RELATO DE CASO

Can the consumption of Seeds, Leaves and Fruit Peels avoid the risk factors for Cardiovascular Disorders?

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Não há conflitos de interesse

ABSTRACT

Changes in the feeding pattern of the population have recently led to a greater occurrence of cardiovascular risk factors that contribute to a high rate of morbidity and mortality worldwide. The presence of beneficial bioactive compounds in fruits and processed sub-products have proven to have a negative association with risk factors, such as blood pressure reduction, plasmatic lipoproteins control and increased resistance of LDL-c to oxidation, in addition to glycemic control and antioxidant effects. The aim of this review is to show that several studies have demonstrated many different chemical compounds in seeds, leaves and fruit peels, including their metabolic and physiologic effects on the risk factors of cardiovascular diseases. We reviewed the relevant literature by searching English-language publications in Pubmed, Google Scholar, Scielo and Lilacs, and references from relevant articles published since 2010, especially in the last five years. Eighty-seven relevant articles were included.

Keywords: phytochemicals, antioxidants, fruit, plants

INTRODUCTION

Epidemiological studies have shown that modernity's diseases affect more and more individuals, being responsible for high rates of mortality and morbidity in the population. Among them, cardiovascular diseases are the main cause of mortality worldwide, which can be explained by the occurrence of associated cardiovascular risk factors, such as visceral obesity, insulin resistance, hypercholesterolemia, smoking and hypertension[1,2,3,4].

Changes in the feeding pattern of the population have visibly contributed to the occurrence of these risk factors, since most of the modifiable factors are directly associated with the individuals' diet and physical activity. The current feeding pattern is characterized by a high intake of high-calorie, high-fat and sodium-rich foods, and by a limited intake of fibers and antioxidant compounds[5,6].

In this context, scientific studies have shown that the regular consumption of fruit and vegetables has been associated with the lower incidence of acute myocardial infarction, blood pressure reduction, lipoprotein control and increased resistance of LDL-c (low-density lipoprotein cholesterol) to oxidation, in addition to reduced levels of adhesion molecules and pro-inflammatory markers, both of which are markers of the endothelial function[7,8,9,10].

In addition to that, studies have widely demonstrated that non-conventional fractions of vegetable raw materials have higher concentrations of phytochemical compounds with beneficial physiological and metabolic properties in experimental models and humans [11,12]. These fractions are composed of seeds, leaves, and peels; they are considered to be domestic or industrial waste and are only sporadically consumed, but present high concentrations of metabolites with beneficial biochemical properties, which may be used to prevent and treat chronic degenerative diseases[13,14,15].

The aim of this review is to show that several studies have found many different chemical compounds in seeds, leaves and fruit peels, including their metabolic and physiologic effects on the risk factors of cardiovascular diseases.

Methods

We reviewed the relevant literature by searching English-language publications in *Pubmed, Google Scholar, Scielo* and *Lilacs*, and references from relevant articles published since 2010, especially in the last five years. Eighty-seven relevant articles were included in the study.

Results and Discussion

Seeds: Benefits for Humans and the Environment

The seeds of fruits and some vegetables stand out as some of the most commonly found agro-industrial waste. They are the byproducts of domestic or industrial processes, but they often have significant contents of antioxidant and anti-inflammatory compounds[15,16,17].

The guava *(Psidium guajava L.)* is one of the most popular tropical fruit, cultivated and consumed throughout the world; the largest part of its production is utilized in pastry, juice, jelly, nectar and the ice-cream industry, which exploit the pulp. The disposal of the seeds and peels corresponds to approximately 30% of the fruit's weight[18]. El Anany[19] identified the presence of phenolic and flavonoid compounds in guava *(P. guajava)* seeds, which showed a high radical-scavenging activity; Farinazzi-Machado et al.[20] identified that the seeds of *P. guajava* significantly decreased glycaemia, triacylglyceride and total cholesterol levels, whilst they increased the levels of HDL-c, when administered in experimental models.

Avocado (Persea americana Mill.) seeds make up a large portion of the fruit, favoring research on the extraction of biologically active compounds to be used in the food and pharmaceutical industries. In 'Hass' avocado seeds, Daiuto et al.[21] observed more expressive contents of total phenolic compounds when compared to the fruit pulp; the Trolox equivalent antioxidant capacity and the antioxidant capacity measured by the ABTS+ ([2,2'-azinobis (3-ethylbenz-thiazoline-6-sulfonic acid]) radical capture method were significantly higher in the seed than in the pulp. Studies have also demonstrated the presence of flavanol monomers, proanthocyanidins, hydroxycinnamic acids and flavonol glycosides in avocado seeds[22]. Pahua-Ramos et al.[23] identified that the fruit seed flour had hypocholesterolemic effects in experimental models; these results were attributed to the antioxidant phenolic compounds and the considerable nutritional fiber contents.

The residue obtained in the wine sector in the grape pressing process corresponds to almost 40%, and it is characterized by its high polluting potential, formed by the stalks of bunches, peels, and seeds. The latter are considerable sources of tocopherols, unsaturated fatty acids, linoleic acid and phenolic compounds[24]. Ngamukote et al.[25] found taurocholic acid, taurodeoxycholic acid, and glycodeoxycholic acid at levels ranging from 38.6% to 28.2% in grape seeds, in addition to gallic acid, catechin, and epicatechin – these are compounds to which inhibitory effects of the pancreatic cholesterol esterase and decreased absorption of intestinal cholesterol are attributed. Another study revealed the antioxidant activity of grape *(Vitis vinifera L.)* seeds through the reduction of lipid oxidation and the inhibition of the production of free radicals induced by ethanol in experimental models[26].

Proanthocyanidins extracted from grape seeds have shown several beneficial effects: reduction of food ingestion and body weight of animals;

significant reduction of the levels of triglycerides, total cholesterol, low density lipoproteins and advanced glycation end products (AGEs); increase of high-density lipoproteins; activity of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase(27,28,29).

Hippophae rhamnoides L. (sea buckthorn) has been used in traditional medicine for a long time due to its multiple biological properties (anticancer, antimicrobial, and cardioprotective) (30). Its fruits are rich in vitamin C (average content of 695mg/100g), vitamin A, vitamin E, amino acids, minerals, β-sitosterol and polyphenolic acids. The administration of sea buckthorn seed waste reduced the body weight as well as the total cholesterol and hepatic triglycerides in experimental models(31).

The passion fruit's peels and seeds (which represent around 40% of the fruit's total weight) resulting from the fruit cutting and extraction process for the extraction of the juice are still mostly discarded. Studies have shown that the seeds are rich in linoleic acid, tocopherols, vitamin E, fiber, and total phenolic content, like gallic acid and quercetin (32,33).

Piceatannol is a polyphenolic antioxidant found in passion fruit (Passiflora edulis) seeds and others plants. In fact, piceatannol has been shown to have various cardioprotective effects, such as inhibition of platelet aggregation, inhibition of LDL-c oxidation, vasorelaxant effects in endothelium-intact aortas and reduction of myocardial tissue damage during ischemic events(34,35). In studies with experimental models, piceatannol reduced fasting blood glucose levels and enhanced the secretion of insulin(36,37).

The seeds of the Amazonian fruit Byrsonima crassifolia, popularly known as muruci, were used in diabetic rats, which revealed the seeds' potential effect in: reducing glucose levels and blood lipids; increasing insulin sensitivity; protecting against the activity of AGEs (advanced glycation end products); they are considered a potential, safe, anti-diabetic agent(38,39).

Other seeds have demonstrated hypoglycemic and lipid-lowering effects in experimental models. The tamarind *(Tamarindus indica)* seed proved to be effective in the control of blood glucose levels and fasting insulin levels, in addition to total cholesterol, triglyceride, and LDL-c levels, when administered to Wistar rats(40, 41). In a study developed by Sharma et al.(42), the seeds of the *Eugenia jambolana* demonstrated an anti-hyperglicemic and hypolipidemic effect in rabbits with severe diabetes induced by alloxan.

Peels: Does their use bring benefits?

Many phenolic compounds present in plants extracts are known for their cardiovascular regulatory properties and many are amply available in fruit and vegetable's peels, including flavones (luteolin, apigenin), flavonols (rutin, quercetin, kaempferol), phenolic acids, catechin, and others(11,43).

Citrus fruit peels have high concentrations of bioactive compounds with antioxidant and anti-inflammatory effects. Loizzo et al.(44) identified the presence of apigenin, rutin, quercetin, kaempferol, and nobiletin in the peel extract of *Citrus aurantifolia*, and Boshtam et al.(45) observed an LDL-c oxidation prevention effect using the peel extract of the same plant.

Extracts of the unripe *Citrus sunki* peels had an anti-obesity effect through the increase in β-oxidation and lipolysis in the adipose tissue, without any observed liver damage, by reducing serum levels of glutamic pyruvic transaminase, glutamic oxaloacetic transaminase and lactate dehydrogenase, hepatic mediators(46). Thirteen flavonoids were quantified in grapefruit peel extracts by HPLC; the main flavonoids occurring in fresh, oven-dried, and freeze-dried grapefruit *(Citrus paradisi Macf.)* peels are naringin and isonaringin(47).

Ajila et al.(48) identified varying concentrations of gallic acid, syringic acid, mangiferin, ellagic acid, gentisyl-protocatechuic acid and quercetin in raw peels of ripe mango *(Mangifera indica L.)*. According to the literature, compounds such as quercetin, gallic acid, and ellagic acid regulate hepatic and enterocyte cholesterol metabolism by controling the key enzymes, including the activity of hepatic 3-hidroxi-3-metil-glutaril-CoA (HMG-CoA) reductase and enzyme acyl-CoA cholesterol acyltransferase (ACAT-2)(49,50). Studies have also shown that the quercetin metabolites, which have an expressive presence in the extracts of apple peels, were responsible for the oxidation inhibition of LDL-c molecules in vitro[51].

Anthocyanins are bioactive compounds responsible for the blue and purple coloring of fruits, flowers, and peels. The jabuticaba *(Myrciaria cauliflora)* peel has high concentrations of anthocyanins, such as cyanidin-3-O-glucoside and delphinidin-3-O-glucoside. The consumption of jabuticaba peels was shown to increase HDL-cholesterol and improve insulin resistance in experimental animals; the tested doses of jabuticaba peels did not present cytotoxic properties in the animals of the study[52,53]. According to Suttirak and Manurakchinakorn[54], the anthocyanin contents increase during the ripening of the fruits, since the peel of ripe mangosteen (Garcinia mangostana), which has an intense purple coloration, shows an expressive concentration of this phytochemical and a high antioxidant activity.

Rai et al.[55], using raw *Psidium guajava* fruit peels, demonstrated their hypolipidemic and hepatoprotective effects, since their use in rats induced to severe diabetes, significantly reducing the plasma levels of triglycerides, total cholesterol, and LDL-c.

The yellow passion fruit *(Passiflora edulis)* peel has been studied for many years because of its hypoglycemic and anti-inflammatory properties, being currently consumed in the form of flour and food additive. Studies have demonstrated the presence of a high concentration of soluble fibers, especially pectin, phenolic compounds, such as isoorientin, coumarin, cyanidin-3-the-glycoside, quercetin-3-O-glycoside and edulic acid, among other yellow flavonoids. The treatment of experimental models and humans with the flour or yellow passion fruit peel extract revealed antihypertensive, antioxidant and antihyperglycaemic effects, in addition to decreased insulin resistance and hypolipidemic activity[56,57,58,59,60,61].

The pitaya is a rustic fruit belonging to the Cactaceae family, known worldwide as “dragon fruit”. Among the species, the white pulp red pitaya *(Hylocereus undatus)* stands out; its peel is considered a residue from the fruit consumption or processing. However, this fruit peel has variable concentrations of phenolic compounds (40.68mg GAE.100g-1 to 116.14mg GAE.100g-1 – the equivalent of gallic acid), in addition to vitamin C and betalains of the betacyanin type – substances derived from betalamic acid, with significant antioxidant activity[62,63,64]. Song et al.[65] observed that the betacyanins present in the peel of the white pulp red pitaya caused a reduction in body weight and an improvement in adipose tissue hypertrophy, in addition to controlling glycemia and insulin resistance in rats treated with a hyperlipidemic diet.

In a study conducted by Jung[66], the peels of pomegranates contained four monoterpenes: beta-thujene; o-cymene; beta-phellandrene; and gamma-terpinene; in addition to various volatile compounds, such as hydrocarbons, alcohols, aldehydes and ketones. Administration of the peel extracts of this fruit, in a study by Sadeghipour et al.[67], significantly decreased total serum cholesterol, triglycerides and LDL-c levels in rats fed on a high-lipid diet, and maintained normal levels of the TGO and TGP enzymes.

Leaves: better than the pulp?

Recent studies have revealed that the leaves of fruit and vegetables have higher nutrient and phytochemical values when compared with their respective edible parts, possibly because they are more exposed to oxidative stress[68].

In a study developed by Wang et al.[69], apple *(Morus alba)* leaves were shown to have higher concentrations of polyphenolic and flavonoid compounds when compared to the levels found in the fruit pulp. Other studies have shown the presence of such phenolic compounds as mulberrofuran, chalcomoracin, kuwanon, isobavachalcone, flavones norartocarpetin, kuwanon and 6-geranylapigenin in leaves of the apple tree[70,71]. Lee et al.[72] used different concentrations of an aqueous extract of *Morus alba* L. in experimental models and observed protective effects against atherogenic diet-induced hypertension, hyperlipidemia and vascular dysfunction. In addition to the anti-atherogenic effect of the apple leaves, Sharma et al.[73] identified a reduction of fasting glycemia in diabetic rats.

By studying the leaves and seeds of the avocado *(Persea americana Mill)* of the Hass and Shepard varieties, Kosińska et al.[22] identified that the total phenolic content and antioxidant activity of these plants was considerably higher in the leaves than in the fruit seeds. Another study identified the presence of catechins, procyanidins and hydroxycinnamic acids in the leaves of the avocado *Persea americana* Mill of the Hass and Fuerte varieties[74].

In the raspberry *(Rubus idaeus L.)* leaves, different phytochemical compounds were identified, including flavonoids, quercetin derivatives, luteolin derivatives, kaempferol derivatives and isorhamnetin derivatives[75]. Another study revealed that the leaves of this plant showed antioxidant activity through its polyphenol contents, in addition to cytotoxic activity against colon adenocarcinoma[76].

Barbalho et al.[77] evaluated the effects of the pulp and leaves of the mountain soursop *(Annona montana)* in the biochemical profile of Wistar rats. They identified that the leaves produced better effects in the reduction of blood glucose and lipid variables in animals when compared to the fruit pulp, and that they didn't provoke an elevation of hepatic mediators in the animals of the experiment.

Liberal et al.[78] found polyphenols, namely ellagitannins, proanthocyanidins, and quercetin and kaempferol glucuronide derivatives in Fragaria vesca leaves extracts. These authors observed that the aqueous extract of strawberry leaves had an anti-inflammatory potential through the inhibition of nitric oxide production and the increased expression of several pro-inflammatory proteins in lipopolysaccharide-triggered macrophages.

The pomegranate *(Punica granatum L.)* leaves also revealed anti-diabetic and antihyperlipidemic effects in Wistar rats induced to diabetes, in concentrations of 500 mg/kg of the plant's leave extract[79]. Balwani et al.[80] isolated the compound 2-methyl-pyran-4-one-3-O-β-d-glucopyranoside from pomegranate leaves, identifying that it inhibits the expression of cell adhesion molecules, suggesting possible anti-inflammatory effects. Bekir et al.[81] also observed the presence of expressive concentrations of total phenols, flavonoids, tannins and anthocyanins in different extracts of *P. granatum* leaves.

Studies performed with Fig (*Ficus carica* Linn) leaves demonstrated an antioxidant and anti-inflammatory activity based on the identification of steroid compounds, flavonoids such as quercetin and luteolin, and phenolic compounds[82,83].

Fagbohun & Odufuwa[84] observed that the leaves of the cashew tree (*Anarcadium occidentale* L.) demonstrated hypoglycemic activity in rats induced to diabetes by streptozotocin. And the leaves of the sapodilla *(Manilkara zapota)* also demonstrated cardioprotective effects by reducing the levels of glucose, insulin, leptin, cholesterol and triglycerides in Wistar rats[85].

Omar et al.[86] demonstrated that the administration of leave extracts from the jackfruit tree *(Artocarpus heterophyllus)* reduced lipid peroxidation, the levels of total cholesterol, LDL-c and triglycerides, in addition to reducing fasting glycemia and glycated hemoglobin values and increasing the HDL-c levels in diabetic rats by 37%. In a similar study, Chackrewarthy et al.[87] observed a reduction in the glucose levels (39%), total cholesterol (23%) and triglycerides (40%) in animals fed with jackfruit leaves.

Conclusion

Considering that there is a high prevalence of cardiovascular disorders in the population, which results in high morbidity and mortality rates, and that their risk factors can be prevented by the regular consumption of vegetable raw materials, studying the ingestion of non-conventional vegetable fractions becomes relevant, since these fractions have numerous bioactive compounds that protect vascular health. It is also relevant to consider that the use of seeds and peels, described as by-products of plant raw materials processing, not only has beneficial effects but could also contribute to less environmental waste.

REFERENCES

1. Cardona D, Cerezo MP, Parra H, Quintero L, Muñoz L, Cifuentes OL et al. Inequalities in mortality by cardiovascular diseases in the Colombian Coffee Growing Region, 2009-2011. Biomedic 2015 Sep; 35(3): 379-794.

2. Kei A, Elisaf MS. Nicotinic acid: clinical considerations. Expert Opin Drug Saf. 2012 May; 11(4): 551-564.

3. Praveen PA, Roy A, Prabhakaran D. Cardiovascular Disease Risk Factors: A Childhood Perspective. Indian J Pediatr. 2012 May; 80(s1):3-12.

4. Ruano GM, Silvestre TV, Aguirregoicoa GE, Criado GL, Duque LY, García-Blanch G. Nutrition, metabolic syndrome and morbid obesity. Nutr Hosp. 2011 Jul-Aug; 26(4):759-64.

5. Same RV, Feldman DI, Shah N, Martin SS, Al Rifai M, Blaha MJ, Graham G7, Ahmed HM. Relationship Between Sedentary Behavior and Cardiovascular Risk. Curr Cardiol Rep. 2016 Jan; 18(1):6.

6. Bezerra IN, Curioni C, Sichieri R. Association between eating out of home and body weight. Nutr Rev. 2012 Feb; 70(2):65-79.

7. Crowe F, Roddam A, Key T, Appleby P, Overvad K, Jakobsen M, et al. Fruit and vegetable intake and mortality from ischaemic heart disease: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)--Heart study. Eur Heart J. 2011; 32:1235-43.

8. Toh JY, Tan VM, Lim PC, Lim ST, Chong MF. Flavonoids from fruit and vegetables: a focus on cardiovascular risk factors. Curr Atheroscler Rep. 2013; 15:368.

9. Leblanc V, Hudon AM, Royer MM, Corneau L, Dodin S, Bégin C, Lemieux S. Differences between men and women in dietary intakes and metabolic profile in response to a 12-week nutritional intervention promoting the Mediterranean diet. J Nutr Sci. 2015 Apr; 4(13):1-11.

10. Sayegh M, Tsiountsioura M, Page P, Rio DD, Ray S. National Safety Associates nutritional supplementation trial of fruit and vegetable extracts and vascular function (NNTV): study protocol for a randomised controlled trial. Trials. 2016 Feb; 17: 67.

11. Parmar HS, Dixit Y, Kar A. Fruit and vegetable peels: Paving the way towards the development of new generation therapeutics. Drug Discov Ther. 2010 Oct; 4(5):314-25.

12. Sousa MSB, Vieira LM, Silva MJM, Lima A. Caracterização nutricional e compostos antioxidantes em resíduos de polpas de frutas tropicais. Cienc Agrotecnol. 2011; 35(3):554-559.

13. Arbos KA, Stevani PC, Castanha RF. Antimicrobial and antioxidant activity and total phenolic content in mango peel and kernel. Rev. Ceres. 2013. Mar/Abr; 60 (2): 161-165.

14. Deng GF, Shen C, Xu XR, Kuang RD, Guo YJ, Zeng LS. et al. Potential of Fruit Wastes as Natural Resources of Bioactive Compounds. Inter J Molec Sciences. 2012; 13(7):8308–8323.

15. Akhtar N, Khan BA, Majid A, Khan HM, Mahmood T, Gulfishan, Saeed T. Pharmaceutical and biopharmaceutical evaluation of extracts from different plant parts of indigenous origin for their hypoglycemic responses in rabbits. Acta Pol Pharm. 2011 Nov-Dec; 68(6):919-25.

16. Melo OS, Bergamaschi KB, TiveronI AP, MassarioliI AP, CadorinTL, OldoniI MC, et al. Composição fenólica e atividade antioxidante de resíduos agroindustriais. Ciênc Rural. 2011 Jun; 41(6):1088-1093.

17. Infante J, Selani MM, Toledo NMV, Silveira-Diniz MF, Alencar SM, Spoto MHF. Atividade antioxidante de resíduos agroindustriais de frutas tropicais. Braz J. Food Nutr. 2013; 24(1):87-91.

18. Chang YP, Tan MP, Wai LL, Pakianathan S, Supramaniam Y. Making Use of Guava Seed (Psidium guajava L): The Effects of Pre-treatments on Its Chemical Composition. Plant Foods for Human Nutrition. 2014 March; 69(1):43-49.

19. El Anany AM. Nutritional composition, antinutritional factors, bioactive compounds and antioxidant activity of guava seeds (Psidium Myrtaceae) as affected by roasting processes. J Food Science Technol. 2015; 52(4):2175-2183.

20. Farinazzi-Machado FMV, Guiguer EL, Souza MSS, Barbalho SM, Bueno PCS, et al. Effects of Psidium guajava on the metabolic profile of Wistar rats. J Medicinal Plants Res. 2012 May; 6(18):3450-3454 16 May, 2012.

21. Daiuto ER, TremocoldiI MG, Alencar SM, Vieites RL, Minarelli PH. Composição química e atividade antioxidante da polpa e resíduos de abacate 'Hass'. Rev Bra Frutic 2012; 36(2): 417-424.

22. Kosińska A, Karamać M, Estrella I, Hernández T, Bartolomé B, Dykes GA.Phenolic Compound Profiles and Antioxidant Capacity of Persea americana Mill. Peels and Seeds of Two Varieties. J Agric Food Chem. 2012 May 9;60(18):4613-9. Epub 2012 Apr 24.

23. Pahua-Ramos ME, Ortiz-Moreno A, Chamorro-Cevallos G, Hernández-Navarro MD, Garduño-Siciliano L, Necoechea-Mondragón H, Hernández-Ortega M. Hypolipidemic effect of avocado (Persea americana Mill) seed in a hypercholesterolemic mouse model. Plant Foods Hum Nutr. 2012 Mar; 67(1):10-6.

24. Sabir A, Unver A, Kara Z. The fatty acid and tocopherol constituents of the seed oil extracted from 21 grape varieties (Vitis spp.). J Sci Food Agric. 2012 Jul; 92(9):1982-7.

25. Ngamukote S, Mäkynen K, Thilawech T, Adisakwattana S. Cholesterol-lowering activity of the major polyphenols in grape seed. Molecules, 2011 Jun; 16(6):5054-61

26. Dogan A, Celik I. Hepatoprotective and antioxidant activities of grapeseeds against ethanol-induced oxidative stress in rats. Br J Nutr. 2012 Jan; 107(1):45-51.

27. Serrano J, Casanova-Martí À, Gual A, Pérez-Vendrell AM, Blay MT, Terra X, et al. A specific dose of grape seed-derived proanthocyanidins to inhibit body weight gain limits food intake and increases energy expenditure in rats. Eur J Nutr. 2016 Apr 2. [Epub ahead of print].

28. Zhang Z, Li Y, Li Y. Grape seed proanthocyanidin extracts prevent hyperglycemia-induced monocyte adhesion to aortic endothelial cells and ameliorates vascular inflammation in high-carbohydrate/high-fat diet and streptozotocin-induced diabetic rats. Int J Food Sci Nutr. 2016 Apr 27:1-11.

29. Mansouri E, Khorsandi L, Zare Moaiedi M. Grape Seed Proanthocyanidin Extract Improved some of Biochemical Parameters and Antioxidant Disturbances of Red Blood Cells in Diabetic Rats. Iran J Pharm Res. 2015 Winter;14(1):329-34.

30. Shivapriya S, Ilango K, Dubey GP. Evaluation of antioxidant and neuroprotective effect of Hippophae rhamnoides (L.) on oxidative stress induced cytotoxicity in human neural cell line IMR32. Saudi Journal of Biological Sciences. 2015; 22(5):645–650.

31. Wang J, Zhang W, Zhu D, Zhu X, Pang X, Qu W. Hypolipidaemic and hypoglycaemic effects of total flavonoids from seed residues of Hippophae rhamnoides L. in mice fed a high-fat diet. J Sci Food Agric. 2011 Jun; 91(8):1446-51.

32. Lourith N, Kanlayavattanakul M. Antioxidant activities and phenolics of Passiflora edulis seed recovered from juice production residue. J Oleo Sci. 2013; 62(4):235-40.

33. Santana FC, Shinagawa FB, Araujo ES, Costa AM, Mancini-Filho J. Chemical Composition and Antioxidant capacity of brazilian Passiflora seed oils. J Food Science. 2015 Dec; 80(12): 647-54, 2015.

34. Sano S, Sugiyama K, Ito T, Katano Y, Ishihata A. Identification of the Strong Vasorelaxing Substance Scirpusin B, a Dimer of Piceatannol, from Passion Fruit (Passiflora edulis) Seeds J. Agric. Food Chem. 2011 Jun; 59(11):6209-13.

35. Tang YL, Chan SW. A Review of the Pharmacological Effects of Piceatannol on Cardiovascular Diseases. Phytother Res. 2014; 28 (11):1581-1588.

36. Uchida-Maruki H, Inagaki H, Ito R, Kurita I, Sai M, Ito T. Piceatannol lowers the blood glucose level in diabetic mice. Biol Pharm Bull. 2015; 38(4):629-33.

37. Oritani Y, Okitsu T, Nishimura E, Sai M, Ito T, Takeuchi S. Enhanced glucose tolerance by intravascularly administered piceatannol in freely moving healthy rats. Biochem Biophys Res Commun. 2016 Feb 12; 70(3):753-8.

38. Perez-Gutierrez RM, Muñiz-Ramirez A, Gomez YG, Ramírez EB. Antihyperglycemic, antihyperlipidemic and antiglycation effects of Byrsonima crassifolia fruit and seed in normal and streptozotocin-induced diabetic rats. Plant Foods Hum Nutr. 2010 Dec; 65(4):350-7.

39. Gutierrez RMP, Flores JMM. Effect of Chronic Administration of Hexane Extract of Byrsonima Crassifolia Seed on B-Cell and Pancreatic Oxidative Parameters in Streptozotocin-Induced Diabetic Rat. African Journal of Traditional, Complementary, and Alternative Medicines. 2014;11(2):231-236.

40. Shahraki MR, Harati M, Shahraki AR. Prevention of high fructose-induced metabolic syndrome in male wistar rats by aqueous extract of Tamarindus indica seed. Acta Med Iran. 2011; 49(5):277-83.

41. Maiti R, Misra DS, Ghosh D. Hypoglycemic and Hypolipidemic Effect of Seed Hydromethanolic Extract of Tamarindus indica L. on Streptozotocin Induced Diabetes Mellitus in Rat. Am J Phytomed Clin Therap. 2014; 2(12):1416-1429.

42. Sharma SB, Tanwar RS, Nasir A, Prabhu KM. Antihyperlipidemic effect of active principle isolated from seed of Eugenia jambolana on alloxan-induced diabetic rabbits. J Med Food. 2011 Apr; 14(4):353-9.

43. Zoungas S, Curtis AJ, McNeil JJ, Tonkin AM. Treatment of Dyslipidemia and Cardiovascular Outcomes: The Journey So Far—Is This the End for Statins? Clin Pharmacol Therap. 2014; 96(2):192–205.

44. Loizzo MR, Tundis R, Bonesi M, Menichini F, De Luca D, Colica C, Menichini F. Evaluation of Citrus aurantifolia peel and leaves extracts for their chemical composition, antioxidant and anti-cholinesterase activities. J Sci Food Agric. 2012; 92(15): 2960-67.

45. Boshtam M, Moshtaghian J, Naderi G, Asgary S, Nayeri H. Antioxidant effects of Citrus aurantifolia (Christm) juice and peel extract on LDL oxidation. J Res Med Sci. 2011 Jul; 16(7):951-5.

46. Kang SI, Shin HS, Kim HM, Hong YS, Yoon SA, Kang SW, et al. Citrus sunki peel extract exhibits antiobesity effects by β-oxidation and lipolysis in high-fat diet-induced obese mice. Biol Pharm Bull. 2012 ;35(2):223-30.

47. Castro-Vazquez L, Alañón ME, Rodríguez-Robledo V, Pérez-Coello MS, Hermosín-Gutierrez I, Díaz-Maroto MC, et al. Bioactive Flavonoids, Antioxidant Behaviour, and Cytoprotective Effects of Dried Grapefruit Peels (Citrus paradisi Macf.) Oxid Med Cell Longev. 2016; 2016: 8915729.

48. Ajila CM, Rao LJ, Rao UJ. Characterization of bioactive compounds from raw and ripe Mangifera indica L. peel extracts. Food Chem Toxicol. 2010 Dec; 48(12):3406-11. Epub 2010 Sep 21.

49. Zhang M, Xie Z, Gao W, Pu L, Wei J, Guo C. Quercetin regulates hepatic cholesterol metabolism by promoting cholesterol-to-bile acid conversion and cholesterol efflux in rats. Nutr Res. 2016 Mar; 36(3):271-9.

50. Torres N, Guevara-Cruz M, Velázquez-Villegas LA, Tovar AR. Nutrition and Atherosclerosis. Arch Med Res. 2015; 46(5):408–426.

51. Thilakarathna SH, Rupasinghe HP, Needs PW. Apple peel bioactive rich extracts effectively inhibit in vitro human LDL cholesterol oxidation. Food Chem. 2013 May; 138(1):463-70.

52. Lenquiste SA, Batista AG, Marineli RS, Dragano NRV, Maróstica Jr MR. Freeze-dried jaboticaba peel added to high-fat diet increases HDL-cholesterol and improves insulin resistance in obese rats. Food Res Inter. 2012 Nov; 49(1): 153-160.

53. Leite-Legatti AV, Batista AG, Dragano NRV, Marquesa AC, Malta LG, et al. Jaboticaba peel: Antioxidant compounds, antiproliferative and antimutagenic activities. Food Res Inter. 2012 Nov; 49(1):596-603.

54. Suttirak W, Manurakchinakorn S. In vitro antioxidant properties of mangosteen peel extract. J Food Sci Technol. 2014 Dec; 51(12):3546-58.

55. Rai PK, Mehta S, Watal G. Hypolipidaemic & hepatoprotective effects of Psidium guajava raw fruit peel in experimental diabetes. Indian J Med Res. 2010 Jun; 131:820-4.

56. Kandandapani S, Balaraman AK, Ahamed HN. Extracts of passion fruit peel and seed of Passiflora edulis (Passifloraceae) attenuate oxidative stress in diabetic rats. Chin J Nat Med. 2015 Sep; 13(9):680-6.

57. Miranda GS, Rennó LN, Machado BB, Silva JL, Pinto P, Oliveira MR. Efeito do consumo da aveia e farinha da casca de maracujá sobre a glicemia e lipemia em um grupo de voluntários. Rev Ciênc Farm Básica Apl. 2014 ;35(2):245-250.

58. Queiroz MS, Janebro DI, da Cunha MA, Medeiros JS, Sabaa-Srur AU, Diniz MF, et al. Effect of the yellow passion fruit peel flour (Passiflora edulis f. flavicarpa deg.) in insulin sensitivity in type 2 diabetes mellitus patients. Nutr J. 2012 Oct; 11(89):1-7.

59. Lewis BJ, Herrlinger KA, Craig TA, Mehring-Franklin CE, Freitas Z, Hinojosa-Laborde C. Antihypertensive effect of passion fruit peel extract and its major bioactive components following acute supplementation in spontaneously hypertensive rats. J Nutr Biochem. 2013; 24(7):1359-1366.

60. Silva DC, Freitas AL, Pessoa CD, Paula RC, Mesquita JX, Leal LK, et al. Pectin from Passiflora edulis shows anti-inflammatory action as well as hypoglycemic and hypotriglyceridemic properties in diabetic rats. J Med Food. 2011 Oct; 14(10):1118-26.

61. Silva LMR, Figueiredo EAT, Ricardo NMPS, Vieira IGP, Figueiredo RW, Brasil IM, et al. Quantification of bioactive compounds in pulps and by-products of tropical fruits from Brazil. Food Chem. 2014 Jan; 143(15):398-404.

62. Abreu WC, Lopes CO, Pinto KM, Oliveira LA, Carvalho GBM, Barcelo MFP. Características físico-químicas e atividade antioxidante total de pitaias vermelha e branca. Rev Instit Adolfo Lutz. 2012; 71(4):656-661.

63. Gregoris E, Pereira Lima GP, Fabris S, Bertelle M, Sicari M, Stevanato R. Antioxidant properties of Brazilian tropical fruits by correlation between different assays. Biomed Res Int. 2013 Sep; 2013:1-8.

64. Mello FR, Bernardo C, Dias CO, Gonzaga L, Amante ER, Fett R, et al. Antioxidant properties, quantification and stability of betalains from pitaya (Hylocereus undatus) peel. Ciênc Rural. 2015; 45(2):323-328.

65. Song H, Chu Q, Xu D, Xu Y, Zheng X. Purified Betacyanins from Hylocereus undatus Peel Ameliorate Obesity and Insulin Resistance in High-Fat-Diet-Fed Mice. J Agric Food Chem. 2016 Jan; 64(1):236-44.

66. Jung JS. Analysis of Volatile Compounds in the Root Peel, Stem Peel, and Fruit Peel of Pomegranate (Punica granatum) by TD GC/MS. Inter J Bio-Science Bio-Technology.2014; 6(3):169-182.

67. Sadeghipour A, Eidi M,Kavgani AI, Ghahramani R, Shahabzadeh S, Anissian A . Lipid Lowering Effect of Punica granatum L. Peel in High Lipid Diet Fed Male Rats. Evid Based Complement Alternat Med. 2014; 2014.

68. Amorim EG. Elaboração alternativa de produtos a partir de resíduos alimentares. Rev Eletr Cien. 2014; 7(1):50-60.

69. Wang W, Zu Y, Fu Y, Efferth T. In vitro antioxidant and antimicrobial activity of extracts from Morus alba L. leaves, stems and fruits. Am J Chin Med. 2012; 40(2):349-56.

70. El-Sayyad HI, El-Sherbiny MA, Sobh MA, Abou-El-Naga AM, Ibrahim MA, Mousa SA. Protective effects of Morus alba leaves extract on ocular functions of pups from diabetic and hypercholesterolemic mother rats. Int J Biol Sci. 2011; 7(6):715-28.

71. Yang Y, Wang HQ, Chen RY. Flavonoids from the leaves of Morus alba L. Yao Xue Xue Bao. 2010 Jan; 45(1):77-81.

72. Lee YJ, Choi DH, Kim EJ, Kim HY, Kwon TO, Kang DG, Lee HS. Hypotensive, hypolipidemic, and vascular protective effects of Morus alba L. in rats fed an atherogenic diet. Am J Chin Med. 2011;39(1):39-52.

73. Sharma SB, Tanwar RS, Rini AC, Singh UR, Gupta S, Shukla SK. Protective effect of Morus rubra L. leaf extract on diet-induced atherosclerosis in diabetic rats. Indian J Biochem Biophys. 2010 Feb; 47(1):26-31.

74. Rodríguez-Carpena JG, Morcuende D, Andrade MJ, Kylli P, Estévez M. Avocado (Persea americana Mill.) phenolics, in vitro antioxidant and antimicrobial activities, and inhibition of lipid and protein oxidation in porcine patties. J Agric Food Chem. 2011 May; 59(10):5625-35.

75. Li ZH, Guo H, Xu WB, Ge J, Li X, Alimu M, He DJ. Rapid Identification of Flavonoid Constituents Directly from PTP1B Inhibitive Extract of Raspberry (Rubus idaeus L.) Leaves by HPLC-ESI-QTOF-MS-MS. J Chromatogr Sci. 2016 May; 54(5):805-10.

76. Durgo K, Belščak-Cvitanović A, Stančić A, Franekić J, Komes D. The bioactive potential of red raspberry (Rubus idaeus L.) leaves in exhibiting cytotoxic and cytoprotective activity on human laryngeal carcinoma and colon adenocarcinoma. J Med Food. 2012 Mar; 15(3):258-68.

77. Barbalho SM, Souza MSS, Bueno PCS, Guiguer EL, Farinazzi-Machado FMV, et al. Annona montana Fruit and Leaves Improve the Glycemic and Lipid Profiles of Wistar Rats. J Med Food. 2012; 15(10):917–922.

78. Liberal J, Francisco V, Costa G, Figueirinha A, Amaral MT, Marques C, et al. Bioactivity of Fragaria vesca leaves through inflammation, proteasome and autophagy modulation. J Ethnopharmacol. 2014 Dec; 158(partA):113-122.

79. Das S, Barman S. Antidiabetic and antihyperlipidemic effects of ethanolic extract of leaves of Punica granatum in alloxan-induced non-insulin-dependent diabetes mellitus albino rats. Indian J Pharmacol. 2012 Mar; 44(2):219-24.

80. Balwani S, Nandi D, Jaisankar P, Ghosh B. 2-Methyl-pyran-4-one-3-O-β-D-glucopyranoside isolated from leaves of Punica granatum inhibits the TNFα-induced cell adhesion molecules expression by blocking nuclear transcription factor-κB (NF-κB). Biochimie. 2011 May; 93(5):921-30.

81. Bekir J, Mars M, Souchard JP, Bouajila J. Assessment of antioxidant, anti-inflammatory, anti-cholinesterase and cytotoxic activities of pomegranate (Punica granatum) leaves. Food Chem Toxicol. 2013 May; 55:470-5.

82. Ali B, Mujeeb M, Aeri V, Mir SR, Faiyazuddin M, Shakeel F. Anti-inflammatory and antioxidant activity of Ficus carica Linn. leaves. Nat Prod Res. 2012; 26(5):460-5.

83. Orhan IE, Ustün O, Sener B. Estimation of cholinesterase inhibitory and antioxidant effects of the leaf extracts of Anatolian Ficus carica var. domestica and their total phenol and flavonoid contents. Nat Prod Commun. 2011 Mar; 6(3):375-8.

84. Fagbohun TR, Odufuwa KT. Hypoglycemic Effect of Methanolic Extract of Anacardium occidentale leaves in Alloxan-Induced Diabetic Rats. Niger J Physiol Sci. 2010 Nov; 25(1):87-90.

85. Barbalho SM, Bueno PCS, Delazari DS, Guiguer EL, Coqueiro DP, Araujo AC, Souza MSS, Farinazzi-Machado FMV, Mendes CG, Groppo M. Antidiabetic and Antilipidemic Effects of Manilkara zapota, J Med Food. 2015 March 18(3): 385-391.

86. Omar HS, El-Beshbishy HA, Moussa Z, Taha KF, Singab AN. Antioxidant activity of Artocarpus heterophyllus Lam. (Jack Fruit) leaf extracts: remarkable attenuations of hyperglycemia and hyperlipidemia in streptozotocin-diabetic rats. ScientificWorldJournal. 2011 Apr; 11:788-800.

87. Chackrewarthy S, Thabrew MI, Weerasuriya MK, Jayasekera S. Evaluation of the hypoglycemic and hypolipidemic effects of an ethylacetate fraction of Artocarpus heterophyllus (jak) leaves in streptozotocin-induced diabetic rats. Pharmacogn Mag. 2010 Jul; 6(23):186-90.

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