

Flavonoid Subclasses in Relation to Cancer Risks: a Review

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Abstract: This paper aims to review data from 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. [Turkistani A. **Flavonoid Subclasses in Relation to Cancer Risks: a Review.** *N Y Sci J* 2018;11(10):46-50]. ISSN 1554-0200 (print); ISSN 2375-723X (online). <http://www.sciencepub.net/newyork>. 7. doi:[10.7537/marsnys111018.07](https://doi.org/10.7537/marsnys111018.07).

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 – 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 compounds 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 decreasing 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 inhibited 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 inhibited renal cancer cell proliferation via inducing 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 sources 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 decreasing 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 association 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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