Dietary Flavonoids

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Over the past few years, interest in health research has increased, making improved health a global goal for 2030. The purpose of such research is to ensure healthy lives and promote wellbeing across individuals of all ages. It has been shown that nutrition plays a key role in the prevention of some chronic diseases such as obesity, cardiovascular disease, diabetes, and cancer. One of the aspects that characterises a healthy diet is a high intake of vegetables and fruits, as both are flavonoid-rich foods. Flavonoids are one of the main subclasses of dietary polyphenols and possess strong antioxidant activity and anti-carcinogenic properties. Moreover, some population-based studies have described a relationship between cancer risk and dietary flavonoid intake.

Keywords: flavonoids ; diet ; antioxidants ; cancer

1. Introduction

Cancer is among the diseases that have the greatest impact on society [1]. Even though its incidence has increased over the years, its mortality has decreased because of advances in treatment [2]. However, efforts to improve cancer prevention are needed. The aetiology of cancer is multifactorial, involving both environmental and genetic factors [3]. Diet is one of the lifestyle factors that affect cancer incidence and mortality [4]. Recently, several studies have reported that diets based on high levels of vegetables and fruits are strongly associated with a significant reduction in cancer risk [5][6].

Furthermore, there are some bioactive compounds in foods that have potential health benefits, such as flavonoids, carotenoids, stilbenes, lignans, and phenolic acids [7][8]. Flavonoids are a large group of phenolic compounds and are usually involved in protection against harsh environmental conditions, UV radiation, and microorganism attacks in plants [9][10]. Because of their potent antioxidant activity against oxidative stress, the interest in flavonoids has recently increased [11]. In vitro and in vivo studies have demonstrated that they have anti-carcinogenic properties against different types of cancers [5][12]. Moreover, many population-based studies have described an association between dietary flavonoids and cancer risk [13][14]. Hence, the goal of this review is to perform an updated evaluation of the association between the risk of different types of cancers and dietary flavonoids, as well as the intake of each flavonoid subclass.

2. Dietary Flavonoids

Flavonoids are widely spread in different foods and beverages (such wine and tea), but the sources with the highest levels are fruits and vegetables [10]. Among the fruits (**Table 1**), the highest levels of flavonoids are found in berries, such as black elderberry (1358.66 mg/100 g) and black chokeberry (1012.98 mg/100 g) [15][16]. In the drupes group, some fruits such as plum and sweet cherry have higher levels of flavonoids than the rest of the group, 101.67 mg/100 g and 185.05 mg/100 g, respectively [17][18]. In the pomes group, apple has the level (56.35 mg/100 g) [18][19]. Furthermore, tropical fruits have a very low flavonoid content [20]. Depending on the type of fruit, the main flavonoid subclass groups vary: anthocyanins predominate in berries, and flavanols predominate in pomes, tropical fruits, and drupes (except in sweet cherry).

Table 1. Flavonoid contents of fruits (mg/100 g food). Data collected from Phenol Explorer [21].

Fruits	ANT	DYC	FVA	FVO	Total
Berries					
Aestivalis grape	**79.74**	**-**	**-**	**1.7**	**81.44**
American cranberry	**49.89**	**-**	**-**	**43.84**	**93.73**
Black chokeberry	**878.11**	**-**	**-**	**134.87**	**1012.98**

Fruits	ANT	DYC	FVA	FVO	Total
Berries					
Black elderberry	1316.66	-	-	42	1358.66
Black raspberry	-	-	-	19	19
Blackberry	172.59	-	13.87	16.87	203.33
Blackcurrant	593.58	-	1.17	13.68	608.43
Black grape	72.15	-	14.03	4.01	90.19
Green grape	-	-	3.78	2.49	6.27
Green currant	-	-	-	11.07	11.07
Highbush blueberry	156.6	-	1.11	54.77	212.48
Lingonberry	60.21	-	-	48.98	109.19
Lowbush blueberry	204.56	-	-	-	204.56
Red raspberry	72.47	-	5.73	16.26	94.46
Redcurrant	33.13	-	4.68	0.77	38.58
Strawberry	26.87	-	9.1075	2.32	38.29
Drupes					
Nectarine	0.86	-	17.65	1.35	19.86
Peach	0.28	-	45.18	1.42	46.88
Plum	47.79	-	46.9	6.98	101.67
Sour cherry	54.43	-	0.2	-	54.63
Sweet cherry	170.18	-	14.87	-	185.05
Pomes					
Apple	0.93	5.38	39.42	10.62	56.35
Pear	-	-	4.98	0.84	5.82
Quince	-	-	7.49	0.67	8.16
Tropical Fruits					
Banana	-	-	1.55	-	1.55
Kiwi	-	-	0.7	-	0.7
Mango	-	-	1.72	-	1.72
Persimmon	-	-	1.28	-	1.28
Pomegranate	-	-	1.1	-	1.1

ANT: Anthocyanins, DYC: Dihydrochalcones, FVA: Flavan-3-ols, FVO: Flavonols.

Regarding vegetables (**Table 2**), the foods with the highest levels of flavonoids are broad bean pod (189.54 mg/100 g) [22], black olive (159.83 mg/100 g) [23], red onion (131.51 mg/100 g) [24], spinach (119.27 mg/100 g), and shallot (112.22 mg/100 g) [25][26]. Except for broad bean pod, the predominate flavonoid subclass in vegetables is flavanols.

Table 2. Flavonoid contents of vegetables (mg/100 g food) [21].

Vegetables	ANT	CHA	FVA	FNE	FVE	FVO	Total
Cabbages							
Broccoli	-	-	-	-	-	27.8	27.8
Fruit Vegetables							

Vegetables	ANT	CHA	FVA	FNE	FVE	FVO	Total
Cabbages							
Avocado	-	-	0.55	-	-	-	0.55
Black olive	82.97	-	-	-	27.43	49.43	159.83
Green olive	-	-	-	-	0.56	-	0.56
Green sweet pepper	-	-	-	-	2.11	5.49	7.6
Red sweet pepper	-	-	-	-	0.05	0.24	0.29
Tomato	-	-	-	0.14	-	0.014	0.15
Leaf Vegetables							
Curly	-	-	-	-	-	24.06	24.06
Escarole	-	-	-	-	-	18.23	18.23
Green lettuce	-	-	-	-	0.4	3.99	4.39
Red lettuce	3.53		-	-	2.51	16.74	22.78
Spinach	-	-	-	-	-	119.27	119.27
Onion-Family Vegetables							
Red onion	9	-	-	-	-	122.51	131.51
White onion	-	-	-	-	-	5.4	5.4
Yellow onion	-	-	-	-	-	59.1	59.1
Shallot	-	-	-	-	-	112.22	112.22
Pod Vegetables							
Broad bean pod	-	0.08	154.45	-	0.37	34.64	189.54
Green bean	-	-	2.42	-	-	5.55	7.97
Shoot Vegetables							
Asparagus	-	-	-	-	-	23.19	23.19
Globe artichoke, heads	-	-	-	-	57.8	-	57.8

ANT: Anthocyanins, CHA: Chalcones, FVA: Flavan-3-ols, FNE: Flavanones, FVE: Flavones, FVO: Flavonols.

Regarding seeds (**Table 3**), although common bean has high levels of flavonoids (from anthocyanins and flavonols), the foods with the highest levels are those derived from soy, and soy products have been suggested to play a key role in the prevention of different diseases [27].

Table 3. Flavonoid contents of seeds (mg/100 g food) [21].

Seeds	ANT	FVA	FNE	FVE	FVO	IFA	Total
Nuts							
Almond	-	4.93	0.5	-	3.81	0.06	9.3
Cashew nut	-	1.1	-	-	-	-	1.1
Chestnut	-	0.05	-	-	-	-	0.05
Hazelnut	-	5.7	-	-	-	-	5.7
Peanut	-	-	-	-	-	0.51	0.51
Pecan nut	-	16.7	-	-	-	-	16.7
Pistachio		6.9	0.12	0.103	0.07		7.193
Common Bean							

Seeds	ANT	FVA	FNE	FVE	FVO	IFA	Total
Nuts							
Black common bean	**41.05**	**-**	**-**	**-**	**10**	**1.4**	**52.45**
Others common bean	**7.42**	**-**	**-**	**-**	**69.58**	**0.2**	**77.2**
White common bean	**0.13**	**-**	**-**	**-**	**49.96**	**0.5**	**50.59**
Other Beans							
Broad bean seed whole	**-**	**49.37**	**-**	**-**	**-**	**-**	**49.37**
Sunflower seed meal	**-**	**-**	**-**	**-**	**-**	**0.02**	**0.02**
LENTILS							
Lentils	**-**	**5.17**		**0.95**	**1.09**	**-**	**7.21**
Soy Products							
Soy paste miso	**-**	**-**	**-**	**-**	**-**	**63.09**	**63.09**
Soy tempeh	**-**	**-**	**-**	**-**	**-**	**147.74**	**147.74**
Soy tofu	**-**	**-**	**-**	**-**	**-**	**39.24**	**39.24**
Soybean roasted	**-**	**-**	**-**	**-**	**-**	**253.11**	**253.11**

ANT: Anthocyanins, FVA: Flavan-3-ols, FNE: Flavanones, FVE: Flavones, FVO: Flavonols, IFA: Isoflavonoids.

Regarding cereals (**Table 4**), some such as barley, buckwheat, and common wheat contain average levels of flavonoids (35.2 mg/100 g, 37.04 mg/100 g, and 77.4 mg/100 g, respectively). However, it is important to note that the highest levels are found in whole grains, and levels are greatly reduced when grains are heat treated or refined [27][28].

Table 4. Flavonoid contents of cereals (mg/100 g food) [21].

Cereals	FVA	FVE	FVO	Total
Cereals				
Barley, whole grain flour	**35.2**	**-**	**-**	**35.2**
Buckwheat groats, thermally treated	**-**	**-**	**8.96**	**8.96**
Buckwheat, refined flour	**-**	**-**	**5.86**	**5.86**
Buckwheat, whole grain flour	**-**	**0.9**	**36.14**	**37.04**
Common wheat, refined flour	**-**	**18.4**	**0.08**	**18.48**
Common wheat, whole grain flour	**-**	**77.29**	**0.11**	**77.4**

FVA: Flavan-3-ols, FVE: Flavones, FVO: Flavonols.

Cocoa and its products, such as dark and milk chocolate, are flavonoid-rich foods (**Table 5**). In these foods, the main flavonoids are flavanols, with cocoa containing 511.63 mg/100 g [29][30].

Table 5. Flavonoid contents of cocoa (mg/100 g food) [21].

Cocoa	FVA	FVO	Total
Cocoa			
Chocolate dark	**212.36**	**25**	**237.36**
Chocolate milk	**19.22**	**-**	**19.22**
Cocoa powder	**511.62**	**-**	**511.62**

FVA: Flavan-3-ols, FVO: Flavonols.

Regarding oils, the data collected from the Phenol Explorer database refer only to oils made from olives (**Table 6**). In ascending order, refined, virgin, and extra virgin olive oil contain 0.15 mg, 0.23 mg, and 1.53 mg of flavones in 100 g, respectively [31][32].

Table 6. Flavonoid contents of oils (mg/100 g oil) [21].

Oils	FVE	Total
Oils		
Extra virgin olive oil	1.53	1.53
Virgin olive oil	0.23	0.23
Refined olive oil	0.15	0.15

FVE: Flavones.

For beverages, a distinction can be made between non-alcoholic (**Table 7**) and alcoholic drinks (**Table 8**). The non-alcoholic drinks with the highest levels of flavonoids are tea infusions, particularly black (83.35 mg/100 g) and green tea (77.44 mg/100 g), and these are mainly flavanols [33][34]. The second most flavonoid-rich beverages are fruit juices, notably pure apple juice (54.99 mg/100 g), pure orange juice (48.02 mg/100 g), pure grapefruit juice (47.12 mg/100 g), and pure lemon juice (37.43 mg/100 g) [35]. The main flavonoids in citrus juices and grapefruit juice are flavanones [36]. However, the main flavonoids in pome juices are flavanols. Regarding alcoholic beverages, wine red contains the highest flavonoid level (83.96 mg/100 mL) [37][38].

Table 7. Flavonoid contents of non-alcoholic beverages (mg/100 g drink) [21].

Non-Alcoholic Beverages	ANT	DYC	FVA	FNE	FVE	FVO	IFA	Total
Cocoa Beverage								
Chocolate, milk	-	-	20.33	-	-	-	-	20.33
Fruit Juices								
Berry Juices								
Fox grape juice	-	-	5.9	-	-	-	-	5.9
Green grape juice	-	-	3.88	-	-	-	-	3.88
Grapefruit juice	-	-	-	46.44	-	0.68	-	47.12
Citrus Juices								
Lemon juice	-	-	-	32.66	4.77	-	-	37.43
Lime juice	-	-	-	19.61	-	-	-	19.61
Orange juice	3.17	-	-	37.63	6.14	1.08	-	48.02
Pummelo juice	-	-	-	8.48	-	-	-	8.48
Red raspberry juice	-	-	-	-	-	9.58	-	9.58
Rowanberry	-	-	-	-	-	7.04	-	7.04
Drupe Juices								
Plum juice	-	5.85	24.7	-	-	-	-	30.55
Pome Juices								
Apple juice	-	4.39	48.45	-	-	2.15	-	54.99
Apple (cider) juice	-	4.78	22.66	-	-	-	-	27.44
Pear juice	-	-	3.24	-	-	-	-	3.24
Tropical Juices								
Kiwi juice	-	-	0.38	-	-	0.09	-	0.47

Non-Alcoholic Beverages	ANT	DYC	FVA	FNE	FVE	FVO	IFA	Total
Cocoa Beverage								
Pomegranate juice	10.13	0.1	-	-	-	0.25	-	10.48
Herb Infusions								
German chamomile, tea	-	-	2.07	-	-	-	-	2.07
Lemon verbena	-	-	10.6	-	-	-	-	10.6
Peppermint, tea	-	-	10.23	-	-	-	-	10.23
Tea Infusion								
Fennel tea	-	-	-	-	-	3.26	-	3.26
Black tea	-	-	73.29	-	-	10.06	-	83.35
Green tea	-	-	71.18	-	-	6.26	-	77.44
Oolong tea	-	-	35.72	-	-	-	-	35.72
Soy Products								
Soy milk	-	-	-	-	-	-	18	18

ANT: Anthocyanins, DYC: Dihydrochalcones, FVA: Flavanols, FNE: Flavanones, FVE: Flavones, FVO: Flavonols, IFA: Isoflavonoids.

Table 8. Flavonoid contents of alcoholic beverages (mg/100 g drink and mg/100 mL wine) [21].

Alcoholic Beverages	ANT	DYC	DYF	FVA	FNE	FVE	FVO	IFA	Total
Beer									
Beer (alcohol free)	-	0.0003	-	0.11	0.01	-	-	-	0.12
Beer (ale)	-	0.01	-	0.38	0.24	-	-	0.02	0.65
Beer (dark)	-	0.03	-	0.03	0.15	-	-	-	0.21
Beer (regular)	-	0.001	-	0.61	0.04	0.004	0.09	0.02	0.77
Wines									
Red wine	23.3	-	5.44	47.02	0.85	-	7.35	-	83.96
Rosé wine	-	-	0.38	2	-	-	-	-	2.38
White wine	0.04	-	0.57	2.07	0.23	-	0.695	-	3.61

ANT: Anthocyanins, DYC: Dihydrochalcones, DYF: Dihydroflavonols, FVA: Flavan-3-ols, FNE: Flavanones, FVE: Flavones, FVO: Flavonols, IFA: Isoflavonoids.

Therefore, a diet rich in fruits, vegetables, seeds, and cereals will provide large amounts of flavonoids. However, it is important to know that there are some foods which contain high quantities of flavonoids, including berries, black olives, spinach, onions, soy products, cocoa, whole grain cereals, tea infusions, and red wine.

3. Pharmacokinetics

In order to determine the biological activity and physiological functions of flavonoids *in vivo*, their bioavailability must be known. Hence, it is necessary to understand the processes of absorption, digestion, metabolism, and excretion in the digestive tract.

Although dietary flavonoids are mostly found in their glucoside form (**Figure 3**), they are not found in plasma [39][40] because, once flavonoids enter the oral cavity, they begin to be hydrolysed [39]. In addition, their absorption throughout the digestive tract is associated with the hydrolysing activity of different enzymes [41]. In the small intestine, deglycosylation occurs in which two enzymes that act as β-glucosidases are involved: lactase-phlorizin hydrolase (LPH) and cytosolic β-glucosidase (CBG), which are located in the brush border of epithelial cells and enterocytes, respectively [39][42].

Flavonoid-O-β-D-glucosides, for which LPH has high specificity, can enter into cells by passive diffusion. However, glucosides enter enterocytes via sodium-glucose co-transporter type 1 (SGLT1)) [39][41][43]. Although β-glucosidases cannot hydrolyse non-monoglucosidic glycosides, gut microbiota compensate for this through the production of absorbable aglycon in the large intestine and cecum (**Figure 3**) [39].

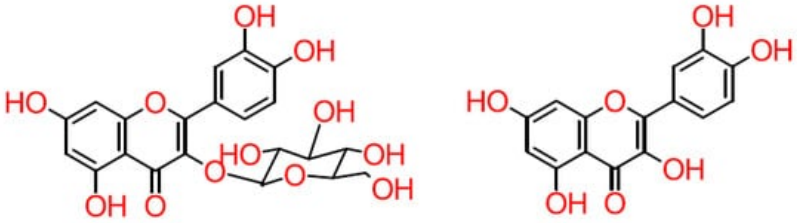

Figure 3. Structure of glycoside and aglycone flavonoids.

Once flavonoids and aglycons are absorbed via the small and the large intestine, respectively, the second phase of enzymatic metabolism begins [39][41]. In this stage, three types of enzymes are involved (uridine-5′-diphosphate-glucuronosyltransferases, sulfotransferases, and catechol-O-methyltransferases) that can conjugate flavonoids with glucuronic acid, sulphate, and methyl groups, making them more water-soluble [13][44]. This phase begins in the wall of the small intestine where metabolites pass to the portal vein and are transported to the liver. In the liver, metabolites are conjugated by sulphation and methylation processes [39]. In the systemic circulation and urine, there are different chemical forms of flavonoids. However, in human plasma, aglycons are rarely detected [39][45][46][47]. Certain plasmatic metabolites are usually excreted into the intestine through bile, and here, they are deconjugated by microbiota and reabsorbed [39][48]. Thus, enterohepatic circulation increases the half-life of flavonoids in human plasma [37].

The gut microbiome plays a main role in the metabolism and absorption of flavonoids. However, these processes could be modified due to flavonoids interaction with other nutrients [49][50]. Among them, flavonoids could alter glucose absorption after high carbohydrate food intake, because inhibit carbohydrate-hydrolyzing enzymes (α-amylase and α-glucosidase) [51]. Besides, flavonoids inhibit glucose transporter in the brush border [51]. However, flavonoid bioavailability is modified with fats intake that improves flavonoid intestinal absorption due to the increment of bile salts secretion which enhances micellar incorporation of flavonoids [51]. However, regarding proteins intake, flavonoid bioavailability became worse [52]. It has been demonstrated that the interaction of phenolic acids with proteins affects antioxidant efficacy and protein digestibility [53].

Depending on the type of flavonoid and its source, bioavailability may differ. Quercetin is one of the most frequently consumed flavonoids (the main sources of quercetin are onions, apples, tea, and wine), being mainly found in its glycosylated form [13]. For example, quercetin glycosides from apples have lower bioavailability than those from onions [13][54]. The plasma levels of quercetin metabolites range from 0.7 to 7.6 μM [13].

Other studies have analysed the levels of flavonoids in human plasma after the intake of flavonoid-rich foods [13]. They could be grouped according to the flavonoid subclass. Flavonols present in apples, onions, and buckwheat tea are found after intake at plasma levels of 0.30 μM, 0.74–7.60 μM, and 2.10 μM, respectively [13][54]. For flavanols in red wine, black tea, green tea, and cocoa, the plasmatic concentration after intake is around 0.08 μM, 0.09–0.34 μM, 1.00–1.80 μM, and 4.92–5.92 μM, respectively [13][55][56][57]. The base plasma levels of flavanones in orange juice and grapefruit juice are around 0.06–0.64 μM and 5.99 μM, respectively, after intake [58]. Finally, the plasma levels of anthocyanidins after consuming red wine, elderberry extract, and blackcurrant juice are around 0.01 μM, 0.10 μM, and 0.11 μM, respectively [13][58][59].

The highest concentration of plasma flavonoids in humans usually occurs 1 to 2 h after the consumption of flavonoid-rich foods [33]. However, the level depends on the type of flavonoid, as anthocyanins and catechins have a half-life elimination that is 5 to 10 times less than that of flavonols [52]. Although data on the concentration of flavonoids in human tissue are scarce, flavonoids have been shown to play an important role in antioxidant defence in both cells and tissues [13].

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