





# Flavonoids


- Flavonoids are secondary metabolites commonly found in fruits, vegetables, nuts, seeds, tea and wine as well as in many products we consume as food.
- Flavonoids are polyphenolic compounds.
- Flavonoids occur either in free or in glycoside form.

# The Richest Sources of Flavonoids

- Citrus species (*Citrus sp.*), originated from China and India, belonging to Rutaceae family, but they are evergreen small trees cultivated in almost all countries with a temperate climate.


- Important citrus species grown in our country;;
- Bitter orange (*Citrus aurantium*),
- Bergamot (*Citrus aurantium*
- var. *bergamia*),
- Lemon (*Citrus limon*),
- Grapefruit (*Citrus paradisi*),
- Mandarin (*Citrus reticulata*),
- Orange (*Citrus sinensis*).

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- Fruits and juices of these plants are used as food and beverage, as well as essential oil is obtained via squeezing from fruit peels, leaves or flowers of these plants, in order to use in the food, perfumery and pharmaceutical industry as fragrance and flavor.
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- In citrus species, mainly flavonoids such as hesperidine, naringin, rutin, and quercetin are found.
  - In general these compounds;
    - Facilitate the absorption of vitamin C
    - Inactivate enzymes responsible for inflammation
    - Strengthen the vascular walls
    - Free radical scavenger
    - Antioxidant
  - Stability of vitamin C




# Hesperidin

- Especially hesperidin has been shown to prevent LDL cholesterol oxidation and formation of atherosclerosis by inhibiting phospholipase A, lipoxygenase and cyclooxygenase enzymes.
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# Diosmin

- Diosmin, diosmetin-7-rutinoside
  - Isolated firstly from *Scrophularia nodosa*
  - Obtained naturally or by semi-synthesis from hesperidin
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# Diosmin


- Used in chronic venous insufficiency,
  - Anti-edema
  - Anti-inflammatory
  - Radical scavenging activity
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# Mechanism of Action

- Increases lymphatic drainage
- Provides microcirculation in capillary
- Shows anti-inflammatory effect
- Reduces capillary permeability
- Prostaglandin E<sub>2</sub> and thromboxane A<sub>2</sub> inhibitor, inhibits the activation, migration and adhesion of leukocytes.




# Rutin

- Flavonoid (glycoside),
  - Firstly isolated from *Ruta graveolens*
  - Found in many food ingredients;
  - Citrus fruits are rich in rutin
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# Effects

- Vasoprotective,
  - Used in hemorrhoids, varicose veins and edema
  - Anti-inflammatory
  - Antioxidant
  - Inhibits angiogenesis
  - Used as food supplement in Turkey
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# Quercetin


- Flavonoid (aglycone)
  - It is found in many foods such as tea, broccoli, sweet potato, blueberry
  - There isn't any prescribed preparation sold in Turkey
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## Vitamin P activity (bioflavonoid):

- Flavonoids increase capillary resistance and reduce permeability by acting on epinephrine metabolism and prolonging the effect of vitamin C.
- In this field, rutin and hesperidin are the mostly known flavonoids.
- Rutin is abundant in *Sophora japonica* and *Eucalyptus macroryncha*, while hesperidin is found in the peels of citrus such as *Pericarpium aurantii* and *P. citri*.



# Diuretic effect

- Some studies suggest that the diuretic effects of flavonoids occur by reducing permeability.
  - Black and green tea has long been known to have diuretic properties.
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## Effects on Cardiyovascular system:

- Flavonoids have vasodilator effect
- Myrcetin, quercetin and rhamnetin have a stimulating effect on the heart, whereas hesperetol is a heart depressant.
- *Viburnum prunifolium*, *Juniperus communis*, *Ginkgo biloba* known as flavonoid containing plants, have vasodilatory effects.




## Antidiabetic and hepatoprotective effects:

- It was determined that the methanol extract of *Gentiana oliveri* revealed high antidiabetic activity and the substance responsible for the activity was isoorientin.
- The hepatoprotective effect of artichoke (*Cynara scolymus*) is due to phenolic acids and flavonoids.
- Flavonolignans which are the main compounds of milk thistle (*Silybum marianum*), are responsible for the hepatoprotective activity of the plant.




# Spasmolithics activity

- Flavonoids have spasmolytic activity on smooth muscles, gastrointestinal and urogenital systems.
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# Estrogenic effects

- Genistein, daidzein and biochanin A are isoflavons with estrogenic activity.
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# Antioxidant activity


- Flavonoids are strong antioxidants.
  - Oxidation takes place in three stages: starting, progress and last stage.
  - Flavonoids are effective at all these stages.
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# Possible Mechanism of Actions of Flavonoids


- Direct free radical scavenging effect
- Depletion of radical product
- Elimination of radical precursors
- Metal chelating
- Xanthine oxidase inhibition
- Increasing endogenous antioxidants




# Tea

- The beverage prepared from the leaves of tea plant (*Camellia sinensis*) is known as «tea» and is one of the most consumed drinks in the world as well as in our country.
  - *Camellia sinensis* is native to China, but recently it is cultivated commonly in India, Sri Lanka, Kenya, Indonesia and Japan. In Turkey, it is grown in and around Rize region.
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- Black tea is produced by controlled fermentation of fresh and young tea leaves.
  - The top bud and the two following leaves of the plant are collected. Afterwards, withering, rolling, fermentation, drying and sieving processes are applied respectively.
- Green tea production is different from black tea production. By applying high temperature to the fresh tea leaves for a short time, the enzymes are destroyed/inactivated so that the tea leaves remain green.

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- Polyphenols in tea are called as catechins. Epigallocatechingallate is the most antioxidant effect bearing compound among catechins found in green tea.
  - Green tea also contains epicatechingallate, epigallocatechin and epicatechin.




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- Free radicals are reactive substances that damage cells in the body and cause various diseases such as cancer and cardiovascular diseases.
  - Clinical trials have shown that catechins inhibit the formation of free radicals and have some preventive effects on the body.
  - Epidemiological studies have shown that tea consumption reduces the risk of heart attacks, coronary heart diseases, certain cancers and liver disorders. Green tea has a stronger antioxidant effect than black tea.




# Pomegranate

- Pomegranate (*Punica granatum*), is one of the most known fruits in recent years due to its strong antioxidant effects.
- It contains high amounts of vitamin C as well as iron, potassium, and strong antioxidant compounds such as ellagic acid, antocyanin.
- One of the most important characteristics of the pomegranate is that it is thought to be effective in general vascular strength, especially in the protection of the heart.



# Isoflavonoids and other phytoestrogens

- Phytoestrogens are divided into different groups according to different sources.
  - These can be divided into four classes:
    - isoflavones,
    - lignans,
    - coumestans and
    - stilbenes
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# Isoflavone contents of some foods

Product class	Product	Isoflavone content <sup>a</sup>	Lignan content <sup>b</sup>
Grain	Whole grain wheat	Trace	0.08
	Wheat bran	0.1	1.1
	Oat bran	0.1	1.1
Seed	Pumpkin seeds	0.02	214
	Linseeds	0	371
	Flaxseed meal <sup>c</sup>	ND	675
	Flaxseed flour <sup>c</sup>	ND	525
	Peanuts <sup>c</sup>	ND	1.7
Legume	Chick peas	0.88	0.08
	Green peas	73	ND
	Lentils <sup>c</sup>	ND	18
	Kidney bean <sup>c</sup>	ND	0.6
Seaweed	Dried seaweed <sup>c</sup>	ND	1.1
Soy	Tofu	532	ND
	Tempah	865	ND
	Miso	300	ND
	Soy milk	44	ND
	Roasted soybeans	2661	ND
	Soy protein isolate	987	ND
	Soy-based infant formula	40	ND

*Sources:* (Thompson et al., 1991; Franke et al., 1995; Reinli and Block, 1996; Lampe 2003).

<sup>a</sup>Isoflavone consumption will result in the excretion of genistein, daidzein, equol and *O*-desmethylangolensin.

<sup>b</sup>Lignan consumption will result in the excretion of enterodiol and enterolactone.

<sup>c</sup>Enterodiol and enterolactone measured after incubation with fecal microbiota.

ND = not determined.

# Isoflavone contents of some foods

Food item	Isoflavone content (mg/100g)		
	Daidzein	Genistein	Isoflavone <sup>2)</sup>
Soybean curd	3.93	5.77	9.70
Uncurdled soybean curd	3.57	3.22	6.79
Soybean curd residue	11.24	13.93	25.18
Fried soybean curd	17.83	28.00	45.83
Bean sprouts	3.81	8.42	12.23
Soybean paste	39.43	42.54	81.97
Dambuk	28.40	27.97	56.37
Miso	16.13	24.56	40.69
Seasoned soybean paste	5.47	6.14	11.61
Soybean	56.22	69.66	125.88
Soy milk	4.51	7.84	12.35
Soybean broth	4.51	7.84	12.35
Red bean	0.00	0.31	0.31
Peanut	0.03	0.24	0.27

Food	Present study		Other studies	
	Daidzein	Genistein	Daidzein	Genistein
Soyabeans, raw	58×10 <sup>4</sup>	84×10 <sup>4</sup>	33×10 <sup>4</sup> †	48×10 <sup>4</sup> †
Soyabeans, raw (ww)	58×10 <sup>4</sup>	84×10 <sup>4</sup>	54×10 <sup>4</sup> ‡	84×10 <sup>4</sup> ‡
Soyabeans, boiled (ww)	15×10 <sup>4</sup>	32×10 <sup>4</sup>	20×10 <sup>4</sup> ‡	31×10 <sup>4</sup> ‡
Miso	59×10 <sup>4</sup>	67×10 <sup>4</sup>	14×10 <sup>4</sup> §	15×10 <sup>4</sup> §
Miso (ww)	59×10 <sup>4</sup>	67×10 <sup>4</sup>	19×10 <sup>4</sup> §	31×10 <sup>4</sup> §
Beansprouts (mung)	39×10 <sup>3</sup>	68×10 <sup>4</sup>	8×10 <sup>3</sup> §	19×10 <sup>3</sup> §
			nd	nd
Broad bean	70	60	240†	tr†
Broccoli, calabrese	nd	nd	50§	70§
Carrot	nd	nd	20§	20§
Cranberry	50	210	0§	0§
Chickpeas	480	770	110§	760§
Green split pea	130	350	80†	tr†
			73×10 <sup>3</sup>	nd
Haricot beans	130	110	140†	4×10 <sup>3</sup> †
Oatmeal	nd	nd	0§	0§
Mung beans	50	110	100§	4×10 <sup>3</sup> §
			nd	nd
Mushroom	10	210	200§	1170§
Red kidney beans	190	210	80†	70†

nd, not detected; tr, isoflavone were identified but could not be quantified; ww, wet weight.


\* Concentrations expressed on a dry weight basis, unless otherwise indicated.


† Mazur *et al.* (1998).



‡ Reinli & Block (1996).

§ Adlercreutz & Mazur (1997).

|| Franke *et al.* (1994).

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- Phytoestrogens and plant-based chemicals in endogenous estrogen-like activities have gained importance in recent years regarding some epidemiological studies.
  - These studies have shown that phytoestrogen-rich diet-fed populations have less frequent complaints of cardiovascular disease, osteoporosis, breast, prostate and bowel cancers, and that postmenopausal women experience less severe estrogen deficiency symptoms.

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- However, the mechanisms related to metabolism, absorption, potential beneficial effects of phytoestrogens, and the optimal and toxic doses required for these effects are insufficient.
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# Biological Potentials and Effects of Phytoestrogens

## a. Estrogenic and Antiestrogenic Activity:


- The estrogenic and anti-estrogenic properties of phytoestrogens are explained primarily by their easy binding to estrogen receptors (ER) due to their structural and functional similarity to endogenous estrogen (17- $\beta$ -estradiol).


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- The activity of phytoestrogens may be related to the endogenous estrogen levels of the media; It is thought that they may show estrogenic effect in low estrogenic environment (such as postmenopause), while they show anti-estrogenic effect in high estrogenic environment (premenopause).

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- It has been suggested that the effects of phytoestrogens on enzymes affecting steroid metabolism may be important in explaining the estrogenic and anti-estrogenic properties of phytoestrogens.
  - ❖ It has been shown that:
    - ❖ isoflavones block the conversion of androgens to estrogens by suppressing aromatase enzyme in microsomes in placenta and ovaries;
    - ❖ cystestrol and genistein suppresses the enzyme 17- $\beta$ -estradiol oxidoreductase, which is responsible for the conversion of estrone to estradiol.




## b. Antioxidant Activity:

- Antioxidant properties of phytoestrogens, especially isoflavones, have been demonstrated by *in vitro* and *in vivo* studies.
  - Isoflavones can prevent oxidative DNA damage either by affecting free radicals directly or by affecting antioxidant-scavenging enzymes. Studies show that dietary isoflavones increase resistance against LDL oxidation.
  - Genistein is known to have the highest antioxidant activity among isoflavones.
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- Isoflavones have potential anticarcinogenic effects, including angiogenesis and inhibition of cell cycle progression.
  - Especially phytoestrogens inhibit the activity of some enzymes playing important role in tumor formation such as;
    - DNA topoisomerase 1 ve 2,
    - tyrosine kinase,
    - ribosomal S6 kinase,
    - 5 $\alpha$ -redüktase.



# Effects of phytoestrogens on bone health:


- Estrogen plays an important role in maintaining bone density by regulating bone formation and mineralization functions.
  - Phytoestrogens have been shown to bind to estrogen receptors in the bone and show estrogenic effect, which reduces bone destruction in menopause.
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# Effects of phytoestrogens on cardiovascular health:

- Estrogen is effective on vascular system either directly by settling at estrogen receptors in vascular tissues or, indirectly by changing the lipoprotein profile.
- Phytoestrogens behave like estrogens and have similar effects.
- Isoflavonoids or soy / soy products and flaxseed have reducing effects on total cholesterol and low-density lipoprotein (LDL) levels while increasing effects on HDL.




# Effects of phytoestrogens on menopausal symptoms


- Menopause causes women to experience hormonal, physiological and psychological changes. The most important effect of hormonal balances during menopause is estrogen hormone. Decreased estrogen levels are responsible for a large number of symptomatic conditions after menopause.
  - It was concluded that phytoestrogens may be protective against vasomotor symptoms such as hot flashes, night sweats, sleep disturbance, insomnia, fainting, depression and irritability.
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# Breast Cancer


- Due to conflicting data on the effect of phytoestrogens on breast cancer, it is not yet possible to make recommendations on phytoestrogen intake to prevent or treat breast cancer.
  - It is known that phytoestrogens may behave differently according to dose, tissue and type of phytoestrogen used →
  - In low concentrations may increase the clinical or subclinical growth of breast tumors and antagonize the antitumor effect of tamoxifen using the possible estrogenic mechanism;
  - At high concentrations can suppress the growth of breast tumors.
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- There is no evidence that phytoestrogens are taken in high-dose tablet form to be protective or safe against breast cancer; however, consuming foods which are the source of phytoestrogens can have beneficial effects on women.



# Prostate cancer


- It has been claimed that the ability of phytoestrogens to suppress enzymes such as aromatase, 17- $\beta$ -hydroxy steroid dehydrogenase, 5- $\alpha$ -reductase and other anticarcinogenic effects in steroid metabolism may be protective against prostate cancer.
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- Does not cause infertility
  - Does not trigger breast cancer
  - Does not cause thyroid diseases by inhibiting the thyroid peroxidase (TPO), which is the key factor in the production of thyroid hormones
  - These concerns are not supported in societies where these compounds are consumed regularly and at high concentrations.

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- No cases of phytoestrogen toxicity have been reported to date in any country in the world, particularly in communities that consume nutrients rich in phytoestrogens.
  - However, it is not known what the consequences of long-term use and / or high doses of concentrated isoflavone supplements, especially in pill, powder or gel form, may be.



# Usages

- Mainly used by women, these products are mainly used to relieve menstrual (PMS) and menopausal (hot flashes, night sweats, vaginal dryness, depression, etc.) symptoms, reduce or partially treat the risk of cardiovascular disease and osteoporosis.
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- *Glycine max,*
  - *Linum usitatissimum,*
  - *Cimicifuga racemosa,*
  - *Trifolium pratense,*
  - *Glycyrrhiza glabra,*
  - *Humulus lupulus,*
  - *Angelica sinensis*

# Weak phytoestrogenic activity

- *Oenothera biennis*,
- *Vitex agnus castus*,
- *Medicago sativa*,
- *Panax spec.*,
- *Eleutherococcus senticosus* ve
- *Coffea arabica*