Chapter 1

Citrus and Health

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Abstract

Citrus has been proposed as an interesting ingredient in the elaboration of food products as soft drinks due to its distinctive aroma and high nutritive value. It is a rich source of nutrients that contains higher amounts of vitamin C, citric acid, minerals, and flavonoids, especially flavanones and flavones (reaching values of 400–600 mg/L) and in lesser amounts flavonols and hydroxycinnamic acids. Citrus flavonoids decrease capillary permeability and are beneficial in the treatment of vascular diseases. Scientific studies suggest that the ingestion of food products based on citrus fruits improves the blood lipid profile, reduces oxidative stress, prevents atherogenic modifications of LDL and platelet aggregation, as well as contributes to the improvement of HDL levels. Other benefits attributed to citrus are antiaging, anticancer, neuroprotective, and antidiabetic. The present revision tries to empathize the most relevant studies regarding citrus and health.

Keywords: citrus, obesity, neurodegeneration, diabetes, cancer, cardiovascular diseases

1. Introduction

There are numerous evidences supporting the crucial influence of diet in the prevention of diseases related to oxidative and inflammatory processes. Citrus are one of the most important foods included in a healthy lifestyle, due to their composition in bioactive compounds. The biological activity of citrus bioactive compounds is mainly their free radical scavenging property, increasing the antioxidant activity which closely related to disease prevention.

Healthy properties of citrus have been linked to its high vitamin content C and flavonoids, mainly attributed to its antioxidant capacity. Citrus are considered adjuvant in the prevention of cardiovascular diseases and metabolic diseases such as obesity, diabetes mellitus or dyslipidemia, as well as certain types of cancer. In citrus (particularly lemon), more than 60 individual flavonoids have been identified.

2. Citrus and their role in different pathologies

The health benefits described with the consumption of these fruits are related to their complete profile on nutrients, including simple sugars, fiber, potassium, high contents of vitamin C and phytochemicals as flavonoids, particularly flavanones that may act synergistically. They are low in fat and proteins, ranging from 0.1 to 0.3 g and from 0.69 to 0.94 g/100 g fresh weight, respectively. Citrus are particularly rich in vitamin C (ascorbic acid), providing amounts in the range of 23–83 g/100 g fresh weight. Considering that the Recommended Dietary Allowance (RDA) is set at 75–80 mg and a medium-sized orange or grapefruit contains from 50 to 70 mg ascorbic acid, it is easy to provide the necessary quantities with these fruits in a daily dietary pattern [1].

Micronutrients are secondary metabolites synthesized in the plant as a defense mechanism against pathogens, parasites, or to protect from UV radiation. We find two main groups in citrus fruits: terpenes and flavanones.

Terpenes are present in the essential aromatic oil produced by cells in the flavedo, and the main compounds are limonene and citral (mixture of isomers geranial and neral) (**Figure 1**). These volatile substances contribute to the flavor of citrics; similar to the protection effect against biotic stress in plants, they have shown antimicrobial activities interesting for food preservation and medicinal purposes [2, 3].

Besides, citrus fruits are especially rich in the flavanones hesperetin, naringenin, and eriodictyol [4]. Flavanones have the characteristic 15-carbon backbone ring structure common in the flavonoids (C6—C3—C6), consisting of two aromatic rings linked by three carbon atoms in an oxygenated structure as pirane derivative [5]. In particular, flavanones have a further degree of oxidation, with a ketone group at position C-4 in C-ring.

These compounds are mainly found glycosylated, with a disaccharide linked by glycosidic bond; common positions are the hydroxyl groups of C3 and C7. The free form (aglycone) can render different flavanones, depending on the position and type of sugar linked. In this sense, grapefruit is abundant in narirutin and naringin, which are both heterosides from the aglycone naringenin, but the glucose moiety is different (rutinoside or neohesperoside, respectively). Orange is rich in hesperidin, that is the glycoside of hesperetin, while lemon is rich in eriocitrin that contains the aglycone eriodictyol [6].

Flavanones are not uniformly distributed in the fruit but are more abundant in the albedo. Because this part is discarded in juice processing, the level of flavanones is lower in citrus juices than in the whole fresh fruit [7]. In fact, levels of in orange fruit range between 35 and 147 mg/100 g of total flavanones and 44 and 106 mg/100 g of naringin and narirutin

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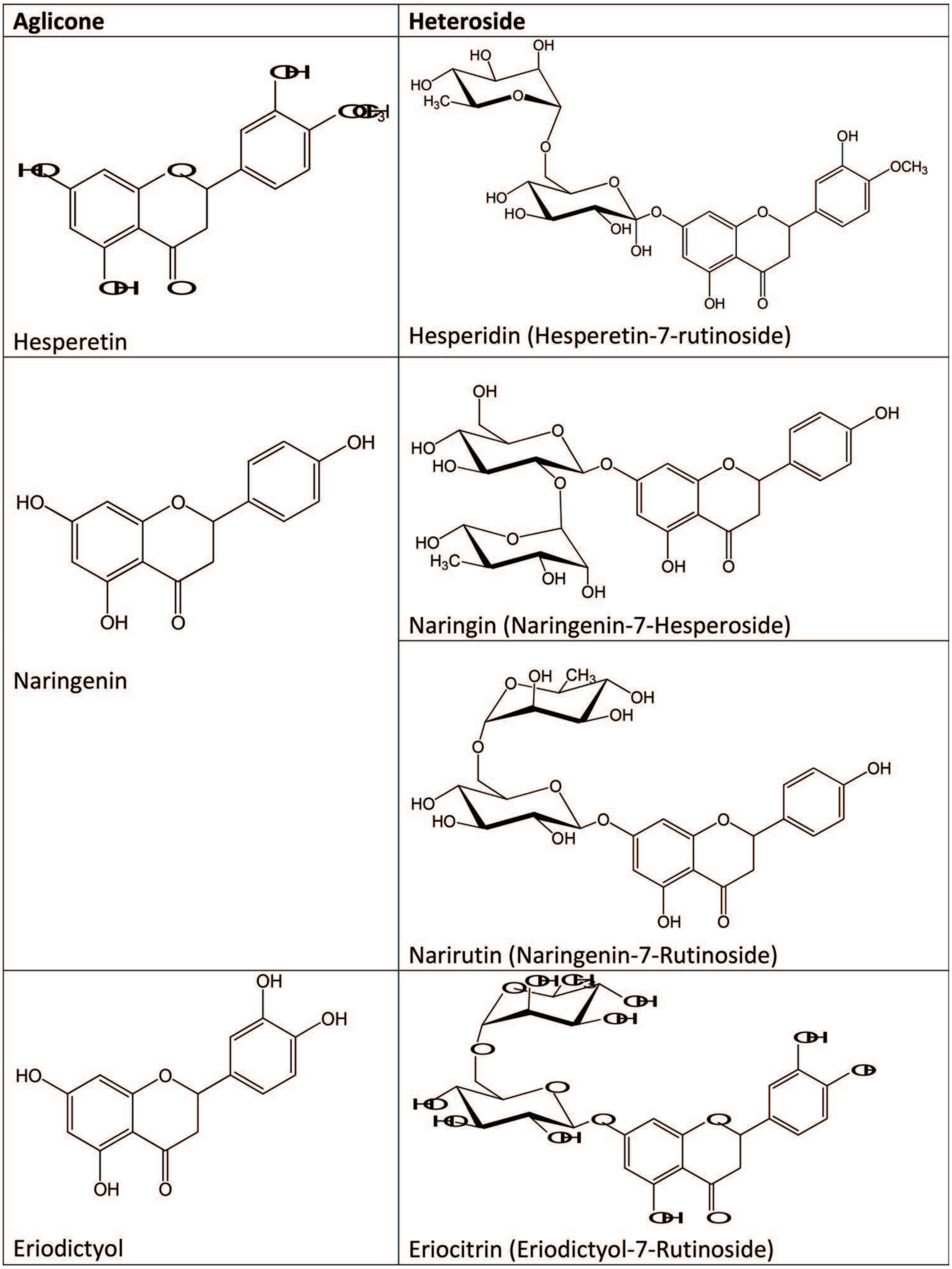

Figure 1. Chemical structures of the main terpenes present in citrus essential oil.

in grapefruit [8]. By contrast, orange and grapefruit juices showed values between 10 and 80 mg/100 g of hesperidin and narirutin [9] and naringenin [10]. Therefore, the pattern of consumption of these fruits greatly affects the flavanone total intake and further biological activities. Moreover, the sugar moiety modifies the in vivo pharmacokinetic properties of the compound. Aglycones are more easily absorbed than their heterosides counterparts, as glycosides are more hydrophilic and need active transport by proteins in gastrointestinal lumen and/or hydrolysis by gut microflora in order to be absorbed [11].

2.1. Citrus and cancer

Flavonoids are major compounds in citrus, and have been investigated since more than 20 years ago. Dietary flavonoids have showed to be able to exert chemopreventive or anticancer capacity [12]. Anticancer capacity of citrus flavonoids takes place through three main mechanisms: defense against DNA injury, inhibition of tumor growth, and inhibition of cell proliferation [13].

The best anticancer compound must exert the most possible inhibition of tumor growth or to able to destroy cancer cells, but origins minimum adverse health collateral effects [14]. Flavonoids are natural and considered innocuous and great compounds for the treatment of cancerous processes [15, 16]. The synthetic molecules that can be used for the treatment of cancer are extremely noxious, and can be able to destroy healthy cells. Due to the safe long-term consumption of flavonoids, and their innate biological activity, flavonoids can be considered as good applicants regarding cancer treatment. In fact, scientific literature has revealed cytotoxic effects of citrus flavonoids on cancer cells, with slightest adverse health effects.

That fact has led the research in order to implement flavonoid-based cancer treatments [17]. As other polyphenols, the presence of aromatic rings in flavonoids leads to pro- and antioxidant capacity that can be useful for chemotherapies [18]. Cancerous cells show an increment on oxidative stress, which leads to the possibility to be attacked by a substance that improves reactive oxygen species level as flavonoids do [19, 20]. As defined by Pacifico et al. [21], pro- or antioxidant capacity of citrus flavonoids is dependent on the concentration, type of cell, and culture condition (*in vitro* models).

Flavonoids exert DNA protection by their ability to absorb ultraviolet light. Some experiments on a UV-irradiated model of plasmidic DNA indicate protecting capacity of naringenin and rutin against UV-induced damage of DNA [22]. Indeed, naringin plays an important role in regulating antioxidative capacity by increasing superoxide dismutase and catalase activities and by upregulating the gene expressions of superoxide dismutase, catalase, and glutathione peroxidase in cholesterol-rich diet-fed rabbits [23].

Apart from UV protection, flavonoids can also diminish tumor promotion at the beginning of carcinogenesis by the intensification of the detoxification processes. In particular, citrus flavonoids inhibit ornithine decarboxylase induction of skin tumor promotion, activating protein kinase C [24, 25]. Miller et al. [26] studied the inhibition of oral carcinogenesis by citrus flavonoids in hamsters and the antineoplastic activity, concluding that hesperetin, neohesperetin, tangeretin, and nobiletin were ineffective, while naringin and naringenin gave good results.

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Citrus flavonoids can inhibit invasion, by rat malignant cells, in cardiac and hepatic tissue of syngenetic rats [27]. Hydroxycinnamates, glycosylated flavonoids, and the polymethoxylated flavones have shown inhibitory activity on several tumoral cell line proliferations [13]. Other studies showed eriocitrin and its aglycone, eriodictyol, as potent inhibitors of lipoxygenases, which are involved in the biosynthesis of various bioregulators that are closely related to the pathogenesis of several diseases such as allergy and atherosclerosis and cancer [28]. Hesperidin in different citrus juices also showed antiproliferative activity [29], reporting lemon in particular potent antiproliferative activities on HepG2 human liver-cancer cell in a dose-dependent manner [30].

Also, the positive effect of vitamin C in reducing the incidence of stomach cancer has been studied, being most probably due to the inhibitory action in the generation of nitrous compounds by interrupting the reaction between nitrites and amine groups [31], although it has recently shown that this effect may be due to a cytotoxic effect of vitamin C on human gastric cancer cell line AGS [32]. Consistent protective effect of vitamin C has also been found in lung and colorectal cancer [33].

One stretched revision done by Turati [34] reported a diminution on cancers of the digestive tract and larynx regarding high intake of citrus. That effect was found to be due to the content on vitamin C, flavanones, and other compounds with antioxidant, antimutagenic, and antiproliferative properties [35]. Subjects consuming more than one portion of citrus fruit per week showed OR between 0·42 and 0·82 for oral cavity and pharyngeal cancer, esophageal cancer, stomach cancer, colorectal cancer, and laryngeal cancer. However, despite the good results obtained, no correlation was found for other neoplasms, including cancers of breast, ovary, endometrium, prostate, or kidney [35].

The most recent and huge research about citrus and cancer was published in 2016. An adaptive meta-analysis of cohort studies revealed that regular dietary intake of citrus prevents the development of gastric cancer, particularly cardia gastric cancer [36].

2.2. Citrus and cardiovascular diseases

Cardiovascular diseases (CVD) are one of the main causes of illness and death in Western countries, and cardiovascular drugs are the most commonly used medications. There are two types of factors involved in the development of CVD. Some factor can be modified, like life style, diet, environment, or smoking. Other cannot be modified: genetic factors, gender, history, or age. Atherosclerotic plaque formation is the most common phenomenon involved in CVD [37].

Consumption of citrus is inversely associated with incidence of CVD, due to the presence of bioactive compounds like flavonoids. Current research has focused on diet containing bioactive compounds, as an alternative to pharmaceutical medication. It can be concluded from the analysis of multiple studies that as the mean consumption of flavonoids increases, mortality due to CVD decreases. Epidemiological evidence of clinical and preclinical studies suggest that flavanones present in the citrus fruits positively influence cardiac and metabolic parameters, preventing CVD [38].

A study performed on approximately 70.000 women highlighted an inverse correlation between the intake of flavanones and the risk of suffering a cerebral ischemia, which is significantly different when contemplate women who consume high levels of flavanones [39]. Another recent meta-analysis study of three randomized clinical trials, including 233 patients, demonstrated a correlation between flavanones intake and a reduction in blood pressure [40].

Another recognized cardiovascular risk factor is metabolic syndrome, characterized by altered glucose metabolism, elevated blood pressure, dyslipidemia, and obesity. In 2016, a study on 10,000 subjects demonstrated an inverse association between polyphenols and metabolic syndrome, which was particularly significant in individuals with the highest intake of polyphenols [41].

Several studies carried out so far support a preventive role of citrus fruits on the main risk factors of CVD, such as hypertension, dyslipidemia, overweight, and hyperglycemia. Among CVDs, the effect of flavonoids on stroke is not clear. Mursu et al. [42] studied the association between intake of flavonoid and risk of stroke and mortality caused by stroke and concluded that a greater intake of flavonoids decreases the chances of ischemic stroke as well as mortality caused by CVD.

Chronic inflammation is caused by the excessive production of chemokines and cytokines. Cytokines and chemokines act as regulatory proteins under normal physiological conditions, but their excessive production disrupts the gradient balance and more reactive oxygen species (ROS) are produced. It has been shown that the grape flavonoids control chronic inflammation by reducing ROS level and by modulating pathways of inflammation. As flavonoids are natural compounds, they can target multiple steps in the inflammation pathway as compared to monotargeted synthetic anti-inflammatory drugs [43].

Atherosclerosis, characterized by the plaque formation in arteries, is one of the major factors contributing to incidence of stroke and myocardial infarction. It is caused by high level of lipoprotein and cholesterol in plasma [37]. High intake of citrus flavonoids reduces several risk factors for development of atherosclerosis including: high tolerance to glucose, maintaining good body mass index, and lowering blood pressure [44].

In another study, patients with metabolic syndrome had reduced cholesterol and ApoB due to the intake of a supplement of hesperidin for 3 weeks [45]. Furthermore, in a 2012 clinical study performed in our laboratory on patients with metabolic syndrome diagnosed, after 4 or 6 months drinking a citrus fruit juice, the glycemic profile was unchanged but the lipid profile improved, as observed by decrease in the cholesterol, LDL-C, and C-reactive protein [46].

Naringenin plays an important role to overcome the metabolic problem that is connected to dyslipidemia and resistance to insulin. It was shown to prevent atherosclerosis development in mice fed a high fat diet. Naringenin treatment attenuated the adverse effects caused by hyperinsulinemia and hyperlipidemia which was induced by western style diet. In mice that were fed a western diet, hyperlipidemia led to development of atherosclerosis in the aortic sinus evidenced by the development of plaque is that increased 10 times as compared to chow-fed animals. Naringenin treatment decreased the incidence of atherosclerosis by 70% [44].

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A clinical study with 500 mg of naringin plus 800 mg of hesperidin did not show a significant improvement in the lipid profile in patients with moderate hypercholesterolemia. This study suggests that citrus flavonoids have no effect on LDL-C in humans, at least not when consumed in a capsule format [47]. A plausible explication of this results could be the inter-individuals variability of pharmacokinetic parameters. Despite preclinical results are clearer, further clinical studies need to be performed.

2.3. Citrus and diabetes

Diabetes is a chronic disease in which metabolic alterations of multiple etiologies characterized by chronic hyperglycemia and disorders in the metabolism of carbohydrates, fats, and proteins occur. These alterations are the result of defects in the secretion of insulin, in the action itself or in both. The long-term manifestation of insulin results in damage and dysfunction of various organs like nerves, kidneys, eyes, blood vessels, and heart. People living with diabetes have a higher risk of morbidity and mortality than the general population [48].

Diabetes is an important public health problem, one of four priority noncommunicable diseases (NCDs) targeted for action by world leaders. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades [49].

A recent report on diabetes by the World Health Organization estimates that 422 million cases in 2014 [49], and an expected number of nearly 650 million subjects in 2040 was estimated [48]. This dramatic rise is largely due to type 2 diabetes (T2D).

The treatment of diabetes consists of pharmacological, dietary, and lifestyle measures. Many trials have effectively tested different lifestyle and pharmacological intervention methods both in terms of prevention and treatment [50].

The use of plants with antidiabetic properties is widely known and described in the scientific literature. A lot of studies have reported that either plant parts or extracts of plant parts possess antidiabetic properties. This antidiabetic activity of plants is due to the presence of phytochemicals which are termed as flavonoids. In this way, several studies reported antidiabetic activities of flavonoids [51, 52].

Citrus fruits are one of the most consumed fruits mainly as fresh or raw materials for juices. Additionally, citrus fruits can also be used in the food, beverage, cosmetic, and pharmaceutical industries [53].

Citrus fruits show several bioactivities of vital importance to human health, like antioxidative and anti-inflammatory activity, cardiovascular protective effects, antidiabetic activity, among others. Citrus species contain a number of secondary metabolites, such as flavonoids, alkaloids, coumarins, limonoids, carotenoids, phenol acids, and essential oils [53]. Of all of them, flavonoids (especially flavanone, flavanonol, and methoxylated flavones) are more active compared to other secondary metabolites in citrus for their remarkable various bioactivities. There are a lot of studies where have been widely reported on plentiful bioactivities from flavonoids.

Flavonoids, a group of natural substances with variable phenolic structures, are well known for their beneficial effects on health. Flavonoids are now considered as an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal, and cosmetic applications [54]. Flavonoids are distinct based on structural characteristics in the following six subclasses: flavonols, flavones, isoflavones, flavanones, anthocyanins, and flavanols (catechins and proanthocyanidins) [6]. In *Citrus* genus, flavanones comprise approximately 95% of the total flavonoids, and these foods are the main source of flavanones [6].

Citrus flavanones are glycosylated in vegetables. The same aglycone can be combined with several glycosides to give different flavanones; for example, the most representative flavanones in grapefruit are narirutin and naringin, those in orange fruit are hesperidin and narirutin, and that in lemon is eriocitrin [6]. Naringin, naringenin, nobiletin, narirutin, and hesperidin are the most important flavonoids thus far isolated from citrus fruits [35].

There has been a substantial body of evidence suggesting that oxidative stress is a key mechanism in pathogenesis of diabetes. Flavanones and flavanones-rich botanical extracts have been a subject of great interest for scientific research. Citrus flavanones like naringin and hesperidin exert a variety of biological activities such as antioxidant, anti-inflammatory, antihyperglycemic, antiapoptotic, etc. Naringin and hesperidin along with their respective aglycones, naringenin, and hesperetin have been shown to attenuate diabetes and its related complications [55]. In this way, Ashafaq et al. [56] demonstrated that hesperidin treatment significantly attenuated the altered levels of oxidative stress and neurotoxicity biomarkers. Their results demonstrate that hesperidin exhibits potent antioxidant and neuroprotective effects on the brain tissue against the diabetic oxidative damage in STZ-induced rodent model.

Iskuender et al. observed that after administration of hesperidin and quercetin in STZ-induced diabetic rats, glucose levels increased and liver and kidney damage markers decreased significantly [57]. In the same way, Akiyama et al. [50] demonstrated that hesperidin normalizes blood glucose by altering the activity of glucose-regulating enzymes, and lowering serum and liver lipid levels in STZ-induced marginal type 1 diabetic rats without any body weight loss due to STZ injection. Thus, hesperidin showed both hypoglycemic and hypolipidemic effects.

In a study, Gupta et al. [58] demonstrate the dipeptidyl peprtidase-4 (DPP-4) inhibition activity of citrus bioflavonoid nutraceuticals as compared to known gliptins (oral antidiabetic agents). The naringin and hesperidin compounds have the best individual activity in comparison to that of the gliptins. Natural gliptin-like alternatives may make these supplements a promising group of natural products for use in improving blood glucose levels in prediabetes and early stages of type 2 diabetes.

The hypoglycemic effect of naringin and naringenin is very well documented in animal and cell studies. So, naringin (30 mg/kg) and vitamin C (50 mg/kg) cotreatment ameliorated streptozotocin-induced diabetes in rats by improving insulin concentration and prevented oxidative stress [59]. Naringenin supplementation (0.2 g/kg of diet) improved glucose intolerance and insulin resistance in a model of high-fat-diet-fed mice [59]. More research is needed to determine the mechanism by which naringenin has hypoglycemic effect. So far, some authors have suggested the following: that is mediated via uptake of glucose in the skeletal muscle [60]; increased activities of hexokinase [61]; decreased production and expression of IL-1b, IL-6, and MCP-1 [62].

Rutin is another flavonoid present in citrus fruits to which many biological activities have been attributed, among them having antihyperglycemic properties. In 2017, Ghorbani [63] in a review discussed the antihyperglycemic property of rutin. Proposed mechanisms for this effect include a decrease of carbohydrates absorption from the small intestine, inhibition of tissue gluconeogenesis, an increase of tissue glucose uptake, stimulation of insulin secretion from beta cells, and protecting Langerhans islet against degeneration. Rutin also decreases the formation of sorbitol, reactive oxygen species, advanced glycation end product precursors, and inflammatory cytokines.

In conclusion, it can be affirmed that flavonoids are useful in the prevention and treatment of diabetes, especially in diabetes type 2, as Xu et al. [64] affirm the meta-analysis of prospective cohort studies carried out in 2018. Now, more studies are needed to elucidate the mechanism or mechanisms by which they carry out this antidiabetic activity.

2.4. Citrus and neurodegenerative diseases

Neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's disease represent rapidly growing causes of disability and death, which have profound economic and social implications; nonetheless, only few effective disease-modifying therapies are available for these diseases [65, 66].

Citrus flavonoids exert little adverse effect and have low or no cytotoxicity to healthy, normal cells. The main citrus flavonoids can also traverse the blood-brain barrier; hence, they are promising candidates for intervention in neurodegeneration and as constituents in brain foods [67].

Assessment of cognitive performance in middle-aged individuals has indicated that consumption of different polyphenols such as catechins, flavonols, and hydroxybenzoic acids is strongly associated with language and verbal memory. Hydroxycinnamates, phenolic acids, and phenolic alcohol are also capable of inducing neuroprotective effects in the same way as flavonoids [68].

Naringenin and hesperidin are abundant polyphenols in citrus fruits and have been shown to have protective effects in Huntington's disease due to their mechanism of nitric acid against 3-nitropropionic acid, which presents neurotoxicity in experimental models with rats [69].

5-Hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone (HHMF) from the *Citrus* genus and nobiletin, the most abundant polymethoxyflavone in orange peel extract are compounds that enhance neuronal survival and exerted prosurvival action in PC12 cells [70].

Ushikubo et al. [71] demonstrated that 3,3′,4′,5,5′-pentahydroxyflavone prevents Aβ fibril formation and that lowering fibril formation decreases Aβ-induced cell death in rat hippocampal neuronal cells. In another study, ursolic acid, *p*-coumaric acid, and gallic acid extracted from *Corni fructus* plant were shown to attenuate apoptotic features such as morphological nuclear changes, DNA fragmentation, and cell blebbing induced by Aβ peptide in PC12 cells [72].

The citrus flavanones hesperidin, hesperetin, and neohesperidin are known to exhibit antioxidant activities and could traverse the blood-brain barrier [73]. These authors showed that hesperetin, hesperidin, and neohesperidin inhibited the decrease of cell viability (MTT reduction), prevented membrane damage (LDH release), scavenged ROS formation, increased catalase activity, and attenuated the elevation of intracellular free Ca^{2+}, the decrease of mitochondrial membrane potential and the increase of caspase-3 activity in H_2O_2-induced PC12 cells. Meanwhile, hesperidin and hesperetin attenuated decreases of glutathione peroxidase and glutathione reductase activities and decreased DNA damage in H_2O_2-induced PC12 cells. These results first demonstrate that the citrus flavanones, such as hesperidin, hesperetin, and neohesperidin, even at physiological concentrations, have neuroprotective effects against H_2O_2-induced cytotoxicity in PC12 cells. These dietary antioxidants are potential candidates for use in the intervention for neurodegenerative diseases.

Antunes et al. [74] demonstrated that hesperidin (50 mg/kg) treatment was effective in preventing memory impairment in the Morris water maze test, as well as depressive-like behavior in the tail suspension test. Hesperidin attenuated the 6-OHDA-induced reduction in glutathione peroxidase and catalase activity, total reactive antioxidant potential, and the dopamine and its metabolite levels in the striatum of aged mice. This study demonstrated a protective effect of hesperidin on the neurotoxicity induced by 6-OHDA in aged mice, indicating that it could be useful as a therapy for the treatment of PD.

Chakraborty et al. [75] showed that hesperidin completely inhibits the amyloid fibril formation which is further supported by atomic force microscopy. Hesperidin exhibited moderate ABTS(+) radical scavenging assay but strong hydroxyl radical scavenging ability, as evident from DNA nicking assay.

3. Conclusions

The Mediterranean diet, considered a good example of a prudent and healthy diet, has undergone important changes in recent years. Factors such as urbanization, pollution, economic development, excessive working hours, and the adoption of inadequate lifestyles cause the population to be exposed to environmental and nutritional factors associated with the onset and progression of diseases related to aging. In this sense, citrus fruits are an important source of bioactive compounds, powerful antioxidants whose health benefits have been scientifically demonstrated in several studies for their protective role against oxidative damage. For this reason, the regular consumption of citrus fruits should be promoted as part of a varied and balanced diet. The absence of sufficient scientific evidence and validated tests to reliably measure the antioxidant activity in vivo of the bioactive compounds present in citrus justifies the need of interventional studies in humans for the correct determination of bioactive properties of citrus and their bioactive compounds.

Conflict of interest

Authors declare that they do not have conflict of interest.

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References

[1] Liu Y, Heying E, Tanumihardjo SA. History, global distribution, and nutritional importance of citrus fruits. Comprehensive Reviews in Food Science and Food Safety. 2012;**11**: 530-545

[2] Aliberti L, Caputo L, De Feo V, De Martino L, Nazzaro F, Souza LF. Chemical composition and in vitro antimicrobial, cytotoxic, and central nervous system activities of the essential oils of Citrus medica L. cv."Liscia"and C. Medica cv."Rugosa"cultivated in southern Italy. Molecules. 2016;**21**:1244

[3] Hsouna AB, Halima NB, Smaoui S, Hamdi N. Citrus lemon essential oil: Chemical composition, antioxidant and antimicrobial activities with its preservative effect against listeria monocytogenes inoculated in minced beef meat. Lipids in Health and Disease. 2017;**16**:146

[4] Spigoni V, Mena P, Fantuzzi F, Tassotti M, Brighenti F, Bonadonna RC, Del Rio D, Dei Cas A. Bioavailability of bergamot (*Citrus bergamia*) flavanones and biological activity of their circulating metabolites in human pro-angiogenic cells. Nutrients. 2017;**9**:1328

[5] Mir IA, Tiku AB. Chemopreventive and therapeutic potential of "naringenin," a flavanone present in citrus fruits. Nutrition and Cancer. 2015;**67**:27-42

[6] Testai L, Calderone V. Nutraceutical value of citrus flavanones and their implications in cardiovascular disease. Nutrients. 2017;**9**:502

[7] Escobedo-Avellaneda Z, Gutiérrez-Uribe J, Valdez-Fragoso A, Torres JA, Welti-Chanes J. Phytochemicals and antioxidant activity of juice, flavedo, albedo and comminuted orange. Journal of Functional Foods. 2014;**6**:470-481

[8] Peterson JJ, Dwyer JT, Beecher GR, Bhagwat SA, Gebhardt SE, Haytowitz DB, Holden JM. Flavanones in oranges, tangerines (mandarins), tangors, and tangelos: A compilation and review of the data from the analytical literature. Journal of Food Composition and Analysis. 2006;**19**:S66-S73

[9] Tomás-Barberán FA, Clifford MN. Flavanones, chalcones and dihydrochalcones–nature, occurrence and dietary burden. Journal of the Science of Food and Agriculture. 2000;**80**:1073-1080

[10] Ross SA, Ziska DS, Zhao K, ElSohly MA. Variance of common flavonoids by brand of grapefruit juice. Fitoterapia. 2000;**71**:154-161

[11] Urpi-Sarda M, Rothwell J, Morand C, Manach C. Bioavailability of Flavanones. New York, NY, USA: CRC Press; 2012

[12] Hertog MG, Feskens EJ, Kromhout D, Hollman P, Katan M. Dietary antioxidant flavonoids and risk of coronary heart disease: The Zutphen elderly study. The Lancet. 1993; **342**:1007-1011

[13] Manthey JA, Guthrie N, Grohmann K. Biological properties of citrus flavonoids pertaining to cancer and inflammation. Current Medicinal Chemistry. 2001;**8**:135-153

[14] Zhao Y, Wang J, Ballevre O, Luo H, Zhang W. Antihypertensive effects and mechanisms of chlorogenic acids. Hypertension Research. 2012;**35**:370-374

[15] Szliszka E, Helewski KJ, Mizgala E, Krol W. The dietary flavonol fisetin enhances the apoptosis-inducing potential of TRAIL in prostate cancer cells. International Journal of Oncology. 2011;**39**:771-779

[16] Yoshimizu N, Otani Y, Saikawa Y, Kubota T, Yoshida M, Furukawa T, Kumai K, Kameyama K, Fujii M, Yano M. Anti-tumour effects of nobiletin, a citrus flavonoid, on gastric cancer include: Antiproliferative effects, induction of apoptosis and cell cycle deregulation. Alimentary Pharmacology and Therapeutics. 2004;**20**:95-101

[17] Sak K. Cytotoxicity of dietary flavonoids on different human cancer types. Pharmacognosy Reviews. 2014;**8**:122-146. DOI: 10.4103/0973-7847.134247

[18] Leung HW, Lin CJ, Hour MJ, Yang WH, Wang MY, Lee HZ. Kaempferol induces apoptosis in human lung non-small carcinoma cells accompanied by an induction of antioxidant enzymes. Food and Chemical Toxicology. 2007;**45**:2005-2013. DOI: 10.1016/j.fct.2007.04.023

[19] Valdameri G, Trombetta-Lima M, Worfel PR, Pires ARA, Martinez GR, Noleto GR, Cadena SMSC, Sogayar MC, Winnischofer SMB, Rocha MEM. Involvement of catalase in the apoptotic mechanism induced by apigenin in HepG2 human hepatoma cells. Chemico-Biological Interactions. 2011;**193**:180-189. DOI: 10.1016/j.cbi.2011.06.009

[20] Yuan L, Wang J, Xiao H, Xiao C, Wang Y, Liu X. Isoorientin induces apoptosis through mitochondrial dysfunction and inhibition of PI3K/Akt signaling pathway in HepG2 cancer cells. Toxicology and Applied Pharmacology. 2012;**265**:83-92. DOI: 10.1016/j.taap.2012.09.022

[21] Pacifico S, Scognamiglio M, D'Abrosca B, Piccolella S, Tsafantakis N, Gallicchio M, Ricci A, Fiorentino A. Spectroscopic characterization and antiproliferative activity on HepG2 human hepatoblastoma cells of flavonoid C-glycosides from *Petrorhagia velutina*. Journal of Natural Products. 2010;**73**:1973-1978. DOI: 10.1021/np100255u

[22] Kootstra A. Protection from UV-B-induced DNA damage by flavonoids. Plant Molecular Biology. 1994;**26**:771-774

[23] Jeon SM, Bok SH, Jang MK, Lee MK, Nam KT, Park YB, Rhee SJ, Choi MS. Antioxidative activity of naringin and lovastatin in high cholesterol-fed rabbits. Life Sciences. 2001; **69**:2855-2866

[24] Manach C, Regerat F, Texier O, Agullo G, Demigne C, Remesy C. Bioavailability, metabolism and physiological impact of 4-oxo-flavonoids. Nutrition Research. 1996;**16**:517-544

[25] Miller E. Neurodegenerative diseases. Advances in Experimental Medicine and Biology. 2012;**724**:228-238

[26] Miller EG, Peacock JJ, Bourland TC, Taylor SE, Wright JM, Patil BS, Miller EG. Inhibition of oral carcinogenesis by citrus flavonoids. Nutrition and Cancer. 2007;**60**:69-74

[27] Bracke ME, Vyncke BM, Van Larebeke NA, Bruyneel EA, De Bruyne GK, De Pestel GH, De Coster WJ, Espeel MF, Mareel MM. The flavonoid tangeretin inhibits invasion of MO 4 mouse cells into embryonic chick heartin vitro. Clinical and Experimental Metastasis. 1989;**7**:283-300

[28] Nogata Y, Ohta H, Ishii T, Sekiya K. Isolation of eriocitrin (eriodictyol 7-O-rutinoside) as an arachidonate lipoxygenase inhibitor from Lumie fruit (*citrus lumia*) and its distribution in citrus species. Journal of the Science of Food and Agriculture. 2007;**87**:82-89

[29] Camarda L, Di Stefano V, Del Bosco SF, Schillaci D. Antiproliferative activity of citrus juices and HPLC evaluation of their flavonoid composition. Fitoterapia. 2007;**78**:426-429

[30] Sun J, Chu Y-F, Wu X, Liu RH. Antioxidant and antiproliferative activities of common fruits. Journal of Agricultural and Food Chemistry. 2002;**50**:7449-7454

[31] You W, Zhang L, Gail MH, Chang YS, Liu WD, Ma JL, Li JY, Jin ML, Hu YR, Yang CS, Blaser MJ, Correa P, Blot WJ, Fraumeni JF Jr, Xu GW. Gastric dysplasia gastric cancer *helicobacter pylori* serum Vitam. C risk factors. Journal of the National Cancer Institute. 2000;**92**:1607-1612

[32] Nagappan A, Park KI, Park HS, Kim JA, Hong GE, Kang SR, Lee DH, Kim EH, Lee WS, Won CK. Vitamin C induces apoptosis in AGS cells by down-regulation of 14-3-3σ via a mitochondrial dependent pathway. Food Chemistry. 2012;**135**:1920-1928

[33] Kojo S. Vitamin C: Basic metabolism and its function as an index of oxidative stress. Current Medicinal Chemistry. 2004;**11**:1041-1064

[34] Turati F, Rossi M, Pelucchi C, Levi F, La Vecchia C. Fruit and vegetables and cancer risk: A review of southern European studies. The British Journal of Nutrition. 2015;**113**:S102-S110. DOI: 10.1017/S0007114515000148

[35] Foschi R, Pelucchi C, Dal Maso L, Rossi M, Levi F, Talamini R, Bosetti C, Negri E, Serraino D, Giacosa A. Citrus fruit and cancer risk in a network of case–control studies. Cancer Causes and Control. 2010;**21**:237-242

[36] Bae JM, Kim EH. Dietary intakes of citrus fruit and risk of gastric cancer incidence: An adaptive meta-analysis of cohort studies. Epidemiology and Health. 2016;**38**

[37] Mendis S, Puska P, Norrving B, World Health Organization. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: World Health Organization; 2011. ISBN 92-4-456437-8

[38] Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke a meta-analysis of cohort studies. Neurology. 2005;**65**:1193-1197

[39] Cassidy A, Rimm EB, O'reilly EJ, Logroscino G, Kay C, Chiuve SE, Rexrode KM. Dietary flavonoids and risk of stroke in women. Stroke. 2012;**43**:946-951

[40] Onakpoya I, O'Sullivan J, Heneghan C, Thompson M. The effect of grapefruits (*Citrus paradisi*) on body weight and cardiovascular risk factors: A systematic review and meta-analysis of randomized clinical trials. Critical Reviews in Food Science and Nutrition. 2017;**57**:602-612

[41] Grosso G, Stepaniak U, Micek A, Stefler D, Bobak M, Pająk A. Dietary polyphenols are inversely associated with metabolic syndrome in polish adults of the HAPIEE study. European Journal of Nutrition. 2017;**56**:1409-1420

[42] Mursu J, Voutilainen S, Nurmi T, Tuomainen T-P, Kurl S, Salonen JT. Flavonoid intake and the risk of ischaemic stroke and CVD mortality in middle-aged Finnish men: The Kuopio Ischaemic heart disease risk factor study. The British Journal of Nutrition. 2008; **100**:890-895

[43] Sung B, Prasad S, Gupta SC, Patchva S, Aggarwal BB. Regulation of inflammation-mediated chronic diseases by botanicals. In Advances in Botanical Research, Elsevier 2012; Vol. 62: pp. 57-132 ISBN 0065-2296

[44] Mulvihill EE, Huff MW. Antiatherogenic properties of flavonoids: Implications for cardiovascular health. The Canadian Journal of Cardiology. 2010;**26**:17A-21A

[45] Roohbakhsh A, Parhiz H, Soltani F, Rezaee R, Iranshahi M. Molecular mechanisms behind the biological effects of hesperidin and hesperetin for the prevention of cancer and cardiovascular diseases. Life Sciences. 2015;**124**:64-74

[46] Mulero J, Bernabé J, Cerdá B, García-Viguera C, Moreno DA, Albaladejo MD, Avilés F, Parra S, Abellán J, Zafrilla P. Variations on cardiovascular risk factors in metabolic syndrome after consume of a citrus-based juice. Clinical Nutrition. 2012;**31**:372-377

[47] Demonty I, Lin Y, Zebregs YE, Vermeer MA, van der Knaap HC, Jäkel M, Trautwein EA. The citrus flavonoids hesperidin and Naringin do not affect serum cholesterol in moderately hypercholesterolemic men and women–3. The Journal of Nutrition. 2010; **140**:1615-1620

[48] Marathe PH, Gao HX, Close KL. American Diabetes Association standards of medical care in diabetes 2017. Journal of Diabetes. 2017;**9**:320-324

[49] Organization WH, Unit, W. H. O. M. of S. A. Global Status Report on Alcohol and Health, 2014; World Health Organization; 2014. ISBN 92-4-156475-X

[50] Akiyama S, Katsumata S, Suzuki K, Ishimi Y, Wu J, Uehara M. Dietary hesperidin exerts hypoglycemic and hypolipidemic effects in streptozotocin-induced marginal type 1 diabetic rats. Journal of Clinical Biochemistry and Nutrition. 2009;**46**:87-92

[51] Brahmachari G. Bio-flavonoids with promising antidiabetic potentials: A critical survey. Opportunity, Challenge and Scope of Natural Products in Medicinal Chemistry. 2011;**2**:187-212

[52] Kaleem M, Ahmad A. Flavonoids as nutraceuticals. Therapeutic, Probiotic, and Unconventional Foods. 2018;137-155

[53] Lv X, Zhao S, Ning Z, Zeng H, Shu Y, Tao O, Xiao C, Lu C, Liu Y. Citrus fruits as a treasure trove of active natural metabolites that potentially provide benefits for human health. Chemistry Central Journal. 2015;**9**:68

[54] Panche AN, Diwan AD, Chandra SR. Flavonoids: An overview. Journal of Nutritional Science. 2016;**5**

[55] Sharma M, Akhtar N, Sambhav K, Shete G, K Bansal A, Sharma S. Emerging potential of citrus flavanones as an antioxidant in diabetes and its complications. Current Topics in Medicinal Chemistry. 2015;**15**:187-195

[56] Ashafaq M, Varshney L, Khan MHA, Salman M, Naseem M, Wajid S, Parvez S. Neuromodulatory effects of hesperidin in mitigating oxidative stress in streptozotocin induced diabetes. BioMed Research International. 2014;**2014**:249031

[57] Iskender H, Dokumacioglu E, Sen TM, Ince I, Kanbay Y, Saral S. The effect of hesperidin and quercetin on oxidative stress, NF-κB and SIRT1 levels in a STZ-induced experimental diabetes model. Biomedicine and Pharmacotherapy. 2017;**90**:500-508

[58] Gupta A, Jacobson GA, Burgess JR, Jelinek HF, Nichols DS, Narkowicz CK, Al-Aubaidy HA. Citrus bioflavonoids possess dipeptidyl peptidase-4 inhibition activity similar to gliptin antidiabetic medication. Biochemical and Biophysical Research Communications. 2018

[59] Alam MA, Subhan N, Rahman MM, Uddin SJ, Reza HM, Sarker SD. Effect of citrus flavonoids, naringin and naringenin, on metabolic syndrome and their mechanisms of action. Advances in Nutrition. 2014;**5**:404-417

[60] Jung UJ, Lee MK, Jeong KS, Choi MS. The hypoglycemic effects of hesperidin and naringin are partly mediated by hepatic glucose-regulating enzymes in C57BL/KsJ-db/db mice. The Journal of Nutrition. 2004;**134**:2499-2503

[61] Punithavathi VR, Anuthama R, Prince PSM. Combined treatment with naringin and vitamin C ameliorates streptozotocin-induced diabetes in male Wistar rats. Journal of Applied Toxicology. 2008;**28**:806-813

[62] Annadurai T, Muralidharan AR, Joseph T, Hsu MJ, Thomas PA, Geraldine P. Antihyperglycemic and antioxidant effects of a flavanone, naringenin, in streptozotocin–nicotinamide-induced experimental diabetic rats. Journal of Physiology and Biochemistry. 2012;**68**:307-318

[63] Ghorbani A. Mechanisms of antidiabetic effects of flavonoid rutin. Biomedicine and Pharmacotherapy. 2017;**96**:305-312

[64] Xu H, Luo J, Huang J, Wen Q. Flavonoids intake and risk of type 2 *diabetes mellitus*: A meta-analysis of prospective cohort studies. Medicine (Baltimore). 2018;**97**

[65] Henry W, Querfurth HW, LaFerla FM. Mechanisms of disease Alzheimer's disease. The New England Journal of Medicine. 2010;**362**:329-344

[66] Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: Clinical trials and drug development. Lancet Neurology. 2010;**9**:702-716

[67] Hwang SJ, Kim YW, Park Y, Lee HJ, Kim KW. Anti-inflammatory effects of chlorogenic acid in lipopolysaccharide-stimulated RAW 264.7 cells. Inflammation Research. 2014;**63**:81-90. DOI: 10.1007/s00011-013-0674-4

[68] Vauzour D, Corona G, Spencer JP. Caffeic acid, tyrosol and p-coumaric acid are potent inhibitors of 5-S-cysteinyl-dopamine induced neurotoxicity. Archives of Biochemistry and Biophysics. 2010;**501**:106-111

[69] Kumar A, Kingdon E, Norman J. The isoprostane 8-iso-PGF2α suppresses monocyte adhesion to human microvascular endothelial cells via two independent mechanisms. The FASEB Journal. 2005;**19**:443-445

[70] Moosavi F, Hosseini R, Saso L, Firuzi O. Modulation of neurotrophic signaling pathways by polyphenols. Drug Design, Development and Therapy. 2016;**10**:23

[71] Ushikubo H, Watanabe S, Tanimoto Y, Abe K, Hiza A, Ogawa T, Asakawa T, Kan T, Akaishi T. 3, 3′, 4′, 5, 5′-Pentahydroxyflavone is a potent inhibitor of amyloid β fibril formation. Neuroscience Letters. 2012;**513**:51-56

[72] Hong SY, Jeong WS, Jun M. Protective effects of the key compounds isolated from *Corni fructus* against β-amyloid-induced neurotoxicity in PC12 cells. Molecules. 2012; **17**:10831-10845

[73] Hwang SL, Shih PH, Yen GC. Neuroprotective effects of citrus flavonoids. Journal of Agricultural and Food Chemistry. 2012;**60**:877-885

[74] Antunes MS, Goes AT, Boeira SP, Prigol M, Jesse CR. Protective effect of hesperidin in a model of Parkinson's disease induced by 6-hydroxydopamine in aged mice. Nutrition. 2014;**30**:1415-1422

[75] Chakraborty S, Bandyopadhyay J, Chakraborty S, Basu S. Multi-target screening mines hesperidin as a multi-potent inhibitor: Implication in Alzheimer's disease therapeutics. European Journal of Medicinal Chemistry. 2016;**121**:810-822