Annals of Nutrition & Food Science

Review Article
Published: 29 Sep, 2017

Coffee Silverskin: A Low-Cost Substrate for Bioproduction of High-Value Health Promoting Products

*Amaia Iriondo-DeHond[1], Beatriz Fernandez-Gomez[1], Nuria Martinez-Saez[1], Danik M Martirosyan[2], María Dolores Mesa Garcia[3]** and María Dolores del Castillo[1]**

[1]Department of Bioactivity and Food Analysis, Universidad Autónoma de Madrid, Spain

[2]Functional Food Center/Functional Food Institute, USA

[3]Deparment of Biochemistry and Molecular Biology II, University of Granada, Spain

Abstract

In the last decade, the valorization of food wastes has become a priority research line in order to achieve a sustainable food industry. Large amounts of by-products are generated during the coffee industrial processing. Coffee Silverskin (CS) is a thin tegument of the outer layer of the coffee bean and it is the only by-product of the roasting process. This agricultural by-product causes an environmental impact in countries dedicated to its cultivation and processing. Our research group patented an aqueous extract of coffee silverskin (CSE) (P201131128) that is rich in different phytochemicals possessing multifunctional properties such as antioxidant capacity and potential for several applications in nutrition, health and cosmetic. Another priority of our society is to find natural and sustainable strategies to reduce the risk of chronic diseases, in particular those considered epidemics of the 21st century: obesity and diabetes. The aim of the present review is to provide scientific evidence of the usefulness of CSE as a sustainable natural bioproduct for chronic diseases.

Keywords: Antioxidants; Chronic diseases; Coffee by-products; Coffee silverskin; Obesity; Oxidative stress; sustainability

OPEN ACCESS

Correspondence:

*Dolores del Castillo, Department of Bioactivity and Food Analysis, Institute of Food Science Research (CIAL, UAM-CSIC), Nicolás Cabrera, 9 Campus Cantoblanco, Universidad Autónoma de Madrid, 28049 Madrid, Spain, Tel: +34 91 0017900 Ext. 953; E-mail: mdolores.delcastillo@csic.es

**María Dolores Mesa Garcia, Department of Biochemistry and Molecular Biology II, Institute of Nutrition and Food Technology, Centre of Biomedical Research, Laboratory 123, University of Granada, Avenida del Conocimiento s/n, 18100 Armilla, Granada, Spain, Tel: +34 958242334; E-mail: mdmesa@ugr.es

Received Date: 09 Jun 2017

Accepted Date: 22 Sep 2017

Published Date: 29 Jul 2017

Citation:

Iriondo-DeHond A, Fernandez-Gomez B, Martinez-Saez N, Martirosyan DM, Garcia MDM, del Castillo MD. Coffee Silverskin: A Low-Cost Substrate for Bioproduction of High-Value Health Promoting Products. Ann Nutr Food Sci. 2017; 1(1): 1005.

Introduction

Today, 415 million people have diabetes and this alarming number is expected to reach 642 million by 2040. Type 2 Diabetes (T2D) is the most common type of diabetes representing 90% to 95% of all cases. This disease is growing rapidly worldwide in both developed and developing nations. This rise is associated with economic development, ageing populations, increasing urbanization, dietary changes, reduced physical activity and changes in other lifestyle patterns [1].

The term T2D designates not a single disease but a heterogeneous collection of hyperglycemic syndromes resulting from the interaction between a genetic predisposition and behavioral and environmental risk factors. There is strong evidence that obesity and physical inactivity are the main non-genetic determinants of the disease. Usually, T2D occurs in adults, but it is increasingly seen in children and adolescents. The development of T2D is usually associated with a combination of insulin resistance and beta cell failure leading to high blood glucose levels. Insulin resistance is defined as a pathophysiological condition in which a normal insulin concentration does not adequately produce a normal insulin response in peripheral tissues, such as adipose, muscle and liver tissues [2]. Under these conditions, pancreatic beta cells secrete more insulin (i.e. hyperinsulinemia) to overcome the hyperglycemia among insulin-resistant individuals. Although hyperinsulinemia may compensate maintaining normoglycemia, it may cause the over-expression of other insulin activities [3,4].

Nowadays, experimental and clinical studies support the role of oxidative stress in the pathogenesis of T2D [5]. In diabetes, free radical formation by non-enzymatic glycation of proteins, glucose oxidation and increased lipid peroxidation, leads to the damage of enzymes and cellular machinery and also increased insulin resistance [6]. Oxidative stress and free radicals play a major role in the onset and progression of late diabetic complications such as coronary artery disease, neuropathy, nephropathy and retinopathy [7]. *In vivo* studies support the role of hyperglycemia in the enhancement of oxidative stress leading to endothelial dysfunction in blood vessels of diabetic patients [8].

Food has a vital role in maintaining our health properly and in helping in the prevention and

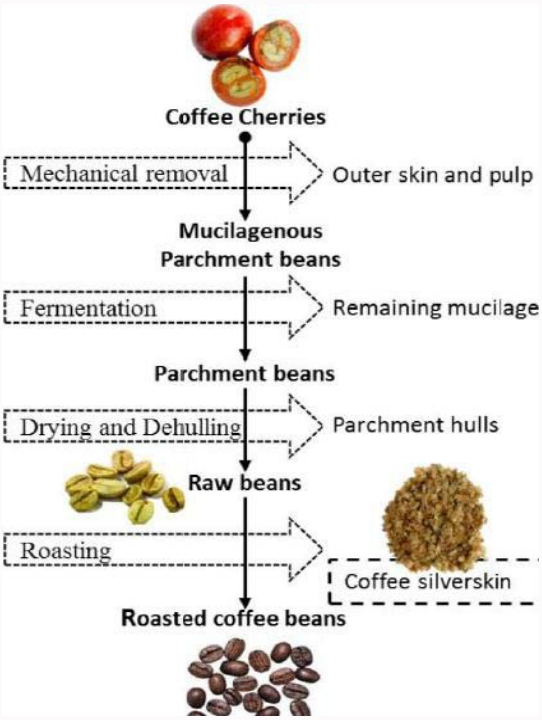

Figure 1: Diagram of coffee silverskin production from wet processing.

cure of some diseases. Nowadays, more than 95% of all chronic disease is caused by food choice, toxic food ingredients, nutritional deficiencies and lack of physical exercise. Many plant extracts and natural compounds are emerging as functional candidates for the reduction of risk of non-communicable chronic diseases, such as T2D [9].

Coffee is considered as an antioxidant beverage with potential beneficial effects on human health [10]. This antioxidant property is due to the presence of bioactive compounds such as caffeine, hydroxycinnamic acids including Chlorogenic Acid (CGA), and melanoidins [11]. Several epidemiological studies have documented the protective effect of coffee components against the risk of chronic diseases due to oxidative stress and inflammation including diabetes [12].

Coffee consumption has been associated with a lower risk of T2D, which may influence different mechanisms such as glucose tolerance, insulin sensitivity, insulin resistance, glucose-6-phosphatase, intestinal glucose absorption, antioxidant activity, inflammatory biomarkers, glucose uptake, glucose homeostasis, glucose metabolism and insulin secretion [13,14]. Although these physiological effects of coffee are related to different components present in the beverage and to the cumulative effects of each compound, most studies on coffee and diabetes clearly associate the observed biological effects to caffeine and CGA [10,13,14].

Coffee silverskin is the thin tegument of the outer layer of the coffee beans and represents about 4.2% (w/w). It is the only by-product produced during the roasting process (Figure 1). This coffee by-product presents phenolic compounds, mainly CGA, and other phytochemicals and bioactive compounds that contribute to its high antioxidant capacity. Our research group patented a CSE from Arabica (*Coffea arabica*) and Robusta (*Coffea canephora*) coffee silverskin (WO 2013004873 A1) enriched in caffeine and CGA [15]. This CSE is extracted with 2 volumes of water per gram of CS at 100°C for at least 10 min, and does not use organic solvents. Thus, CSE is obtained using an environment-friendly technology [15]. The extraction of bioactive compounds from natural products like CS is increasingly being used to prepare dietary supplements (nutraceuticals), food ingredients and some pharmaceutical products (Figure 2) [16].

The patented CSE is rich in total dietary fiber (28% to 36%), which includes about 4% to 9% insoluble dietary fiber and 24% to 26% soluble dietary fiber. CSEs are a good source of polyphenols, particularly CGA (1% to 6%); the most relevant are 5-O-, 3-O- and 4-O-caffeoylquinic acids [9]. CSE is also a good source of caffeine (3%), and melanoidins (17% to 23%) which are formed during the roasting process [17]. The chemical composition of the patented CSE has been described by [9]. Recent studies [18] have shown that CSE contained 11.42 µg/L of acrylamide; which is approximately 10 times lower than that reported in coffee beverages. After *in vitro* digestion under mimicked human conditions acrylamide was not bioaccesible. Therefore, CS may be used as a safe and natural source of health promoting compounds for chronic diseases.

Coffee Silverskin Extract, Oxidative Stress and Aging

Generally, cells are able to balance the production of oxidants and antioxidants. However, when cells are subjected to excessive levels of ROS or as a result of antioxidant depletion, oxidative stress occurs [19]. Under normal conditions, ROS are natural byproducts produced in mitochondria, peroxisome and in the plasma membrane which have positive physiological effects on cells, such as killing microorganisms, acting as a second messenger (H_2O_2) in cellular differentiation and proliferation and regulating signal transduction [20]. However, ROS are also induced by exogenous sources (UV radiation or chemical agents) and cause DNA, protein and lipid damage. The combination of DNA mutations, protein oxidation and lipid peroxidation induces a cellular progressive decline as a result of insufficient supply of energy leading to oxidative stress-induced aging [21]. In the process of aging, there is a deficiency of the endogenous antioxidant defenses of cells and the residual ROS generate oxidative stress, even in physiological conditions [22]. Large epidemiological studies support the relationship between oxidative state and global health, while high consumption of foods rich in antioxidants is associated with lower disease rates and preventive protection [23]. The anti-aging effect of CSE has been investigated *in vivo* employing as an animal model *Caenorhabditis elegans* [24].

Chlorogenic acid has been described as an anti-aging compound in *C. elegans*. A recent study has demonstrated that CGAs, caffeine, melanoidins and other bioactive compounds all together in the CSE may act in a synergic manner when protecting from UV-induced accelerated aging on *C. elegans* [24]. The nematodes that were treated with CSE (1 mg/mL) showed a significantly increased longevity compared to those cultured on a standard diet. The increased longevity observed was similar to that of the nematodes fed on CGA or vitamin C (0.1 µg/mL). The antiaging properties of the CSE observed in this study are due to its antioxidant character caused by phenols among other bioactive compounds present in the botanical material. Some plant extracts containing CGA and other polyphenols are able to exert an antiaging effect on *C. elegans*. For instance, crude blueberry extract and blueberry polyphenols (including an hydroxycinnamic ester fraction containing CGA) have lengthened the nematode's mean lifespan by 28% [25]. Moreover, Vayndorf et

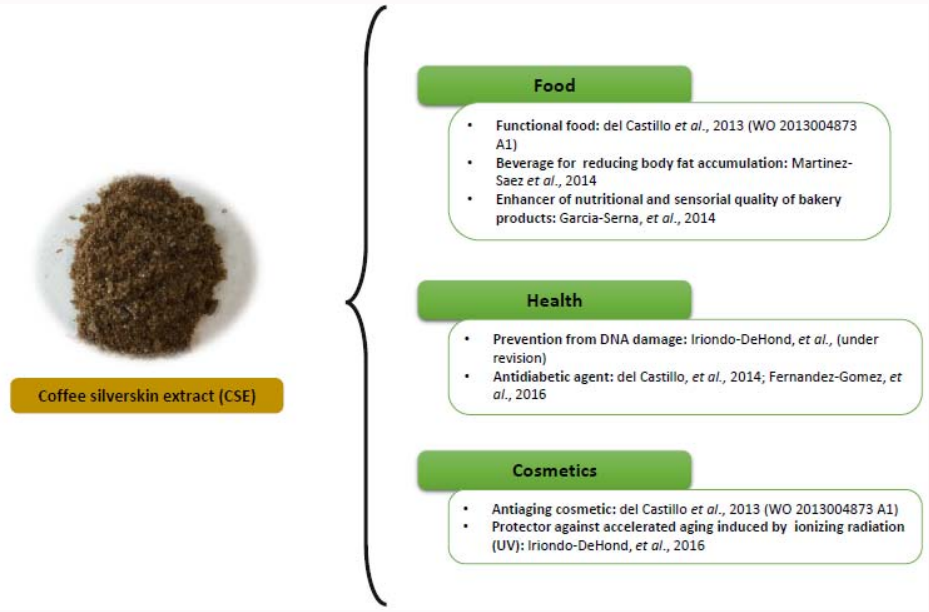

Figure 2: Applications of the patented CSE (WO 2013004873 A1) in food, health and cosmetics.

al. [26] observed that when *C. elegans* was pre-treated with whole apple extracts, worms were more resistant to stresses such as heat, UV radiation and pathogenic infection, suggesting that cellular defense and immune system functions were improved. The authors suggest a possible antioxidant mechanism underlying the antiaging effects of whole apple phytochemicals [26]. Coffee silverskin extract has the potential to be used as an ingredient in skin care products for topical use and as nutricosmetic to prevent accelerated skin aging induced by oxidative stress caused either by exogenous sources (photoaging).

Oxidative stress can also lead to DNA lesions such as DNA strand breaks and oxidized bases [27]. Considering the high antioxidant power of CSE, this extract could protect cells from DNA damage when induced by an oxidative agent. Benzo(a)pyrene (B(a)P) is a carcinogenic Polycyclic Aromatic Hydrocarbon (PAH) found in air, water, soils and in thermally processed foods and cigarette smoke [28,29]. Benzo(a)pyrene induces the production of ROS in cells during the metabolism of this food mutagen, which leads to DNA damage [30].

Have evaluated the protective effect of CSE and CGA against B(a)P induced DNA damage (strand breaks and oxidized purines/pyrimidines) in HepG2 cells. Results showed a significant decrease ($p \leq 0.05$) in DNA strand breaks when cells were pretreated with CSE and CGA [31]. Several authors have confirmed the protective effect of roasted coffee consumption on DNA integrity in humans [32,33]. The reduction of spontaneous DNA strand breaks observed may be attributed to the presence of antioxidants with chemo preventive properties (such as CGAs and roast-associated constituents) [32]. Considering that CS keeps part of the polyphenolic compounds that are normal constituents of coffee beans, such as CGA, it is likely that this effect described for coffee brews is also maintained in CS. These results indicate that CSE protects human cells from DNA strand breaks and oxidative DNA damage effects of B(a)P, and that free CGA or linked to other chemical structures seem to be contributors to the observed chemo protective effect of CSE [31]. This extract presents potential as a natural and sustainable food ingredient.

Coffee Silverskin, Obesity and Dyslipidemia

Overweight and obesity are the major cause of the metabolic syndrome, which is increasing rapidly in modern societies [34]. Therefore, treatment should focus on weight loss by increasing exercise and improving dietary habits; and medical treatment can be used if lifestyle changes are insufficient. Novel foods from natural sources have attracted much attention as potential therapeutic agents in the prevention and treatment of obesity [35].

Recently, the impact of CSE on obesity and diabetes has been evaluated. CSEs from Arabica and Robusta coffees have been used for the preparation of antioxidant novel beverages to study the inhibitory effect on fat accumulation *in vivo* using as animal model *C. elegans* [36]. A significant dose-response effect on reducing accumulation of body fat was found for pure CGA (3.54 mg/L) and caffeine (4.85 mg/L), achieving 30% and 29% reduction of lipid deposits, respectively. The brews of Arabica and Robusta CSE (100 µg/mL), which contained physiologically active doses of CGA and caffeine, were effective reducing body fat 21% and 24%, respectively. Furthermore, similar results in body fat reduction by Robusta CSE beverage were found when a commercial dietary supplement made from Robusta decaffeinated green coffee extract was studied. Therefore, CSE is a natural alternative to dietary supplements for the prevention of overweight and obesity [18,36].

In addition, CSE reduced total cholesterol and triglycerides plasma levels in rats after 45 days of treatment with CSE (2.2 mg caffeine/kg body weight and 0.8 mgCGA/kg body weight). CSE also reduced 41.73% the activity of pancreatic lipase *in vitro* at concentration of 36 mg/mL. This could explain the mechanism of action of the observed reduction of total cholesterol and triglycerides, since pancreatic lipase is a key enzyme in fat digestion [37]. These results support the lyporegulatory character of CSE through the inhibition of pancreatic lipase and therefore its preventive and therapeutic effect in the obesity disease.

The anti-obesity effect of coffee may be due to its bioactive compounds, such as caffeine, CGAs and melanoidins, which are

also present in coffee silverskin [17,37]. CGA and caffeine can regulate lipid metabolism by modulating cell signaling, reducing lipid accumulation and size of adipocytes [38], inhibiting pancreatic lipase [39], regulating hepatic lipid metabolism-related enzymes [40], and by down regulating genes involved in adipogenesis [41]. The combination of these effects leads to the suppression of body fat accumulation [42]. In addition, coffee melanoidins have showed to protect against non-alcoholic fatty liver disease by reducing the hepatic fat accumulation in the rat model [43].

Coffee Silverskin and Diabetes

Type 2 diabetes is usually associated to a combination of insulin resistance and beta cell failure leading to high blood glucose levels. Hyperglycemia is a major factor contributing to accelerated protein glycation and the formation of Advanced Glycation End Product (AGEs) [44]. In diabetes, free radical formation by non-enzymatic glycation of proteins, glucose oxidation and increased lipid peroxidation, leads to damage of enzymes, cellular machinery and also increases insulin resistance [6]. Oxidative stress plays a major role in the development of late diabetic complications such as coronary artery disease, neuropathy, nephropathy, and retinopathy [7].

Studies suggest that moderate intake of coffee may lower risk of T2D [45]. The effects observed on diabetes biomarkers may be associated to the synergic effect of different bioactive compounds present in coffee such as CGA, caffeine, their metabolites and others coffee components. Some of these compounds are also present in CSE [9] and have an effect in diabetes biomarkers.

Caffeine concentrations present in CSE range between 3% and 3.4% [9]. Studies performed in rats suffering streptozotocin-induced diabetes showed that caffeine in CSE was metabolized and the metabolites protected the pancreas against oxidative stress [46]. In addition, caffeine can also reduce glucose levels and insulin sensitivity [47,48]. Other authors have also observed a protective effect of caffeine in pancreatic beta cells [49,50].

Coffee silverskin extract also contains CGA in a range of 1.1% to 6.8% [9]. Results obtained by our research group suggest that CGA and its metabolites have a greater effect on T2D biomarkers than caffeine. CGA and its roasting-formed derivates present in CSE have been proposed as the main contributors to the beneficial effects of CSE on T2D [14,51]. The different mechanisms by which CGA exerts its antidiabetic effect are: a) regulation of glucose metabolism [45,52], b) enhancement of insulin action [52,53]. c) Inhibition of α-glucosidase activity [54,55], d) protection against oxidative stress [56] and e) inhibition of AGEs formation [57]. Different studies demonstrate that the formation of fluorescent AGEs is inhibited by different pathways such as carbonyl trapping, antioxidant effect and the formation of protein-phenols conjugates [57-59].

Other coffee constituents relevant in the prevention of T2D are melanoidins, melatonin, lignans and lignin, tannic acid, isoflavones and trigonelline, all of which may be present in CSE. These compounds may exert synergic effects being responsible for the health-promoting properties of CSE. Further research should be carried out in order to confirm the presence of these compounds in CSE and to prove their effect in the prevention of T2D.

In conclusion, CSE contains a number of coffee components able to reduce the risk of accelerated aging and chronic metabolic disorders such as T2D. These effects may be associated to its antioxidant power and capacity to inhibit enzymes involved in the metabolism of nutrients.

Acknowledgements

This research was supported by the NATURAGE (AGL2010-17779) and SUSCOFFEE (AGL2014-57239-R) projects. Fernandez-Gomez, B. (BES-2011-046827) and Iriondo-DeHond, A. (BES-2015-072191), thanks the Spanish Ministry of Economy and Competitiveness (MINECO) for their pre-doctoral research fellowship (FPI) and Martinez-Saez, N. thanks the Autonomous University of Madrid (U.A.M) for her FPI-predoc fellow.

References

1. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001;414(6865):782-7.
2. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev. 2013;93(1):137-88.
3. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2016;39:S13-22.
4. Hameed I, Masoodi SR, Mir SA, Nabi M, Ghazanfar K, Ganai BA. Type 2 diabetes mellitus: From a metabolic disorder to an inflammatory condition. World J Diabetes. 2015;6(4):598-612.
5. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, et al. Impaired fasting glucose and impaired glucose tolerance. Diabetes Care. 2007;30(3):753-9.
6. Maritim AC, Sanders RA, Watkins JB. Diabetes, oxidative stress, and antioxidants: A review. J Biochem Mol Toxicol. 2003;17(1):24-38.
7. Oguntibeju O. Antioxidant-antidiabetic agents and human health. Croatia: InTech; 2014.
8. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010;107(9):1058-70.
9. del Castillo MD, Fernandez-Gomez B, Martinez-Saez N, Iriondo-DeHond A, Martirosyan DM, Mesa MD. Coffee silverskin extract for aging and chronic diseases. In: Martirosyan DM, editor. Functional Foods in Health and Disease. CreateSpace Independent Publishing Platform; 2016.
10. Moreira ASP, Nunes FM, Domingues MR, Coimbra MA. Coffee melanoidins: structures, mechanisms of formation and potential health impacts. Food Funct. 2012;3:903-15.
11. Fava F, Totaro G, Diels L, Reis M, Duarte J, Carioca OB, et al. Bio waste bio refinery in Europe: opportunities and research & development needs. N Biotechnol. 2015;32(1):100-8.
12. Bisht S, Sisodia S. Coffea arabica: A wonder gift to medical science. J Nat Pharm. 2010;1(1):58-65.
13. Akash MS, Rehman K, Chen S. Effects of coffee on type 2 diabetes mellitus. Nutrition. 2014;30(7-8):755-63.
14. Ludwig IA, Clifford MN, Lean MEJ, Ashihara H, Crozier A. Coffee: biochemistry and potential impact on health. Food Funct. 2014;5(8):1695-717.
15. del Castillo MD, Ibañez ME, Amigo M, Herrero M, Plaza del Moral M, Ullate M. Application of products of coffee silverskin in anti-ageing cosmetics and functional food. 2013.
16. Dai J, Mumper RJ. Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. Molecules. 2010;15(10):7313-52.
17. Mesías M, Navarro M, Martínez-Saez N, Ullate M, del Castillo MD, Morales FJ. Antiglycative and carbonyl trapping properties of the water soluble fraction of coffee silverskin. Food Res Int. 2014;62:1120-6.
18. Garcia-Serna E, Martinez-Saez N, Mesias M, Morales FJ, del Castillo MD.

Use of coffee silverskin and stevia to improve the formulation of biscuits. Polish J Food Nutr Sci. 2014;64(4):243-51.

19. Hancock JT, Desikan R, Neill SJ. Role of reactive oxygen species in cell signalling pathways. Biochem Soc Trans. 2001;29:345-50.

20. Klaunig JE, Kamendulis LM, Hocevar BA. Oxidative stress and oxidative damage in carcinogenesis. Toxicol Pathol. 2010;38(1):96-109.

21. Baumann L. Skin ageing and its treatment. J Pathol. 2007;211(2):241-51.

22. Momtaz S, Abdollahi M. A comprehensive review of biochemical and molecular evidences from animal and human studies on the role of oxidative stress in aging: An epiphenomenon or the cause. Asian J Anim Vet Adv. 2012;7(1):1-19.

23. Prior RL. Oxygen radical absorbance capacity (ORAC): New horizons in relating dietary antioxidants/bioactives and health benefits. J Funct Foods. 2015;18:797-810.

24. Iriondo-DeHond A, Martorell P, Genovés S, Ramón D, Stamatakis K, Fresno M, et al. Coffee silverskin extract protects against accelerated aging caused by oxidative agents. Molecules. 2016;21(6):1-14.

25. Wilson MA, Shukitt-Hale B, Kalt W, Ingram DK, Joseph JA, Wolkow CA. Blueberry polyphenols increase lifespan and thermo tolerance in Caenorhabditis elegans. Aging Cell. 2006;5(1):59-68.

26. Vayndorf EM, Lee SS, Liu RH. Whole apple extracts increase lifespan, health span and resistance to stress in Caenorhabditis elegans. J Funct Foods. 2013;5(3):1236-43.

27. Xue W, Warshawsky D. Metabolic activation of polycyclic and heterocyclic aromatic hydrocarbons and DNA damage: A review. Toxicol Appl Pharmacol. 2005;206(1):73-93.

28. Brinkmann J, Stolpmann K, Trappe S, Otter T, Genkinger D, Bock U. Metabolically competent human skin models: activation and genotoxicity of benzo[a]pyrene. Toxicol Sci. 2013;131(2):351-9.

29. International Agency for Research on Cancer. Chemical agents and related occupations. In: A review of human carcinogens. Lyon: IARC, France; 2012.

30. Haza AI, Morales P. Spanish honeys protect against food mutagen-induced DNA damage. J Sci Food Agric. 2013;93(12):2995-3000.

31. Iriondo-DeHond A, Haza AI, Avalos A, del Castillo MD, Morales P. Validation of coffee silverskin extract as a food ingredient by the analysis of cytotoxicity and genotoxicity. Food Res Int. 2017;100:791-7.

32. Bakuradze T, Lang R, Hofmann T, Eisenbrand G, Schipp D, Galan J, et al. Consumption of a dark roast coffee decreases the level of spontaneous DNA strand breaks: a randomized controlled trial. Eur J Nutr. 2014;54(1):149-56.

33. Bakuradze T, Boehm N, Janzowski C, Lang R, Hofmann T, Stockis JP, et al. Antioxidant-rich coffee reduces DNA damage, elevates glutathione status and contributes to weight control: Results from an intervention study. Mol Nutr Food Res. 2011;55(5):793-7.

34. Tsai YJ, Wu MP, Hsu YW. Emerging health problems among women: Inactivity, obesity, and metabolic syndrome. Gynecol Minim Invasive Ther. 2014;3(1):12-14.

35. Boqué N, Campión J, de la Iglesia R, de la Garza AL, Milagro FI, San Román B, et al. Screening of polyphenolic plant extracts for anti-obesity properties in Wistar rats. J Sci Food Agric. 2013;93(5):1226-32.

36. Martinez-Saez N, Ullate M, Martin-Cabrejas MA, Martorell P, Genovés S, Ramon D. A novel antioxidant beverage for body weight control based on coffee silverskin. Food Chem. 2014;150:227-34.

37. del Castillo MD, Fernandez-Gomez B, Ullate M, Mesa MD. Use of coffee husk products for the prevention and treatment of the pathologies that make up the metabolic syndrome and its metabolic factors. Risk. 2014;P201431848.

38. Kim J, Jang JY, Cai J, Kim Y, Shin K, Choi EK, et al. Ethanol extracts of unroasted Coffea canephora robusta beans suppress adipogenesis in preadipocytes and fat accumulation in rats fed a high-fat diet. Food Sci Biotechnol. 2014;23(6):2029-35.

39. Narita Y, Iwai K, Fukunaga T, Nakagiri O. Inhibitory activity of chlorogenic acids in decaffeinated green coffee beans against porcine pancreas lipase and effect of a decaffeinated green coffee bean extract on an emulsion of olive oil. Biosci Biotechnol Biochem. 2012;76(12):2329-31.

40. Zheng G, Qiu Y, Zhang QF, Li D. Chlorogenic acid and caffeine in combination inhibit fat accumulation by regulating hepatic lipid metabolism-related enzymes in mice. Br J Nutr. 2014;112(6):1034-40.

41. Song SJ, Choi S, Park T. Decaffeinated green coffee bean extract attenuates diet-induced obesity and insulin resistance in mice. Evid Based Complement Altern Med. 2014;2014:718379.

42. Murase T, Misawa K, Minegishi Y, Aoki M, Ominami H, Suzuki Y, et al. Coffee polyphenols suppress diet-induced body fat accumulation by down regulating SREBP-1c and related molecules in C57BL/6J mice. Am J Physiol Endocrinol Metab. 2011;300(1):E122-33.

43. Vitaglione P, Morisco F, Mazzone G, Amoruso DC, Ribecco MT, Romano A, et al. Coffee reduces liver damage in a rat model of steatohepatitis: the underlying mechanisms and the role of polyphenols and melanoidins. Hepatology. 2010;52(5):1652-61.

44. Vlassara H, Uribarri J. Advanced glycation end products (AGE) and diabetes: cause, effect, or both? Curr Diab Rep. 2014;14(1):453.

45. van Dijk AE, Olthof MR, Meeuse JC, Seebus E, Heine RJ, van Dam RM. Acute effects of decaffeinated coffee and the major coffee components chlorogenic acid and trigonelline on glucose tolerance. Diabetes Care. 2009;32(6):1023-5.

46. Fernandez-Gomez B, Lezama A, Amigo-Benavent M, Ullate M, Herrero M, Martín MA, et al. Insights on the health benefits of the bioactive compounds of coffee silverskin extract. J Funct Foods. 2016;25:197-207.

47. Kagami K, Morita H, Onda K, Hirano T, Oka K. Protective effect of caffeine on streptozotocin-induced beta-cell damage in rats. J Pharm Pharmacol. 2008;60(9):1161-5.

48. Urzua Z, Trujillo X, Huerta M, Trujillo-Hernandez B, Rios-Silva M, Onetti C, et al. Effects of chronic caffeine administration on blood glucose levels and on glucose tolerance in healthy and diabetic rats. J Int Med Res. 2012;40(6):2220-30.

49. Abunasef SK, Amin HA, Abdel-hamid GA. A histological and immunohistochemical study of beta cells in streptozotocin diabetic rats treated with caffeine. Folia Histochem Cytobiol. 2014;52(1):42-50.

50. Chen L, Yu M, Shen T, Xia J, Xu BL. Impact of caffeine on β cell proliferation and apoptosis under the influence of palmitic acid. Genet Mol Res. 2015;14(2):5724-30.

51. Cano-Marquina A, Tarín JJ, Cano A. The impact of coffee on health. Maturitas. 2013;75(1):7-21.

52. Li SY, Chang CQ, Ma FY, Yu CL. Modulating effects of chlorogenic acid on lipids and glucose metabolism and expression of hepatic peroxisome proliferator-activated receptor-alpha in golden hamsters fed on high fat diet. Biomed Environ Sci. 2009;22(2):122-9.

53. Ma Y, Gao M, Liu D. Chlorogenic acid improves high fat diet-induced hepatic steatosis and insulin resistance in mice. Pharm Res. 2015;32(4):1200-9.

54. Ishikawa A, Yamashita H, Hiemori M, Inagaki E, Kimoto M, Okamoto M, et al. Characterization of inhibitors of postprandial hyperglycemia from the leaves of Nerium indicum. J Nutr Sci Vitaminol (Tokyo). 2007;53(2):166-73.

55. Tateishi E, Han LK, Okuda H. Effect of a hot-water extract from coffee beans on the postprandial blood glucose concentration in rats. Japanese J Nutr Diet. 2004;62:323-7.

56. Karthikesan K, Pari L, Menon VP. Combined treatment of tetrahydrocurcumin and chlorogenic acid exerts potential antihyperglycemic effect on streptozotocin-nicotinamide-induced diabetic rats. Gen Physiol Biophys. 2010;29(1):23-30.

57. Kim J, Jeong IH, Kim CS, Lee YM, Kim JM, Kim JS. Chlorogenic acid inhibits the formation of advanced glycation end products and associated protein cross-linking. Arch Pharm Res. 2011;34(3):495-500.

58. Fernandez-Gomez B, Ullate M, Picariello G, Ferranti P, Mesa MD, del Castillo MD. New knowledge on the antiglycoxidative mechanism of chlorogenic acid. Food Funct. 2015;6(6):2081-90.

59. Gugliucci A, Bastos DH, Schulze J, Souza MF. Caffeic and chlorogenic acids in Ilex paraguariensis extracts are the main inhibitors of AGE generation by methylglyoxal in model proteins. Fitoterapia. 2009;80(6):339-44.