Review Article

Flavonoids and breast cancer prevention as well as treatment: a review on growing evidence.

ABSTRACT

Background: There is mounting evidence linking certain lifestyle factors such as food, weight, and physical activity to an increased risk of breast cancer. Flavonoids are commonly used in traditional medicine. Plenty of studies have investigated the relationship between flavonoid consumption and breast cancer in humans. This review aimed to examine the association between flavonoids, each flavonoid subclass and the risk of breast cancer besides therapeutic use of flavonoids to break the multidrug resistance in breast cancer.

Materials and methods: Prospective cohort, case-control, and laboratory-based studies published between around 1990's to date and referred to the impact of flavonoids on breast cancer prevention, treatment, or other roles were included. Odd Ratio (OR)/Risk Ratio (RR) and Hazard ratio (HR) along 95% CI were carefully reviewed to reveal the association between different subgroups of flavonoids and breast cancer risk. Other adjustments (e.g. age, menopausal status, food habits, race, BMI, etc.) were also considered.

Results and discussion: The antioxidant properties of flavonoids, as well as their ability to inhibit apoptosis, suppress estrogen activity, and limit the proliferation of breast cancer cells, all contribute to a significant reduction in the risk of developing breast cancer.

Conclusion: There are linings enough that some polyphenolic compounds are found as effective drugs for treating breast cancer.

Keywords: Polyphenolic compounds; mammary carcinogenesis; antioxidants; multi-drug resistance (MDR); phytoestrogen; CYP1A1 inhibitors; ATP-binding cassette.

INTRODUCTION

Breast cancer (or mammary carcinogenesis) is the most frequently detected cancer in women worldwide. It has emerged as a growing global health concern in recent decades (Ganesan et al., 2022). According to GLOBOCAN (2020), the prevalence of new instances of breast cancer among women is expected to be 24.5% (Sung et al., 2021). The number of women who were diagnosed with breast cancer worldwide reached 2.3 million in the year 2020, leading to 685,000 confirmed deaths. With 7.8 million confirmed cases in the previous five years, breast cancer exceeded all other cancers in terms of prevalence by the end of 2020 (WHO, 2023). Human mammary carcinoma is the consequence of cumulative exposure of the mammary cells to endogenous estrogens (Colditz, 1998). Having greater levels of estrogen is associated with an increased chance of developing breast cancer. A wide variety of biological processes, including cell proliferation, cancer progression, apoptosis, and others, are made easier as a result of the interaction between estrogen and the estrogen receptor that is present in breast cells. This phenomenon is the result of this interaction (Thomas and Gustafsson, 2011). The Estrogen Receptor primarily occurs in two distinct forms: Estrogen Receptor-α and Estrogen Receptor-β. Estrogen receptor-α (ER-α) is mostly found in the uterus, vagina, mammary gland, liver, and pituitary gland (Takahashi et al., 1998).

Diet is the most pronounced modifiable factor for breast cancer occurrence, recurrence, and mortality (Hamer and Warner, 2017). Several studies in the last few decades have looked at the relationship between breast cancer and certain foods, such as beans, endive, tomatoes, strawberries, grapes, meat, soy products, and a variety of vegetables, fruits, and teas (Peterson and Dwyer, 1998). Jang H. *et al.* in 2018 reported an association between anti-inflammatory diets and cancer recurrence as well as overall mortality in breast cancer patients. Experimental evidence suggests that flavonoids can both inhibit and stimulate a wide array of enzyme systems found in mammals. Enzymes like these have an impact on processes including cell proliferation and division, detoxification, platelet aggregation, inflammation, and immunological responses (Franke et al., 1998). Flavonoids have gone under number of investigations for their anti-carcinogenic mechanisms and antiproliferative effects on human lymphocytes as well as breast cancer cells and have also been reported (Peterson et al., 2003). Laboratory and animal studies suggest that dietary flavonoids may be protective against breast cancer risk. On the other hand, there are limited epidemiological studies on this concern. An increased consumption of fruits and vegetables rich in flavonoids has been linked to a decreased risk of cancer, according to data from epidemiological studies. Which bioactive chemicals, if any, are responsible for this correlation remains unknown. This review aims at a clear idea about the 1990-to-date study pattern, interest in flavonoid subclasses, and major findings in both epidemiological and laboratory-based studies.

What is breast cancer?

Cancer is a cluster of abnormally grown/growing cells in a tissue. This anomaly is caused by a genetic mutation or other environmental factors that let them divide/grow out of control. These out-of-control cells form ball-shaped lumps of mutated tissue which is termed as tumor(s). When these forms of tumors are from breasts, they're classified as breast cancer. Most breast cancers begin in the milk glands (lobules) or the tubes (ducts) by which the nipple is connected to the milk glands. According to WHO (2023), the female gender has come up as the strongest risk factor for the occurrence of breast cancer. But in males, 1% or less of breast cancer cases are occurred. The main variables that increase the likelihood of breast cancer, both in terms of incidence and mortality, include being older (40 or older), having a higher body mass index (BMI), smoking, not being physically active, eating a diet rich in fat, experiencing menstruation at a young age, having a first full-term pregnancy late, breastfeeding for shorter periods or not at all, using oral contraceptives, using menopausal hormone therapy, breast density, and genetic predisposition (Zhang et al., 2020). A woman's chance of getting breast cancer is increased by both behavioral and genetic factors. Age (above 40 years), family history of cancer, hormone levels (late menopause or early menarche), dense breast tissue, race, and genetics (particularly, mutations in the genes BCRA1 and BCRA2, TP53, and genes encoding enzymes involved in estrogen metabolism pathways COMT, CYP1A1, CYP1B1, estrogen receptors ERα/ERβ, CYP17A1, and CYP19A1) are some of the immutable factors. Some examples of lifestyle issues are obesity, abortion, using birth control pills, or not having children at all (Anderson et al., 2014). Signs and symptoms of breast cancer include; thickening or lump in the breast, sometimes without pain, change in overall appearance (size and shape) of the breast, creek, reddish appearance, pit, or other changes in the skin, change in the physiognomy of nipples or areola (the darkish area around the breast), and abnormal fluid (may be bloody) from the nipple (WHO, 2023).

Molecular subtypes of breast cancer

Physiologically, the human female mammary gland is under the primary control of different hormones. It is established that among them, estrogen appears to play the central role. There are mainly four molecular subtypes of breast cancer, characterized by hormone receptors (HR) in addition to protein involvement (or not involvement) in each cancer: (I) Luminal A or HR+/HER2- (HR-positive/HER2-negative), (II) Luminal B or HR+/HER2+ (HR-positive/HER2-positive), (III) HER2 enriched and (IV) Triple-negative (TNBC) or basal-like (HR/HER2-negative) (Fragomeni et al., 2018). Each of the subtypes of breast cancer is described in Table 1, which includes their characteristics.

Table 1: Distinctive characteristics of the various subtypes of breast cancer

Attribute	Luminal A	Luminal B	HER2	TNBC	References
Frequency (%)	50	15	20	15	Barzaman et al., 2020
ER	Yes	Yes	Some cases	No	Gao and Swain, 2018

PR	Yes	Some cases	Some cases	No	Barzaman et al., 2020
HER	No	No	Yes	No	Engel and Kaklamani, 2007
Mutations	No	BRCA2	p53	p53 and BRCA1	Duffy et al., 2018
Prognosis	Good	Middle	Middle/Bad	Bad	Ahrn et al., 2014
Therapy	Hormonal	Hormonal / Chemo	Hormonal/Chemo/ Herceptin	Chemo/ Experimental	Loibl and Gianni, 2017
ER: estrogen receptor, PR: progesterone receptor, HER: human epidermal receptor, HER2: human epidermal growth factor receptor 2, and TNBC: triple-negative breast cancer					

Cancer Growth and Clinical Stages

The female breast consists of 15 to 20 lobes of tissue, each of which contains lobules that house milk-producing glands and ducts. The nipple receives milk from the lobules via the ducts. Cancers can begin anywhere. However, the lymph nodes are often the sites of spreading after beginning in the ducts or lobules. Lymph nodes are like bus stations for cancer cells; they transport the disease throughout the body. There are many lymph nodes close to the breasts- around the chest, neck, and armpits. Cancer can spread regionally to these nodes from the breasts (Regionally spreading). Metastatic breast cancer spreads beyond those nodes. During diagnosis with breast cancer, cancer is categorized termed as "staged". Staging lets healthcare providers to make decision on treatment mechanisms and conditions after treatment. There are three distinct categories used to classify breast cancer stages: clinical prognostic, pathologic, and anatomic.

1. **Clinical prognostic stage**:

Based on tumor size, lymph node colonization, and metastasis, the American Joint Committee on Cancer assigned breast cancer a stage ranging from 0 to IV in the AJCC Cancer Staging Manual (Eighth Edition) of the American College of Surgeons (ACS). A greater number indicates that the cancer has spread to more parts of the breast and blood vessels. As a preliminary step, it uses the patient's medical history, physical exam, imaging results (if any), and biopsies to determine the patient's diagnostic stage. Based on tumor grade, TNM system, and biomarker status (ER, PR, HER2), the Clinical Prognostic Stage is determined. Clinical staging involves evaluating the lymph nodes for malignancy using imaging techniques like mammography or ultrasound. The "TNM" system is another name for this staging method. Where "T" denotes the cm-scale tumor size, the number of lymph nodes impacted by malignancy, denoted as "N", and "M" stands for "metastasis," where 0 means no spread and 1 means cancer has spread to other organs. The TNM system is the most often used staging system for breast cancer.

Table 2: TNM classification of breast cancer (Alfonse et al., 2014; Gaur, 2013)

Overall Stage	T category	N category	M category	Additional Information
Stage 0	Tis	N0	M0	• Non-invasive breast cancer
Stage I	T1	N0	M0	• Invasive breast cancer
Stage IIA	T0	N1	M0	• Invasive breast cancer • Pain in the nipple(s) • Dry or flaky nipples or breast skin
	T1	N1	M0	
	T2	N0	M0	
Stage IIB	T2	N1	M0	
	T3	N0	M0	
Stage IIIA	T0	N2	M0	• Invasive breast cancer. Reddening, dimples, or puckering of the breast skin • Unexplained rash, nipple non-milk fluid • Lump under arms or in breast(s)
	T1	N2	M0	
	T2	N2	M0	
	T3	N1	M0	
	T3	N2	M0	
Stage IIIB	T4	Any N	M0	
Stage IIIC	Any T	N3	M0	
Stage IV	Any T	Any N	M1	• Inflammatory breast cancer. • Bones, lungs, brain, liver, distant lymph nodes, and chest wall are all impacted as well

Tx: The tumor can't be measured or found **T0:** No evidence of the primary tumor
Tis: The cancer is "in situ"
T1: Tumor size < 2 centimeters
T2: Tumor size is 2 - 5 centimeters
T3: Tumor size >5 centimeters
T4: Tumor of any size has broken through the skin, or is attached to the chest wall
Nx: The nearby lymph nodes can't be measured or found
N0: Nearby lymph nodes are not affected
N1: Metastasis to movable, same-side, axillary (armpit) lymph node(s)
N2: Metastasis to same-side lymph node(s) fixed to one another or other structures
N3: Metastasis to same-side lymph nodes beneath the breastbone
Mx: Metastasis can't be measured or found.
M0: There are no distant metastases
M1: Distant metastases were found

Clinical and pathologic breast cancer staging systems were incorporated into the most recent AJCC cancer staging system in January 2018.

2. **Pathological prognostic stage (also called surgical staging)**

This staging system is used for patients who have surgery as their first treatment. Laboratory data from lymph nodes and breast tissue that were removed after surgery, along with all available clinical information and biomarker status, are used to determine the Pathological Prognostic Stage.

3. **Anatomical stage**

This is based on the TNM system (size and spread of tumors). In regions without access to biomarker testing, the anatomic stage is utilized.

Breast cancer scenario worldwide

Taking aside lung cancer from the title of “most commonly diagnosed cancer globally”, breast cancer has emerged as the most prevalent cancer type. The year

2020 had an estimated 2.3 million cases and 685,000 fatalities due to breast cancer and among eight cancer diagnoses one cancer case was diagnosed as breast cancer case (Sung et al., 2021)**.** Over 2.3 million new instances of breast cancer are added annually. As more and more instances have been reported, breast cancer has outpaced all others among adults. More than 95% of countries have determined that breast cancer is either the first or second major cause of mortality among females due to cancer (WHO, 2023). The majority of countries throughout the world have breast cancer as their primary cause of mortality and morbidity in the year 2020. Breast cancer was responsible for more than a quarter of all cancer diagnoses in women and approximately fifteen percent of all deaths that were caused by cancer (Sung et al., 2021). Low- and middle-income nations account for almost 80% of breast cancer and cervical cancer deaths because of their larger populations (WHO, 2023). By 2070, the anticipated number of breast cancer cases will have risen to 4.4 million (Soerjomataram and Bray, 2021).

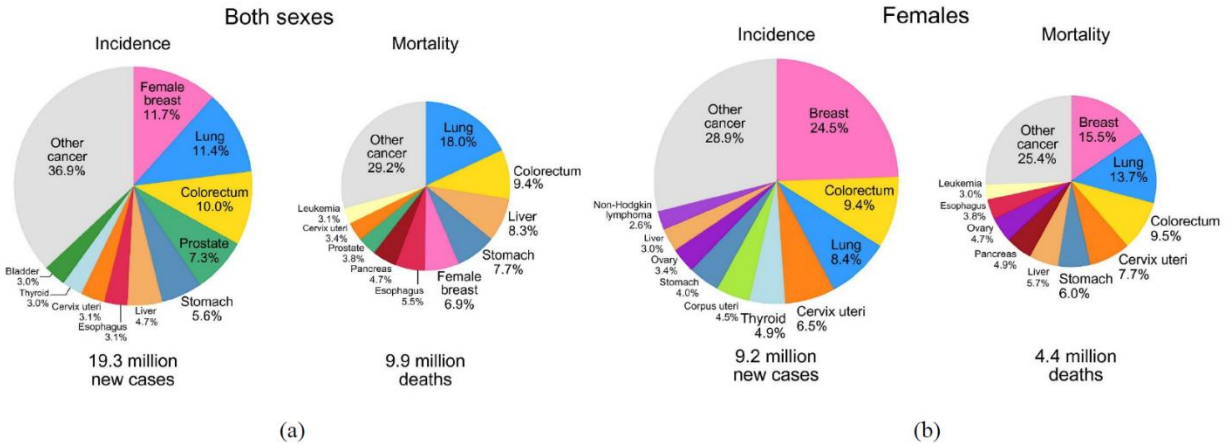

Figure 1: Death and case distributions for the 10 most frequent malignancies in 2020; (a) Both sexes and (b) Females. The percentage of cases or deaths is shown by the area of the pie chart. The "other" group includes nonmelanoma skin cancers, which do not include basal cell carcinoma for incidence. Data source: GLOBOCAN 2020. Pie chart: Sung et al., 2021.

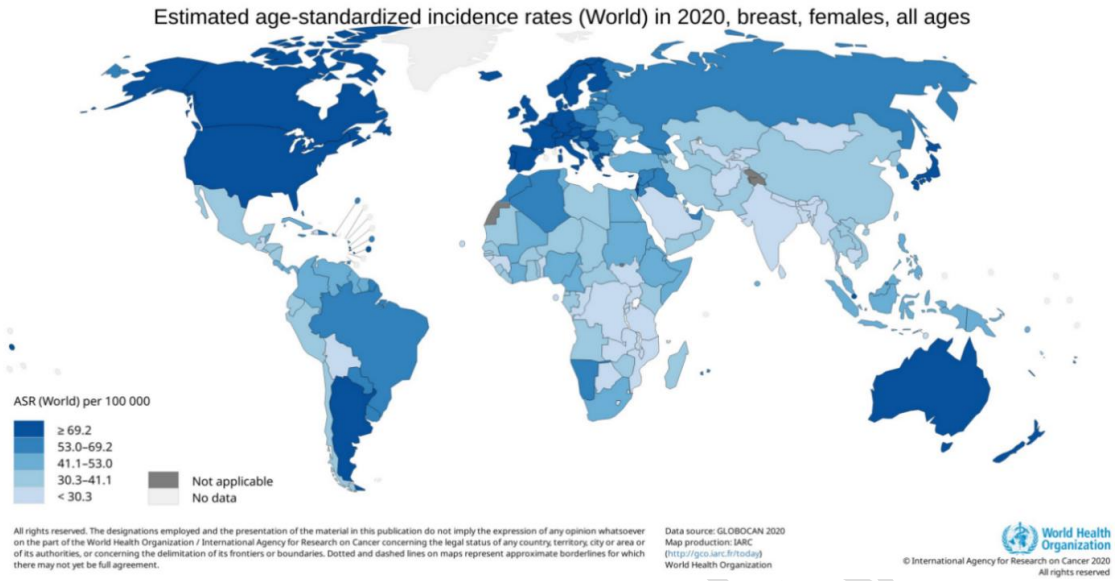

Figure 2: Estimated age-standard female breast cancer incidence rates in 2020. Data source: GLOBOCAN 2020, Map production: IARC, World Health Organization.

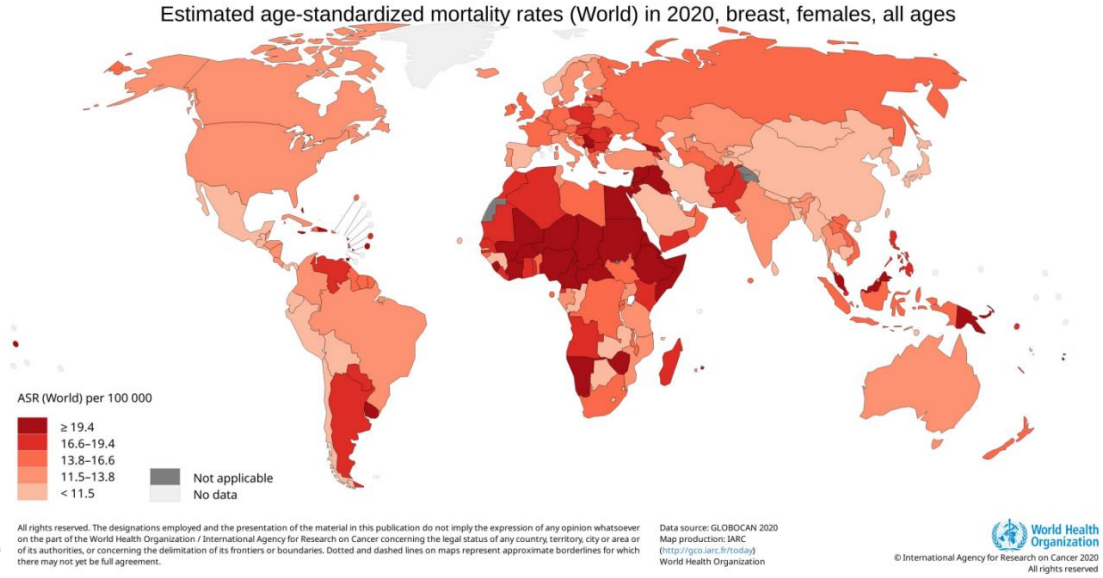

Figure 3: Estimated age-standard female breast cancer mortality rates in 2020. Data source: GLOBOCAN 2020, Map production: IARC, World Health Organization.

Flavonoids, Classification, and Distribution

Flavonoids, whose name derives from the Latin word "flavus" signifying yellow, are ubiquitous secondary metabolites found in plants. They are most recognizable as the anthocyanin pigments, which are red, blue, and purple in color, that cover plant

tissues (Winkel-Shirley 2000). Flavonoids generally consist of a 15-carbon skeleton comprising two benzene rings joined by a 3-carbon linkage chain (Navabi et al., 2018). They are therefore shown as C6-C3-C6 compounds. The production of these compounds is accomplished by two distinct pathways: the shikimic acid pathway and the acetate pathway (Navabi et al., 2018). Over six thousand distinct flavonoids have been identified. These chemicals are found in many different types of plants and serve multiple purposes, including protecting plants from various biotic and abiotic challenges, acting as signal molecules, detoxifying the body, and fighting microbes (Liu *et al.* 2021). The degree of oxidation, the connection location of ring B, the annularity of ring C, and the position of hydroxy groups in the carbon skeleton all contribute to the classification of flavonoids into several subgroups, which include isoflavones, flavones, flavonols, flavanones, flavanonols, and flavones (Wang et al., 2018). Because of their extraordinary health advantages, foods rich in flavonoids are called superfoods. Beverages, fruits, vegetables, cereals, beans, nuts, and tea make up the vast majority of these plant-based items (Harborne and Williams, 2000). Westerners get most of their flavonoids from wine, while Easterners get most of theirs from tea. Green vegetables, onions, apples, berries, cherries, soybeans, and citrus fruits are also believed to have a high concentration of dietary flavonoids (Butt et al., 2014).

Flavonoid biosynthesis in plants

The shikimate, phenylpropanoid, and polyketide pathway is the main pathway for higher plant species to synthesize flavonoids. These processes lead to the formation of numerous different types of flavonoids, with chalcones and flavanones serving as intermediates (Rehan, 2021). Plant species and sets of enzymes including hydroxylases, reductases, and isomerases are essential for this principal process to generate different forms of flavonoid skeletons. The flavanone is the progenitor of many flavonoid groups, including anthocyanins, isoflavonoids, and proanthocyanidins, which are condensed tannins (Figure 4). Typically, the phenylpropanoid pathway is where flavonoid synthesis gets started. Following the completion of the shikimate pathway, the phenylpropanoid pathway will eventually start. Erythrose 4-phosphate and phosphoenol pyruvate condense, which is the first step in the shikimate pathway.

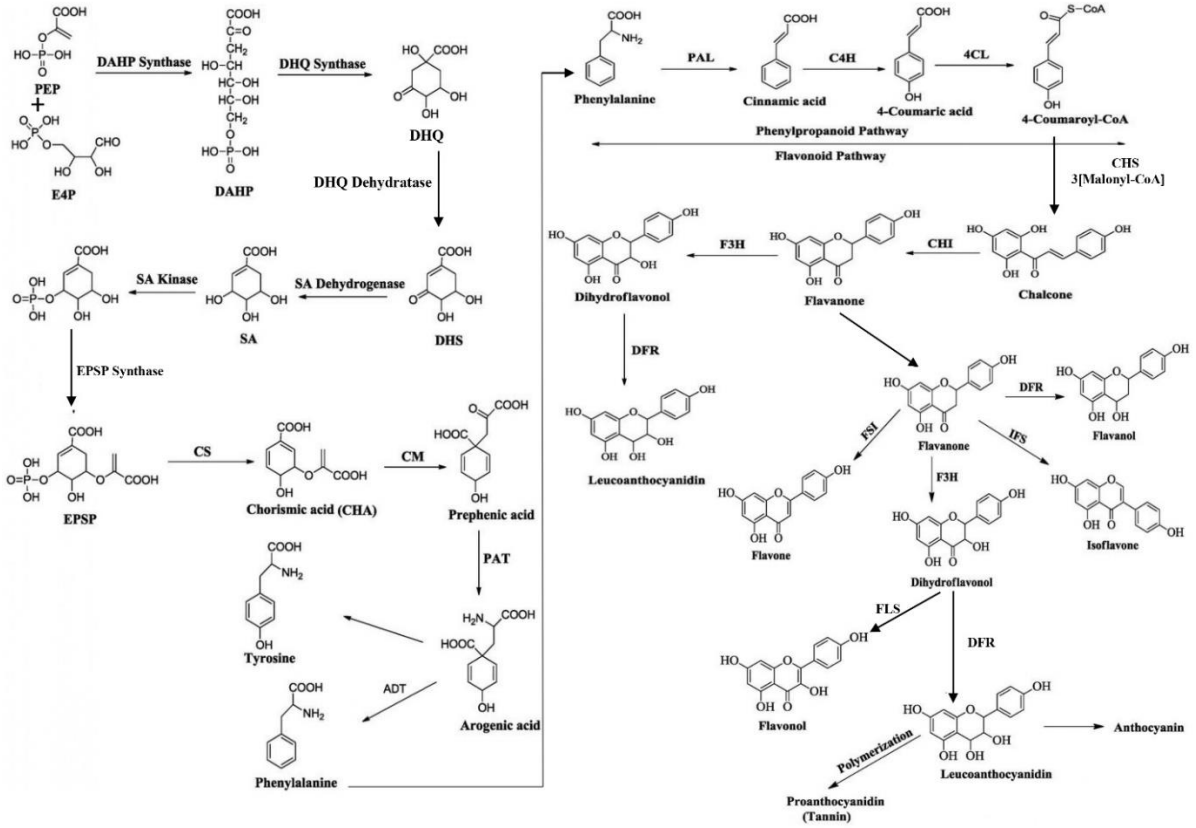

Figure 4: Biosynthesis of various classes of flavonoids through the phenylpropanoid and shikimate pathways (Rehan, 2021).

METHODOLOGY

Selection of articles: Article search was performed in PubMed and Google Scholar using combinations of keywords relating to “breast cancer” AND (“dietary flavonoids” OR “flavonoids rich foods” OR “flavonols” OR “flavonones” OR “anthocyanidins” OR “flavones” OR “isoflavones” OR “soy flavonoids” OR “quercetin” OR “flavonoid subclasses” OR “polyphenolic compounds” OR “flavonoids rich foods” OR “flavonoids rich fruits and vegetables”) AND (“preventive role” OR “treatment” OR “flavonoids in drug” OR “flavonoids as chemoprotective agent”) etc.

Inclusion criteria: The eligible criteria included studies in the English language published between around 1990’s to date. Prospective cohort, case-control, and laboratory-based studies that referred to the impact of flavonoids on breast cancer prevention, treatment, or other roles were included. Titles and abstracts were independently screened. Hence, I included articles that linked flavonoids to (a) breast cancer incidence, (b) breast cancer-specific mortality, (c) the role of flavonoids, (d) therapeutic use of flavonoids, (e) multidrug resistance, etc.

The menopausal phase, cancer subtype, and type of anti-cancer medication received by patients were not subject to any restrictions.

Retrieval of information: Odd Ratio (OR)/Risk Ratio (RR)/Hazard ratio (HR) along 95% CI and p-value were carefully reviewed to reveal the association between different subgroups of flavonoids and breast cancer risk. Other adjustments (e.g. age, menopausal status, food habits, education level, race, BMI, multi-vitamin use, smoking habit, energy intake, age at first live birth, physical activity level, lifetime lactation, etc.) were also considered.

How flavonoids fight against breast cancer

Flavonoids, a plant source of polyphenolic compounds have grown its evidence from the 1990's to date that can fight against breast cancer.

1. Flavonoids as antioxidants

Flavonoids demonstrate their antioxidant action in a variety of ways, including activating antioxidant enzymes, scavenging reactive oxygen species (ROS), metal-chelating activity etc. Enzymes including catalase, glutathione peroxidase (GPX), and superoxide dismutase (SOD) constitute the backbone of this antioxidant defense system; they deactivate free radicals generated by metabolic processes. (Jeeva et al., 2015). In 1999, Nacaia *et al.* demonstrated that flavonoids' intracellular antioxidative effect is dependent on their interaction with GSH-PO, at least in cells expressing the enzyme, and concluded that quercetin and catechin-activate glutathione peroxidase (GSH-PO) clearly. Superoxide dismutase (SOD) levels were increased and glutathione peroxidase (GPx) levels were potently decreased upon intraperitoneal dose of catechins.

Flavonoids, being polyphenols, have a high reactivity due to the hydroxyl substituents, which makes them effective at scavenging free radicals through a process called hydrogen atom abstraction (Korkina, and Afanas'Ev, 1997). Flavonoids possess the ability to effectively capture the highest levels of active solar wavelengths (namely, UV-B and UV-A). Not only that, but they are equally adept at halting the creation of ROS and removing them once they've formed (Agati et al., 2012). Troxerutin, a flavonoid, exhibited its cytoprotective efficacy by protecting various cell types (intestinal epithelial cells, fibroblasts, and lymphocytes) against oxidative stress (Panat et al., 2016). The antioxidant properties of silibinin and quercetin stem from their capacity to bind to iron or copper ions and inhibit oxidases, in addition to scavenging free radicals and other oxidizing chemicals (de Groot and Rauen, 2009). Diniz *et al.* in 2015 suggested that flavonoids have the potential for neuroprotection in epilepsy.

Rutin and quercetin were found to be more effective in suppressing iron ion-dependent lipid peroxidation systems due to their ability to form stable compounds with iron ions, which are incapable of initiating lipid peroxidation (Afanas'Ev et al., 1989). Apigenin, luteolin, kaempferol, quercetin, myricetin, and rutin, isoflavones (daidzein and genistein), flavanones (taxifolin, naringenin, and naringin; and catechin) were found to have a greater ability to reduce copper ions compared to iron ions (Mira et al., 2012).

2. **Flavonoids as phytoestrogens:**

High consumption of phytoestrogens can result in increased amounts of phytoestrogens in the bloodstream, which have been empirically shown to exhibit estrogen-like actions. Breast cancer risk is lower in women who regularly consume phytoestrogens, especially throughout childhood (Lee et al., 2009). Korde *et al.* in 2009 also concluded a correlation

between breast cancer risk reduction with higher soy consumption during childhood, adolescence, and adulthood the most potent protective effect was shown in childhood. According to Rice and Whitehead (2006), phytoestrogens have the ability to change estrogen production by inhibiting aromatase (known as cytochrome P450 19 aromatase (Cyp19)) as well as 17β-hydroxysteroid dehydrogenases (HSD), estrone sulfatase, and sulfotransferase. In breast tissue, these enzymes play a role in the generation of estradiol, and when they are overexpressed, they are associated with an increased risk of breast cancer. Research has shown that a number of flavonoids can significantly lower estrogen levels in the blood. They may be useful in treating malignancies that are resistant to other treatments, even though their efficacy is lower than that of steroidal aromatase inhibitors often employed in clinical practice.

3. Flavonoids as CYP1A1 inhibitors/substrates

Inhibiting CYP1A is a plausible approach to preventing the development of cancer. The selective metabolism of dietary flavonoids by CYP1 enzymes, resulting in the production of conversion products that limit the proliferation of cancer cells, is the key mechanism behind cancer prevention. Cytochrome P450 enzymes (CYP450s) are the primary enzyme group accountable for the metabolism and detoxification of foreign substances, which are commonly referred to as xenobiotics. They are also involved in the biosynthesis as well as metabolism of endogenous compounds like fatty acids and steroids. CYP450s in the liver where they are highly expressed catalyze reactions that are responsible for converting lipophilic compounds into more hydrophilic derivatives. Most drugs follow this biotransformation pathway to be catabolized and eliminated from the body (Gonzalez, 1988). But other xenobiotic substances, such as dietary flavonoids, can modulate the CYP450 enzyme function, either increasing or decreasing the catalytic activity. As a result, drug detoxification or functionality could be interrupted (Hodek et al., 2002).

It has been established that the CYP1 family is involved in the process of carcinogenesis and the advancement of cancer and demonstrated through several research that flavonoids, such as resveratrol, have the ability to effectively inhibit the activation of CYP1 in both in-vivo and ex-vivo environments because of their function as competitive antagonists for the aryl hydrocarbon receptor AhR, which plays a role in the activation of CYP1 expression (Ciolino et al., 1999). For instance, quercetin and myricetin are potent CYP1B1 inhibitors, but they appear to have a lesser impact on the CYP1A1 and CYP1A2 variants (Arroo et al., 2009).

4. Flavonoids as ABC (ATP-binding cassette) transporter regulators

ATP-binding cassette superfamily comprises P-glycoprotein (P-gp), ABCG2, multidrug resistance proteins 1 and 2 (MRP1 and 2) and breast cancer resistance protein (BCRP). Several xenobiotic-related compounds rely on these membrane proteins for absorption, distribution, and excretion. These transporters are essential for the distribution of pharmaceuticals often used in medical therapy, and they are the principal family responsible for removing drugs from cells (Tan et al., 2013). In recent years, there has been a significant amount of focus placed on the role that ATP-binding cassette (ABC) transporters play role in the biology of cancer cells (Nobili et al., 2019) and for this reason they are the subject of substantial investigation. The development of multidrug resistance, which is predominantly driven by factors related to ABC transporter genes, is the primary

obstacle that stands in the way of effective cancer treatment. There are several examples of ATP-binding cassette (ABC) transporters that impart resistance to particular chemotherapy medications. Some of these transporters include breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), and multidrug resistance-associated protein 1 (MRP1). Intestinal efflux ABC (ATP binding cassette) transporters, some of which include P-glycoprotein, breast cancer resistance protein, and multidrug resistance-related proteins, perform the function of "pumping doors" to regulate the elimination of flavonoids from intestinal epithelial cells into either the intestinal cavity or the systemic circulation. Breast cancer resistance protein (BCRP) is an ATP-binding cassette transporter that has recently come to light due to the report that it can regulate drug disposition and induce multidrug resistance (MDR) to certain important anticancer treatments. Flavonoids serve as inhibitors of transporters and restrict the ATP hydrolysis activity that leads to the elimination of anticancer drugs from tumor tissues (Zhang et al., 2004). Presumably, this occurs through the interaction with the nucleotide-binding domain (NBD), which is the specific site of action for flavonoids in both BCRP and P-gp (Morris and Zhang, 2006). The complete understanding of the interaction between flavonoids and BCRP, despite their ability to effectively modify medication pharmacokinetics, remains incomplete.

5. Flavonoids' impact on cell death, cell cycle reversal, and other signaling mechanisms

Flavonoids are well acknowledged for their significance as anti-carcinogenic substances and have shown remarkable efficacy as cytotoxic anti-cancer medicines, triggering apoptosis in most cancer cells. A number of flavonoids have shown promise in inducing cell death in cancers, including breast cancer (Huang et al., 2012) via means of the two primary apoptotic pathways: internal apoptosis involving caspase-9 and mitochondria, and extrinsic apoptosis involving caspase-8 and death receptors (Kamsteeget al., 2003). Brusselmans *et al.* proposed the ability of flavonoids to inhibit fatty acid synthase (FAS) is closely linked to their potential to cause apoptosis in cancer cells.

6. Effect of flavonoids on multi-drug resistance

The primary factor contributing to the failure of the majority of cancer chemotherapy is drug resistance. The fundamental cause of chemoresistance is believed to be the dysregulation of the epigenetic machinery. It was reported that the dysregulation of DNA methylation in resistant cancer cells leads to the abnormal expression of genes involved in cancer proliferation, apoptosis, DNA repair, and drug efflux. The dysregulation of many enzymes that catalyze histone post-translational modifications can also lead to changes in chromatin structure. Moreover, expression of numerous drug-resistance genes is regulated by this imbalance. Alterations in the patterns of microRNA play a role in the development of drug resistance in cancer cells (To Kenneth and Cho, 2021). Curcumin, stilbenes, ellagitannins, phenol carboxylic acids, and flavones are all examples of phytochemicals that possess antioxidant, anti-inflammatory, and anti-cell-growth activities. These features make them useful chemo-preventive agents. In addition to this, they prevent the development of new blood vessels and the spread of cancer cells, regulate immune and inflammatory responses, and deactivate substances that can cause cancer. Furthermore, preclinical and clinical investigations have revealed that these drugs successfully change several pathways, which prevents cancer from developing multidrug

resistance (Costea et al., 2020). Researchers are now interested in the effect of flavonoids on drug resistance in chemotherapies. To overcome treatment resistance in breast cancer, flavonoids have been suggested as a potential medication by many studies. According to Rao et al. (2012), luteolin effectively reverses multidrug resistance (MDR) in breast cancer cells that are resistant to mitoxantrone.

Table 3: **Summary of epidemiological studies investigating the association of flavonoid intake with breast incidence and mortality.**					
Author(s)	**Method**	**Subject(s)**	**Cancer type**	**Exposer**	**Conclusion**
Zheng et al., 1998	Case-control study Structured questionnaire Urinary excretion rates In-person interviews	Sixty (60) breast cancer cases and individually matched controls examined for rates of excretion in urine Face-to-face interviews conducted for 746 urbane Chinese women in Shanghai	Breast cancer	Total phenols and five major isoflavonoids (glycitein, daidzein, genistein, equol and *O*-desmethylangolensin)	● Breast cancer cases had lower urinary total phenols and all isoflavonoids. ● The disparity between the case and control groups became more apparent when comparing the median levels of these compounds ● Individuals with the greatest levels of daidzein, glycitein, and total isoflavonoids had around 50% lower risk of cancer compared to those with the lowest levels.
Horn-Ross et al., 2001	Case-control study Food Frequency Questionnaire (FFQ) Ontario phytoestrogen database Multivariate logistic regression	1,326 cases and 1,657 controls non-Asian US women (35–79 years) residing in the San Francisco Bay Area	Breast cancer	Isoflavones, total isoflavones, lignans, total lignans, total phytoestrogens	● Phytoestrogen was found not to be protective against breast cancer risk (odds ratio = 1.0 and 95% CI = 0.80, 1.3 for the highest versus lowest quartile)
Peterson et al., 2003	Case-control study in Greece Semi-quantitative food frequency questionnaire US Department of Agriculture-Iowa State University Database	820 women diagnosed with breast cancer against 1548 control women	Breast cancer	Flavones, flavonols, flavanones, flavan-3-ols, isoflavones and anthocyanidins	● A significant negative correlation between flavone consumption and breast cancer was observed. The odd ratio for an increment in daily flavone consumption equal to one standard deviation (0.5 mg/day) was 0.87 (95% CI = 0.77, 0.97.
Silva et al., 2004	Case-control study Face-to-face interview with food frequency questionnaire (FFQ) Conditional logistic regression models	240 South Asians diagnosed with breast cancer residing in England against 477 population-based controls matched for age	Breast Cancer	Total isoflavones, (genistein, daidzein) as well as total lignans (secoisolariciresinol,matairesinol)	● After controlling for known and established risk factors for breast cancer, there is moderate evidence of a dose-response relationship between isoflavone consumption and the likelihood of developing breast cancer (P value for trend 0.08).

Bosetti et al., 2005	Case-control study Standard structured questionnaire Food Frequency Questionnaire (FFQ)	2,569 women with histologically confirmed breast cancer and 2,588 hospital controls (age range 23-74 years, median age 55) from six Italian areas	Breast Cancer	Flavanones, flavones, anthocyanidins, flavan-3-ols, flavonols, and isoflavones	● Increased intake of flavones reduced the risk of breast cancer (OR = 0.81 for the highest versus the lowest quintile with a P-trend of 0.02). ● Significant association of risk reduction of breast cancer was not found for other flavonoids
Fink et al., 2006	Case-control study Interviewed about known as well as suspected risk factors Food Frequency Questionnaire (FFQ)	1,434 female cases (English-speaking and newly diagnosed with breast cancer) and 1,440 control. Both are from Long Island, New York, USA	Breast Cancer	Flavonols, flavan-3-ols, flavones, flavanones, isoflavones, lignans anthocyanidins,	● Flavonoid intake was associated with breast cancer risk reduction. ● The reduction was most pronounced among postmenopausal women for flavonols (odds ratio (OR) ¼ 0.54 with 95% CI = 0.40, 0.73).
Cotterchio et al., 2007	Case-control study Block food frequency questionnaire (FFQ) expanded to include foods containing phytoestrogen	3,063 breast cancer cases (age range 25-74 years and diagnosed in 2002 and 2003) and 3430 controls were identified by using the Ontario Cancer Registry	Breast cancer	Lignans and isoflavones	● Lignan intake was found to be effective in reducing breast cancer risk. ● A significant reduction in breast cancer risk was observed in overweight pre-menopausal women who had a high consumption of phytoestrogens
Cutler et al., 2008	Prospective cohort Food frequency questionnaire Food composition databases Baseline questionnaire (1985) and 5 follow-up questionnaires (1987, 1989, 1992, 1997, 2004) Followed for cancer incidence from 1986 through 2004	34,708 postmenopausal women (55-69 years) in the Iowa Women's Health Study	Pancreati, lung, breast, colorectal and upper aerodigestive cancer	Seven flavonoid subclasses along with total flavonoids	● Isoflavone intake and overall cancer incidence were inversely associated (HR = 0.93; 95% CI = 0.86−1.00).
Torres-Sanchez	Case-control study	A total of 198 women with breast cancer (age range 21–79	Breast cancer	Onion, lettuce, tea, apple, and spinach	● The adjusted odds ratio was 0.27 (95% CI = 0.16, 0.47) with a statistically significant

et al., 2009	Semiquantitative food frequency questionnaire (FFQ) Logistic regression models	years) and age-matched control (±3yr) for each case			trend (P<0.001) for the consumption of more than one slice of onion per day. ● Consumption of lettuce and spinach had a substantial preventive impact.
Ha et al., 2009	Cross-sectional study Dietary questionnaire	128 women aged 40–79 year and newly diagnosed with invasive breast cancer.	Breast cancer	Isoflavonoids and lignans	● The chance of getting a cancer diagnosis at any stage other than stage 1 was 32% lower in women who consumed a higher level of phytoestrogens.
Pantavos et al., 2014	Prospective cohort study Semiquantitative FFQ Ferric reducing antioxidant potential (FRAP) Follow-up of 17 years Crude and multivariate Cox proportional hazard models	Women aged 55 years and older (n = 3,209) and 199 breast cancer cases, identified from the Rotterdam study	Breast cancer	Vitamin A, C and E, selenium, flavonoids and carotenoids	● No correlation between total antioxidant intake and the risk of breast cancer was found. ● A reduced consumption of flavonoids was linked to an increased risk of breast cancer in women aged 70 and above (HR = 1.80; 95% CI = 1.09, 2.99).
Wang et al., 2014	Prospective cohort study Self-administered questionnaires Modified Willett FFQ Cox proportional hazards regression	56,630 postmenopausal women from the CPS-II Nutrition Cohort were included in the analytical cohort	Breast cancer	Total flavonoids anthocyanidins flavan-3-ols flavanones flavones etc	● Total flavonoid intake was not associated with breast cancer risk. ● Despite this, the total risk of breast cancer was somewhat inversely related to flavone consumption.
Feng et al., 2020	Case-control study Food frequency questionnaire (Face-to-face) Multivariable logistic regression models.	1522 breast cancer cases and 1547 frequency-matched controls (both cases and controls ar**e** selected Chinese population)	Breast cancer	Total flavonoids anthocyanidins flavanols flavan-3-ol etc.	● After considering possible influencing factors, a clear inverse relationship was shown between the risk of developing breast cancer and the intake of various types of flavonoids,

Table 4: Summary of laboratory-based studies investigating the association of flavonoid intake with breast incidence and mortality.

Author	Cell line	Model	Flavonoids exposer	Conclusion
Miksicek, 1993	MCF7, HeLa, COS-7	Transfection studies, competition binding studies	Chalcones, flavanones,	● Selected hydroxylated flavonoiods interacted directly with the estrogen receptor based on their ability to

			flavones, and isoflavones	compete for binding 17β-[^{3}H]estradiol to the receptor in the free cell extracts. ● These substances exhibited lower activity, when measured on a molar basis, compared to 17β-[3H]estradiol or the synthetic dihydroxystilbene estrogens.
So et al., 1996	Human breast carcinoma cell line, MDA-MB-435.	Proliferation assay, growth curve at $ic_{50,}$ MTT viability assay, tumorigenicity experiments	Two citrus flavonoids along with four noncitrus flavonoids	● Among the six individual flavonoids tested, baicalein had the highest potency to effectively suppress the proliferation of the cells. ● Hesperetin and naringenin (found in citrus fruits) exhibited moderate inhibitory effects.
Zand et al., 2000	BT-474 human breast cancer cells	ELISA-type immunofluorometric assays,	72 flavonoids and structurally related compounds.	● Flavonoids exhibited significant steroid hormone activity. Based on the findings they concluded that flavonoids may have an effect on cancer risk, prevention and cancer therapeutics.
Imai et al., (2004)	K562 (K562/BCRP), LLC/BCRP, K562/MDR, and KB/MRP Cell Lines.	Cell growth inhibition assay, cellular [3H]genistein accumulation in K562/BCRP Cells, transcellular transport assay of [3H]genistein	Estrone, kaempferol, naringenin, naringenin-7-glucoside	● Phytoestrogens/flavonoids, including genistein, naringenin, acacetin, and kaempferol, boosted the toxicity of SN-38 and mitoxantrone in BCRP-transduced K562 (K562/BCRP) cells.
Zhang et al., 2004	MCF-7, NCI-H460	Western blot analysis of BCRP, P-gp, and MRP1, mitoxantrone accumulation studies, mitoxantrone cytotoxicity studies.,	Apigenin, biochanin a, chrysin, daidzein, fisetin, morin, myricetin, genistein etc.	● Many of the tested flavonoids (50 M) are BCRP inhibitors. ● Chrysin and biochanin A exhibited the highest level of potency as inhibitors of BCRP.
Katayama et al., 2007	Human leukemia K562 cells and human epidermoid carcinoma KB-3-1 cells	Growth inhibition assay, topotecan uptake	Flavone, flavonol, flavanone, isoflavone, chalcone	● 3,4,7-trimethoxyXavone demonstrated the most potent anti-BCRP activity for SN-38 and mitoxantrone respectively. ● 3,4,7-trimethoxyXavone and acacetin, exhibited minimal anti-P-gp activity, while the others did not demonstrate any inhibitory effects on P-gp.
Chen et al., 2007	MDA-MB-231 breast cancer cell cultures and xenografts	Proteasomal chymotrypsin-like and caspase-3/caspase-7 activity assays, MTT assay, western blot analysis and human breast tumor xenograft experiments	Apigenin	● Apigenin suppresses the proteasomal chymotrypsin-like activity and induces apoptosis in both cultured MDA-MB-231 cells and MDA-MB-231 xenografts.

Yang et al., 2012	MCF-7, MDA-MB-231, MCF-10A cells	MTT colorimetric assay, Luminescence ATP detection assay, Western blot analysis	Fisetin (3,3',4',7-tetrahydroxyflavone)	• Fisetin exhibited greater cytotoxicity in MCF-7 human breast cancer cells compared to MDA-MB-231 cells. • Fisetin can trigger a novel atypical apoptosis in caspase-3-deficient MCF-7 cells.
Shan et al., 2013	MCF-7 and MDA-MB-231	MTT, clonogenicity assay, apoptosis assay, western blot analysis	Triticuside A from wheat bran	• Triticuside A dose-dependently suppressed the growth of human breast cancer cells (MCF-7 and MDA-MB-231).
Pradhan et al., 2015	MCF-7 cell lines and MCF-7 xenografts	Proteasomal chymotrypsin-like and caspase-3/ caspase-7 activity assays, cell viability assay, xenograft experiments	Quercetin	• Quercetin suppresses the proteasomal chymotrypsin-like activity and triggers apoptosis in both cultivated MCF-7 cell lines and MCF-7 xenografts.
Vrhovac Madunic et al., 2017	ER-positive MCF-7, triple-negative MDA MB-231	MTT assay, cell viability, comet and lipid peroxidation assays,	Apigenin	• Apigenin caused cell death in both cell lines resulting in significant toxicity and apoptosis. • No significant cytogenotoxic effects were detected in normal cells.
Santes-Palacios et al., 2019	*Escherichia coli* DH5α cells	Ethoxyresorufin O-deethylase activity (EROD) assay, bacterial mutagenicity assay	Quercetin, myricetin, luteolin, fisetin, kaempferol, 5-hydroxyflavone, flavone etc.	• 5-hydroxyflavone, 3 hydroxy-flavone and flavone exerted the most potent inhibitory activity with IC50 values of 0.07, 0.10 and 0.08 μM respectively.

DISCUSSION

Flavonoid consumption may have an association with a lower risk of cancer development, according to the findings of the cohort and case-control studies that were reviewed in this article (Table 4). The fact that flavonoids have been shown to have an inverse correlation with cancer risk may be explained by the fact that flavonoids have an effect on a number of critical biological activities. The capacity of flavonoids to scavenge free radicals has been characterized in experimental settings to a satisfactory degree.

More recently, flavonoids have been shown to influence the signal transduction pathway (Melnik et al., 2002), accelerate apoptosis (Choi et al., 2001), suppress inflammation and impede proliferation in human cancer cell lines (Manthey et al., 2002). The in vitro and animal model systems were used to publish these findings. Some flavonoids can also enhance the transcription of phase II detoxifying enzymes, which would help eliminate pro-carcinogenic substances. This would reinforce the idea that flavonoids prevent cancer. Flavonoids were shown to dramatically reduce the number of focal areas of dysplasia that were caused by exposure to azoxymethane (AOM), according to the findings of a study that employs mice that were subjected to treatment with azoxymethane (AOM) and fed either a standard diet, a standard diet plus rutin, or a standard diet plus quercetin (Yang et al., 2000). This kind of research is noteworthy because it suggests that flavonoids could be related to a number of early-stage processes in the cascade that result in cancer development.

The development of multidrug resistance (MDR) in cancer cells through transporter-mediated active efflux of cytotoxic drugs is one of the processes that has been studied and characterized the most. Previous studies have demonstrated that BCRP (Breast Cancer resistance protein) bestows resistance upon several significant anticancer agents, including doxorubicin, topotecan, mitoxantrone, SN38, methotrexate, and flavopiridol (Doyle et al., 1998). Therefore, to potentially reverse multidrug resistance (MDR), it is necessary to identify inhibitors of BCRP that are both potent and nontoxic. Flavonoids, which have a lengthy history of human ingestion and a stellar safety record, are an essential component of the average diet (Havsteen, 2002). Furthermore, these compounds have been linked to numerous anticancer mechanisms (Havsteen, 2002), as well as synthetic compounds that are analogous to them, including flavone acetic acid and flavopiridol (Senderowicz et al., 1998).

In addition to its role in regulating drug distribution, the ATP-binding cassette transporter breast cancer resistance protein (BCRP), which was only recently discovered, has been shown to impart multidrug resistance (MDR) to many important anticancer drugs. Flavonoids, a group of polyphenolic chemicals, are widely present in botanical products and dietary sources. It has been reported that flavonoids interact with P-glycoprotein and multidrug resistance-associated protein 1; nevertheless, the nature of their interaction with BCRP remains unknown. The objective of this study was to evaluate the effects of twenty naturally derived flavonoids on the cytotoxicity and cellular accumulation of mitoxantrone in human cell lines that exhibit BCRP expression but lack BCRP. These investigations utilized human breast cancer cells (MCF-7) that overexpressed BCRP and large-cell lung carcinoma cells (NCI-H460) that lacked BCRP.

A considerable number of the flavonoids that were assessed (50 μM) exhibited an augmentation in mitoxantrone accumulation in cells that overexpressed BCRP, while also effectively reversing the development of mitoxantrone resistance. It is important to note

that these flavonoids did not have any effect on the BCRP-negative cells that corresponded to them, which suggests that they act as antioxidants. The impact of these flavonoids on the cellular accumulation and cytotoxicity of mitoxantrone was found to be concentration-dependent, with the majority of the flavonoids exhibiting significant modifications at concentrations below 10 μM (Hung et al., 2015). Additional research is required to optimize the compounds' bioavailability, biodistribution, and safety in preparation for future human studies. In particular, it is imperative to elucidate how every flavonoid, in accordance with its distinct chemical composition, can traverse the membrane.

Based on the available research, it may be concluded that flavonoids have a negative correlation with the chance of developing cancer. Further research utilizing up-to-date dietary databases with HPLC results for flavonoid estimations from food will offer conclusive information about the correlation between plant chemicals and the risk of cancer. Furthermore, conducting feeding experiments that can accurately describe the process of how plant flavonoids are absorbed, metabolized, and eliminated from the body, as well as their interaction with important enzyme systems, would be crucial in comprehending the underlying biological reasons for the negative relationship between flavonoid consumption and the risk of developing cancer. Meanwhile, it is strongly recommended that the public adhere to dietary recommendations for cancer prevention, which involve consuming five or more servings of fruits and vegetables daily. Moreover, the findings of the researcher might offer significant backing for additional exploration into evaluating the effectiveness and safety of flavonoid chemicals whether included in a nutritious diet or used as a supplementary treatment for human malignancies.

CONCLUSION

There is evidence that dietary flavonoids can lower the risk of cancer, especially breast cancer. This review briefly discussed about that the different sources of flavonoid and their subclasses which are the polyphenolic compounds mainly present in plant sources like fruits, vegetables, and cereals. They mainly reduce the risk of breast cancer by antioxidant activity, anti-carcinogenic effect, inhibiting apoptosis, reducing estrogen activity, and inhibiting the growth of breast cancer cells. Researchers are enthusiastic about revealing the therapeutic properties of flavonoids to treat breast cancer cases. There are linings enough that some polyphenolic compounds are found as effective drugs for treating breast cancer.

COMPLETING INTERESTS

The authors of this manuscript certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

REFERENCES

1. Ganesan, K., Du, B., & Chen, J. (2022). Effects and mechanisms of dietary bioactive compounds on breast cancer prevention. Pharmacological Research 178: 105974. https//DOI: 10.1016/j.phrs.2021.105974
2. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 71: 209-249. https//doi: 10.3322/caac.21660
3. WHO (2023). Breast cancer. Link: https://www.who.int/news-room/fact-sheets/detail/breastcancer#:~:text=Overview,producing%20lobules%20of%20the%20breast.
4. Colditz, G. A. (1998). Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. Nat Rev Cancer 90: 814-32. https//doi 10.1093/jnci/90.11.814
5. Thomas, C., & Gustafsson, J. A. (2011). The different roles of ER subtype in cancer biology and therapy. Journal of Nature Reviews Cancer 11: 597-608. https//doi: 10.1038/nrc3093.
6. Takahashi, T., Kobori, M., Shinmoto, H., & TsUsHIDA, T. (1998). Structure-activity relationships of flavonoids and the induction of granulocytic- or monocytic differentiation in HL60 human myeloid leukemia cells. Biosci Biotechnol Biochem 62: 2199-204. https//doi: 10.1271/bbb.62.2199.
7. Hamer, J. & Warner, E. (2017). Lifestyle modifications for patients with breast cancer to improve prognosis and optimize overall health. CMAJ 189: E268–e274. https//doi: 10.1503/cmaj.160464.
8. Peterson, J. & Dwyer, J. (1998). Flavonoids: dietary occurrence and biochemical activity. Nutr Res. 18: 1995-2018.
9. Jang, H., Chung, M. S., Kang, S. S., & Park, Y. (2018). Association between the dietary inflammatory index and risk for cancer recurrence and mortality among patients with breast cancer. Nutrients 10: 1095. https//doi: 10.3390/nu10081095.
10. Franke, A. A., Cooney, R. V., Custer, L. J., Mordan, L. J., & Tanaka, Y. (1998). Inhibition of neoplastic transformation and bioavailability of dietary flavonoid agents. Adv Exp Med Biol. 439: 237-48. https//DOI: 10.1007/978-1-4615-5335-9_17
11. Peterson, J., Lagiou, P., Samoli, E., Lagiou, A., Katsouyanni, K., La Vecchia, C. *et al.* (2003). Flavonoid intake and breast cancer risk: a case-control study in Greece. British Journal of Cancer 89: 1255–1259. https//doi:10.1038/sj.bjc.6601271
12. Who (2023). WHO launches new roadmap on breast cancer. Link: https://www.who.int/news/item/03-02-2023-who-launches-new-roadmap-on-breast-cancer
13. Zhang, Y., Zhou, Y., Mao, F., Yao, R., & Sun, Q. (2020). Ki-67 index, progesterone receptor expression, histologic grade and tumor size in predicting breast cancer recurrence risk: A consecutive cohort study. Cancer Commun (Lond) 40(4): 181-93.
14. Anderson, K. N., Schwab, R. B., & Martinez, M. E. (2014). Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast cancer research and treatment, 144, 1-10. PMCID: PMC4026199. https//DOI: 10.1007/s10549-014-2852-7

15. Fragomeni, S. M., Sciallis, A., & Jeruss, J. S. (2018). Molecular subtypes and local-regional control of breast cancer. Surg Oncol Clin N Am. 27(1): 95-120. https//DOI: 10.1016/j.soc.2017.08.005
16. Barzaman, K., Karami, J., Zarei, Z., Hosseinzadeh, A., Kazemi, M. H., Moradi-Kalbolandi, S., ... & Farahmand, L. (2020). Breast cancer: Biology, biomarkers, and treatments. International immunopharmacology, 84, 106535. PMID: 32361569. https//DOI: 10.1016/j.intimp.2020.106535
17. Gao, J. J., & Swain, S. M. (2018). Luminal a breast cancer and molecular assays: a review. Oncologist. 23(5): 556–565. https://doi.org/10.1634/theoncologist.2017-0535
18. Engel, R. H. &, Kaklamani, V. G. (2007). HER2-positive breast cancer: current and future treatment strategies. Drugs. 67(9): 1329-1341. https://doi.org/10.2165/00003495-200767090-00006
19. Duffy, M. J., Synnott, N. C., & Crown, J. (2018). Mutant p53 in breast cancer: potential as a therapeutic target and biomarker. Breast Cancer Res Treat. 170(2): 213-219. https://doi.org/10.1007/s10549-018-4753-7
20. Ahern, T. P., Lash, T. L., Damkier, P., Christiansen, P. M., & Cronin-Fenton, D. P. (2014). Statins and breast cancer prognosis: evidence and opportunities. The lancet oncology, 15(10), e461-e468. PMCID: PMC4167822. https//doi 10.1016/S1470-2045(14)70119-6
21. Loibl, S. & Gianni, L. (2017). HER2-positive breast cancer. Lancet. 389(10087): 2415-2429. https://doi.org/10.1016/S0140-6736(16)32417-5
22. AJCC Cancer Staging Manual, Eighth Edition (2017). The American College of Surgeons (ACS), Chicago, Illinois.
23. Alfonse, M., Aref, M. M., & Salem, A. B. M. (2014). An ontology-based system for cancer diseases knowledge management. International Journal of Information Engineering and Electronic Business, 6(6), 55-63.
24. Gaur, R. (2013). Breast Cancer Biomarkers. https//doi:10.1201/b14289-13.
25. Soerjomataram, I. & Bray, F. (2021). Planning for tomorrow: global cancer incidence and the role of prevention 2020-2070. Nat Rev Clin Oncol. 18(Suppl. 1). https//doi-10.1038/s41571-021-00514-z
26. Winkel-Shirley, B. (2001). Flavonoid biosynthesis. A colorful model for genetics, biochemistry, cell biology, and biotechnology. *Plant physiology*, *126*(2), 485-493. https://doi.org/10.1104/pp.126.2.485
27. Nabavi, S. M., Šamec, D., Tomczyk, M., Milella, L., Russo, D., Habtemariam, S. *et al.* (2018). Flavonoid biosynthetic pathways in plants: Versatile targets for metabolic engineering. Biotechnol. Ad. 38: 107316. https//DOI: 10.1016/j.biotechadv.2018.11.005
28. Liu, W., Feng, Y., Yu, S., Fan, Z., Li, X., Li, J., & Yin, H. (2021). The Flavonoid Biosynthesis Network in Plants. *Int J Mol Sci*. 22(23):12824. https//DOI: 10.3390/ijms222312824
29. Wang, T. Y., Li, Q., & Bi, K. S. (2018). Bioactive flavonoids in medicinal plants: Structure, activity and biological fate. Asian J. Pharm. Sci. 13:12-23. doi: 10.1016/j.ajps.2017.08.004.
30. Harborne, J.B. & Williams, C. A. (2000). Advances in flavonoid research since 1992. Phytochemistry 55: 481-504. https//DOI: 10.1016/s0031-9422(00)00235-1

31. Butt, M. S., Imran, A., Sharif, M. K., Ahmad, R. S., Xiao, H., Imran, M., & Rsool, H. A. (2014). Black Tea Polyphenols: A Mechanistic Treatise. Critical Reviews in Food Science and Nutrition, 54(8), 1002–1011. https://doi.org/10.1080/10408398.2011.623198
32. Rehan, M. (2021). Biosynthesis of Diverse Class Flavonoids via Shikimate and Phenylpropanoid Pathway. Intech Open. https//doi: 10.5772/intechopen.96512
33. Jeeva, J. S., Sunitha, J., Ananthalakshmi, R., Rajkumari, S., Ramesh, M., & Krishnan, R. (2015). Enzymatic antioxidants and its role in oral diseases. J Pharm Bioallied Sci. 7(Suppl 2): S331-3. https//doi: 10.4103/0975-7406.163438
34. Korkina, L. G, Afanas'ev, I. B (1997). Antioxidant and chelating properties of flavonoids. Adv Pharmacol. 38:151-63. doi: 10.1016/s1054-3589(08)60983-7.
35. Nacaia, H., Takekoshi, S., Takagi, T., Honma, T., & Watanabe, K. (1999). Antioxidative Action of Flavonoids, Quercetin and Catechin, Mediated by the Activation of Glutathione Peroxidase. Tokai J Exp Clin Med. 24(1): 1-11. PMID: 10530620
36. Agati, G., Azzarello, E., Pollastri, S., & Tattini, M. (2012). Flavonoids as antioxidants in plants: location and functional significance. Plant science, 196, 67-76. PMID: 23017900. https//doi: 10.1016/j.plantsci.2012.07.014
37. Panat, N. A., Maurya, D. K., Ghaskadbi, S. S., & Sandur, S. K. (2016). Troxerutin, a plant flavonoid, protects cells against oxidative stress-induced cell death through radical scavenging mechanism. Food Chemistry 94: 32-45. https//DOI: 10.1016/j.foodchem.2015.07.078
38. de Groot, H. D. & Rauen, U. (1998). Tissue injury by reactive oxygen species and the protective effects of flavonoids. Fundamental and clinical Pharmacology 12(3): 249-255. https//DOI: 10.1111/j.1472-8206.1998.tb00951.x
39. Diniz, T. C., Silva, J. C., Lima-Saraiva, S. R. G. D., Ribeiro, F. P. R. D. A., Pacheco, A. G. M. *et al.* (2015). The role of flavonoids on oxidative stress in epilepsy. *Cell Longev* 2015:171756. https//doi:10.1155/2015/171756
40. Afanas' ev, I. B., Dcrozhko, A. I., Brodskii, A. V., Kostyuk, V. A., & Potapovitch, A. I. (1989). Chelating and free radical scavenging mechanisms of inhibitory action of rutin and quercetin in lipid peroxidation. Biochemical pharmacology, 38(11), 1763-1769. PMID: 2735934. https//doi 10.1016/0006-2952(89)90410-3
41. Mira, L., Tereza Fernandez, M., Santos, M., Rocha, R., Helena Florêncio, M., & Jennings, K. R. (2002). Interactions of Flavonoids with Iron and Copper Ions: A Mechanism for their Antioxidant Activity. Free Radical Research 36(11): 1199-1208. https//doi: 10.1080/1071576021000016463
42. Lee, S. A., Shu, X. O., Li, H., Yang, G., Cai, H., Wen, W. *et al.* (2009). Adolescent and adult soy food intake and breast cancer risk: results from the Shanghai Women's Health Study. *The American Journal of Clinical Nutrition* 89 (6): 1920-6. https//doi:10.3945/ajcn.2008.27361
43. Korde, L. A., Wu, A. H., Fears, T., Nomura, A. M., West, D. W., Kolonel, L. N. *et al.* (2009). Childhood soy intake and breast cancer risk in Asian American women. *Cancer Epidemiology, Biomarkers & Prevention* 18(4): 1050-9. https://doi:10.1158/1055-9965.EPI-08-0405.
44. Rice, S. & Whitehead, S. (2006). Phytoestrogens and breast cancer--promoters or protectors? Endocr. Relat. Cancer 13: 995-1015. https//doi: 10.1677/erc.1.01159.

45. Gonzalez, F. J. (1988). The molecular biology of cytochrome P450s. Pharmacol. Rev. 40: 243-288. PMID: 3072575
46. Hodek, P., Trefil, P., & Stiborová, M. (2002). Flavonoids-potent and versatile biologically active compounds interacting with cytochromes P450. Chem. Biol. Interact. 139: 1-21. https// DOI: 10.1016/s0009-2797(01)00285-x
47. Ciolino, H. P., Daschner, P. J., & Yeh, G. C. (1999). Dietary flavonols quercetin and kaempferol are ligands of the aryl hydrocarbon receptor that affect CYP1A1 transcription differentially. Biochem. J. 340: 715–722. PMID: 10359656. PMCID: PMC1220303
48. Arroo, R. R., Androutsopoulos, V., Beresford, K., Ruparelia, K., Surichan, S. *et al.* (2009). Phytoestrogens as natural prodrugs in cancer prevention: Dietary flavonoids. Phytochem. Rev. 8: 375–386.
49. Tan, K. W., Li, Y., Paxton, J. W., Birch, N. P., & Scheepens, A. (2013). Identification of novel dietary phytochemicals inhibiting the efflux transporter breast cancer resistance protein (BCRP/ABCG2). Food Chem. 138: 2267–74. https//doi: 10.1016/j.foodchem.2012.12.021
50. Nobili, S., Lapucci, A., Landini, I., Coronnello, M., Roviello, G., & Mini, E. (2020). Role of ATP-binding cassette transporters in cancer initiation and progression. Semin Cancer Biol. 60: 72-95. doi: https://doi.org/10.1016/j.semcancer.2019.08.006
51. Zhang, S., Yang, X., & Morris, M. E (2004). Flavonoids are inhibitors of breast cancer resistance protein (ABCG2)-mediated transport. Molecular pharmacology 65(5): 1208–1216. https//doi.org/10.1124/mol.65.5.1208
52. Morris, M. E., & Zhang, S. (2006). Flavonoid-drug interactions: effects of flavonoids on ABC transporters. Life Sci. 78: 2116–30. https//DOI: 10.1016/j.lfs.2005.12.003
53. Huang, C., Chen, X., Guo, B., Huang, W., Shen, T., Sun, X., ... & Zhou, Q. (2012). Induction of Apoptosis by Icariside II through Extrinsic and Intrinsic Signaling Pathways in Human Breast Cancer MCF7 Cells. Biosci. Biotechnol. Biochem. 76: 1322–1328. https//DOI: 10.1271/bbb.120077
54. Kamsteeg, M., Rutherford, T., Sapi, E., Hanczaruk, B., Shahabi, S., Flick, M. *et al.* (2003). Phenoxodiol - An isoflavone analog - Induces apoptosis in chemoresistant ovarian cancer cells. Oncogene 22; 2611–2620. https//DOI: 10.1038/sj.onc.1206422
55. Brusselmans, K., Vrolix, R., Verhoeven, G., & Swinnen, J. V. (2005). Induction of cancer cell apoptosis by flavonoids is associated with their ability to inhibit fatty acid synthase activity. Journal of Biological Chemistry, 280(7), 5636-5645. https//doi 10.1074/jbc.M408177200.
56. To, K. K., & Cho, W. (2021). Flavonoids Overcome Drug Resistance to Cancer Chemotherapy by Epigenetically Modulating Multiple Mechanisms. Current Cancer Drug Targets 21(4): 289-305(17). https//doi: 10.2174/1568009621666210203111220.
57. Costea, T., Vlad, O. C., Miclea, L. C., Ganea, C., Szöllősi, J., & Mocanu, M. M. (2020). Alleviation of Multidrug Resistance by Flavonoid and Non-Flavonoid Compounds in Breast, Lung, Colorectal and Prostate Cancer. International Journal of Molecular Sciences 21(2): 401. https://doi.org/10.3390/ijms21020401
58. Rao, P. S., Satelli, A., Moridani, M., Jenkins, M., & Rao, U. S. (2012). Luteolin induces apoptosis in multidrug resistant cancer cells without affecting the drug transporter function:

Involvement of cell line-specific apoptotic mechanisms. Int. J. Cancer 130: 2703-2714. https//doi: 10.1002/ijc.26308

59. Zheng, W., Dai, Q., Custer, L. J., Shu, X. O., Wen, W. Q., Jin, F., & Franke, A. A. (1999). Urinary excretion of isoflavonoids and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 8(1) :35-40.
60. Horn-Ross, P. L., John, E. M., Lee, M., Stewart, S. L., Koo, J., Sakoda, L. C. *et al.* (2001). Phytoestrogen consumption and breast cancer risk in a multiethnic population: the Bay Area Breast Cancer Study. Am J Epidemiol. 154(5): 434-441. https//doi:10.1093/aje/154.5.434
61. Silva, I. D. S., Mangtani, P., McCormack, V., Bhakta, D., McMichael, A. J., & Sevak, L. (2004). Phyto-oestrogen intake and breast cancer risk in South Asian women in England: findings from a population-based case-control study. Cancer causes & control: CCC 15(8): 805–818. https//doi: 10.1023/B:CACO.0000043431.85706.d8.
62. Bosetti, C., Spertini, L., Parpinel, M., Gnagnarella, P., Lagiou, P., Negri, E., ... & La Vecchia, C. (2005). Flavonoids and breast cancer risk in Italy. Cancer Epidemiology Biomarkers & Prevention, 14(4), 805-808. https//doi:10.1158/1055-9965.EPI-04-0838.
63. Fink, B. N., Steck, S. E., Wolff, M. S., Britton, J. A., Kabat, G. C., Schroeder, J. C. *et al.* (2007). Dietary flavonoid intake and breast cancer risk among women on Long Island. American journal of epidemiology 165(5): 514-523. https://doi.org/10.1093/aje/kwk033
64. Cotterchio, M., Boucher, B. A., Kreiger, N., Mills, C. A., & Thompson, L. U. (2008). Dietary phytoestrogen intake--lignans and isoflavones--and breast cancer risk (Canada). Cancer causes & control: CCC 19(3): 259-272. https://doi.org/10.1007/s10552-007-9089-2
65. Cutler, G. J., Nettleton, J. A., Ross, J. A., Harnack, L. J., Jacobs Jr, D. R., Scrafford, C. G. *et al.* (2008). Dietary flavonoid intake and risk of cancer in postmenopausal women: the Iowa Women's Health Study. International journal of cancer 123(3): 664-671. https://doi.org/10.1002/ijc.23564
66. Torres-Sanchez, L., Lopez--Carrillo, L., Lo--Cervantes, M., Rueda-Neria, C., & Wolff, M. S. (2000). Food sources of phytoestrogens and breast cancer risk in Mexican women. Nutrition and cancer 37(2): 134-139. https://doi.org/10.1207/S15327914NC372-3
67. Ha, T. C., Lyons-Wall, P. M., Moore, D. E., Tattam, B. N., Boyages, J. *et al.* (2006). Phytoestrogens and indicators of breast cancer prognosis. Nutrition and cancer 56(1): 3-10. https//DOI: 10.1207/s15327914nc5601_2
68. Pantavos, A., Ruiter, R., Feskens, E. F., de Keyser, C. E., Hofman, A., Stricker, B. H. *et al.* (2015). Total dietary antioxidant capacity, individual antioxidant intake and breast cancer risk: the Rotterdam Study. International journal of cancer 136(9): 2178-2186. https//DOI: 10.1002/ijc.29249
69. Wang, Y., Gapstur, S. M., Gaudet, M. M., Peterson, J. J., Dwyer, J. T., & McCullough, M. L. (2014). Evidence for an Association of Dietary Flavonoid Intake with Breast Cancer Risk by Estrogen Receptor Status Is Limited. J. Nutr. 144: 1603-1611. https//doi: 10.3945/jn.114.196964
70. Feng, X. L., Ho, S. C., Mo, X. F., Lin, F. Y., Zhang, N. Q., Luo, H. *et al.* (2020). Association between flavonoids, flavonoid subclasses intake and breast cancer risk: a case-control study in China. Eur J Cancer Prev. 29(6): 493-500. https//DOI: 10.1097/CEJ.0000000000000561

71. Miksicek, R. J. (1993). Commonly occurring plant flavonoids have estrogenic activity.The American Society of Pharmacology. Molecular Pharmacology 44(1): 37-43. PMID: 8341277
72. So, F. V., Guthrie, N., Chambers, A. F., Moussa, M., & Carroll, K. K. (1996). Inhibition of human breast cancer cell proliferation and delay of mammary tumorigenesis by flavonoids and citrus juices. Nutrition and cancer 26(2): 167-181. https// doi: 10.1080/01635589609514473.
73. Zand, R. S. R., Jenkins, D. J., & Diamandis, E. P. (2000). Steroid hormone activity of flavonoids and related compounds. Breast cancer research and treatment 62(1): 35–49. https://doi.org/10.1023/a:1006422302173
74. Imai, Y., Tsukahara, S., Asada, S., & Sugimoto, Y. (2004). Phytoestrogens/flavonoids reverse breast cancer resistance protein/ABCG2-mediated multidrug resistance. Cancer research 64(12): 4346-4352. https://doi.org/10.1158/0008-5472.CAN-04-0078
75. Katayama, K., Masuyama, K., Yoshioka, S., Hasegawa, H., Mitsuhashi, J., & Sugimoto, Y. (2007). Flavonoids inhibit breast cancer resistance protein-mediated drug resistance: transporter specificity and structure-activity relationship. Cancer chemotherapy and pharmacology 60(6): 789-797. https://doi.org/10.1007/s00280-007-0426-7
76. Chen D, Landis-Piwowar KR, Chen MS, Dou QP (2007). Inhibition of proteasome activity by the dietary flavonoid apigenin is associated with growth inhibition in cultured breast cancer cells and xenografts. Breast cancer research: BCR 9(6): R80. https://doi.org/10.1186/bcr1797
77. Yang, P. M., Tseng, H. H., Peng, C. W., Chen, W. S., & Chiu, S. J. (2012). Dietary flavonoid fisetin targets caspase-3-deficient human breast cancer MCF-7 cells by induction of caspase-7-associated apoptosis and inhibition of autophagy. International journal of oncology 40(2): 469–478. https://doi.org/10.3892/ijo.2011.1203
78. Shan, Y., Cheng, Y., Zhang, Y., Guan, F. Q., Sun, H. *et al.* (2013). Triticuside A, a dietary flavonoid, inhibits proliferation of human breast cancer cells via inducing apoptosis. Nutrition and cancer 65(6): 891-899. https://doi.org/10.1080/01635581.2013.802001
79. Pradhan, D., Pradhan, R. K., Tripathy, G., & Pradhan, S. (2015). Inhibition of proteasome activity by the dietary flavonoid Quercetin associated with growth inhibition in cultured breast cancer cells and xenografts. Journal of Young Pharmacists 7(3). https//doi: 10.5530/jyp.2015.3.13
80. Vrhovac Madunić, I., Madunić, J., Antunović, M., Paradžik, M., Garaj-Vrhovac, V., Breljak, D. *et al.* (2018) Apigenin, a dietary flavonoid, induces apoptosis, DNA damage, and oxidative stress in human breast cancer MCF-7 and MDA MB-231 cells. Naunyn-Schmiedeberg's archives of pharmacology 391(5): 537-550. https://doi.org/10.1007/s00210-018-1486-4
81. Santes-Palacios, R., Marroquín-Pérez, A. L., Hernández-Ojeda, S. L., Camacho-Carranza, R., Govezensky, T., & Espinosa-Aguirre, J. (2020). Human CYP1A1 inhibition by flavonoids. Toxicology in vitro: an international journal published in association with BIBRA. Toxicology in Vitro 62: 104681. https://doi.org/10.1016/j.tiv.2019.104681
82. Melnik, L. I., Collins-Burow, B. M., Pace, D. K., McLachlan, J. A., Burow, M. E., Frigo, D. E. *et al.* (2002). Flavonoid phytochemicals regulate activator protein-1 signal

transduction pathways in endometrial and kidney stable cell lines. J Nutr. 132: 1848-185. https//DOI: 10.1093/jn/132.7.1848

83. Choi, J. A., Kim, J.Y., Lee, J.Y., Kang, C.M., Kwon, H.J., Yoo, Y.D., Kim, T.W., Lee, Y.S., Lee, S. J. (2001). Induction of cell cycle arrest and apoptosis in human breast cancer cells by quercetin. Int J Oncol.19(4):837-44. https//doi :10.3892/ijo.19.4.837. PMID: 11562764.
84. Manthey, J. A., & Guthrie, N. (2002). Antiproliferative activities of citrus flavonoids against six human cancer cell lines. J Agril Food Chem. 50: 5837-5843. https//DOI: 10.1021/jf020121d
85. Yang, K., Lamprecht, S. A., Liu, Y., Shinozaki, H., Fan, K., Leung, D. *et al.* (2000). Chemoprevention studies of the flavonoids: quercetin and rutin in normal and azoxymethane-treated mouse colon. Carcinogenesis 21: 1655-1660. https//doi: 10.1093/carcin/21.9.1655.
86. Doyle, L. A., Yang, W., Abruzzo, L. V., Krogmann, T., Gao, Y., Rishi, A. K., & Ross, D. D. (1998). A multidrug resistance transporter from human MCF-7 breast cancer cells. Proc Natl Acad Sci USA 95:15665-15670. https//DOI: 10.1073/pnas.95.26.15665
87. Havsteen, B. H. (2002). The biochemistry and medical significance of the flavonoids. Pharmacol Ther. 96: 67202. https//DOI: 10.1016/s0163-7258(02)00298-x
88. Senderowicz, A. M., Headlee, D., Stinson, S. F., Lush, R. M., Kalil, N., Villalba, L. *et al.* (1998). Phase I trial of continuous infusion flavopiridol, a novel cyclin-dependent kinase inhibitor, in patients with refractory neoplasms. J Clin Oncol. 16: 2986-2999. https//doi: 10.1200/JCO.1998.16.9.2986
89. Hung, C. H., Chan, S. H., Chu, P. M., & Tsai, K. L. (2015). Quercetin is a potent anti-atherosclerotic compound by activation of SIRT1 signaling under oxLDL stimulation, Mol. Nutr. Food Res. 59: 1905-1917. https//DOI: 10.1002/mnfr.201500144