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Effect of Flavonoids in Preventing Breast Cancer: A Review

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Abstract

Epidemiological research has found a wide range of environmental and dietary risk factors for different cancers nowadays. The four most prevalent cancers—breast, colorectal, lung, and prostate—have all been linked to lifestyle factors in affluent nations. Flavonoids are a significant group of phenolic plant compounds made up of derivatives of 2-phenyl-benzopyrone. Flavonoids, foods such as fruits, vegetables, cereals, bark, roots, stems, flowers, tea, and wine include a group of chemical compounds with different phenolic structures. There are currently efforts being made to separate the purported flavonoids from the other components because these natural chemicals have numerous beneficial health effects. The various sources of flavonoids, their subclasses, and how they aid in the prevention of breast cancer will be outlined in this review article.

Keywords: *2-phenyl-benzo-γ-pyrone, breast cancer, fruits, phenolic compounds, vegetables, wine.*

1. Introduction:

Cancer is a disorder when some certain cells of the human body grow uncontrollably and spread to other body regions (Steck and Murphy, 2020). Without our knowledge numerous types of cancer including lung, breast, stomach, esophageal can occur anywhere of the body. The immune system of the body prevents these tumors to initially go away but if it does not happen then the tumor grows and damages the body and transforms into cancer (Nardin *et al*., 2020). The most prevalent type of cancer worldwide among those that are a concern for the entire world is breast cancer (Ferlay *et al*., 2021). Woman in their age of forties and fifties are likely to get breast cancer which has a mortality rate of 20% and morbidity rate of 30% (Petroni *et al*., 2021). Despite of developments in early detection techniques and comprehensive therapies of breast cancer survivors frequently battle with comorbidities brought on by ongoing treatment. Thats why finding new therapies and preventative measures is still essential for reducing breast cancer. According to epidemiological study a nutritious diet full of fruits and vegetables and a healthy body weight are linked to prevalence of breast cancer (Ferrini 2015;

Nattenmuller *et al*., 2018). Fruits and vegetable including in the dietary intake have some antioxidant effects like ascorbic acid tocopherols, carotenoids, phenolic compound (Pennington and Fisher, 2009). Flavonoids is also a group of polyphenolic compounds which mainly present in fruits and vegetable and cereals (Leopoldini *et al*., 2006). Due to phenolic nature, it is also known as antioxidant (Cao *et al*., 1997).

Breast cancer begins as a malignant tumor in breast cells. The likelihood of developing breast cancer might rise due to a variety of variables. Typically, breast cancer has two targets in its pathogenesis: (A) The steroid hormone [estrogen receptor] activates carcinogenic pathway (B) Epidermal growth factor (Waks and Winer, 2019). Breast cancer can also develop as a result of estrogen exposure since it alters the genes and damages DNA. Breast cancer develop as a result of immune system failure. Sometimes it can also be brought on by DNA flaws or cancer-causing genes like BRC-A1 and BRC-A2 (Panche *et al*., 2016).

2. Flavonoids and it's subclasses:

2.1 Flavonoid

Fruits& vegetables including in the dietary intake have some antioxidant effects, like - ascorbic acid tocopherols, carotenoids phenolic compound (Pennington and Fisher, 2009). Flavonoid is a group of polyphenolic compounds which mainly found in fruits, vegetables, and cereals (Leopoldini *et al*., 2006). Due to phenolic nature, it's also known as antioxidant (Cao *et al*., 1997).

2.2 Structure of flavonoid

Naturally flavonoids are producing from plant source and from their different parts (Havsteen, 2002). Alpinia galanga is an example of rich source of flavonoids, it's also a well-known medicinal plant in Southeast Asia (Jirovetz *et al*., 2003). In to the flavonoids molecule there is two a carbons aromatic rings (assembled in to two benzene ring). These two rings are attached with another third number, which is oxygen connected pyrene Ring, and formation a bridge like structure (c6-c3-c6). This flavonoid presented as a derivative of 2-phenyl-benzo-γ-pyrone (Barve *et al*., 2006; Symonowicz *et al*., 2012).

2.3 Sub classes of Flavonoids:

In the base of carbon skeleton structure of flavonoid is C6-C3-C6, flavonoids are structurally subdivided in major six groups. This groups are -flavanols or catechins, flavones, flavonol, flavanone, anthocyanins, isoflavones (Williamson *et al*., 2018).

2.3.1 Flavanols

In the list raw food charts flavanols are widely found into the simple form of Flavan-3-ols (Andúja *et al*., 2012). Types of fruit like pome fruit like apples, pears & stone fruit, berries are source of catechin. Green tea, legumes good source of gloocate chains. Coca, bean nuts are good source of anthocyanidins (Arts *et al*., 2000; Gu *et al*., 2004). Grape juice where is flavanol are present are shown that, they did not inhibit testosterone 8nduced cell proliferation, there was a synergistic inhibitory effect when it's combined with tamoxifen. The grape juice as a dietary intake helps in prevention on breast cancer by potentially improve response to the treatment of tamoxifen (Chen *et al*., 1998).

2.3.2 Flavones

Chemical structure of Flavones is 2- phenyl-1,4- benzopyrone with hydroxyl group (Tung *et al*., 2019). Flavones have very low dietary source, they are represented in to dietary source as - apigenin, luteolin. The source of flavones are celery, parsley, and artichoke (Crozier *et al*., 2006). Flavones have anti-cancerogenic effect flavones have shown and helps to inhibit tumor development in cancer cells by inducing apoptosis. (Apoptosis is a circular process help in removal of undesirable cells physiological helps in condition. In active apoptosis pathway in cancer cells through different mechanisms (Yan *et al*., 2017).

2.3.3 Flavonols

Chemical structure of flavonol is 3hydroxy-2-phenyl chromen-4-one. The major source of flavonoids is quercetin, kaempferol, myricetin, luteolin apigenin. Example are Apple berries, brassica capres, grape, onion tea, tomato. Flavonol have mechanical effects -17B-estradiol (E2), KEMas, a phytoestrogen, that inhibits the proliferation of MCF-7 breast cancer cells, and eliminating its effects. And after the treatment of the PMC42 line with KEM are from a relationship between the inhibition of proliferation and reduction into the expression of the Ki-67 antigen. Which helps in prevention of breast cancer (Kim *et al*., 2016).

2.3.4 Flavanone

Flavanone are mainly found in citrus fruits & fruit juices. The three major source of flavanone - eriodictyol hesperitin, naringenin. Dietary sources are tomatoes, orange lemon (Hu *et al*., 1999). Flavonone have anti-cancer properties, the flavanone naringenin and hesperitin are inhibited effect of HER2-TK, into their antitumor activity against HER2-positive tumors. Pinocembrin is another source of flavanone which reduced breast cancer by induces cell cycle and arrested MCF-7, SKBR3, and MDA-MB-231 cells into G2/M phase by downregulation process

of the pro-survival proteins as cyclinB1, Cdc2 and Bcl-2 **(Chandrika *et al*., 2021; Zhu *et al*., 2021)**.

2.3.5 Isoflavones

Legumes from the Fabaceae family are the principal food sources of isoflavones. Sources of daidzein, genistein, and glycitein include soybean (Glycine max) and red clover (Trifolium pratense), which also include formononetin and biochanin (Ko *et al*., 2014). Isoflavones have a negligible estrogenic effect. a result of their steroid composition. The isoflavone genistein, which is found in soy products, has a two-stage action on the ER found on breast cancer cells. One is that it enhances the growth of positive-ER breast cancer cells at low doses, whereas genistein inhibits the growth of breast cancer cells at greater concentrations. The second is the inhibition of a tyrosine kinase system, which can be used to stop excessive cell growth by blocking signalling pathways linked to tyrosine kinase receptors. Genistein prevents DNA topoisomerase from functioning (Varinska *et al*., 2015; Zalega *et al*., 2013; Ziaei *et al*., 2017).

2.3.6 Anthocyanin

Anthocyanin mainly presents in red-blue color of berries, fruits, and certain vegetables-based products, natural pigments of anthocyanin are blue, purple, red and orange colors present in fruits and vegetables. Strawberry, blueberry orange, apple, cabbage, cauliflower, ginger, peach, pepper is the example of Anthocyanidin. Blueberry source of anthocyanins and in the addition anthocyanin-pyruvic acid antiinvasive potential effect in both breasts. Grape seeds also promoted the pathway of CDKI Cip1/p21 and a decrease in CDK4, resulting is G1 arrested (Faria *et al*., 2010; Agarwal *et al*., 2000).

2.4 Effects of flavonoids in preventing breast cancer

Genetic makeup and age are adaptable risk factors for breast cancer while alcohol use, occupational exposure to tobacco, smoke and nutrition are adaptable risk factors (Ghasemzadeh and Ghasemzadeh, 2011). The factors that enhance the mortality rate of breast cancer patients include obesity, sedentary life style and unhealthy meals. It is controversial if eating foods high in polyphenols can prevent ERalpha+BC and ERalpha cells from growing whereas eating foods low in polyphenols can promote the growth of ERalpha+ cells (Briguglio *et al*., 2020). Flavonoid that has a preventive activity on both ER-positive and ER-negative cells can be beneficial against tumor because the majority of breast cancer cells are ER negative and positive (Poschner *et al*., 2019). Many biological and pharmacological actions such as antioxidative, antibacterial, antiviral and anti-inflammatory properties have been associated with phytocompounds such as flavonoid and phenolic acid (Middleton *et al*., 2000). A compound's antioxidant capability is determined by its structural characteristics such as the quantity and position of double bonds, hydroxyl groups and modification

such as coupling to sugar moieties (Kozikowski *et al*., 2003). Strong antioxidant like flavonoids stop the development of cells. Depending on the substance's ability to scavenge free radicals, cell development can be inhibited. In order to neutralize free radicals and chelate redox active metals and due to the structure, flavonoid function as antioxidant (Rice-Evans *et al*., 1995; Rice-Evans and Miller, 1996). Due to the antioxidant property flavonoids have been demonstrated to inhibit macrophage's ability to produce reactive oxygen species which in turn enhance the immune defence and lower the risk of breast cancer (Nicholas *et al*., 2007; Lin *et al*., 2007; Peluso *et al*., 2015).

A flavonoid called naringenin which is found in citrus fruits has comparable cytostatic effect on human BC cells. High flavone intake which is found in aromatic plants has been linked to decreased risk of BC (Fenga *et al*., 2016).

The majority of epidemic research conducted on human populations focuses on the isoflavones contained in soy products, saying that they are protective against breast cancer (Schwingshackl *et al*., 2014; Hui *et al*., 2013).

A dietary flavonoid called quercetin prevents tumor growth by impeding protein tyrosine kinase. Similar cancer cell lines show anticancer activity when exposed diosmin. In comparison to other polyphenols tangeretin, a flavone, has higher anticancer activity against melanoma cell lines (Veeramuthu *et al*., 2017; Rodriguez *et al*., 2002) human lungs cell line, human hepatoma and in breast cell lines. Lutein is one flavone that appears to also prevent prostate cancer cell growth and proliferation in addition to other types of cancer. A cancer preventive agent is kaempferol. Leukaemia, prostate, lung, pancreatic and specially breast cancer was some of the tumors types for which it was developed to inhibit the growth of tumor cells. In tumor cells, it recognizes the cell cycle. Most of the time, kaempferol is effective against angiogenesis. Breast cancer is prevented by anthocyanin-rich extract from black rice (Abdullah *et al*., 2018). Flavones have an inhibitory effect on several cancer cell types that affect apoptosis. Studies conducted both vivo and in vitro came to conclusion that flavanones like naringin, 2-hydroxyflavone and hesperidin enhance programmed cell death of cancer cells by activating death receptors and the mitochondrial and cascade-dependent pathway (Malik *et al*., 2003).

3. Conclusion:

There is evidence that a diet high in the polyphenol founds in fruits and vegetables can lower the risk of cancer. This review briefly discussed about that the different sources of flavonoid and their subclasses which are the polyphenolic compounds mainly present in plant source like fruits, vegetable and cereals and they are mainly reduce the risk of breast cancer by antioxidant activity, anti-carcinogenic effect, inhibiting apoptosis, reducing estrogen activity, and by inhibiting the growth of breast cancer cell.

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