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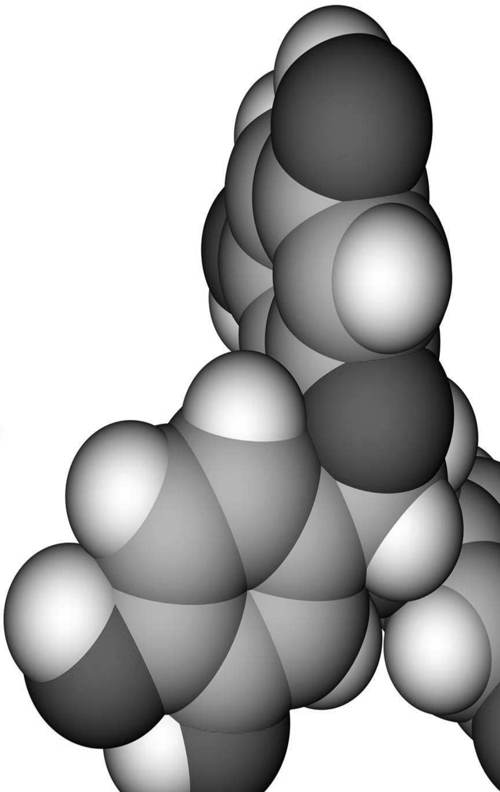
NATURAL BIOACTIVE COMPOUNDS FROM FRUITS AND VEGETABLES AS HEALTH PROMOTERS

PART 1



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Part I

Edited by

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FOREWORD

For centuries, humans have considered food only as an “energy” source for survival. Clarification of nutritional relevant components, as protein, fat, carbohydrates, minerals and vitamins, was determinant to understand metabolic needs, and to adjust consumption patterns. However, this oversimplified definition of food resulted in processed foods composed by mixtures of ingredients rich in these components, while diet is increasingly claimed as being responsible for the most common diseases of modern society: cardiovascular diseases, obesity, and cancer.

When we look upon food from this simplified perspective, it is as if we are regarding food without its “soul”. Indeed, although being difficult to demonstrate causality between food and health, there is now appreciable epidemiologic evidence for the protective role of diets rich in fruits and vegetables, being the Mediterranean diet an interesting example. These foods have thousands of components without nutritional essentiality that have been neglected. The interest in these components has increased tremendously in the last two decades, seeking to identify the dietary bioactive components (*i.e.*, those that have a measurable impact on human health), their amounts, and availability. Simultaneously, it is also becoming clear that each one of these components has different effects and potencies when ingested alone or when taking its part in the complex network of molecules present in whole foods. These are amazing days for food scientists because we are closer to understand these bioactive compounds, while the consumer is following closely scientific advances, being increasingly interested in the health properties of foods.

The editors took an enormous and successful effort to assemble a huge variety of knowledge on different natural bioactive components in foods, bringing together experts working in different fields of food composition and health. This first issue was written to provide readers a comprehensive review of bioactive constituents in fruits from different parts of the world. This assembled knowledge allows the reader to attribute a “health-value” to these foods in a more clear way, understand the care needed to preserve their bioactivity, while also adding value to fruits residues (peels, pulp, seeds, and stones) that are frequently neglected by industry. Therefore, this book is designed for food scientists, nutritionists, pharmaceuticals, physicians, food industrials, as well as for health-conscious consumers. More similar comprehensive reviews on other natural food products will be certainly welcomed by readers.

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PREFACE

Plants have been widely used as food and medicines, since they provide, not only essential nutrients required for human life, but also other bioactive compounds which play important roles in health promotion and disease prevention, commonly known as phytochemicals. Moreover, in the recent years, the impact of lifestyle and dietary choices for human health has increased the interest in fruits and vegetables, as well as in foods enriched with bioactive compounds and nutraceuticals. In fact, epidemiological studies have consistently shown that the Mediterranean diet, characterized by the daily consumption of fruits and vegetables, is strongly associated with reduced risk of developing a wide range of chronic diseases, such as cancer, diabetes, neurodegenerative and cardiovascular diseases.

Phytochemicals are secondary metabolites present in fruits and vegetables in low concentrations that have been hypothesized to reduce the risk of several pathological conditions. There are thousands of dietary phytochemicals, namely flavonoids, phenolic acids, glucosinolates, terpenes, alkaloids, between many other classes of compounds, which present different bioactivities, such as antioxidant, antimutagenic, anticarcinogenic, antimicrobial, anti-inflammatory, hypocholesterolemic, hypoglycemic and other clinically relevant activities. The evidence suggests that the health benefits of consuming fruits and vegetables are attributed to the additive and synergistic interactions between these phytocomponents. Therefore, nutrients and bioactive compounds present in fruits and vegetables should be preferred instead of unnatural and expensive dietary supplements.

In this ebook, we provide an overview about the different classes of phytochemicals commonly found in fruits and vegetables, highlighting their chemical structures, occurrence in fruits and vegetables, biological importance and mechanisms of action. Part (I) is particularly focused on Mediterranean and Tropical fruits.

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CHAPTER 4

Stone Fruits as a Source of Bioactive Compounds

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Abstract: Fruits constitute one of the most important sources of phytochemicals in human diet. Stone fruits, such as peaches, plums, almonds, apricots and cherries have been investigated concerning their therapeutic effects in the prevention of a range of diseases. The consumption of these fruits is related with the lower prevalence of diabetes, overweight or general obesity, lower risk for estrogen receptor-negative tumors and cardiovascular protection among others. Phenolic compounds, predominantly flavonoids and phenolic acids, are the main phytochemicals in stone fruits. Considering the importance of stone fruits as a source of biologically active compounds the present chapter aims to provide the current findings in this field and the main implications to human health associated with its consumption.

Keywords: Almond, Anticancer, Antidiabetic, Antiinflammatory, Antioxidant, Apricot, Bioactive Compounds, Cardiovascular protection, Cherry, Flavonoids, Nectarine, Obesity, Peach, Phenolic acids, Phenolic compounds, Plum, Prunus, Stone fruits.

INTRODUCTION

Different studies have demonstrated that a diet rich in fruits and vegetables may decrease the risk of diabetes, cancer, cardiovascular and neurodegenerative diseases (*i.e.* Alzheimer and Parkinson) [1 - 4]. This beneficial effect is associated to

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Luís Rodrigues da Silva and Branca Silva (Eds.)

the nutrients they contain such as fibers, minerals, vitamins and the presence of phytochemicals. Phytochemicals are secondary metabolites produced by plants, in relatively small amounts, where they are responsible for a variety of functions. The ecological role of secondary metabolites production can be related to the potential medicinal effect observed in humans. For example, secondary metabolites in plant defense through cytotoxicity towards microbial pathogens could be useful as antimicrobial drugs in humans, if not very toxic [5].

Phytochemicals compounds have been extensively investigated since they possess a range of activities, which may be involved in the protection against chronic diseases (Fig. **1**). They may also regulate inflammatory and immune responses, inhibit cancer cell proliferation, and protect cells against oxidative damages, caused by free radicals and reactive oxygen species, to macromolecules such as lipids, proteins, and DNA [6]. Examples of phytochemicals present in fruits are phenolic, terpenoids, alkaloids and organosulfur compounds.

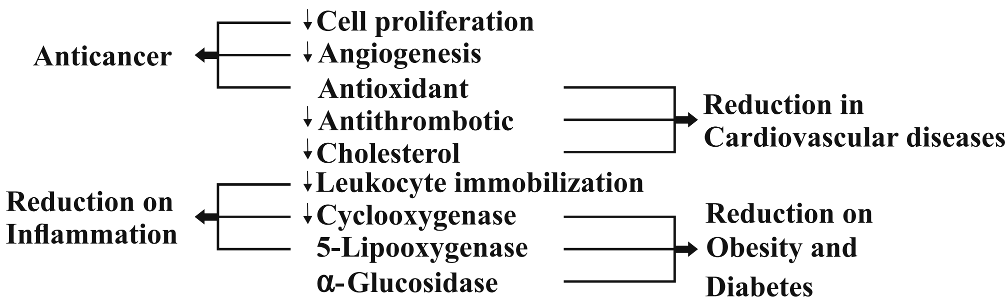

Fig. (1). Relation of phytochemicals actions on different diseases (adapted from [7]).

Stone fruits, also known as drupes, are trees and shrubs members of Prunus genus. Peaches (*Prunus persica* (L.) Batsch), nectarines (*P. persica*, var. nectarine), European plum (*P. domestica* L.), Japanese plum (*P. salicina*), apricot (*P. armeniaca* L.), mume or Japanese apricot (*P. mume*), sweet cherry (*P. avium*), sour cherry (*P. cerasus*) and almond (*P. amygdalus*) are examples of stone fruits with economical interest and are highly consumed worldwide [8]. Good nutritional properties are described for these fruits which are also a good source of phytochemicals affording considerable amounts of bioactive phenolic compounds, mainly flavonoids and phenolic acids.

In the last years, the consumption of fruits has been investigated in different epidemiological studies. Stone fruits consumption was correlated with lower prevalence of diabetes and obesity [9 - 11], cardiovascular protection [12 - 17] and inversely associated with estrogen receptor-negative (ER−) breast cancer [18, 19] and risk of esophageal squamous carcinomas [20]. Moreover, *in vivo* and *in vitro* studies with stone fruits, their extracts, purified fractions and their phytochemicals have been related with these epidemiological evidences on chronic diseases. Considering these facts, we intend to present in this chapter recent research, mostly from the past 10 years, related with epidemiological evidences of the consumption of stones fruits and their health benefits as well as the relationship between these effects and the phytochemicals, mainly phenolic compounds, present in these matrices.

Stone Fruits Bioactive Compounds

Stone fruits can provide different bioactive phytochemicals such as terpenoids, mainly carotenoids, tocopherols and phenolic compounds. In this chapter greater attention will be given to phenolic compounds, since these are the most abundant compounds found in stone fruits. Nevertheless, stone fruits carotenoids and tocopherols, their amounts and their role to human health will be briefly commented.

Carotenoids

Carotenoids are C_{40} terpenoids pigments present in all stone fruits. The carotenoids α- and β-carotene, capsantine, β-cryptoxanthin, lycopene, lutein and zeaxantin, have been reported [21 - 24]. However, there is a large variation on the amounts of these compounds that is dependent of the specie and variety studied. Apricots is the most abundant stone fruit concerning carotenoids with 1512-16500 µg/100g of fresh weight, followed by peaches (up to 1160 µg/100g of fresh weight), plums (231 µg/100g of fresh weight), nectarines (162 µg/100g of fresh weight), being cherries (1.1 µg/100g of fresh weight) the poorest one [25 - 27]. Carotenoids are important to human health since they are precursors of vitamin A, that are implicated in the production of retinoids, vital for human vision [28].

Besides, different studies report carotenoids as antioxidants [29, 30], a very important activity linked with the protection of cells from the damage caused by free radicals and reactive oxygen species which can result in damage to proteins, DNA and lipids resulting in cell death and neoplasia, which are probably in the origin of many human diseases [6].

Tocopherols

Tocopherols and tocotrienols (vitamin E) are natural liposoluble compounds that exist as a mixture of 8 homologues, Alpha, Beta, Gamma and Delta. Almonds are the richest provider of tocopherols (26 mg α-TOC/100g), followed by apricots, nectarines and peaches (0.89, 0.75 and 0.73 mg α-TOC/100g, respectively), plums (0.26 mg α-TOC/100g) and cherries (0.07 mg α-TOC/100g) [8]. The main contribution of tocopherols and tocotrienols for human health are their antioxidant properties [31], that can protect cells against oxidative injury as mentioned for carotenoids. Nevertheless, others properties have been related to vitamin E, such as gene regulation and antiproliferative effects, prevention of platelet aggregation, enhancement of vasodilation and modulation of enzymes associated with the immune system as recently reviewed by [8, 32].

Phenolic Compounds

Phenolic compounds are the main phytochemical compounds found in stone fruits. They are formed *via* the shikimic acid pathway, responsible by the production of the phenylpropanoids, and the acetic acid pathway, in which the simple phenol is mainly formed [33, 34]. Phenolic compounds are structurally characterized by the presence of at least one aromatic ring with one or more hydroxyl groups attached. They represent the largest and wide group of compounds, accounting for more than 8000 phenolic structures, and are classified according with the number of carbons atoms and their basic structure [35, 36] or as flavonoids and non-flavonoids. Non-flavonoids include phenol, benzoquinones and phenolic acids, while flavonoids are the remaining ones. Flavonoids can be divided into classes including mainly flavan-3-ols, flavones, flavonols, anthocyanins, flavanones and isoflavones, and phenolic acids are represented by hydroxybenzoic and hydroxycinnamic acids. Flavonoids and phenolic acids are the two major classes of dietary polyphenols [37]. Stone fruits are a good source of phenolic compounds being peaches capable of providing up to 1260 mg/100 g of fresh weight (FW) (Table **1**).

Table 1. Stone fruits phenolic composition (mg/ 100g of fresh weight).

Total	Peach	Nectarine	Plum	Almond	Apricot	Cherry
	mg/100 g FW					
Phenolic compounds	21.0-1260.0	13.6-102.4	42.0-563.0	45.0-241.0	32.0-211.0	27.8-312.4
Flavonoids	76.4	6.5-21.7	5.4-257.5	14.0-26.7	78.5-139.0	30.2-109.2
Phenolic acids	163.0	10.0	0.1-58.4	0.3-0.5	12.3-40.4	11.0-33.6
Refs	[22, 25, 38-41]	[9, 25, 42]	[25, 40, 41, 43-45]	[46-48]	[46, 47, 49, 50]	[27, 51, 52]

Daily intake of phenolic compounds has been estimated in different studies from different countries. Total phenolic intake can reach 1193 mg/day where flavonoids contribute with 42% (506 mg/day) and phenolic acids with 53% (639 mg/day) [53]. Fruits were reported to contribute with 17% (206 mg/day) of phenolic compounds, being mostly represented by flavonoids (83%, 172 mg/day), and with small contribution of phenolic acids (15%, 32 mg/day) [53]. The median total flavonoids intake was reported to be 166.0-193.3 mg/day, where flavon-3-ols were the most representative group (85.0-161.7 mg/day), followed by flavonone (15.5-46.4 mg/day), flavonols (12.9-20.7 mg/day) and anthocyanins (2.6-7.6 mg/day) [54, 55].

Hydroxycinnamic acids were the main contributors to the total phenolic acid intake, accounting for 84-95% of intake [53, 71]. Fruits, vegetables and nuts are the main food sources of hydroxycinnamic acids, after coffee [53, 71, 72]. Concerning stone fruits, plums and cherries were found among the fruits with high contributions for phenolic compounds intake in this food group (8%) [53]. The type and amounts of phenolic compounds on stone fruits can range significantly inter and intra species since it is dependent of edaphoclimatic factors (Table **2**) [73, 74].

Table 2. Stone fruits phenolic composition (mg/ 100g of fresh weight).

	Peach	Nectarine	Plum	Almond	Apricot	Cherry
	mg / 100 g FW					
Catechin	1.0-42.0	0.3-4.7	3.3-31.8	0.5-22.7	2.8-23.2	0.6-6.8
Epicatechin	1.4-9.2	2.5	0.6-15.6	0.3-4.0	1.1-14.5	13.0-15.0
Epigallocatechin	0.3-1.5			2.6	1.3-9.6	0.05-0.2
Procyanidin B1	14.7	9.9	2.4-31.8		0.09	0.2
Procyanidin B2	2.3		0.7-10.1			2.1
Cyanidin-3-*O*-glucoside	2.4		0.1-48.4		0.8-1.2	1.43-18.7
Cyanidin-3-*O*-rutinoside			0.2-33.8			6.9-143.2
Naringenin			0.2-2.5	0.01-28.1		
Naringenin-7-*O*-glucoside				0.08-10.5		
Eriodictyol				0.03-0.5		
Quercetin		0.1	0.2-6.6	0.02-3.5	0.8-1.6	
Quercetin-3-*O*-glucoside		0.1	0.02-14.3	0.09	0.6-3.6	0.2-0.7
Quercetin-3-*O*-rutinoside	10.2	0.1	0.2-7.9	0.05-0.5	6.7-37.1	0.9-4.6
Quercetin-3-*O*-galactoside			0.3	0.2-1.2		
Quercetin-3-*O*-rhaminoside					2.0-73.0	
Kaempferol			0.3-1.1	0.003	0.6	
Kaempferol-3-*O*-rutinoside	7.0	0.12		0.2-7.0		0.3-1.39
Myricetin					0.6	
Isorhamnetin-3-O-glucoside				0.1-1.0		0.09-2.65
2,5-Dihydroxy benzoic	98.5					
Protocatechuic acid				0.1-12.2	12.6	
Vanillic acid				0.09-9.3	0.2-3.8	
Gallic acid				0.2-1.6	35.0	
p-Coumaric acid			0.2-2.6		0.2-8.8	0.8-6.84
Ferulic acid			0.5-2.2		0.3-1.6	
Caffeic acid			0.3-6.1	0.2-3.2	0.2-7.3	
3-*O*-Caffeoylquinic acid	4.0-29.3	3.9	3.5-75.8	0.03-2.2	2.4-94.0	0.13-19.1
5-*O*-Caffeoylquinic acid	2.5-25.0	6.1	1.1-43.4		3.6-18.6	2.9-53.0
Refs	[21, 22, 25, 38-40, 42, 56, 57]	[42, 58]	[24, 25, 40, 42-45, 57-62]	[42, 46-48, 63, 64]	[46, 47, 49, 57, 58, 65-68]	[42, 51, 52, 57, 58, 69, 70]

Stone fruits are responsible to provide 1% of the intake of caffeic acid and 6% of *p*-coumaric acid [71]. More specifically peaches can provide 1 mg/day of catechin and 4.5 mg/day of procyanidin B1, plums 4.2 mg/day of caffeic acid and 1.6 mg/day of cyanidin-3-*O*-rutinoside, almonds contributes with 0.02 mg/day of epigallocatechin and cherries with 2.8 mg/day of caffeic acid and 9.0 mg/day of cyanidin-3-*O*-rutinoside [53].

Health Benefits of Stone Fruits

In Vivo Studies and Their Mechanism of Action

Diabetes and Obesity

Diabetes mellitus and obesity are becoming a major public health concern with high social and health care costs both in developed and developing countries [75]. Type 2 diabetes mellitus (T2DM) is characterized by individuals with post-prandial hyperglycemia associated with low production of insulin, resistance to insulin or both. The T2DM accounts for 90% of cases of diabetes mellitus and is directly related to obesity, since 80 and 90% of obese individuals have T2DM. Concerning obesity its etiology is multifactorial, with a combination of genetic and environmental factors. This metabolic disorder is characterized by the combination of hyperglycemia, dyslipidemia, abdominal obesity and hypertension. Both, diabetes and obesity, are risk factors in several other pathologies such as coronary heart disease, stroke, diabetic ophthalmopathy, diabetic neuropathy and chronic renal failure [76].

Experiments on obese Zucker and lean rats fed with peach (47.5 mL/day) and plum (45.2 mL/day) juices revealed protective effect against a combination of obesity-induced metabolic disorders including hyperglycemia, insulin and leptin resistance, dyslipidemia and low-density lipoprotein oxidation [75]. In addition, a decrease on the expression of pro-atherogenic and pro-inflammatory biomarkers in plasma and heart tissues including intercellular cell adhesion molecule-1, monocyte chemotactic protein-1, nuclear factor-κB (NF-κB) and foam cell adherence to aortic arches was reported. A reduction on levels of angiotensin II in plasma and its receptor Agtr1 in heart tissues was also reported, suggesting a role of peach and plum polyphenols as peroxisome proliferator-activated receptor-γ agonists. Nevertheless, only plum juice prevented body weight gain and increased the ratio high-density lipoprotein cholesterol/total cholesterol in plasma [75].

Insulin-resistant obese Wistar rats fed with plum concentrated (0.25%) were reported to present a decrease in blood glucose and plasma triglyceride concentrations. Besides, a reduction on the areas under the curve for glucose and insulin during a glucose tolerance test was also reported. Authors suggest that plum treatment may increase insulin sensitivity in Wistar obese rats *via* adiponectin-related mechanisms [77].

These effects can be related to the presence of phenolic compounds that can act on diabetes and obesity by different mechanisms. Cyanidin-3-*O*-glucoside (Table **2**, Fig. **2**) reduces blood glucose and increases glucose tolerance [78], improves insulin sensitivity and reduces white adipose tissue messenger RNA levels and serum concentrations of inflammatory cytokines [79], preserves insulin sensitivity [80] and may exert insulin-like activities [81]. These properties have direct effect on reduction of free fatty acids in plasma and improvement on insulin resistance that represents a risk factor for metabolic, cardiovascular, and neoplastic disorders [82]. Cyanidin-3-*O*-rutinoside retards *in vivo* absorption of carbohydrates by inhibition of α-glucosidase [83], fact that was also observed for this compound and for cyanidin-3-*O*-glucoside and cyanidin-3-*O*-galactoside by different authors in *in vitro* studies[83 - 85]. Naringenin and quercetin-3-*O*-glucoside lower mean levels of fasting blood glucose [86, 87], glycosylated hemoglobin, and elevated serum insulin levels [87], plasma C-peptide, triglyceride, total cholesterol and blood urea nitrogen levels and improves glucose tolerance and the immunoreactive of pancreatic islets β-cells [86]. Quercetin-3-*O*-glucoside lowers the biochemical changes and delays paw and tail withdrawal latency in hyperalgesia and allodynia, showing beneficial effects in preventing the progression of early diabetic neuropathy in rats [88]. Quercetin reduces glycaemia and diminishes total cholesterol, triglycerides (TG) and low density lipoprotein (LDL) and increases high density lipoprotein (HDL) levels by inhibition of 11β-hydroxysteroid dehydrogenase type 1 [89]. Myricetin protects the diabetic nephrotoxic rats on all the biochemical parameters studied [90], alters their lipid metabolism [91] and improves carbohydrate metabolism, subsequently enhancing glucose utilization and renal function [92]. Protocatechuic acid activates the nuclear factor erythroid 2-related factor (Nrf2) system [93] *in vivo*, but this compound was also reported with *in vitro* protective effect on insulin sensitivity [80]. Ferulic acid increases insulin release and reduces hepatic glycogenolysis *in vitro*, while caffeic acid affects only the last [94]. Moreover, caffeic acid decreases the hepatic glucose output along with the increased level of adipocyte glucose disposal [94] and induced a decrease of blood glucose and glycosylated hemoglobin levels [95]. 3-*O*-Caffeoylquinic acid inhibits protein tyrosine phosphatase 1B, a negative regulator of the insulin signaling pathway [96].

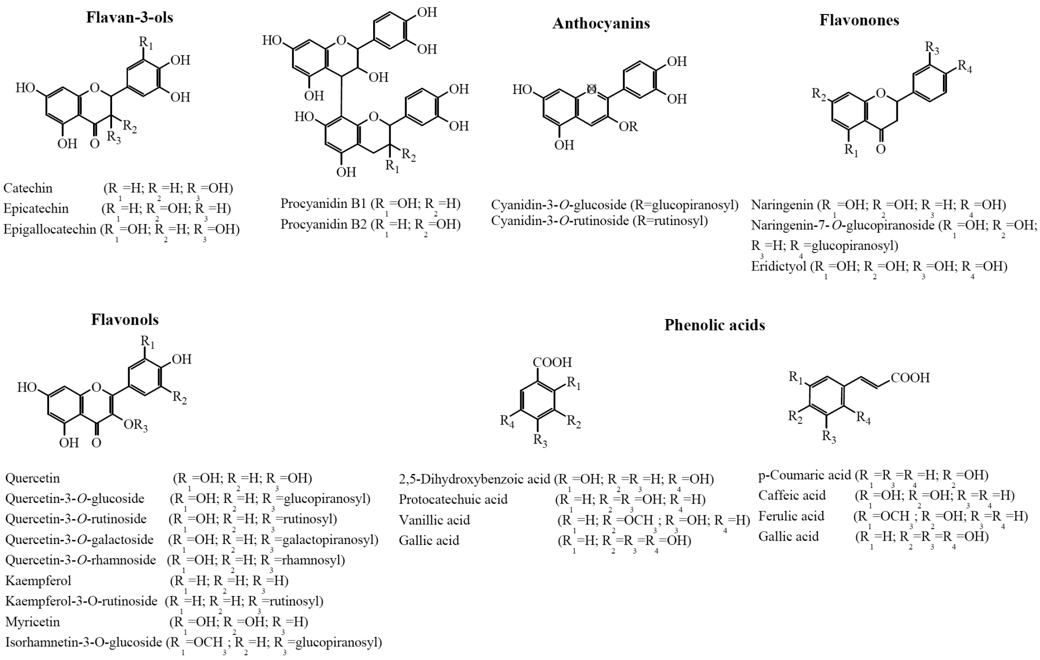

Fig. (2). Chemical structures of biological active phenolic compounds present in stone fruits.

Concerning obesity consumption of catechins and phenolic acids (Fig. **2**), Table **2**) has been associated with a variety of beneficial effects including increased plasma antioxidant activity, blood vessel expansion, fat oxidation, and resistance of LDL to oxidation [97 - 100]. Epicatechin and epigallocatechin lower lymphatic cholesterol absorption in rats, and decrease lymphatic absorption of triacylglycerols [101]. Cyanidin-3-*O*-glucoside reduced obesity, accumulation of fat in tissues, and plasma triglyceride levels, by inhibiting lipoprotein lipase [82], activating of protein kinase phosphorylation [102], and upregulating hepatic cholesterol 7α-hydroxylase expression [103]. Quercetin can protect LDL against oxidation [104]. Quercetin and kaempferol could significantly improve insulin-stimulated glucose uptake [105] and regulates hepatic apolipoprotein A-I (apo A-I) and HDL synthesis by inducing apo A-I gene expression in HepG2 and Caco-2 cells [106].

Cardiovascular Disease

Cardiovascular diseases are a group of disorders of the heart and blood vessels and is the number 1 cause of death globally [107]. Cardiovascular disease is usually resulting from a vascular dysfunction, such as atherosclerosis, thrombosis and hypertension, which can compromises heart function.

The cardio-protective potential of apricot-feeding in the ischemia-reperfusion model of rats *in vivo* was evaluated by [108]. Rats were fed with 10% or 20% dried apricot during 3 months and ischemia-reperfusion produced by occlusion of the left main coronary artery for 30 min, followed by 120 min reperfusion, in anesthetized rats. Significant and similar decrease on infarct sizes were observed in 10% (55%) and 20% (57%) apricot-fed groups compared to control group (68%). Besides, Cu, Zn superoxide dismutase (SOD) and catalase (CAT) activities were increased, and lipid peroxidation was decreased in the hearts of 20% apricot-fed group after ischemia-reperfusion [108].

Phenolic compounds present in stone fruits can have *in vivo* protective effect on cardiovascular diseases by exerting for instance anti-atherosclerotic activity, as reported for catechin [109]. Other example is preventive effect of cyanidin-3-*O*-glucoside on formation of glycated-LDL products on aortic endothelial cells induced by NADPH, the impairment of mitochondrial electron transport chain enzymes and cell viability in cultured vascular endothelial cells [110]. Naringenin-7-*O*-glucoside, prevent cardiomyocytes from doxorubicin-induced toxicity by induction of endogenous antioxidant enzymes *via* phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) and nuclear translocation of Nrf2 [111] and by stabilizing the cell membrane and reducing reactive oxygen species generation [112]. Quercetin has been shown to induce a progressive reduction in blood pressure when given chronically in several rat models of hypertension. A high dose of quercetin also reduced blood pressure in stage 1 hypertensive patients in a randomized, double-blind, placebo-controlled, crossover study [113]. In addition, it can protect isolated vessels by activation of adenosine monophosphate-activated protein kinase and nitric oxide synthase (eNOS) in human aortic endothelial cells [114]. Quercetin-3-*O*-glucoside improve cell survival in the oxygen-glucose deprivation model of ischemia and increase neurite outgrowth in differentiated PC12 cells subjected to ischemic insult [115].

Cancer

Cancer is a multifactorial disease and a progressive process involving gene-environment interactions which can cause dysfunction in multiple systems, including DNA repair, apoptotic and immune functions.

Peaches and plums extracts have been reported with antiproliferative effects in estrogen-receptor negative breast cancer cells but not in estrogen positive breast cancer line or the normal breast cell line [18, 19, 116, 117]. Crude extracts and fractions rich in flavonoids for peach and plum [19] and hydroxycinnamic acids for peach [18] showed to be very effective against cell proliferation. Further, *in vivo* studies on peach polyphenolic extracts revealed inhibitory and anti-metastatic action on female athymic mice implanted with MDA-MB-435 breast cancer cell line. Inhibition was achieved by feeding mices with 0.8-1.6 mg/day, this effect was mediated by inhibition of metalloproteinases gene expression [118]. Sour cherry extracts were also reported with antiproliferative activity and induction of apoptosis in mammary adenocarcinoma (MCF-7) and mouse mammary tumour cell (4T1) breast cancer cells lines [119]. Moreover, peach and plum extracts and purified phenolic compounds can inhibit growth and induce differentiation of colon cancer cells [120], and plums extracts have similar beneficial effect *in vivo* [121].

A Japanese apricot extract (MK615), has shown strong antiproliferative and antitumorigenic effects in different cancer cell lines and *in vivo* model [122 - 126]. MK615 also inhibit A375 melanoma cells growth by reducing the mRNA- and protein expression levels of DNA binding 1, a basic helix-loop-helix transcription factor family that is essential for DNA binding and the transcriptional regulation of various proteins that play important roles in the development, progression and invasion of tumour [122]. SK-MEL28 cell line, another melanoma cell model, has also their growth inhibited by MK615 in a dose-dependent manner, by increasing the proportion of cells in sub-G1 phase and inducing apoptosis. Inhibition of advanced glycation end products and suppression of the release of a specific cytokine (high mobility group box protein 1) indicates the MK615 for the treatment of malignant melanoma [124]. MK615 also showed strong growth suppression effect mainly in human cancer cells while sparing normal cells such as human umbilical vein endothelial cells (HUVEC) and mouse bone marrow cells [123]. Moreover, MK615 induce the accumulation of reactive oxygen species in cancer cells but not in HUVEC indicating that the antiproliferative effect is due to a reactive oxygen species-dependent mechanism. *In vivo* tests showed that MK615, in both the presence and absence of gemcitabine, significantly inhibited the growth of human pancreatic cancer cells as xenografts without apparent adverse effects [123]. Japanese apricot extract combined with anticancer drugs 5-fluorouracil, irinotecan and cisplatin showed synergistic cytotoxic effects on esophageal squamous carcinoma cells. The effect was observed in both *in vitro* model using YES-2 cells and *in vivo* model by the injection of YES-2 cells into the peritoneal cavity of a severe combined immuno-deficiency mouse. The Japanese apricot extract and 5-fluorouracil induced cell cycle arrest at G2/M phase and at S phase, respectively, and caused apoptosis in YES-2 cells *in vitro* [125]. *In vivo* results showed that the addition of Japanese apricot extract to 5-fluorouracil augmented the suppression of experimental metastasis of the peritoneum. Also a decrease in the number of peritoneal nodules in mice treated with 5-fluorouracil and Japanese apricot extracts was observed when compared with the individual treatment [125]. In other study the Japanese apricot extract inhibited A549 lung cancer cell proliferation at non-cytotoxic doses and suppressed NF-κB activation induced by tumor necrosis factor α (TNF-α) at a dose of 1 mg/mL and blocked proteasome activities in a dose-dependent manner at concentrations of 0.67 and 1 mg/mL [126].

Stone fruits anticancer properties can be also associated to their antioxidant and antiinflammatory effects. At physiological levels antioxidants may protect important cells macromolecules (proteins, DNA and lipids) from oxidative injury, preventing cell death and neoplasia, which are probably in the origin of many human diseases [6]. Moreover, by preventing inflammation, which is an adaptive immune response to tissue injury or infection [127], stone fruits can have a positive effect on chronic diseases such as cancer, Alzheimer's disease, diabetes among others that are related with inflammatory process [128 - 131]. In fact, peaches are responsible for attenuation on the oxidative stress and the inflammation *in vitro*, *ex vivo* and *in vivo* [132, 133]. The mechanism of action was found to be through its protective effect against lipids and proteins damage, increase of antioxidant enzymatic activities and blocking the induction of inflammatory mediators [133].

Several mechanisms of action can be used by different bioactive compounds from stone fruits. Catechin can induced apoptosis and inhibited G2/M phase in cell cycle in HepG2 cells [134]. In addition, catechin and epicatechin, present in all stone fruits, were reported as antioxidants, a possible anticancer mechanism. Inhibition of radicals [135] and prevention of the oxidative injure, induced by palmitic acid in rats, protecting the mitochondrial membrane from collapse and cell death [136]. Oxidative protection was also observed in rats pretreated with this compound [134, 137] that was capable to restore their antioxidant parameters (glutathione, SOD, CAT and lipid peroxidation).

Anthocyanins, present in all stone fruits, can suppress lipid peroxidation in Caco-2 cells [138] and attenuate ethanol-induced migration/invasion of breast cancer cells by blocking ethanol-induced activation of the ErbB2/cSrc/FAK pathway, which is necessary for cell migration/invasion [139]. Moreover, they also suppresses Benzo[a]pyrene-7,8-diol-9,10-epoxide-induced cyclooxygenase-2 (COX-2) expression mainly by blocking the activation of the Fyn (a proto-oncogene tyrosine-protein kinase) signaling pathway [140], inhibit nitric oxide synthase and COX-2 and decrease in nitric oxide and prostaglandin E2 production (PGE2) [141], and inhibit IκBα phosphorylation, thereby suppressing NF-κB activity in cell models [142] and *in vivo* models [143, 144], which may contribute to its chemopreventive potential. In addition, protective effect on DNA cleavage, free radical scavenging activity [145], reduction of reactive oxygen species generation [146], protection against oxidative injure by decreasing mitochondrial reactive oxygen species production and cell necrosis [78] and decreasing lipid peroxidation by increasing cell enzymatic levels [147 - 149] are other possible anticancer mechanisms.

The Flavanone, naringenin, and the flavonol, myricetin, exert a cytostatic effect by the impairment of cell cycle progression and inhibition of the cell migration [150]. Quercetin exerts an apoptotic activity in cancer cell lines mediated by the dissociation of Bax from Bcl-xL and the activation of caspase families [151]; and can also inhibits precursors of cellular differentiation; stimulates phagocytosis [152], antimitotic activity [153], suppression of COX-2 expression by inhibiting the p300 signaling and blocking the binding of multiple transactivators to COX-2 promoter [154], and interferes with cell cycle progression [155]. Moreover, flavonones were reported to have *in vitro* and *in vivo* antioxidant capacity [111, 112, 156, 157]. Reduction of ROS generation and induction of the cellular antioxidant enzymatic system are the *in vitro* and *in vivo* mechanisms described for these compounds [87, 158]. They can reduce nitric oxide production and prevent peroxinitrite formation in LPS-stimulated RAW 264.7 cells by strongly suppressing the phagocytic activity of activated macrophages, thus reducing the expression of mRNA and the secretion of pro-inflammatory cytokines by blockage of nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) activation and phosphorylation of p38 mitogen-activated protein kinase, ERK1/2 and c-Jun N terminal kinase [159].

The flavonol, quercetin-3-*O*-rutinoside, isolated from the ethyl acetate fraction of *P. domestica*, showed antiproliferative activity in MCF-7 and MDA-MB-468 at 80×10^{-3} mg/mL with inhibitions of 22 and 32%, respectively [117]. One possible mechanism of action of quercetin-3-*O*-rutinoside can be due to its antioxidant activity which has been reported in different *in vitro* and *in vivo* tests. This compound has scavenging activity against peroxyl radicals *in vitro* [160] and *in vivo* [88, 161, 162], recover levels of glutathione [160, 161] and antioxidant enzymes SOD, NO and CAT [88]. Quercetin, is also able to scavenge radicals [163] and have *in vitro* and *in vivo* ability to decrease the tumor necrosis factor-α production [164, 165] and increase total plasma antioxidant status [165] was reported for quercetin and quercetin-3-*O*-galactoside. Quercetin and quercetin-3-*O*-glucoside protect Caco-2 cells [166] and PC12 cells [167] against oxidative stress caused by different agents probably by their free radicals inhibitory effects [157]. In addition, they possess anti-inflammatory action by inhibition of 5-lipoxygenase [157], raft disrupting and anti-oxidant effects [105, 168].

Protocatechuic, 3-*O*-caffeoyl quinic and 5-*O*-caffeoyl quinic acids, isolated from *P. domestica and P. persica*, have been identified as potential chemopreventive dietary compounds due to their antiproliferative effect on the human breast cancer cell line MCF-7 and the estrogen-independent MDA-MB-435 breast cancer cell line [19, 117]. 3-*O*-Caffeoyl quinic and 5-*O*-caffeoyl quinic acids also presents low toxicity on normal cells [19]. Gallic acid also showed *in vitro* (DU145 cells) and *in vivo* (DU145 and 22Rv1 xenograft growth in nude mice) inhibitory and apoptotic activities against prostate cancer [169, 170]. These effects were also observed in other cancers models [171, 172]. Protocatechuic, vanilic, *p*-coumaric, ferulic and 3-*O*-caffeoylquinic (isolated from *P. domestica*), 2,5-dihydroxy benzoic and caffeic acids were reported with antioxidant activity in different models [117, 173 - 175]. *In vivo* tests indicate that hydroxycinnamic acids increases the antioxidants enzymes activities (*i.e.* SOD, CAT and glutathione peroxidase) and decreases levels of liver lipid peroxidation [95, 176 - 178]. Concerning their anti inflammatory properties, *p*-coumaric and ferulic acids showed inhibition of nitric oxide production and inducible nitric oxide synthase (iNOS) expression [179].

Epidemiological Studies

Diabetes and Obesity

Consumption of fruits and their role in the treatment of diabetes and obesity have been investigated in humans [16]. In respect to stone fruits, a study performed on overweight and obese individuals (n=123) fed with hypocaloric almond-enriched diet (56 g/day) resulted in a significant loss of weight when compared with individuals under a hypocaloric nut-free diet after 6 months with no significant weight gain after 18 months. In addition, a reduction on total cholesterol (4%), total:high density lipoprotein (HDL) cholesterol (5%) and triglycerides (12%), and an improvement of the lipid profile was also observed in the almond-enriched diet [11]. The same trend was observed in other study with prediabetes individuals subjected to an 20% almond-enriched diet (approximately 62 g/day) [10]. A clinically significant decline in human low density lipoprotein-cholesterol (LDL-C) was found in the almond-enriched intervention group (-12.4 mg/dl *vs*. -0.4 mg/dl) as compared with the nut-free control group after sixteen weeks of dietary modification. Besides, the almond-enriched intervention group showed improved markers of insulin sensitivity such as reductions in insulin, homeostasis model analysis for insulin resistance, and homeostasis model analysis for beta-cell function compared with the nut-free control group [10].

Cardiovascular Disease

The antithrombotic properties of anthocyanin-rich Queen Garnet plum juice (QGPJ) supplementation with and without exercise-induced oxidative stress was investigated in thirteen healthy participants in a randomized, double-blind, placebo-controlled, cross-over trial. The experiment was carried out during 28 days where participants consumed 200 mL/day of QGPJ and placebo juice, with treatments separated by a two-week wash-out period. QGPJ supplementation inhibited adenosine diphosphate-induced platelet aggregation in both groups (10.7 and 12.7%), reduced platelet activation-dependent P-selectin expression (32.9 and 38.7%) and exhibited favorable effects on coagulation parameters. The arachidonic acid-induced aggregation was reduced under oxidative stress by 28.8% [12]. Daily intake of a single dose of plums was reported to significantly reduce blood pressure in a placebo controlled clinical trial with 259 pre-hypertensive volunteers [13]. Consumption of plum as juice, whole fruit (dried plums), or 3 (about 11.5 g) or 6 plums soaked overnight in a glass of water, with control group (glass of plain water in the morning on empty stomach) also showed significantly reduction on serum cholesterol and LDL [13].

The cardiovascular risk of 108 overweight and obese women, under an almond-enriched diet during 3 months has been studied in a clinical study. Body mass index, waist circumference, waist to hip circumference ratio, total cholesterol, and triglyceride, total: High density lipoprotein-cholesterol, fasting blood sugar and diastolic blood pressure were significantly decreased in almond-enriched diet (50 g/day) group compared to the nut-free group [14]. In a study performed by Choudhury and co-workers [15], healthy young and middle-aged men subjected to a enriched almond diet (50 g/day) during 4 weeks showed an improvement on flow mediated dilatation and a reduction on systolic blood pressure for men with cardiovascular risk factors, but diastolic blood pressure was reduced only in healthy men [15].

Cancer

Epidemiological data reports that consumption of stone fruits has been inversely associated with estrogen receptor-negative (ER−) breast cancer [180, 181]. Breast cancer is a major concern worldwide and is responsible for one of the highest causes of death. ER-negative tumour growth is not estrogen-dependent; consequently, such tumors are not sensitive to hormones treatment that prevents the estrogen binding. Jung *et al.* 2013 [180], evaluated the association between fruit and vegetable intake and risk of ER− breast cancer. Authors analyzed 20 cohort studies that followed 993,466 women by 11 to 20 years and documented 4821 ER− breast cancers. They found that, for vegetable consumption, there is an inverse association with risk of ER− breast cancer, while for fruits only specific ones shows the same behaviour as the case of apples/pears, peaches/ nectarines/apricots, and strawberries [180]. In other study [181], the association of intake of specific fruits and vegetables with risk of ER- postmenopausal breast cancer has been checked. A total of 75,929 women aged 38-63 years at baseline where followed for up to 24 years and 792 incident cases of ER- postmenopausal breast cancer were found. The multivariate relative risk (RR) of ER− breast cancer was 0.82 for every 2 servings of berries/week, 0.69 for at least one serving of blueberries/week and 0.59 for 2 servings of peaches/nectarines per week compared with non-consumers [181].

The association of fruit and vegetable intake and risk of esophageal squamous cell carcinoma and esophageal adenocarcinoma was evaluated by Freedman 2007 [20]. A total of 490,802 participants of the National Institutes of Health - American Association of Retired Persons Diet and Health Study were followed 103 participants were diagnosed with esophageal squamous cell carcinoma and

213 with esophageal adenocarcinoma. A significant inverse association between total fruit and vegetable intake and esophageal squamous cell carcinoma risk was found. Protective effects were stronger for fruits being the Rosacea (apples, peaches, nectarines, plums, pears and strawberries) and Rutaceae (citrus fruits) those with higher action [20].

CONCLUDING REMARKS

The evidences found in the epidemiological studies, which relate the consumption of stone fruits and effects on chronic diseases, corroborate with the reported results for *in vitro* and *in vivo* tests with these fruits and their products (juices and extracts). Moreover, these effects can be attributed to the phenolic compounds present in stone fruits since the individual compounds exert similar effects at low concentrations. In conclusion, stone fruits are a good source of bioactive phenolic compounds and its consumption may have remarkable beneficial effects on human health due to their positive results in the treatment of diabetes and obesity, cardiovascular diseases and cancer.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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REFERENCES

[1] Loef M, Walach H. Fruit, vegetables and prevention of cognitive decline or dementia: a systematic review of cohort studies. J Nutr Health Aging 2012; 16(7): 626-30. [http://dx.doi.org/10.1007/s12603-012-0097-x] [PMID: 22836704]

[2] Woodside JV, Young IS, McKinley MC. Fruits and vegetables: measuring intake and encouraging increased consumption. Proc Nutr Soc 2013; 72(2): 236-45. [http://dx.doi.org/10.1017/S0029665112003059] [PMID: 23324158]

[3] Barnes DE. The mediterranean diet: good for the heart = good for the brain? Ann Neurol 2011; 69(2): 226-8. [http://dx.doi.org/10.1002/ana.22376] [PMID: 21387364]

[4] Smith-Warner SA, Spiegelman D, Yaun SS, *et al.* Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. JAMA 2001; 285(6): 769-76.
[http://dx.doi.org/10.1001/jama.285.6.769] [PMID: 11176915]

[5] Briskin DP. Medicinal plants and phytomedicines. Linking plant biochemistry and physiology to human health. Plant Physiol 2000; 124(2): 507-14.
[http://dx.doi.org/10.1104/pp.124.2.507] [PMID: 11027701]

[6] Praticò D, Delanty N. Oxidative injury in diseases of the central nervous system: focus on Alzheimer's disease. Am J Med 2000; 109(7): 577-85.
[http://dx.doi.org/10.1016/S0002-9343(00)00547-7] [PMID: 11063960]

[7] Tapas AR, Sakarkar DM, Kakde RB. Flavonoids as nutraceuticals: A Review. Trop J Pharm Res 2008; 7(3): 1089-99.
[http://dx.doi.org/10.4314/tjpr.v7i3.14693]

[8] Vicente AR, Manganaris GA, Cisneros-Zevallos L, Crisosto CH. Health-promoting Properties of Fruits and Vegetables In: Terry LA, Ed. Prunus. CABI 2011; pp. 59-238.

[9] Abidi W, Jiménez S, Moreno MÁ, Gogorcena Y. Evaluation of antioxidant compounds and total sugar content in a nectarine [*Prunus persica* (L.) Batsch] progeny. Int J Mol Sci 2011; 12(10): 6919-35.
[http://dx.doi.org/10.3390/ijms12106919] [PMID: 22072927]

[10] Wien M, Bleich D, Raghuwanshi M, *et al.* Almond consumption and cardiovascular risk factors in adults with prediabetes. J Am Coll Nutr 2010; 29(3): 189-97.
[http://dx.doi.org/10.1080/07315724.2010.10719833] [PMID: 20833991]

[11] Foster GD, Shantz KL, Vander Veur SS, *et al.* A randomized trial of the effects of an almond-enriched, hypocaloric diet in the treatment of obesity. Am J Clin Nutr 2012; 96(2): 249-54.
[http://dx.doi.org/10.3945/ajcn.112.037895] [PMID: 22743313]

[12] Santhakumar AB, Kundur AR, Sabapathy S, Stanley R, Singh I. The potential of anthocyanin-rich Queen Garnet plum juice supplementation in alleviating thrombotic risk under induced oxidative stress conditions. J Funct Foods 2015; 14: 747-57.
[http://dx.doi.org/10.1016/j.jff.2015.03.003]

[13] Ahmed T, Sadia H, Batool S, Janjua A, Shuja F. Use of prunes as a control of hypertension. J Ayub Med Coll Abbottabad 2010; 22(1): 28-31.
[PMID: 21409897]

[14] Abazarfard Z, Salehi M, Keshavarzi S. The effect of almonds on anthropometric measurements and lipid profile in overweight and obese females in a weight reduction program: A randomized controlled clinical trial. J Res Med Sci 2014; 19(5): 457-64.
[PMID: 25097630]

[15] Choudhury K, Clark J, Griffiths HR. An almond-enriched diet increases plasma α-tocopherol and improves vascular function but does not affect oxidative stress markers or lipid levels. Free Radic Res 2014; 48(5): 599-606.
[http://dx.doi.org/10.3109/10715762.2014.896458] [PMID: 24555818]

[16] Savory LA, Griffin SJ, Williams KM, *et al.* Changes in diet, cardiovascular risk factors and modelled cardiovascular risk following diagnosis of diabetes: 1-year results from the ADDITION-Cambridge

trial cohort. Diabet Med 2014; 31(2): 148-55.
[http://dx.doi.org/10.1111/dme.12316] [PMID: 24102972]

[17] WHO. Cardiovascular diseases. World Health Organization Available from: http://www.who.int/mediacentre/factsheets/fs317/en/ , 2015 [[Accessed on 14/01/2015]];

[18] Vizzotto M, Porter W, Byrne D, Cisneros-Zevallos L. Polyphenols of selected peach and plum genotypes reduce cell viability and inhibit proliferation of breast cancer cells while not affecting normal cells. Food Chem 2014; 164: 363-70.
[http://dx.doi.org/10.1016/j.foodchem.2014.05.060] [PMID: 24996346]

[19] Noratto G, Porter W, Byrne D, Cisneros-Zevallos L. Identifying peach and plum polyphenols with chemopreventive potential against estrogen-independent breast cancer cells. J Agric Food Chem 2009; 57(12): 5219-26.
[http://dx.doi.org/10.1021/jf900259m] [PMID: 19530711]

[20] Freedman ND, Park Y, Subar AF, *et al.* Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. Int J Cancer 2007; 121(12): 2753-60.
[http://dx.doi.org/10.1002/ijc.22993] [PMID: 17691111]

[21] Campbell OE, Padilla-Zakour OI. Phenolic and carotenoid composition of canned peaches (*Prunus persica*) and apricots (*Prunus armeniaca*) as affected by variety and peeling. Food Res Int 2013; 54(1): 448-55.
[http://dx.doi.org/10.1016/j.foodres.2013.07.016]

[22] Oliveira A, Pintado M, Almeida DP. Phytochemical composition and antioxidant activity of peach as affected by pasteurization and storage duration. LWT - Food. Sci Tech (Paris) 2012; 49(2): 202-7.

[23] Bohoyo-Gil D, Dominguez-Valhondo D, García-Parra JJ, González-Gómez D. UHPLC as a suitable methodology for the analysis of carotenoids in food matrix. Eur Food Res Technol 2012; 235(6): 1055-61.
[http://dx.doi.org/10.1007/s00217-012-1838-0]

[24] Bobrich A, Fanning KJ, Rychlik M, Russell D, Topp B, Netzel M. Phytochemicals in Japanese plums: impact of maturity and bioaccessibility 2014.
[http://dx.doi.org/10.1016/j.foodres.2014.06.030]

[25] Gil MI, Tomás-Barberán FA, Hess-Pierce B, Kader AA. Antioxidant capacities, phenolic compounds, carotenoids, and vitamin C contents of nectarine, peach, and plum cultivars from California. J Agric Food Chem 2002; 50(17): 4976-82.
[http://dx.doi.org/10.1021/jf020136b] [PMID: 12166993]

[26] Ruiz D, Egea J, Tomás-Barberán FA, Gil MI. Carotenoids from new apricot (*Prunus armeniaca* L.) varieties and their relationship with flesh and skin color. J Agric Food Chem 2005; 53(16): 6368-74.
[http://dx.doi.org/10.1021/jf0480703] [PMID: 16076120]

[27] Valero D, Díaz-Mula HM, Zapata PJ, *et al.* Postharvest treatments with salicylic acid, acetylsalicylic acid or oxalic acid delayed ripening and enhanced bioactive compounds and antioxidant capacity in sweet cherry. J Agric Food Chem 2011; 59(10): 5483-9.
[http://dx.doi.org/10.1021/jf200873j] [PMID: 21506518]

[28] von Lintig J. Metabolism of carotenoids and retinoids related to vision. J Biol Chem 2012; 287(3):

1627-34.
[http://dx.doi.org/10.1074/jbc.R111.303990] [PMID: 22074927]

[29] Stahl W, Sies H. Antioxidant activity of carotenoids. Mol Aspects Med 2003; 24(6): 345-51. [http://dx.doi.org/10.1016/S0098-2997(03)00030-X] [PMID: 14585305]

[30] Fiedor J, Burda K. Potential role of carotenoids as antioxidants in human health and disease. Nutrients 2014; 6(2): 466-88.
[http://dx.doi.org/10.3390/nu6020466] [PMID: 24473231]

[31] Traber MG, Atkinson J. Vitamin E, antioxidant and nothing more. Free Radic Biol Med 2007; 43(1): 4-15.
[http://dx.doi.org/10.1016/j.freeradbiomed.2007.03.024] [PMID: 17561088]

[32] Engin KN. Alpha-tocopherol: looking beyond an antioxidant. Mol Vis 2009; 15: 855-60.
[PMID: 19390643]

[33] Hollman PC. Evidence for health benefits of plant phenols: local or systemic effects? J Sci Food Agric 2001; 81(9): 842-52.
[http://dx.doi.org/10.1002/jsfa.900]

[34] Sánchez-Moreno C. Compuestos polifenólicos: estructura y classificación: presencia en alimentos y consumo: biodisponibilidad y metabolismo. Alimentaria 2002; 329: 19-28.

[35] Robards K, Prenzler PD, Tucker G, Swatsitang P, Glover W. Phenolic compounds and their role in oxidative processes in fruits. Food Chem 1999; 66(4): 401-36.
[http://dx.doi.org/10.1016/S0308-8146(99)00093-X]

[36] Strack D, Wray V. The Flavonoids: Advances in Research Since 1986. London: Chapman and Hall 1992.

[37] Tapiero H, Tew KD, Ba GN, Mathé G. Polyphenols: do they play a role in the prevention of human pathologies? Biomed Pharmacother 2002; 56(4): 200-7.
[http://dx.doi.org/10.1016/S0753-3322(02)00178-6] [PMID: 12109813]

[38] Durst RW, Weaver GW. Nutritional content of fresh and canned peaches. J Sci Food Agric 2013; 93(3): 593-603.
[http://dx.doi.org/10.1002/jsfa.5849] [PMID: 22968977]

[39] Abidi W, Cantin CM, Buhner T, Gonzalo MJ, Moreno MÁ, Gogorcena Y. Genetic control and location of QTLs involved in antioxidant capacity and fruit quality traits in peach. Acta Hortic 2012; 962: 129-34. [*Prunus Persica* (L.) BATSCH].
[http://dx.doi.org/10.17660/ActaHortic.2012.962.17]

[40] Cevallos-Casals BA, Byrne D, Okie WR, Cisneros-Zevallos L. Selecting new peach and plum genotypes rich in phenolic compounds and enhanced functional properties. Food Chem 2006; 96(2): 273-80.
[http://dx.doi.org/10.1016/j.foodchem.2005.02.032]

[41] Vizzotto M, Cisneros-Zevallos L, Byrne DH, Ramming DW, Okie WR. Large variation found in the phytochemical and antioxidant activity of peach and plum germplasm. J Am Soc Hortic Sci 2007; 132(3): 334-40.

[42] Neveu V, Perez-Jiménez J, Vos F, *et al.* Phenol-Explorer: an online comprehensive database on polyphenol contents in foods 2010.
[http://dx.doi.org/10.1093/database/bap024]

[43] Kim D-O, Chun OK, Kim YJ, Moon H-Y, Lee CY. Quantification of polyphenolics and their antioxidant capacity in fresh plums. J Agric Food Chem 2003; 51(22): 6509-15.
[http://dx.doi.org/10.1021/jf0343074] [PMID: 14558771]

[44] Cosmulescu S, Trandafir I, Nour V, Botu M. Total phenolic, flavonoid distribution and antioxidant capacity in skin, pulp and fruit extracts of plum cultivars. J Food Biochem 2015; 39(1): 64-9.
[http://dx.doi.org/10.1111/jfbc.12112]

[45] Jaiswal R, Karaköse H, Rühmann S, *et al.* Identification of phenolic compounds in plum fruits (*Prunus salicina* L. and *Prunus domestica* L.) by high-performance liquid chromatography/tandem mass spectrometry and characterization of varieties by quantitative phenolic fingerprints. J Agric Food Chem 2013; 61(49): 12020-31.
[http://dx.doi.org/10.1021/jf402288j] [PMID: 24152059]

[46] Kamiloglu S, Pasli AA, Ozcelik B, Capanoglu E. Evaluating the *in vitro* bioaccessibility of phenolics and antioxidant activity during consumption of dried fruits with nuts. LWT - Food. Sci Tech (Paris) 2014; 56(2): 284-9.

[47] Kiat VV, Siang WK, Madhavan P, Chin JH, Ahmad M, Akowuah GA. FT-IR Profile and antiradical activity of dehulled kernels of apricot, almond and pumpkin. Res J Pharm Biol Chem Sci 2014; 5(2): 112-20.

[48] Milbury PE, Chen C-Y, Dolnikowski GG, Blumberg JB. Determination of flavonoids and phenolics and their distribution in almonds. J Agric Food Chem 2006; 54(14): 5027-33.
[http://dx.doi.org/10.1021/jf0603937] [PMID: 16819912]

[49] Roussos PA, Sefferou V, Denaxa N-K, Tsantili E, Stathis V. Apricot (*Prunus armeniaca* L.) fruit quality attributes and phytochemicals under different crop load. Sci Hortic (Amsterdam) 2011; 129(3): 472-8.
[http://dx.doi.org/10.1016/j.scienta.2011.04.021]

[50] Ruiz D, Egea J, Gil MI, Tomás-Barberán FA. Characterization and quantitation of phenolic compounds in new apricot (*Prunus armeniaca* L.) varieties. J Agric Food Chem 2005; 53(24): 9544-52.
[http://dx.doi.org/10.1021/jf051539p] [PMID: 16302775]

[51] Kim D-O, Heo HJ, Kim YJ, Yang HS, Lee CY. Sweet and sour cherry phenolics and their protective effects on neuronal cells. J Agric Food Chem 2005; 53(26): 9921-7.
[http://dx.doi.org/10.1021/jf0518599] [PMID: 16366675]

[52] Melicháčová S, Timoracká M, Bystrická J, Vollmannová A, Čéry J. Relation of total antiradical activity and total polyphenol content of sweet cherries (*Prunus avium* L.) and tart cherries (*Prunus cerasus* L.). Acta Agric Slov 2010; 95(1): 21-8.
[http://dx.doi.org/10.2478/v10014-010-0003-3]

[53] Pérez-Jiménez J, Fezeu L, Touvier M, *et al.* Dietary intake of 337 polyphenols in French adults. Am J Clin Nutr 2011; 93(6): 1220-8.

[http://dx.doi.org/10.3945/ajcn.110.007096] [PMID: 21490142]

[54] Mullie P, Clarys P, Deriemaeker P, Hebbelinck M. Estimation of daily human intake of food flavonoids. Int J Food Sci Nutr 2008; 59(4): 291-8. [http://dx.doi.org/10.1080/09687630701539293] [PMID: 17852474]

[55] Chun OK, Chung SJ, Song WO. Estimated dietary flavonoid intake and major food sources of U.S. adults. J Nutr 2007; 137(5): 1244-52. [PMID: 17449588]

[56] Andreotti C, Ravaglia D, Ragaini A, Costa G. Phenolic compounds in peach (*Prunus persica*) cultivars at harvest and during fruit maturation. Ann Appl Biol 2008; 153(1): 11-23. [http://dx.doi.org/10.1111/j.1744-7348.2008.00234.x]

[57] de Pascual-Teresa S, Santos-Buelga C, Rivas-Gonzalo JC. Quantitative analysis of flavan-3-ols in Spanish foodstuffs and beverages. J Agric Food Chem 2000; 48(11): 5331-7. [http://dx.doi.org/10.1021/jf000549h] [PMID: 11087482]

[58] Arts IC, van de Putte B, Hollman PC. Catechin contents of foods commonly consumed in The Netherlands. 1. Fruits, vegetables, staple foods, and processed foods. J Agric Food Chem 2000; 48(5): 1746-51. [http://dx.doi.org/10.1021/jf000025h] [PMID: 10820089]

[59] Ozturk B, Yıldız K, Kucuker E. Effect of pre-harvest methyl jasmonate treatments on ethylene production, water-soluble phenolic compounds and fruit quality of Japanese plums. J Sci Food Agric 2015; 95(3): 583-91. [http://dx.doi.org/10.1002/jsfa.6787] [PMID: 24930710]

[60] Ozturk B, Kucuker E, Karaman S, Yıldız K, Kılıc K. Effect of aminoethoxyvinylglycine and methyl jasmonate on individual phenolics and post-harvest fruit quality of three different Japanese plums (*Prunus salicina* Lindell). Int J Food Eng 2013; 9(4): 421. [http://dx.doi.org/10.1515/ijfe-2012-0257]

[61] Venter A, Joubert E, de Beer D. Characterisation of phenolic compounds in South African plum fruits (*Prunus salicina* Lindl.) using HPLC coupled with diode-array, fluorescence, mass spectrometry and on-line antioxidant detection. Molecules 2013; 18(5): 5072-90. [http://dx.doi.org/10.3390/molecules18055072] [PMID: 23644975]

[62] Venter A, Joubert E, de Beer D. Nutraceutical value of yellow- and red-fleshed South African plums (*Prunus salicina* Lindl.): evaluation of total antioxidant capacity and phenolic composition. Molecules 2014; 19(3): 3084-109. [http://dx.doi.org/10.3390/molecules19033084] [PMID: 24619353]

[63] Bolling BW, Dolnikowski G, Blumberg JB, Chen CO. Polyphenol content and antioxidant activity of California almonds depend on cultivar and harvest year. Food Chem 2010; 122(3): 819-25. [http://dx.doi.org/10.1016/j.foodchem.2010.03.068] [PMID: 25544797]

[64] Yıldırım AN, San B, Koyuncu F, Yıldırım F. Variability of phenolics, α-tocopherol and amygdalin contents of selected almond (*Prunus amygdalus* Batsch.) genotypes. J Food Agric Environ 2010; 8(1): 76-9.

[65] Čanadanović-Brunet JM, Vulic J, Cetkovic G, Djilas S, Tumbas-Saponjac V. Bioactive compounds

and antioxidant properties of dried apricot. Acta Per Technol 2013; 44: 193-205.
[http://dx.doi.org/10.2298/APT1344193C]

[66] Campbell OE, Merwin IA, Padilla-Zakour OI. Characterization and the effect of maturity at harvest on the phenolic and carotenoid content of Northeast USA Apricot (*Prunus armeniaca*) varieties. J Agric Food Chem 2013; 61(51): 12700-10.
[http://dx.doi.org/10.1021/jf403644r] [PMID: 24328399]

[67] Madrau MA, Piscopo A, Sanguinetti A, *et al.* Effect of drying temperature on polyphenolic content and antioxidant activity of apricots. Eur Food Res Technol 2009; 228(3): 441-8.
[http://dx.doi.org/10.1007/s00217-008-0951-6]

[68] Sochor J, Zitka O, Skutkova H, *et al.* Content of phenolic compounds and antioxidant capacity in fruits of apricot genotypes. Molecules 2010; 15(9): 6285-305.
[http://dx.doi.org/10.3390/molecules15096285] [PMID: 20877223]

[69] Mozetic B, Trebse P, Hribar J. Determination and quantitation of anthocyanins and hydroxycinnamic acids in different cultivars of sweet cherries (*Prunus avium* L.) from Nova Gorica Region (Slovenia). Food Technol Biotechnol 2002; 40(3): 207-12.

[70] Macheix JJ, Fleuriet A. Fruit Phenolics. Taylor & Francis 1990.

[71] Zamora-Ros R, Rothwell JA, Scalbert A, *et al.* Dietary intakes and food sources of phenolic acids in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Br J Nutr 2013; 110(8): 1500-11.
[http://dx.doi.org/10.1017/S0007114513000688] [PMID: 23507418]

[72] Grosso G, Stepaniak U, Topor-Mądry R, Szafraniec K, Pająk A. Estimated dietary intake and major food sources of polyphenols in the Polish arm of the HAPIEE study. Nutrition 2014; 30(11-12): 1398-403.
[http://dx.doi.org/10.1016/j.nut.2014.04.012] [PMID: 25280419]

[73] Brandi F, Liverani A, Giovannini D, *et al.* Molecular and biochemical studies on phytonutrient accumulation in peach fruit. Acta Hortic 2013; 976: 389-95.
[http://dx.doi.org/10.17660/ActaHortic.2013.976.53]

[74] Veberic R, Stampar F. Selected polyphenols in fruits of different cultivars of genus Prunus. Phyton - Ann Rei Bot 2005; 45(3): 83-375.

[75] Noratto G, Martino HS, Simbo S, Byrne D, Mertens-Talcott SU. Consumption of polyphenol-rich peach and plum juice prevents risk factors for obesity-related metabolic disorders and cardiovascular disease in Zucker rats. J Nutr Biochem 2015; 26(6): 633-41.
[http://dx.doi.org/10.1016/j.jnutbio.2014.12.014] [PMID: 25801980]

[76] Després J-P, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006; 444(7121): 881-7.
[http://dx.doi.org/10.1038/nature05488] [PMID: 17167477]

[77] Utsunomiya H, Yamakawa T, Kamei J, Kadonosono K, Tanaka S. Anti-hyperglycemic effects of plum in a rat model of obesity and type 2 diabetes, Wistar fatty rat. Biomed Res 2005; 26(5): 193-200.
[http://dx.doi.org/10.2220/biomedres.26.193] [PMID: 16295695]

[78] Sun C-D, Zhang B, Zhang J-K, *et al.* Cyanidin-3-glucoside-rich extract from Chinese bayberry fruit protects pancreatic β cells and ameliorates hyperglycemia in streptozotocin-induced diabetic mice. J

Med Food 2012; 15(3): 288-98.
[http://dx.doi.org/10.1089/jmf.2011.1806] [PMID: 22181073]

[79] Guo H, Xia M, Zou T, Ling W, Zhong R, Zhang W. Cyanidin 3-glucoside attenuates obesity-associated insulin resistance and hepatic steatosis in high-fat diet-fed and db/db mice *via* the transcription factor FoxO1. J Nutr Biochem 2012; 23(4): 349-60.
[http://dx.doi.org/10.1016/j.jnutbio.2010.12.013] [PMID: 21543211]

[80] Guo H, Ling W, Wang Q, Liu C, Hu Y, Xia M. Cyanidin 3-glucoside protects 3T3-L1 adipocytes against H_2O_2- or TNF-α-induced insulin resistance by inhibiting c-Jun NH_2-terminal kinase activation. Biochem Pharmacol 2008; 75(6): 1393-401.
[http://dx.doi.org/10.1016/j.bcp.2007.11.016] [PMID: 18179781]

[81] Scazzocchio B, Varì R, Filesi C, *et al.* Cyanidin-3-*O*-β-glucoside and protocatechuic acid exert insulin-like effects by upregulating PPARγ activity in human omental adipocytes. Diabetes 2011; 60(9): 2234-44.
[http://dx.doi.org/10.2337/db10-1461] [PMID: 21788573]

[82] Guo H, Guo J, Jiang X, Li Z, Ling W. Cyanidin-3-*O*-β-glucoside, a typical anthocyanin, exhibits antilipolytic effects in 3T3-L1 adipocytes during hyperglycemia: involvement of FoxO1-mediated transcription of adipose triglyceride lipase. Food Chem Toxicol 2012; 50(9): 3040-7.
[http://dx.doi.org/10.1016/j.fct.2012.06.015] [PMID: 22721980]

[83] Adisakwattana S, Yibchok-Anun S, Charoenlertkul P, Wongsasiripat N. Cyanidin-3-rutinoside alleviates postprandial hyperglycemia and its synergism with acarbose by inhibition of intestinal α-glucosidase. J Clin Biochem Nutr 2011; 49(1): 36-41.
[http://dx.doi.org/10.3164/jcbn.10-116] [PMID: 21765605]

[84] Akkarachiyasit S, Charoenlertkul P, Yibchok-Anun S, Adisakwattana S. Inhibitory activities of cyanidin and its glycosides and synergistic effect with acarbose against intestinal α-glucosidase and pancreatic α-amylase. Int J Mol Sci 2010; 11(9): 3387-96.
[http://dx.doi.org/10.3390/ijms11093387] [PMID: 20957102]

[85] Akkarachiyasit S, Yibchok-Anun S, Wacharasindhu S, Adisakwattana S. *In vitro* inhibitory effects of cyandin-3-rutinoside on pancreatic α-amylase and its combined effect with acarbose. Molecules 2011; 16(3): 2075-83.
[http://dx.doi.org/10.3390/molecules16032075] [PMID: 21368719]

[86] Zhang R, Yao Y, Wang Y, Ren G. Antidiabetic activity of isoquercetin in diabetic KK -A y mice. Nutr Metab 2011; 8(1): 1.

[87] 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. J Physiol Biochem 2012; 68(3): 307-18.
[http://dx.doi.org/10.1007/s13105-011-0142-y] [PMID: 22234849]

[88] Niture NT, Patil DG, Somani RS, Sahane RS. Effect of rutin on early diabetic neuropathy in experimental animals J Nat Prod Plant Resour 2014.

[89] Torres-Piedra M, Ortiz-Andrade R, Villalobos-Molina R, *et al.* A comparative study of flavonoid analogues on streptozotocin-nicotinamide induced diabetic rats: quercetin as a potential antidiabetic agent acting *via* 11β-hydroxysteroid dehydrogenase type 1 inhibition. Eur J Med Chem 2010; 45(6):

2606-12.
[http://dx.doi.org/10.1016/j.ejmech.2010.02.049] [PMID: 20346546]

[90] Kandasamy N, Ashokkumar N. Myricetin, a natural flavonoid, normalizes hyperglycemia in streptozotocin-cadmium-induced experimental diabetic nephrotoxic rats. Biomed Prev Nutr 2012; 2(4): 246-51.
[http://dx.doi.org/10.1016/j.bionut.2012.04.003]

[91] Kandasamy N, Ashokkumar N. Renoprotective effect of myricetin restrains dyslipidemia and renal mesangial cell proliferation by the suppression of sterol regulatory element binding proteins in an experimental model of diabetic nephropathy. Eur J Pharmacol 2014; 743(0): 53-62.
[http://dx.doi.org/10.1016/j.ejphar.2014.09.014] [PMID: 25240712]

[92] Kandasamy N, Ashokkumar N. Protective effect of bioflavonoid myricetin enhances carbohydrate metabolic enzymes and insulin signaling molecules in streptozotocin-cadmium induced diabetic nephrotoxic rats. Toxicol Appl Pharmacol 2014; 279(2): 173-85.
[http://dx.doi.org/10.1016/j.taap.2014.05.014] [PMID: 24923654]

[93] Harini R, Pugalendi KV. Antihyperglycemic effect of protocatechuic acid on streptozotocin-diabetic rats. J Basic Clin Physiol Pharmacol 2010; 21(1): 79-91.
[http://dx.doi.org/10.1515/JBCPP.2010.21.1.79] [PMID: 20506690]

[94] Azay-Milhau J, Ferrare K, Leroy J, *et al.* Antihyperglycemic effect of a natural chicoric acid extract of chicory (*Cichorium intybus* L.): a comparative *in vitro* study with the effects of caffeic and ferulic acids. J Ethnopharmacol 2013; 150(2): 755-60.
[http://dx.doi.org/10.1016/j.jep.2013.09.046] [PMID: 24126061]

[95] Jung UJ, Lee M-K, Park YB, Jeon S-M, Choi M-S. Antihyperglycemic and antioxidant properties of caffeic acid in db/db mice. J Pharmacol Exp Ther 2006; 318(2): 476-83.
[http://dx.doi.org/10.1124/jpet.106.105163] [PMID: 16644902]

[96] Muthusamy VS, Saravanababu C, Ramanathan M, *et al.* Inhibition of protein tyrosine phosphatase 1B and regulation of insulin signalling markers by caffeoyl derivatives of chicory (*Cichorium intybus*) salad leaves. Br J Nutr 2010; 104(6): 813-23.
[http://dx.doi.org/10.1017/S0007114510001480] [PMID: 20444318]

[97] Muramatsu K, Fukuyo M, Hara Y. Effect of green tea catechins on plasma cholesterol level in cholesterol-fed rats. J Nutr Sci Vitaminol (Tokyo) 1986; 32(6): 613-22.
[http://dx.doi.org/10.3177/jnsv.32.613] [PMID: 3585557]

[98] Mangiapane H, Thomson J, Salter A, Brown S, Bell GD, White DA. The inhibition of the oxidation of low density lipoprotein by (+)-catechin, a naturally occurring flavonoid. Biochem Pharmacol 1992; 43(3): 445-50.
[http://dx.doi.org/10.1016/0006-2952(92)90562-W] [PMID: 1540202]

[99] Stevens JF, Miranda CL, Wolthers KR, Schimerlik M, Deinzer ML, Buhler DR. Identification and *in vitro* biological activities of hop proanthocyanidins: inhibition of nNOS activity and scavenging of reactive nitrogen species. J Agric Food Chem 2002; 50(12): 3435-43.
[http://dx.doi.org/10.1021/jf0116202] [PMID: 12033808]

[100] Cheng J-C, Dai F, Zhou B, Yang L, Liu Z-L. Antioxidant activity of hydroxycinnamic acid derivatives in human low density lipoprotein: Mechanism and structure–activity relationship. Food Chem 2007;

104(1): 132-9.
[http://dx.doi.org/10.1016/j.foodchem.2006.11.012]

[101] Ikeda I, Imasato Y, Sasaki E, *et al.* Tea catechins decrease micellar solubility and intestinal absorption of cholesterol in rats 1992.
[http://dx.doi.org/10.1016/0005-2760(92)90269-2]

[102] Wei X, Wang D, Yang Y, *et al.* Cyanidin-3-*O*-β-glucoside improves obesity and triglyceride metabolism in KK-Ay mice by regulating lipoprotein lipase activity. J Sci Food Agric 2011; 91(6): 1006-13.
[http://dx.doi.org/10.1002/jsfa.4275] [PMID: 21360538]

[103] Wang D, Xia M, Gao S, *et al.* Cyanidin-3-*O*-β-glucoside upregulates hepatic cholesterol 7α-hydroxylase expression and reduces hypercholesterolemia in mice. Mol Nutr Food Res 2012; 56(4): 610-21.
[http://dx.doi.org/10.1002/mnfr.201100659] [PMID: 22495986]

[104] Gong M, Garige M, Varatharajalu R, *et al.* Quercetin up-regulates paraoxonase 1 gene expression with concomitant protection against LDL oxidation. Biochem Biophys Res Commun 2009; 379(4): 1001-4.
[http://dx.doi.org/10.1016/j.bbrc.2009.01.015] [PMID: 19141295]

[105] Fang X-K, Gao J, Zhu D-N. Kaempferol and quercetin isolated from *Euonymus alatus* improve glucose uptake of 3T3-L1 cells without adipogenesis activity. Life Sci 2008; 82(11-12): 615-22.
[http://dx.doi.org/10.1016/j.lfs.2007.12.021] [PMID: 18262572]

[106] Haas MJ, Onstead-Haas LM, Szafran-Swietlik A, *et al.* Induction of hepatic apolipoprotein A-I gene expression by the isoflavones quercetin and isoquercetrin. Life Sci 2014; 110(1): 8-14.
[http://dx.doi.org/10.1016/j.lfs.2014.06.014] [PMID: 24963805]

[107] WHO. Cardiovascular diseases. World Health Organization Available from: http://www.who.int/mediacentre/factsheets/fs317/en/ , 2015 [[Accessed on 2015 14/01/2015]];

[108] Parlakpinar H, Olmez E, Acet A, *et al.* Beneficial effects of apricot-feeding on myocardial ischemia-reperfusion injury in rats. Food Chem Toxicol 2009; 47(4): 802-8.
[http://dx.doi.org/10.1016/j.fct.2009.01.014] [PMID: 19271314]

[109] Auclair S, Milenkovic D, Besson C, *et al.* Catechin reduces atherosclerotic lesion development in apo E-deficient mice: a transcriptomic study. Atherosclerosis 2009; 204(2): e21-7.
[http://dx.doi.org/10.1016/j.atherosclerosis.2008.12.007] [PMID: 19152914]

[110] Xie X, Zhao R, Shen GX. Impact of cyanidin-3-glucoside on glycated LDL-induced NADPH oxidase activation, mitochondrial dysfunction and cell viability in cultured vascular endothelial cells. Int J Mol Sci 2012; 13(12): 15867-80.
[http://dx.doi.org/10.3390/ijms131215867] [PMID: 23443099]

[111] Han X, Pan J, Ren D, Cheng Y, Fan P, Lou H. Naringenin-7-O-glucoside protects against doxorubicin-induced toxicity in H9c2 cardiomyocytes by induction of endogenous antioxidant enzymes. Food Chem Toxicol 2008; 46(9): 3140-6.
[http://dx.doi.org/10.1016/j.fct.2008.06.086] [PMID: 18652870]

[112] Han XZ, Gao S, Cheng YN, *et al.* Protective effect of naringenin-7-*O*-glucoside against oxidative stress induced by doxorubicin in H9c2 cardiomyocytes. Biosci Trends 2012; 6(1): 19-25.

[PMID: 22426099]

[113] Perez-Vizcaino F, Duarte J, Jimenez R, Santos-Buelga C, Osuna A. Antihypertensive effects of the flavonoid quercetin. Pharmacol Rep 2009; 61(1): 67-75. [http://dx.doi.org/10.1016/S1734-1140(09)70008-8] [PMID: 19307694]

[114] Shen Y, Croft KD, Hodgson JM, *et al.* Quercetin and its metabolites improve vessel function by inducing eNOS activity *via* phosphorylation of AMPK. Biochem Pharmacol 2012; 84(8): 1036-44. [http://dx.doi.org/10.1016/j.bcp.2012.07.016] [PMID: 22846602]

[115] Orbán-Gyapai O, Raghavan A, Vasas A, Forgo P, Hohmann J, Shah ZA. Flavonoids isolated from Rumex aquaticus exhibit neuroprotective and neurorestorative properties by enhancing neurite outgrowth and synaptophysin. CNS Neurol Disord Drug Targets 2014; 13(8): 1458-64. [http://dx.doi.org/10.2174/1871527313666141023154446] [PMID: 25345505]

[116] Byrne DH, Noratto G, Cisneros-Zevallos L, Porter W, Vizzotto M. Health benefits of peach, nectarine and plums. Acta Hortic 2009; 841: 267-73. [http://dx.doi.org/10.17660/ActaHortic.2009.841.32]

[117] Dhingra N, Sharma R, Kar A. Antioxidative and antiproliferative activities of isolated compounds from *Prunus domestica*: an *in vitro* study. Int J Phytomed 2013; 5(3): 6.

[118] Noratto G, Porter W, Byrne D, Cisneros-Zevallos L. Polyphenolics from peach (*Prunus persica* var. Rich Lady) inhibit tumor growth and metastasis of MDA-MB-435 breast cancer cells *in vivo.* J Nutr Biochem 2014; 25(7): 796-800. [http://dx.doi.org/10.1016/j.jnutbio.2014.03.001] [PMID: 24745759]

[119] Ogur R, Istanbulluoglu H, Korkmaz A, Barla A, Tekbas OF, Oztas E. Report: investigation of anti-cancer effects of cherry in vitro. Pak J Pharm Sci 2014; 27(3): 587-92. [PMID: 24811821]

[120] Lea MA, Ibeh C, desBordes C, *et al.* Inhibition of growth and induction of differentiation of colon cancer cells by peach and plum phenolic compounds. Anticancer Res 2008; 28(4B): 2067-76. [PMID: 18751377]

[121] Yang Y, Gallaher DD. Effect of dried plums on colon cancer risk factors in rats. Nutr Cancer 2005; 53(1): 117-25. [http://dx.doi.org/10.1207/s15327914nc5301_14] [PMID: 16351514]

[122] Tada K, Kawahara K, Matsushita S, Hashiguchi T, Maruyama I, Kanekura T. MK615, a *Prunus mume* Steb. Et Zucc (‘Ume’) extract, attenuates the growth of A375 melanoma cells by inhibiting the ERK1/2-Id-1 pathway. Phytother Res 2012; 26(6): 833-8. [http://dx.doi.org/10.1002/ptr.3645] [PMID: 22076920]

[123] Hattori M, Kawakami K, Akimoto M, Takenaga K, Suzumiya J, Honma Y. Antitumor effect of Japanese apricot extract (MK615) on human cancer cells *in vitro* and *in vivo* through a reactive oxygen species-dependent mechanism. Tumori 2013; 99(2): 239-48. [PMID: 23748821]

[124] Matsushita S, Tada KI, Kawahara KI, *et al.* Advanced malignant melanoma responds to *Prunus mume* Sieb. Et Zucc (Ume) extract: Case report and *in vitro* study. Exp Ther Med 2010; 1(4): 569-74. [PMID: 22993577]

[125] Yamai H, Sawada N, Yoshida T, *et al.* Triterpenes augment the inhibitory effects of anticancer drugs on growth of human esophageal carcinoma cells *in vitro* and suppress experimental metastasis *in vivo.* Int J Cancer 2009; 125(4): 952-60.
[http://dx.doi.org/10.1002/ijc.24433] [PMID: 19462449]

[126] Yoon H. Japanese apricot extract attenuates nuclear factor-κB activation and proteasomal activity in A549 lung cancer cells. Food Sci Biotechnol 2012; 21(5): 1507-10.
[http://dx.doi.org/10.1007/s10068-012-0200-4]

[127] Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454(7203): 428-35.
[http://dx.doi.org/10.1038/nature07201] [PMID: 18650913]

[128] Bastard JP, Maachi M, Lagathu C, *et al.* Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 2006; 17(1): 4-12.
[PMID: 16613757]

[129] Pearson TA, Mensah GA, Alexander RW, *et al.* Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107(3): 499-511.
[http://dx.doi.org/10.1161/01.CIR.0000052939.59093.45] [PMID: 12551878]

[130] Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420(6917): 860-7.
[http://dx.doi.org/10.1038/nature01322] [PMID: 12490959]

[131] Rakoff-Nahoum S. Why cancer and inflammation? Yale J Biol Med 2006; 79(3-4): 123-30.
[PMID: 17940622]

[132] Gasparotto J, Somensi N, Bortolin RC, *et al.* Effects of different products of peach (*Prunus persica* L. Batsch) from a variety developed in southern Brazil on oxidative stress and inflammatory parameters *in vitro* and *ex vivo.* J Clin Biochem Nutr 2014; 55(2): 110-9.
[http://dx.doi.org/10.3164/jcbn.13-97] [PMID: 25320458]

[133] Gasparotto J, Somensi N, Bortolin RC, *et al.* Preventive supplementation with fresh and preserved peach attenuates CCl4-induced oxidative stress, inflammation and tissue damage. J Nutr Biochem 2014; 25(12): 1282-95.
[http://dx.doi.org/10.1016/j.jnutbio.2014.07.004] [PMID: 25287815]

[134] Jain P, Kumar N, Josyula VR, *et al.* A study on the role of (+)-catechin in suppression of HepG2 proliferation *via* caspase dependent pathway and enhancement of its *in vitro* and *in vivo* cytotoxic potential through liposomal formulation. Eur J Pharm Sci 2013; 50(3-4): 353-65.
[http://dx.doi.org/10.1016/j.ejps.2013.08.005] [PMID: 23954456]

[135] Iacopini P, Baldi M, Storchi P, Sebastiani L. Catechin, epicatechin, quercetin, rutin and resveratrol in red grape: Content, *in vitro* antioxidant activity and interactions. J Food Compos Anal 2008; 21(8): 589-98.
[http://dx.doi.org/10.1016/j.jfca.2008.03.011]

[136] Wong K-L, Wu Y-R, Cheng K-S, *et al.* Palmitic acid-induced lipotoxicity and protection by (+)-catechin in rat cortical astrocytes. Pharmacol Rep 2014; 66(6): 1106-13.
[http://dx.doi.org/10.1016/j.pharep.2014.07.009] [PMID: 25443742]

[137] Teixeira MD, Souza CM, Menezes AP, *et al.* Catechin attenuates behavioral neurotoxicity induced by 6-OHDA in rats. Pharmacol Biochem Behav 2013; 110: 1-7. [http://dx.doi.org/10.1016/j.pbb.2013.05.012] [PMID: 23714698]

[138] Elisia I, Kitts DD. Anthocyanins inhibit peroxyl radical-induced apoptosis in Caco-2 cells. Mol Cell Biochem 2008; 312(1-2): 139-45. [http://dx.doi.org/10.1007/s11010-008-9729-1] [PMID: 18327700]

[139] Xu M, Bower KA, Wang S, *et al.* Cyanidin-3-glucoside inhibits ethanol-induced invasion of breast cancer cells overexpressing ErbB2. Mol Cancer 2010; 9(1): 285. [http://dx.doi.org/10.1186/1476-4598-9-285] [PMID: 21034468]

[140] Lim T-G, Kwon JY, Kim J, *et al.* Cyanidin-3-glucoside suppresses B[a]PDE-induced cyclooxygenase-2 expression by directly inhibiting Fyn kinase activity. Biochem Pharmacol 2011; 82(2): 167-74. [http://dx.doi.org/10.1016/j.bcp.2011.03.032] [PMID: 21501596]

[141] Wang Q, Xia M, Liu C, *et al.* Cyanidin-3-*O*-β-glucoside inhibits iNOS and COX-2 expression by inducing liver X receptor alpha activation in THP-1 macrophages. Life Sci 2008; 83(5-6): 176-84. [http://dx.doi.org/10.1016/j.lfs.2008.05.017] [PMID: 18619979]

[142] Zhang Y, Lian F, Zhu Y, *et al.* Cyanidin-3-O-β-glucoside inhibits LPS-induced expression of inflammatory mediators through decreasing IkappaBalpha phosphorylation in THP-1 cells. Inflamm Res 2010; 59(9): 723-30. [http://dx.doi.org/10.1007/s00011-010-0183-7] [PMID: 20309718]

[143] Min S-W, Ryu S-N, Kim D-H. Anti-inflammatory effects of black rice, cyanidin-3-*O*-β-D-glycoside, and its metabolites, cyanidin and protocatechuic acid. Int Immunopharmacol 2010; 10(8): 959-66. [http://dx.doi.org/10.1016/j.intimp.2010.05.009] [PMID: 20669401]

[144] Hassimotto NMA, Moreira V. Nascimento NGd, Souto PCMdC, Teixeira C, Lajolo FM. Inhibition of carrageenan-induced acute inflammation in mice by oral administration of anthocyanin mixture from wild mulberry and cyanidin-3-glucoside. Bio Med Res Int 2013; 2013: 10.

[145] Acquaviva R, Russo A, Galvano F, *et al.* Cyanidin and cyanidin 3-*O*-beta-D -glucoside as DNA cleavage protectors and antioxidants. Cell Biol Toxicol 2003; 19(4): 243-52. [http://dx.doi.org/10.1023/B:CBTO.0000003974.27349.4e] [PMID: 14686616]

[146] Song J, Zhao M, Liu X, Zhu Y, Hu X, Chen F. Protection of cyanidin-3-glucoside against oxidative stress induced by acrylamide in human MDA-MB-231 cells. Food Chem Toxicol 2013; 58(0): 306-10. [http://dx.doi.org/10.1016/j.fct.2013.05.003] [PMID: 23685245]

[147] Li C-Y, Xu H-D, Zhao B-T, Chang H-I, Rhee H-I. Gastroprotective effect of cyanidin 3-glucoside on ethanol-induced gastric lesions in rats. Alcohol 2008; 42(8): 683-7. [http://dx.doi.org/10.1016/j.alcohol.2008.08.009] [PMID: 19038699]

[148] Nasri S, Roghani M, Baluchnejadmojarad T, Rabani T, Balvardi M. Vascular mechanisms of cyanidin-3-glucoside response in streptozotocin-diabetic rats. Pathophysiology 2011; 18(4): 273-8. [http://dx.doi.org/10.1016/j.pathophys.2011.03.001] [PMID: 21546226]

[149] Nasri S, Roghani M, Baluchnejadmojarad T, Balvardi M, Rabani T. Chronic cyanidin-3-glucoside administration improves short-term spatial recognition memory but not passive avoidance learning and memory in streptozotocin-diabetic rats. Phytother Res 2012; 26(8): 1205-10.

[http://dx.doi.org/10.1002/ptr.3702] [PMID: 22228592]

[150] Maggioni D, Nicolini G, Rigolio R, *et al.* Myricetin and naringenin inhibit human squamous cell carcinoma proliferation and migration *in vitro*. Nutr Cancer 2014; 66(7): 1257-67. [http://dx.doi.org/10.1080/01635581.2014.951732] [PMID: 25256786]

[151] Lee D-H, Szczepanski M, Lee YJ. Role of Bax in quercetin-induced apoptosis in human prostate cancer cells. Biochem Pharmacol 2008; 75(12): 2345-55. [http://dx.doi.org/10.1016/j.bcp.2008.03.013] [PMID: 18455702]

[152] Yu C-S, Lai K-C, Yang J-S, *et al.* Quercetin inhibited murine leukemia WEHI-3 cells *in vivo* and promoted immune response. Phytother Res 2010; 24(2): 163-8. [PMID: 19449452]

[153] Boly R, Gras T, Lamkami T, *et al.* Quercetin inhibits a large panel of kinases implicated in cancer cell biology. Int J Oncol 2011; 38(3): 833-42. [PMID: 21206969]

[154] Xiao X, Shi D, Liu L, *et al.* Quercetin suppresses cyclooxygenase-2 expression and angiogenesis through inactivation of P300 signaling. PLoS One 2011; 6(8): e22934. [http://dx.doi.org/10.1371/journal.pone.0022934] [PMID: 21857970]

[155] Choi EJ, Bae SM, Ahn WS. Antiproliferative effects of quercetin through cell cycle arrest and apoptosis in human breast cancer MDA-MB-453 cells. Arch Pharm Res 2008; 31(10): 1281-5. [http://dx.doi.org/10.1007/s12272-001-2107-0] [PMID: 18958418]

[156] Cavia-Saiz M, Busto MD, Pilar-Izquierdo MC, Ortega N, Perez-Mateos M, Muñiz P. Antioxidant properties, radical scavenging activity and biomolecule protection capacity of flavonoid naringenin and its glycoside naringin: a comparative study. J Sci Food Agric 2010; 90(7): 1238-44. [http://dx.doi.org/10.1002/jsfa.3959] [PMID: 20394007]

[157] Wijaya S, Jin KT, Nee TK, Wiart C. *In vitro* 5-LOX inhibitory and antioxidant activities of extracts and compounds from the aerial parts of *Lopholaena coriifolia* (Sond.) E. Phillips & C.A. Sm. J Complement Integr Med 2012; 9(1): 11. [http://dx.doi.org/10.1515/1553-3840.1615] [PMID: 22728459]

[158] Jayaraman J, Veerappan M, Namasivayam N. Potential beneficial effect of naringenin on lipid peroxidation and antioxidant status in rats with ethanol-induced hepatotoxicity. J Pharm Pharmacol 2009; 61(10): 1383-90. [http://dx.doi.org/10.1211/jpp.61.10.0016] [PMID: 19814872]

[159] Lee JK. Anti-inflammatory effects of eriodictyol in lipopolysaccharide-stimulated raw 264.7 murine macrophages. Arch Pharm Res 2011; 34(4): 671-9. [http://dx.doi.org/10.1007/s12272-011-0418-3] [PMID: 21544733]

[160] Dhanya R, Arun KB, Syama HP, *et al.* Rutin and quercetin enhance glucose uptake in L6 myotubes under oxidative stress induced by tertiary butyl hydrogen peroxide. Food Chem 2014; 158: 546-54. [http://dx.doi.org/10.1016/j.foodchem.2014.02.151] [PMID: 24731381]

[161] Mahmoud M, Hamdan D, Wink M, El-Shazly A. Naringin and rutin prevent d-galactosamine-induced hepatic injury in rats via attenuation of the inflammatory cascade and oxidative stress. Eur Sci J 2013; 9(30): 55-141.

[162] Dixit S. Anticancer effect of rutin isolated from the methanolic extract of *Triticum aestivum* straw in mice. Med Sci 2014; 2(4): 153-60.

[163] Owolabi MA, Coker HA, Jaja SI. Bioactivity of the phytoconstituents of the leaves of *Persea americana.* J Med Plants Res 2010; 4(12): 1130-5.

[164] Kim SJ, Um JY, Lee JY, Lee JY. Anti-inflammatory activity of hyperoside through the suppression of nuclear factor-κB activation in mouse peritoneal macrophages. Am J Chin Med 2011; 39(1): 171-81. [http://dx.doi.org/10.1142/S0192415X11008737] [PMID: 21213407]

[165] Boots AW, Wilms LC, Swennen EL, Kleinjans JC, Bast A, Haenen GR. *In vitro* and *ex vivo* anti-inflammatory activity of quercetin in healthy volunteers. Nutrition 2008; 24(7-8): 703-10. [http://dx.doi.org/10.1016/j.nut.2008.03.023] [PMID: 18549926]

[166] Carrasco-Pozo C, Mizgier ML, Speisky H, Gotteland M. Differential protective effects of quercetin, resveratrol, rutin and epigallocatechin gallate against mitochondrial dysfunction induced by indomethacin in Caco-2 cells. Chem Biol Interact 2012; 195(3): 199-205. [http://dx.doi.org/10.1016/j.cbi.2011.12.007] [PMID: 22214982]

[167] Liu Z, Tao X, Zhang C, Lu Y, Wei D. Protective effects of hyperoside (quercetin-3-*o*-galactoside) to PC12 cells against cytotoxicity induced by hydrogen peroxide and *tert*-butyl hydroperoxide. Biomed Pharmacother 2005; 59(9): 481-90. [http://dx.doi.org/10.1016/j.biopha.2005.06.009] [PMID: 16271843]

[168] Kao T-K, Ou Y-C, Raung S-L, Lai C-Y, Liao S-L, Chen C-J. Inhibition of nitric oxide production by quercetin in endotoxin/cytokine-stimulated microglia. Life Sci 2010; 86(9-10): 315-21. [http://dx.doi.org/10.1016/j.lfs.2009.12.014] [PMID: 20060843]

[169] Veluri R, Singh RP, Liu Z, Thompson JA, Agarwal R, Agarwal C. Fractionation of grape seed extract and identification of gallic acid as one of the major active constituents causing growth inhibition and apoptotic death of DU145 human prostate carcinoma cells. Carcinogenesis 2006; 27(7): 1445-53. [http://dx.doi.org/10.1093/carcin/bgi347] [PMID: 16474170]

[170] Kaur M, Velmurugan B, Rajamanickam S, Agarwal R, Agarwal C. Gallic acid, an active constituent of grape seed extract, exhibits anti-proliferative, pro-apoptotic and anti-tumorigenic effects against prostate carcinoma xenograft growth in nude mice. Pharm Res 2009; 26(9): 2133-40. [http://dx.doi.org/10.1007/s11095-009-9926-y] [PMID: 19543955]

[171] Lu Y, Jiang F, Jiang H, *et al.* Gallic acid suppresses cell viability, proliferation, invasion and angiogenesis in human glioma cells. Eur J Pharmacol 2010; 641(2-3): 102-7. [http://dx.doi.org/10.1016/j.ejphar.2010.05.043] [PMID: 20553913]

[172] You BR, Moon HJ, Han YH, Park WH. Gallic acid inhibits the growth of HeLa cervical cancer cells *via* apoptosis and/or necrosis. Food Chem Toxicol 2010; 48(5): 1334-40. [http://dx.doi.org/10.1016/j.fct.2010.02.034] [PMID: 20197077]

[173] Mori H, Iwahashi H. Antioxidant activity of caffeic acid through a novel mechanism under UVA irradiation. J Clin Biochem Nutr 2009; 45(1): 49-55. [http://dx.doi.org/10.3164/jcbn.08-258] [PMID: 19590707]

[174] Ashidate K, Kawamura M, Mimura D, *et al.* Gentisic acid, an aspirin metabolite, inhibits oxidation of low-density lipoprotein and the formation of cholesterol ester hydroperoxides in human plasma. Eur J

Pharmacol 2005; 513(3): 173-9.
[http://dx.doi.org/10.1016/j.ejphar.2005.03.012] [PMID: 15862799]

[175] Gülçin I. Antioxidant activity of caffeic acid (3,4-dihydroxycinnamic acid). Toxicology 2006; 217(2-3): 213-20.
[http://dx.doi.org/10.1016/j.tox.2005.09.011] [PMID: 16243424]

[176] Yeh Y-H, Lee Y-T, Hsieh H-S, Hwang D-F. Dietary caffeic acid, ferulic acid and coumaric acid supplements on cholesterol metabolism and antioxidant activity in rats. J Food Drug Anal 2009; 17(2): 123-32.

[177] Koriem KM, Abdelhamid AZ, Younes HF. Caffeic acid protects tissue antioxidants and DNA content in methamphetamine induced tissue toxicity in Sprague Dawley rats. Toxicol Mech Methods 2013; 23(2): 134-43.
[http://dx.doi.org/10.3109/15376516.2012.730561] [PMID: 22992185]

[178] Koriem KMM, Soliman RE. Chlorogenic and Caftaric acids in liver toxicity and oxidative stress induced by methamphetamine. J Toxicol 2014; 2014: 10.
[http://dx.doi.org/10.1155/2014/583494]

[179] Kim EO, Min KJ, Kwon TK, Um BH, Moreau RA, Choi SW. Anti-inflammatory activity of hydroxycinnamic acid derivatives isolated from corn bran in lipopolysaccharide-stimulated Raw 264.7 macrophages. Food Chem Toxicol 2012; 50(5): 1309-16.
[http://dx.doi.org/10.1016/j.fct.2012.02.011] [PMID: 22366099]

[180] Jung S, Spiegelman D, Baglietto L, *et al.* Fruit and vegetable intake and risk of breast cancer by hormone receptor status. J Natl Cancer Inst 2013; 105(3): 219-36.
[http://dx.doi.org/10.1093/jnci/djs635] [PMID: 23349252]

[181] Fung TT, Chiuve SE, Willett WC, Hankinson SE, Hu FB, Holmes MD. Intake of specific fruits and vegetables in relation to risk of estrogen receptor-negative breast cancer among postmenopausal women. Breast Cancer Res Treat 2013; 138(3): 925-30.
[http://dx.doi.org/10.1007/s10549-013-2484-3] [PMID: 23532538]