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A review of significant molecular mechanisms of flavonoids in prevention of prostate cancer

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ABSTRACT

Prostate cancer is the third most common cancer among men. Risk factors for prostate cancer contain environmental factors such as diet rich of reactive oxygen species. Epidemiological studies recommend dietary consumption of plant-derived foods may decrease the risk of prostate, colon, pancreas, breast and lung cancers. However, it has been difficult to identify specific components responsible for this effect. Many phytochemicals have been shown to be biologically active compounds and they may act as a protective factor against cancer. Recent researches have revealed that diets based on flavonoids have the potential benefits for cancer prevention. Flavonoids are part of a large class of polyphenols that are found widely in diet. Nowadays, experimental researches have suggested developing proof for the valuable action of flavonoids on multiple cancer-related biological pathways. Although the outcomes of studies about flavonoids and prostate cancer are still limited and conflicting, some protective associations have been suggested for flavonoid-rich foods. The current review presented molecular mechanism of the main flavonoids on prostate cancer. The main mechanisms are in three different directions. These mechanisms contain antioxidant activity and inhibition of DNA damage of its oxidizing agents, anti-cell proliferation and induction of apoptosis.

KEY WORDS: prostate cancer, flavonoids, oxidative stress, molecular mechanisms.

1. INTRODUCTION

Worldwide, Prostate cancer (PCa) is the sixth cancer, and the third most common cancer among men. Risk factors for PCa include environmental factors, age, race/ethnicity, and family history. Very few men are diagnosed younger than age 50, with the mean age of diagnosis in the beginning 70's. Incidence varies widely by country and racial/ethnic origin. The highest rate has been achieved in western countries while the lowest rates have seen in Asian countries (Grönberg, 2003). Other probable risk factors include hormonal factors, body mass index, and diet. Several researches have proven positive associations between PCa and BMI incidence, although not all results have been consistent (Crawford, 2003). With the great abundance of incidence worldwide, differences in diet, especially fat intake, have been increasingly studied. Because the growth of the prostate is directed by androgens, these hormones may be another risk factor (Prins and Korach, 2008). PCa remains the most commonly diagnosed cancer and second leading cause of cancer mortality among men in several national groups in the United States. Lower PCa occurrence among Asian population has been attributed to increased intake of herbal rich diet. On the other hand, the environmental factors such as some diet changes the patterns of epigenetic and leading to changes in gene expression. Some of the genes associated with creating and advancing PCa (Labbé, 2014). Plants have been consumed as medicines for thousands of years (Sewell and Rafieian-Kopaei, 2014, Bahmani, 2014, Asadbeigi, 2014, Asgari, 2012).

Recent researches have also presented promising results in the prevention and treatment of diseases (Fasihzadeh, 2016, Lorigooini, 2015, Lorigooini, 2014, Heidarian and Rafieian-Kopaei, 2012). These medicines primarily took the form of crude drugs such as teas, powders, poultices, tinctures and other natural formulations (Balunas and Kinghorn, 2005, Rafieian-Kopaei and Nasri, 2014). The particular herbal drugs to be used and the methods of application for specific diseases were passed down via oral history. Eventually information regarding medicinal plants was documented in herbals. In latest history, the consumption of plants as drugs has included the isolation of active phytochemicals, beginning with the separation of morphine from *Papaver somniferum* in the early 19th century (Kinghorn, 2001, Samuelsson, 1992). Drug finding from medicinal herbs lead to the separation of novel natural drugs (Balunas and Kinghorn, 2005). Isolation and characterization of pharmacologically active compounds from medicinal herbs continue these days (Di Carlo, 1999, Rahnama, 2015, Nasri and Rafieian-Kopaei, 2014b). One of these active secondary metabolites are flavonoids (Rabiei, 2015).

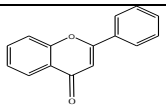
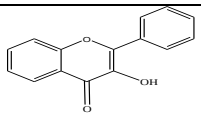
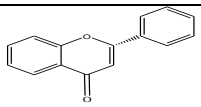
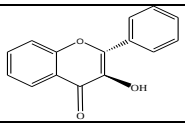
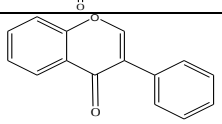
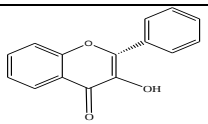
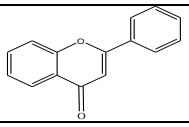
Flavonoids are part of a large classes of polyphenols that are originated widely in vegetables and fruits. This class of secondary metabolites has been of significant medical attentiveness due to their anti-inflammatory, analgesic and anti-tumor activities (Asgary, 2013, Bahmani, 2014, Shayganni, 2015). Recent studies also have revealed that flavonoids possess medicinal specification, especially antioxidant activities. Some environmental factors are the cause of oxidative stress (Apel and Hirt, 2004, Mirhosseini, 2014). Oxidative stress can do extensive damage to all components of cells, and subsequently causing variety of diseases such as cancer. Studies have shown that oxidative stress can potentially lead to development of cancer. Namely, the oxidative agents cause DNA damage. DNA

damages can be carcinogenic (Loft and Poulsen, 1997). Today, it has been proved that some foods are natural anti-cancer or prevent cancer agents (Ren, 2003, Samani, 2015).

Nowadays, dietary patterns worldwide vary greatly, especially between the countries that differ widely in PCa incidence (Crawford, 2003, Grönberg, 2003). Studies reveal how important diet can be in PCa etiology. Flavonoid intake is one aspect of diet that has not been sufficiently researched. Some studies have assessed the relationship between cancers and flavonoid intake, but very few have examined flavonoids and PCa specifically. One cohort study found that get a greater degree of the flavonoid myricetin was associated with less risk of PCa (Knekt, 1996), while another study found no association between flavonoids and PCa (Rossi, 2010). Experimental data support at least a role for flavonoids in PCa progression prevention and expansion.

Flavonoids are one of plant secondary metabolites; which are present in the foods of herbal origin as well as in medicinal herbs and have various medicinal effects (Sedighi, 2014, Delfan, 2014, Karimi and Moradi, 2015). They are categorized into flavones, flavonols, isoflavones, flavonols, flavonones, and flavononols. Currently herbal treatments including flavonoids are used in many areas of the world (Craig, 1999, Di Carlo, 1999, Samuelsen, 2000). Flavonoids are polyphenolic compounds; define chemically as substances composed of a common phenylchromanone structure (C6-C3-C6), with one or more hydroxyl substituents, including derivatives (Table 1). In marked contrast to flavonoids, isoflavonoids have a 3-phenylchroman skeleton that is biogenetically derived from the 2-phenylchroman skeleton of the flavonoids. Isoflavonoids are available from different family of plants. In mammals, flavonoids and isoflavonoids occur only through dietary intake. Isoflavonoids and Flavonoids have shown many biological properties that may account for cancer or other therapeutic effects (Bravo, 1998, Birt, 2001, Messina, 1999). Today, special attention has been paid to their potential to inhibit the oxidative stress, cell proliferation, cell cycle, to induce detoxification, apoptosis, and the immune system. Building upon this foundation will facilitate development of new strategies and approaches for cancer control (Apel and Hirt, 2004).

Table.1. Chemical structures, Classification and food sources of certain commonly dietary flavonoids aglycones (Kumar and Pandey, 2013).

Group of flavanoid	Structure backbone	Flavonoid	Dietary source
Flavones		Rutin Luteolin luteolin glucosides	Fruit skins red wine buckwheat red pepper tomato skin
Flavonols		Kaempferol Quercetin Myricetin tamarixetin	Onion red wine olive oil berries grapefruit
Flavanones		Naringin Naringenin Taxifolin Hesperidin	Citrus fruits Grapefruits Lemons Oranges
Flavanonol		-	-
Isoflavones		Genistin daidzin	Soyabean
Flavan-3-ols		(+)-Catechin (−)-Epicatechin Epigallocatechin Chrysin apigenin	Tea
Flavones		Anthocyanidin cyanidin	Cherry Easberry Strawberry

Although widespread attempt has been made to recognize the biological effects responsible for the chemopreventive activity of these compounds, the accurate molecular mechanisms involved are not fully understood. Anyway, researchers have found there is a deep connection between the defect detoxification and cancer (Liska, 1998). For example, it has already been established that the oxidative stress can increase the level of Akt expressed within cells. The overexpression of Akt can lead to development of cancer (Yang, 2006). One of the most vital functions of natural products in prevention or inhibition of cancer is detoxification and elimination of free radicals (Lobo, 2010).

Briefly, different flavonoids are safe natural compounds that with diverse mechanisms can carry out their anti-cancer roles. For example, it has been found that some flavonoids have potential as a complementary therapy in PCa. In contrast the various molecular mechanisms involved in carcinogenesis and cancer progression. Therefore, in this review presented the main known anti-cancer mechanisms of flavonoids. It is clear that finding effective flavonoids also detection of their molecular mechanisms is essential to create synergistic effects that can be used to reduce the dose of chemotherapy drugs and their side effects and better treatment effects.

Mechanisms and Discussion: Some studies showed that South East Asian countries have a much lower risk of prostate, breast, colon and other cancers than their Western counterparts (Dorai and Aggarwal, 2004), and it is thought that their diet may have significant function in protection. The Phenolic compounds are in fruit and vegetables, and in medicinal herbs, have chemo-preventive activities in tumors (Surh, 1999, Mahmoud, 2000). Flavonoids have been linked with a reduced risk of digestive tract, lung and certain hormone-related cancers (Bosetti, 2006). Epidemiologic researches have shown an inverse association between high flavonoid intake in men and low PCa risk. Diet of East Asian have very rich in flavonoids and, correspondingly, men in these countries have the lowest incidence of PCa (Haddad, 2006). For anti-cancer flavonoids roll was known different molecular mechanisms. The main mechanisms are in three different classes. These mechanisms contain antioxidant activity and prevent damage to DNA of its oxidizing agents, inhibition of cell proliferation and induction of apoptosis (Hertzogi and Tica, 2012).

Flavonoids may play their anti-oxidant and anti-inflammatory roles via direct inhibition of prooxidant enzymes (Rafieian-Kopaei, 2013b, Baradaran and Rafieian-kopaei, 2014). The antioxidant activity is usually performed through the direct removal of the free radicals (Nasri and Rafieian-Kopaei, 2014a, Rafieian-Kopaei, 2013a, Nasri and Rafieian-Kopaei, 2013). Formation of ROS (reactive oxygen species) is a major step in stages of tumor progression. NADPH oxidase I (NOX 1), is down expressed during tumor growth (Fukuyama, 2005, Lim, 2005, Arnold, 2007). ROS is mutagenic and play important role in DNA damage (Poli, 2004, Valko, 2004). Liu and, showed that ROS could induce and increase cell proliferation, apoptosis resistance, and overexpression of some oncogenes such as cFOS, cJUN and cMyc (Liu, 2002). Some flavonoids inhibit ornithine decarboxylase enzyme that induced by tumor promoters, and thereby inhibiting proliferation (Dangles, 2006, Sandhar, 2011). The flovonoids interact with the pathways signaling cell growth and apoptosis (Khan, 2015). Knekt and, estimated that men with higher myricetin intake had a lower PCa incidence (Knekt, 1996). Many flavonoids that tested in vitro exerted anti proliferative effect in the some cell lines of PCa compared to the non-PCa cells. As an example, PC3 cell line was arrested in cell cycle (Haddad, 2006). The flavonoids targets are some regulator proteins in cell cycle such as CDKs and their inhibitors, p53, E2Fs, Rb, ATM/ATR and stay in transition-control points G1/S and G2/M (Singh and Agarwal, 2006). Dalu, have shown that in male rats genistein decreases the amount of prostate EGF (Epidermal Growth Factor) receptor. Genistein may be effect on expression or turnover of receptor of EGF (Lamartiniere, 2000, Peterson and Barnes, 1993). The growth factor hormones are connected to extracellular domains of receptors. These receptors display a tyrosine kinase (TK) activity in their intracellular portion. After hormone–receptor binding, the receptor, then triggering a substantial number of signaling pathways involving some PKs, for example, PKC, and MAPKs (mitogen-activated PKs) (Batra and Sharma, 2013). In cell cycle, DNA replication and chromosomes built is controlled by cyclin-dependent kinases (CDKs) phosphorylation. Flavonoids inhibit some PKs, so inhibit cell proliferation. Also, Lutein appears as a specific inhibitor of TKs (Yang, 1998, Yang, 2006). Quercetin was induced some tumor suppressor genes expression (TS). Beside, quercetin inhibited the expression of some oncogenes expression and control gene in phases of the cell division cycle significantly. The achievements of researches provided an important potential for use of some flavonoids in the chemoprevention of cancers (Nair, 2004; Azadmehr , 2011).

2. CONCLUSION

According to the various results of studies in this area seems moreover chemotherapy drugs, flavonoids might be beneficial in the cancer treatment or inhibition (Hertzogi and Tica, 2012). Flavonoids induce apoptosis mechanisms in cancer cells. Polyphenols activate cell-death signalling pathways and stimulate apoptosis in cells before they become cancerous. Finally inhibit cancer development or progression (Hertzogi and Tica, 2012).

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