**Flavonoid Subclasses in Relation to Cancer Risks: a Review**

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**Abstract:** This paper aims to review data form recent different studies addressing flavonoids subclasses potential benefits in reducing cancer risks. Flavonoids subclasses includes flavones, flavonols, flavanones, flavan-3-ols, isoflavones and anthocyanidins. Many epidemiological studies suggest flavonoids dietary intake may reduce the risk of the breast, ovarian, colorectal and prostate cancers. However, some studies have reported inconsistent results**.**

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**Keywords:** flavonoids; cancer; risk; prevention; intake

**1. Introduction**

Cancers are now the second leading cause of death throughout the world after CVD, with increasing potential of surpassing it (WHO, 2017). Plant compounds ــ flavonoids have been reported to exert beneficial effects in the prevention of cancer. This review examines recent research on the effects of specific flavonoids in the prevention of cancer.

**2. Cancer**

About 7 million deaths occurred in 2015 due to cancer (WHO, 2017). Cancer deaths in the world are predicted to continue to increase to over 11 million in 2030 (WHO, 2008). Lung, liver, colorectal, stomach and breast cancers currently are the most common causes of cancer death. Quality of diet plays an important role in preventing or causing cancer (Parkin, 2001; A. Boutayeb & S. Boutayeb, 2005; WHO, 2017). Dietary factor is one of the major cancer risk factors worldwide (WHO, 2017).

**3. Flavonoid Subclasses**

Flavonoids are plant compounds with yellow pigments in flower or red/blue in petals (Hertog & Katan, 1998). They are found in fruits, tea, wines and vegetables (Zamora-Ros et al., 2013). More than 8,000 types of flavonoids that have been discovered (Watson, 2009). They divided into six subclasses: flavones, flavonols, flavanones, flavan-3-ols, anthocyanidins and isoflavones (USDA, 2005; Beecher, 2003; Nishiumi et al., 2011). Flavonols compounds includes quercetin, kaempferol, myricetin and isorhamnetin that available in yellow onions, leek, cherries, tomato, broccoli, buckwheat, blueberries, black grapes & beans. While flavones includes apigenin and luteolin, which can be found in herbs and green leaves. Flavanones includes hesperetin, naringenin and eriodictyol that available in citrus fruits. Flavan-3-ols are subdivided to catechins group existing in green & white tea, cocoa, grapes, apples, red wine and theaflavins group existing in black & oolong tea. Cyanidin, malvidin, delphinidin, peonidin, pelargonidin and petunidin are examples of anthocyanidins compounds that available in blueberries, raspberries, blackcurrants, black grapes, cherries, rhubarb, plum, elderberries, strawberries & red cabbage. Finally, genistein, daidzein and glycitein are isoflavones compunds that soybeans are the most common source of them (USDA, 2011).

Research to date established certain associations between nutrients and cancer risks, and flavonoid is one of the important nutrients associated with cancer prevention. They act on different targets including scavenging reactive oxygen species (ROS), regulation of the cell cycle, and initiation of DNA repair mechanisms, apoptotic induction and inhibition of metastasis.

**4. Flavonoids and Cancers**

**Flavonols and Cancers**

*Hormone-Sensitive Cancer*

A case-control study found that high intake of total flavonoids, flavonols, flavones and flavanols was associated with decreasing breast cancer risk among postmenopausal women (Fink et al., 2007). In addition, a network of case-control studies conducted in Italy reporting a decrease in breast and ovarian cancers risk with increasing intake of flavonols (Rossi et al., 2010). A meta-analysis also suggested that consumption of isoflavones and flavonols together could lower ovarian cancer risk (Hua et al., 2016). Moreover, Wilsher et al. (2017) explained the anti-cancer activity of apigenin, luteolin, scutellarein, kaempferol and quercetin by inhabiting cytochrome P450 (CYP)1 enzymes in breast cancer cells. Xin et al. (2017) also indicated that fisetin, a bioactive flavonol molecule, was effective in suppressing on the activity of CYP1B1 in vivo model of estrogen tissues. In vitro model study, Kim et al. (2016) also concluded that flavonol-enriched extract from the American cranberry may offer protective effects against human prostate tumor cell lines. A retrospective cohort study also found that high flavonols intake were associated with degreasing prostate cancer mortality after diagnosis it (Taborelli et al., 2017). However, Adebamowo et al. (2005) showed no association of breast cancer risk with high intake of most major food sources of ﬂavonols. In follow-up study, Wang et al. (2009) also reported no significant association of quercetin, kaempferol, and myricetin with breast, ovarian and endometrial cancers risk.

*Colorectal Cancer*

Nimptsch et al. (2016) reported from two large prospective cohorts including 2519 cases of colorectal cancer that high intake of flavonoid including flavonols did not play any roles with colon or rectal cancer risk. Moreover, there was no significant association between flavonols intake and the incidence of specific cancers including colorectal cancer among women aged ≥45 y (Wang et al., 2009). On the other hand, an Italian network case-control study found a negative association between colorectal cancer and high intake of anthocyanidins, flavonols, flavones and isoflavones intakes (Rossi et al., 2010). Similarly, a Korean study indicated that high flavonol intake may reduce colorectal cancer risk, especially among carriers of the CYP1A1 CC homozygous variant (Cho et al., 2017). Raja et al. (2017) also found that quercetin inhibits human colonic tumor cell lines.

*Other Cancers*

A meta-analysis of epidemiological studies suggest that increasing intake of dietary flavonols among smokers may reduce risk of gastric and esophageal cancer, especially in women (Xie et al., 2016). Nöthlings et al. (2007) also found negative association between total flavonols intake and pancreatic cancer risk among current smokers. Moreover, a meta-analysis study showed negative association between flavonoids, especially flavonols, intake and risk of smoking related cancer, which includes oral cavity, nasal cavity, paranasal sinuses, larynx, pharynx, esophagus, lung, gastric, pancreas, liver, kidney, bladder, uterine cervix and myeloid leukemia (Woo & Kim, 2013). In a cell culture study, Liao et al. (2016) found that kaempferol inversely associated with proliferative activity on human cancer cell lines including breast, gastric, cervical and lung cells. In vitro and in vivo models, quercetin also inhabited lung cancer cells as an aurora B inhibitor (Xingyu et al., 2016).

**Flavones and Cancers**

*Hormone-Sensitive Cancer*

A meta-analysis of epidemiologic studies suggested that high consumption of flavones and flavonols, but not total flavonoids or other flavonoid subclasses, was associated with a decreased breast cancer risk, specifically among post-menopausal women. (Hui et al., 2013). In Mexican population, Sanchez (2009) also observed that high intake of flavones and flavonols reduced the risk of developing breast cancer, especially among post-menopausal women.

A meta-analysis study including five cohort and seven case-control studies failed to find an association between flavones intake and ovarian cancer risk (Hua et al., 2016). Moreover, there was no significant association between flavones consumption and the incidence of specific cancers including breast, ovarian and endometrial cancers among middle-aged and older women (Wang et al., 2009).

*Digestive System Cancers*

The Chinese case-control study observed that high intake of anthocyanin, ﬂavone and flavanones from vegetables and fruits reduced the risk of developing colorectal cancer. However, the study did not find any association between tea flavonoids and colorectal cancer risk (Xu et al., 2016). In addition, a meta-analysis of five studies found no reduction in colorectal cancer risk with high intake of flavone (He & Sun, 2016). In the Women's Health Study, there also was no significant association between intake of flavones and colorectal cancer incidence among women aged ≥45 y (Wang et al., 2009).

A meta-analysis including seven prospective cohort or case-control studies suggested that high intake of total flavonoids, flavones, flavanones and anthocyanidins may decrease the esophageal cancer risk (Cui et al, 2016). However, Sun et al. (2017) study failed to find an association between any flavonoid intake and esophageal or gastric cancers risk.

*Other Cancers*

In vitro and in vivo models, apigenin inhabited renal cancer cell proliferation via inducinmg DNA damage and G2/M phase cell cycle arrest (Meng et al., 2017). (Li et al., 2015) indicated that isorhamnetin, a flavone compound, suppressed lung cancer in vitro and in vivo model. However, Wang et al. (2009) did not find any association between intake of flavones and the lung cancer incidence among women aged ≥45 y from the Women's Health Study.

**Flavanones and Cancers**

*Digestive System Cancers*

The Chinese case-control study observed that high intake of anthocyanin, ﬂavone and flavanones from vegetables and fruits reduced the risk of developing colorectal cancer (Xu et al., 2016). A meta-analysis including seven prospective cohort or case-control studies, published from 1990 to 2016, suggested that high intake of total flavonoids, flavones, flavanones and anthocyanidins may lower the esophageal cancer risk (Cui et al, 2016). However, Sun et al. (2017) study failed to find an association between any flavonoid intake and esophageal or stomach cancers risk.

*Other Cancers*

In a prospective cohort study, Sun et al. (2017) found that flavanones were associated with reducing head and neck cancer risk by 22%. In the Nurses’ Health Study I and II, Cassidy et al. (2014) found a significant negative association between ovarian cancer risk and high intake of flavonols and flavanones. Sánchez-Marzo et al. (2017) indicated that citrus and olive flavonoids might decrease skin cancer risk by inhibiting UVB-induced reactive oxygen species generation and decreasing apoptosis and DNA damage.

**Flavan-3-ols and Cancers**

*Digestive System Cancers*

A Korean study including 923 cases and 1,846 controls found that flavan-3-ols and flavonols intake had a stronger negative association with a risk of colorectal cancer than other flavonoids subclasses (Cho et al., 2017). Additionally, a meta-analysis study of 43 epidemiologic studies on flavan-3-ols consumption indicated the protective effect of flavan-3-ols intake on rectal cancer, oropharyngeal and laryngeal cancer, while stomach cancer was specifically in women (Lei et al., 2016).

*Breast Cancer*

Meta-analysis showed that consuming flavan-3-ols may reduce the risk of breast cancer (Lei et al., 2016). In addition, Mérida-Ortega et al. (2016) found that high intake of vegetables with high sours of flavan-3-ols and anthocyanidins raised the negative association between butyl benzyl phthalate (BBzP) and breast cancer in northern Mexico population.

**Anthocyanidins and Cancers**

*Digestive System Cancers*

The Chinese case-control study observed that high intake of anthocyanin, ﬂavone and flavanones from vegetables and fruits reduced the risk of developing colorectal cancer (Xu et al., 2016). In addition, a meta-analysis of five studies found a potential reduction in colorectal cancer risk with high intake of procyanidins, which formed from catechin and epicatechin (He & Sun, 2016). However, Nimptsch et al. (2016) reported from two large prospective cohorts including 2519 cases of colorectal cancer that high intake of flavonoid subclasses including anthocyanins did not play any roles with colon or rectal cancer risk.

A meta-analysis including seven prospective cohort or case-control studies compared the total flavonoids and each flavonoid subclass highest-intake with the lowest-intake of esophageal cancer patients. The study results suggested that high intake of total flavonoids, flavones, flavanones and anthocyanidins may decrease the esophageal cancer risk (Cui et al, 2016).

*Other Cancers*

A retrospective cohort study also found that high proanthocyanidins intake were associated with degreasing prostate cancer mortality after diagnosis it (Taborelli et al., 2017). In a prospective cohort study, Sun et al. (2017) found that anthocyanidins intake were associated with reducing head and neck cancer risk by 28% (HR: 0.72; 95% CI: 0.62, 0.82; BH-adjusted 95% CI: 0.59, 0.87; P-trend = 0.0005).

**Isoflavone and Cancer**

*Colorectal Cancer*

A meta-analysis of five studies found a potential reduction in colorectal cancer risk with high intake of isoflavones (He & Sun, 2016). In addition, a meta-analysis of 13 case-control and 4 prospective cohort studies observed an inverse association between soy isoflavone consumption and colorectal cancer risk among Asian populations (Yu et al., 2016).

*Hormone-Sensitive Cancer*

A meta-analysis also suggested that consumption of isoflavones and flavonols together could lower ovarian cancer risk (Hua et al., 2016). However, a follow up study including 2,598 cases of prostate cancer reported no significant associations between total isoflavones intake and risk of non-advanced prostate cancer and total prostate cancer, while the researchers observed an associated between isoflavones intake and elevated risk of advanced prostate cancer (Reger et al. 2018).

**5. Conclusion**

The current review demonstrates that flavonoids intake has protective effects against various types of cancer including colorectal, oral, larynx, pharynx, esophagus, pancreas, liver, prostate, ovarian, endometrial, breast, head with neck, skin, stomach, kidney, bladder, uterine cervix, lung and leukemia. Recent epidemiological studies suggest dietary intake of about all flavonoids subclasses may reduce the risk of the colorectal, breast, ovarian and prostate cancers. Most recent studies support the prevention effects of flavones, flavonols, flavanones, flavan-3-ols, isoflavones and anthocyanidins on colorectal cancer. However, some studies have reported inconsistent results. These differentiate between studies’ findings can be caused by various reasons, including the study design, study duration, dose, population and type of tumor. These findings suggest also the importance role of flavonoids habitual intake in cancer prevention. Not to be hidden, large sample studies among populations are needed to reduce bias and further investigate the effects of specific flavonoids and interactions on the specific cancer response.

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**References**

1. World Health Organization (2017) Cancer fact sheet. http://www.who.int/mediacentre/factsheets/fs297/en/ (accessed November 2017).
2. Hertog MGL and Katan MB (1998) Quercetin in food, cardiovascular disease, and cancer. In: Flavonoids in Health and Disease (Rice-Evans C and Packer L eds), Marcel Dekker, New York. 483-522.
3. Wang Y, Chen S, and Yu O (2011) Metabolic engineering of flavonoids in plants and microorganisms. Appl Microbiol Biotechnol, 91(4): 949-956.
4. Zamora-Ros R, Fedirko V, Trichopoulou A et al. (2013) Dietary Flavonoid, Lignan and Antioxidant Capacity and Risk of Hepatocellular Carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. International journal of cancer 133(10):2429-2443.
5. United State Department of Agriculture (2013) USDA Database for the Flavonoid Content of Selected Foods. https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/nutrient-data-laboratory/docs/usda-database-for-the-flavonoid-content-of-selected-foods-release-31-december-2013/ (accessed November 2017).
6. Fink BN, Steck SE, Wolff MS et al. (2007) Dietary flavonoid intake and breast cancer risk among women on Long Island. Am J Epidemiol. 165, 514-23.
7. Rossi M, Bosetti C, Negri E et al. (2010) Flavonoids, Proanthocyanidins, and Cancer Risk: A Network of Case-Control Studies From Italy. Nutrition and Cancer 62(7):871-7.
8. Hua X, Yu L, You R et al. (2016) Association among Dietary Flavonoids, Flavonoid Subclasses and Ovarian Cancer Risk: A Meta-Analysis. Association among Dietary. PLoS ONE 11(3):e0151134.
9. Wilsher NE, Arroo RR, Matsoukas MT et al. (2017) Cytochrome P450 CYP1 metabolism of hydroxylated ﬂavones and ﬂavonols: Selective bioactivation of luteolin in breast cancer cells. Food and Chemical Toxicology 110: 383-394.
10. Kim J, Patel K, Catalli A et al. (2016) Cranberry Flavonols Modulate Cell Cyclerelated Protein Expression In Human Prostate Cancer Cells In Vitro. International Journal of Cancer Research and Prevention. 9(2): 1554-1134.
11. Taborelli M, Polesel J, Parpinel M, et al. (2017) Fruit and vegetables consumption is directly associated to survival after prostate cancer. Mol Nutr Food Res. 61(4).
12. Adebamowo CA, Cho E, Sampson L et al. (2005) Dietary flavonols and flavonol-rich foods intake and the risk of breast cancer. Int. J. Cancer 114:628-633.
13. Wang L, Lee IM, Zhang SM et al. (2009) Dietary intake of selected flavonols, flavones, and flavonoid-rich foods and risk of cancer in middle-aged and older women. Am J Clin Nutr. 89(3):905-12.
14. Nimptsch K, Zhang X, Cassidy A et al. (2016) Habitual intake of flavonoid subclasses and risk of colorectal cancer in 2 large prospective cohorts. Am J Clin Nutr. 103(1):184-91.
15. Cho YA, Lee J, Oh JH et al. (2017) Dietary Flavonoids, CYP1A1 Genetic Variants, and the Risk of Colorectal Cancer in a Korean population. Scientific Reports. 7: 128.
16. Raja SB, Rajendiran V, Kasinathan NK et al. (2017) Differential cytotoxic activity of Quercetin on colonic cancer cells depends on ROS generation through COX-2 expression. Food Chem Toxicol. 106(Pt A):92-106.
17. Xie Y, Huang S, and Su Y (2016) Dietary Flavonols Intake and Risk of Esophageal and Gastric Cancer: A Meta-Analysis of Epidemiological Studies. Nutrients. 8: 91.
18. Nöthlings U, Murphy SP, Wilkens LR et al. (2007) Flavonols and pancreatic cancer risk: the multiethnic cohort study. Am J Epidemiol. 166(8):924-31.
19. Woo HD and Kim J (2013) Dietary Flavonoid Intake and Smoking-Related Cancer Risk: A Meta-Analysis. PLoS ONE 8(9): e75604.
20. Liao W, Chen L, Ma X et al. (2016) Protective effects of kaempferol against reactive oxygen species-induced hemolysis and its antiproliferative activity on human cancer cells. Eur J Med Chem. 114:24-32.
21. Xingyu Z, Peijie M, Dan P et al. (2016) Quercetin suppresses lung cancer growth by targeting Aurora B kinase. Cancer Med. 5(11):3156-3165.
22. Hui C, Qi X, Qianyong Z et al. (2013) Flavonoids, flavonoid subclasses and breast cancer risk: a meta-analysis of epidemiologic studies. PLoS One. 8(1):e54318.
23. Torres-Sanchez L, Galvan-Portillo M, Wolff MS et al. (2009) Dietary consumption of phytochemicals and breast cancer risk in Mexican women. Public Health Nutr. 12:825–31.
24. Xu M, Chen YM, Huang J et al. (2016) Flavonoid intake from vegetables and fruits is inversely associated with colorectal cancer risk: a case–control study in China. British Journal Of Nutrition. 116(7): 1275-1287.
25. He X and Sun LM (2016) Dietary intake of flavonoid subclasses and risk of colorectal cancer: evidence from population studies. Oncotarget. 7(18).
26. Cui L, Liu X, Tian Y et al. (2016) Flavonoids, Flavonoid Subclasses, and Esophageal Cancer Risk: A Meta-Analysis of Epidemiologic Studies. Nutrients. 8(6): 350.
27. Sun L, Subar AF, Bosire C et al. (2017) Dietary Flavonoid Intake Reduces the Risk of Head and Neck but Not Esophageal or Gastric Cancer in US Men and Women. American Society for Nutrition. 147(9):1729-1738.
28. Meng S, Zhu Y, Li JF et al. (2017) Apigenin inhibits renal cell carcinoma cell proliferation. Oncotarget. 8(12):19834-19842.
29. Li Q, Ren FQ, Yang CL et al. (2015) Anti-proliferation effects of isorhamnetin on lung cancer cells in vitro and in vivo. Asian Pac J Cancer Prev. 16(7):3035-42.
30. Cassidy A, Huang T, Rice MS et al. (2014) Intake of dietary flavonoids and risk of epithelial ovarian cancer. Am J Clin Nutr. 100(5):1344-51.
31. Sánchez-Marzo N, Pérez-Sánchez A, Castillo J et al. (2017) P 187 - Prevention of UVB-induced Oxidative Stress and DNA damage in human keratinocytes by citrus and olive formulations. Free Radical Biology and Medicine. 108(1): S82.
32. Lei L, Yang Y, He H et al. (2016) Flavan-3-ols consumption and cancer risk: a meta-analysis of epidemiologic studies. Oncotarget. 7(45): 73573–73592.
33. Mérida-Ortega Á, Hernández-Alcaraz C, Hernández-Ramírez RU et al. (2016) Phthalate exposure, flavonoid consumption and breast cancer risk among Mexican women. Environ Int. 96:167-172.
34. Yu Y, Jing X, Li H et al. (2016) Soy isoflavone consumption and colorectal cancer risk: a systematic review and meta-analysis. Scientific Reports. 6: 25939.
35. Reger MK, Zollinger TW, Liu Z et al. (2018) Dietary intake of isoflavones and coumestrol and the risk of prostate cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Int J Cancer. 142(4):719-728.

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