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Review Article

NATURAL FLAVONOIDS: A NOVEL APPROACH TO BREAST CANCER (REVIEW)

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ABSTRACT

Cancer is a hereditary disease and is caused due to the abnormal growth of the cells. Cancer can be of many forms, but the most prevalent is breast cancer. Breast cancer is most common among women and can be treated by radiation therapy, surgery, hormone therapy, chemotherapy, and natural therapy. The present review presents an overview about the role of flavonoids in curing cancer. This review gives a detailed account of classification of flavonoids. The *in vivo* and *in vitro* studies show the action of flavonoids on cancer. Various natural flavonoids can be extracted and can be used for various therapeutic effects apart from cancer.

Keywords: Flavonoids, Cancer, Breast cancer, Classification of flavonoids.

INTRODUCTION

Cancer is a hereditary disease. The agents causing cancer are known as carcinogens. These can be present in food, water, and air. It is a virulent disease which leads to the genetic mutations bringing a change in regulating proteins. The resultant abnormal cell behavior leads to extensive growth of cells affecting various surrounding cells and organs resulting into cancer and ultimately leads to the death of the patient [1].

Breast cancer is the most prevailing disease in women. It is the second common disease after lung cancer. The disclosure, medication, and avoidance of breast cancer are one of the burning issues in public health and medical practices [2].

Breast cancer patients can be diagnosed by surgery, radiation therapy, chemotherapy, hormone therapy, and natural therapy. These therapies are employed to wipe out cancer, avert the production of metastases, and counter the exoneration [3].

HISTORICAL PERSPECTIVE

A new flavonoid called rutin was isolated from oranges in the year 1930 which reduced the capillary permeability [4]. Flavonoids are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine [5]. Flavonoids are found in various medicinal plants and found to be a great use in various treatments used worldwide, especially China. Flavonoids extracted from licorice have been found to show there therapeutic effects against peptic ulcers and gastric cancer in *Helicobacter pylori*-infected individuals [6]. Genistein present in soy was tested with various other natural flavonoids and was found to inhibit cell proliferation in estrogen receptor-positive breast cancer cells. Another such flavonoid is quercetin which is found effective against breast cancer and is effective only in water soluble form [7]. It was also found in cell culture studies that many flavonoids could inhibit breast cancer resistance protein (BCRP, ABCG2) [8]. Flavonoids are also reported to show chemopreventive effects in estrogen-dependent or -independent breast cancer [9]. Many fruits and leafy vegetables are found to contain kaempferol. Onion and pears are found to contain isorhamnetin whereas myricetin is found in berries, maize, and tea. Citrus fruits and vegetables are rich sources of anthocyanidins. Soy and soy products mainly include daidzein and genistein which are the isoflavonones [10]. Black tea is the rich source of flavan-3-ols. The red skin peanuts are also reported to contain some amount of flavanones.

OVERVIEW (FLAVONOIDS)

Flavonoids are the subclass of polyphenols which are extensively dispersed in plants such as citrus fruits, berries, onions, parsley, legumes, green tea, red wine, sea buckthorn, and dark chocolate. It consists of a diphenylpropane skeleton, consisting of two aromatic rings (i.e., A-ring and B-ring), each contains at least one hydroxyl group, and the two aromatic rings are connected through a three-carbon bridge, which becomes a part of the six-member heterocyclic ring (Fig. 1) [11].

GENERAL STRUCTURE OF FLAVONOID

On the basis of their chemical structures, flavonoids are classified into following (Table 1):

1. Flavonoids (2-phenylbenzopyrans)
2. Isoflavonoids (3-benzopyrans)
3. Neoflavonoids (4-benzopyrans) [12,13].

Flavonoids

These are further divided into the following depending on degree of oxidation and saturation present in the heterocyclic ring as shown Fig. 2.

Isoflavonoids

These are also of following categories as shown in Fig. 3.

Neoflavonoids

These comprise the following in Fig. 4.

Flavonoids and cancer

Flavonoids display an exceptional spectrum of biological activities which may affect cancer activities. These can be antiallergic, anti-inflammatory, antioxidant, antimutagenic, anticarcinogenic, and modulation of enzymatic activities [13-15]. These are benign in cancer chemoprevention and may act as potential therapeutic agents [16].

Carcinogenesis is a multistep process. Its steps can be summarized as follows.

a. Initiation: It is an accelerated phase which includes interaction of DNA with carcinogenic material.
b. Promotion: The abnormal cells flourish and grow.
c. Progression: It is the final stage, in which premalignant cells into neoplastic cells (Fig. 5) [11].

STAGES OF GROWTH OF CELLS IN TUMOR

Flavonoids are most widely found in photosynthesizing plant cells. These are the indispensable part in human and animal diet and cannot be synthesized within body. In recent years, there has been an upswing concern in the therapeutic potential of flavonoids. These are mainly due to the presence of phenolic groups [17,18]. Various edible plants have been linked to the treatment of cancer [19]. Various plant-derived agents such as paclitaxel, docetaxel; vinblastine, vincristine; and topotecan, irinotecan, and etoposide are currently being used for the treatment of cancer [20-22].

Plants have various flavonoids which are biologically very active and possess various therapeutic properties, which outline its necessity for determination [23]. Flavonols such as catechin, epicatechin, and epigallocatechin from tea have been extracted [24]. Certain flavones such as chrysin, apigenin, rutin, luteolin, and luteolin glucosides are found in the fruit skins, red wine, buckwheat, red pepper, and tomato skin [25-28]. Flavanols such as kaempferol, quercetin, myricetin, and tamarixetin are found in onion, red wine, olive oil, berries, and grapefruit [29]. Citrus fruits, grapefruits, lemons, and oranges possess flavonones such as naringin, naringenin, taxifolin, and hesperidin [30,31]. Soybean consists of isoflavone such as genistein and daidzein [32].

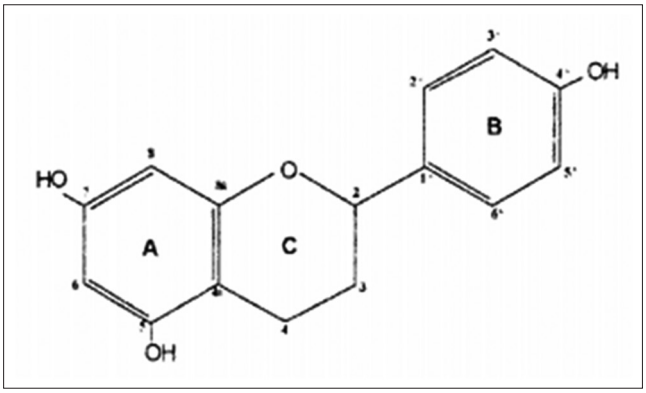

Fig. 1:

Polyphenols found in tea especially in green tea have shown to reduce the risk of cancer [33]. Curcumin in turmeric has been found to affect various multicellular signaling pathways, which are involved in proliferation, invasion, survival, apoptosis, and inflammation [34]. Various other plants and their phytochemicals effective against cancer are listed in Table 2.

Table 1: Classification of flavonoids

S. No.	Groups	Subgroups
1.	Flavonoids	Flavan Flavanone Flavone Flavonol Dihydroflavonol Flavan-3-ol Flavan-4-ol Flavan-3,4-diol
2.	Isoflavonoids	Isoflavan Isoflavone Isoflavanone Isoflav-3-ene Isoflavanol Rotenoid Coumestan 3-aryl-coumarin Coumaronochremene Coumaronochromone Pterocarpan
3.	Neoflavonoids	4-aryl-coumarin 3,4-dihydro-4-aryl-coumarin Neoflavene

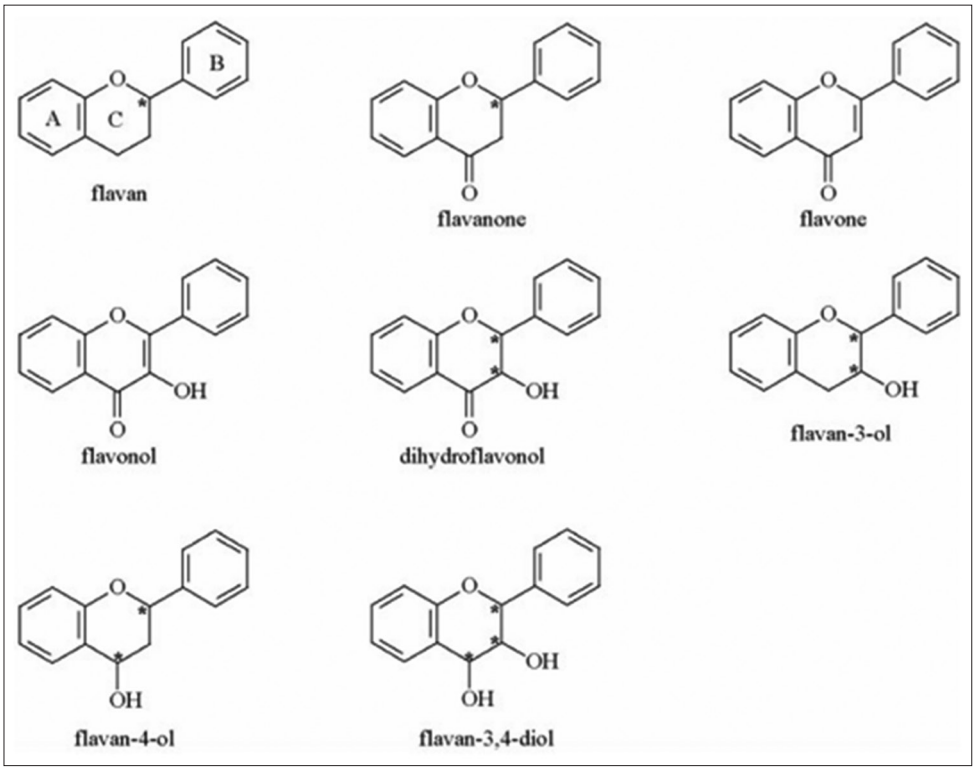

Fig. 2:

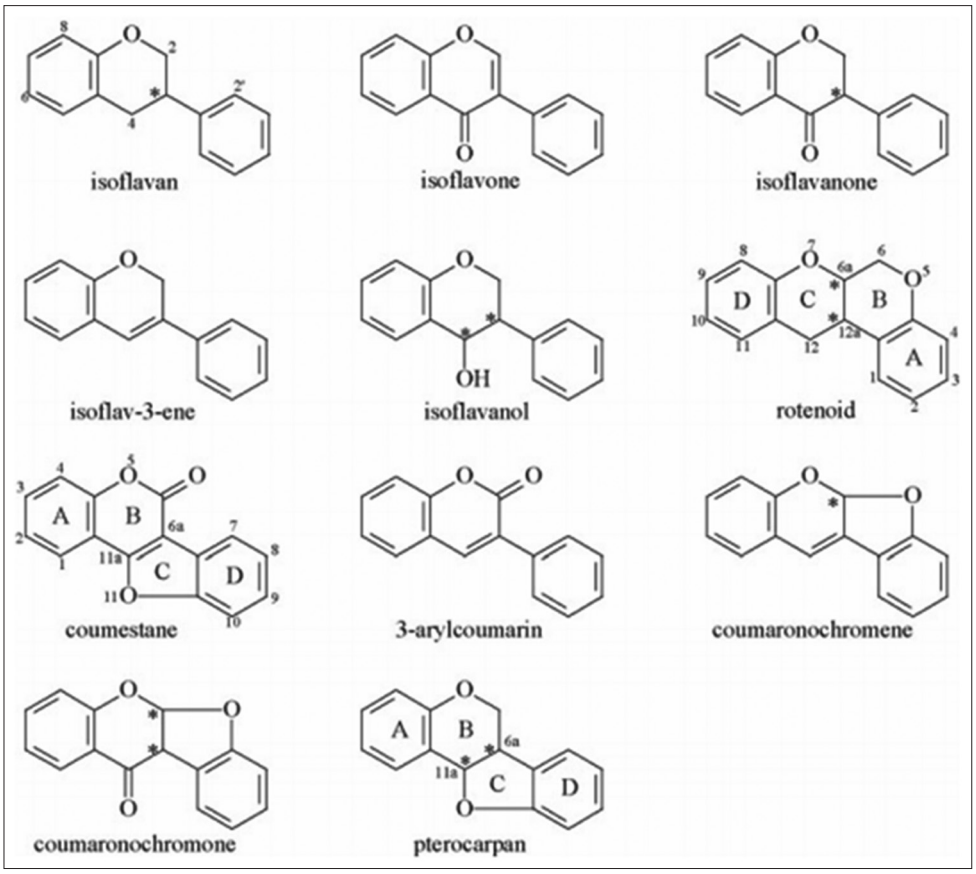

Fig. 3:

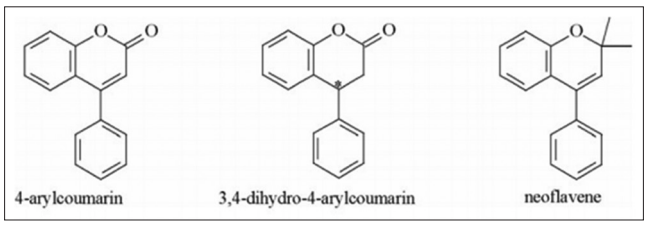

Fig. 4:

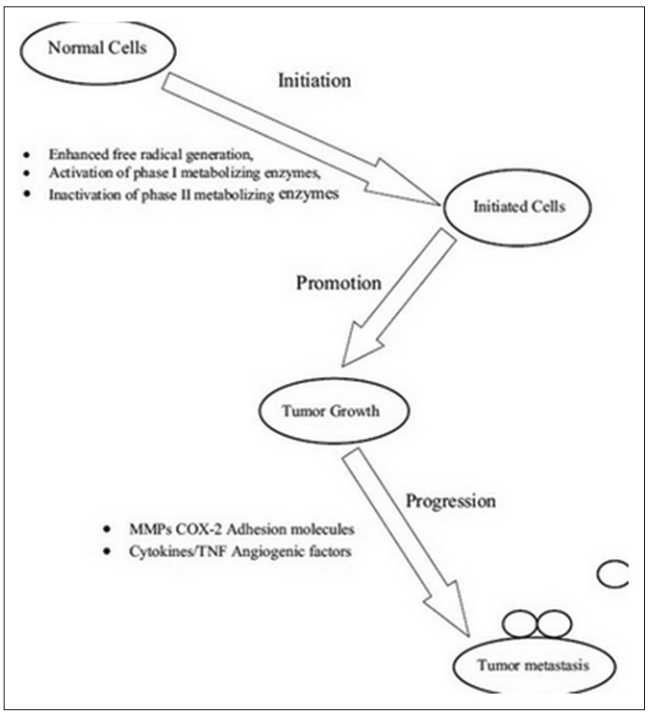

Fig. 5:

VARIOUS FLAVONOIDS IN FOOD

In vitro studies

Many researchers have conducted various *in vitro* studies on the potential anticancer activity of flavonoids. Biphasic effects of isoflavones have been seen in proliferation of breast cancer cell culture. At concentration above 5 mM, genistein showed concentration-dependent ability to inhibit growth and estrogen stimulated breast cancer cell proliferation. 28 flavonoids were studied by Hirano *et al.* against acute myeloid cell line HL 60 and were compared with antiproliferative activity and cytotoxicity with four clinical anticancer agents. Out of these 28 flavonoids, eight shows suppressive effects on HL 60 cell growth. The rest had potent anticancer activity [42]. 55 flavones were evaluated by Cushman and Nagarthnam and studied their toxicity in five cancer cell cultures and were found effective against A-549 lung carcinoma, MCF-7 breast carcinoma, HT-29 colon adenocarcinoma, SKMEL-5 melanoma, and MLM melanoma [43]. 27 out of these were of citrus origin and were found to inhibit tumor cell proliferation.

In vivo studies

Flavonoids have also shown to exhibit anticancerous activities *in vivo* studies. They may inhibit carcinogenesis in any stage of carcinoma. Animal and other cellular model investigations showed that certain flavonoids inhibit tumor initiation and progression. A novel research showed that fermented soy milk which contains large amounts of genistein and daidzein which were given to rats

Table 2:

S. No.	Source	Phytochemicals	References
1.	Broccoli, sprouts, cabbage, kale	Sulforaphane	[35]
2.	Broccoli, cabbage, cauliflower, mustard, and radish	Indole-3 carbinol, diindolylmethane	[36]
3.	Soy compounds	Genistein, Soy isoflavones	[37]
4.	Wasabi, horseradish, mustard, radish, Brussels sprouts, watercress, nasturtiums, capers	Isothiocyanate	[38]
5.	Red wine, peanuts, and certain berries	Resveratrol	[39]
6.	Garlic, chives, and leeks	Organosulfur compounds	[40]
7.	Tomato products	Lycopene	[41]
8.	Citrus fruits and buckwheat	Quercetin	

of 7 weeks of age showed to inhibit mammary tumorigenesis which was induced artificially by 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine [44].

Mammographic breast density can be used as biomarkers for estrogenic and anti-estrogenic effects of a particular treatment in breast tissue. Consuming dietary supplements including red clover-derived isoflavonones for 12 months did not show any increase in mammographic breast density in women experiencing menopause suggesting that there are no effects of estrogenic and anti-estrogenic effects on the breast [45].

CONCLUSION

Flavonoids have a wide range of therapeutic effects. The impact of flavonoids has been seen widely during the avalanche of immunological events which are correlated with the advancement and progression of cancer. They have regulatory role on various hormones [46]. A methodical mechanism is to be developed so as to understand mechanism of action of flavonoids, when they enter various cell organelles and tissues. Flavonoids are probable to inflect various biological events in cancer including apoptosis, vascularization, cell differentiation, and cell proliferation. Various dietary flavonoids show antitumor activity during *in vivo* studies whereas these show repression *in vivo* studies.

Various potent flavonoids are to be studied and extracted for elucidating various other natural ways in treating cancer. They are gaining interest due to their wide variants and number of members. These are reported to be effective in pathogenesis of majority of diseases [47]. Further studies should be conducted so as to validate the traditional ways of treating cancer. In the past, many efforts are made to get various anticancerous plants containing flavonoids and further studies are to be made to get satisfactory results. For these, a number of medicinal plants can be screened and can be further worked on so that *in vitro* and *in vivo* studies can be conducted providing new insights for fighting against cancer.

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