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].

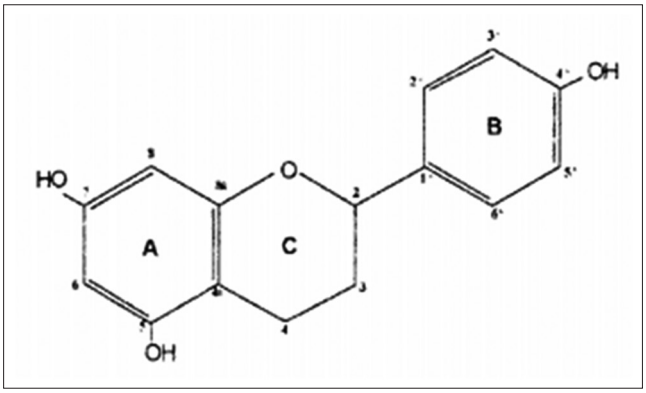

Fig. 1:

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

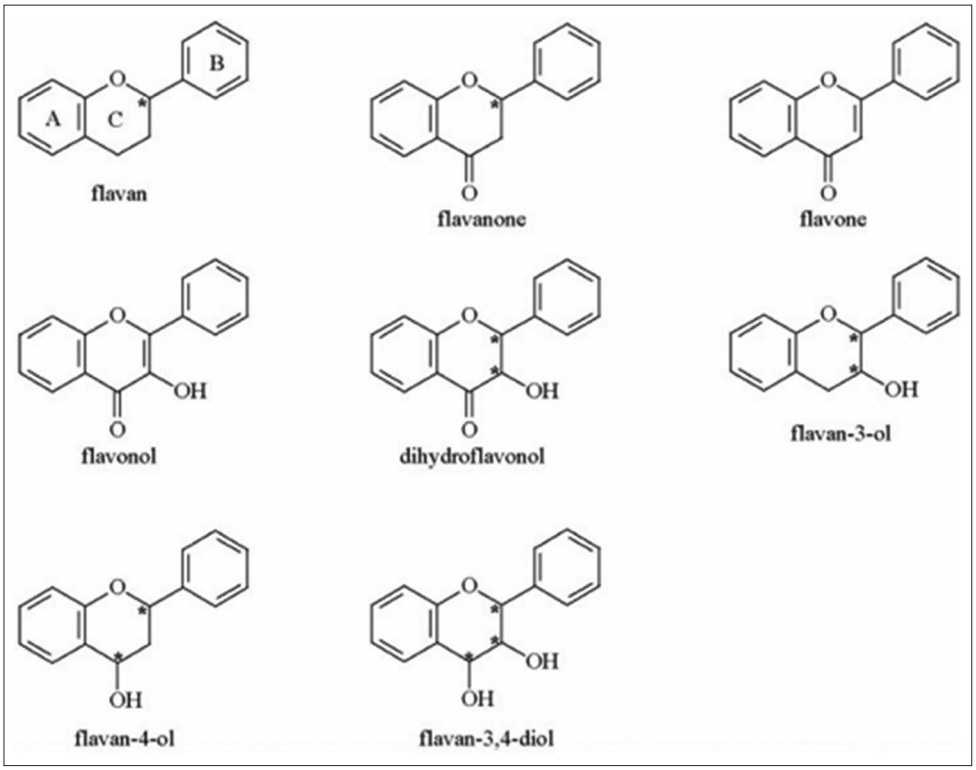

Fig. 2:

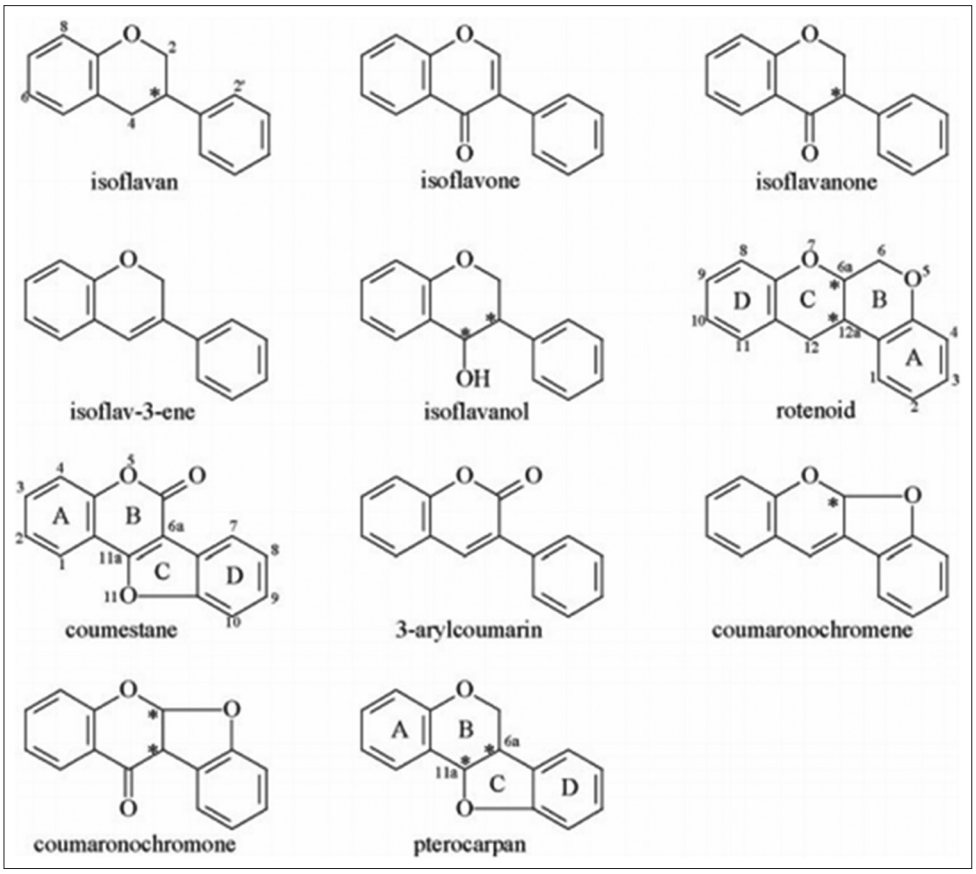

Fig. 3:

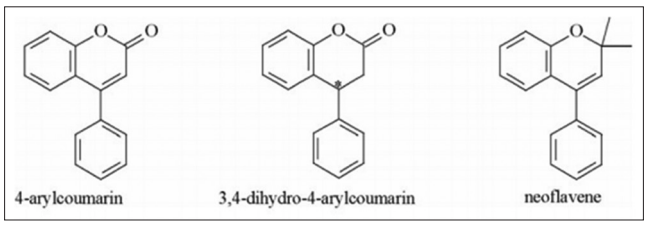

Fig. 4:

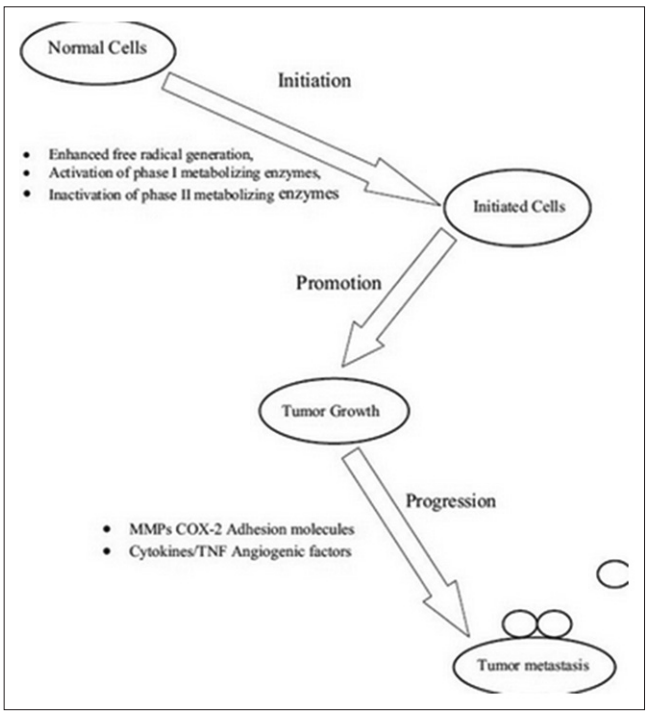

Fig. 5:

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.

REFERENCES

1. Alison MR. Cancer; Imperial College School of Medicine. London, UK. Encyclopaedia of Life Sciences, Nature Publishing Group; 2001. Available from: http://www.els.net.
2. Breast Cancer and the Environment a Life Course Approach. Available from: http://www.iom.nationalacademies.org/~/media/Files/Report%20Files/2011/Breast-Cancer-Environment/breastcancerreportbrief_2.pdf.
3. Breast Cancer Treatment Options: Surgery and Radiation Therapy: A Literature Review. Breast Cancer Treatment Options: A Literature Review, December; 2012.
4. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet 1992;339(8808):1523-6.
5. Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA. Flavonoids: A review of probable mechanisms of action and potential applications. Am J Clin Nutr 2001;74(4):418-25.
6. Fukai T, Marumo A, Kaitou K, Kanda T, Terada S, Nomura T. Anti - *Helicobacter pylori* flavonoids from liquorice extract. Life Sci 2002;71:1449-63.
7. Available from: http://www.allcancerguide.com/2015/07/flavonoids-in-breast-cancer.html.
8. Available from: http://www.dmd.aspetjournals.org/content/33/3/341.full.
9. Takemura H, Sakakibara H, Yamazaki S, Shimoi K. Breast cancer and flavonoids-a role in prevention. Curr Pharm Des 2013;19(34):6125-32.
10. Peterson J, Lagiou P, Samoli E, Lagiou A, Katsouyanni K, La Vecchia C, *et al.* Flavonoid intake and breast cancer risk: A case-control study in Greece. Br J Cancer 2003;89(7):1255-9.
11. Liu P, Jackie S. Effects of Flavonoids on Proliferation of Breast Cancer Cells and Vascular Smooth Muscle Cells, A Thesis Submitted for the Degree of Master of Medical Sciences, The University of Hong Kong; 2007.
12. Available from: http://www.files.rushim.ru/books/mechanizms/the-science-of-flavonoids.pdf.
13. Jannie S, Marais PJ, Deavours B, Dixon RA, Ferriera D. The Science of Flavonoids, the Stereochemistry of Flavonoid. New York: Springer, Springer Science Business Media Inc.; 2006.
14. Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease, and cancer. Pharmacol Rev 2000;52(4):673-751.
15. Galati G, Teng S, Moridani MY, Chan TS, O'Brien PJ. Cancer chemoprevention and apoptosis mechanisms induced by dietary polyphenolics. Drug Metabol Drug Interact 2000;17:311-49.
16. Yang CS, Landau JM, Huang MT, Newmark HL. Inhibition of carcinogenesis by dietary polyphenolic compounds. Annu Rev Nutr 2001;21:381-406.
17. Birt DF, Hendrich S, Wang W. Dietary agents in cancer prevention: Flavonoids and isoflavonoids. Pharmacol Ther 2001;90(2-3):157-77.
18. Chahar MK, Sharma N, Dobhal MP, Joshi YC. Flavonoids: A versatile source of anticancer drugs. Pharmacogn Rev 2011;5(9):1-12.
19. Pourmorad F, Hosseinimehr SJ, Shahabimajd N. Antioxidant activity, phenol and flavonoid contents of some selected Iranian medicinal plants. Afr J Biotechnol 2006;5(11):1142-5.
20. Kumar S, Pandey AK. Antioxidant, lipo-protective and antibacterial activities of phytoconstituents present in *Solanum xanthocarpum* root. Int Rev Biophys Chem 2012;3(3):42-7.
21. Mignet N, Seguin J, Ramos Romano M, Brullé L, Touil YS, Scherman D, *et al.* Development of a liposomal formulation of the natural flavonoid fisetin. Int J Pharm 2012;423:69-76.
22. Kim JH, Jung CH, Jang BH, Go HY, Park JH, Choi YK, *et al.* Selective cytotoxic effects on human cancer cell lines of phenolic-rich ethyl-acetate fraction from *Rhus verniciflua* stokes. Am J Chin Med 2009;37:609-20.
23. Li YL, Gan GP, Zhang HZ, Wu HZ, Li CL, Huang YP, *et al.* A flavonoid glycoside isolated from *Smilax china* L. Rhizome *in vitro* anticancer effects on human cancer cell lines. J Ethnopharmacol 2007;113:115-24.
24. Attoub S, Hassan AH, Vanhoecke B, Iratni R, Takahashi T, Gaben AM, *et al.* Inhibition of cell survival, invasion, tumour growth and histone deacetylase activity by the dietary flavonoid luteolin in human epithelioid cancer cells. Eur J Pharmacol 2011;651:18-25.
25. Sulaiman CT, Balachandran I. Total phenolics and total flavonoids in selected Indian medicinal plants. Indian J Pharm Sci 2012;74(3):258-60.
26. Lopez M, Martinez F, Del-Valle C, Orte C, Miro M. Analysis of phenolic constituents of biological interest in red wines by high-performance liquid chromatography. J Chromatogr A 2001;922(1-2):359-63.
27. Hara Y, Luo SJ, Wickremasinghe RL, Yamanishi T. Special issue on tea. Food Rev Int 1995;11:371-542.
28. Kreft S, Knapp M, Kreft I. Extraction of rutin from buckwheat (*Fagopyrum esculentum* Moench) seeds and determination by capillary electrophoresis. J Agric Food Chem 1999;47(11):4649-52.
29. Stewart AJ, Bozonnet S, Mullen W, Jenkins GI, Lean ME, Crozier A.

Occurrence of flavonols in tomatoes and tomato-based products. J Agric Food Chem 2000;48:2663-9.
30. Hertog MG, Hollman PC, Katan MB. Content of potentially anti-carcinogenic flavonoids of 28 vegetables and 9 fruits commonly consumed in the Netherlands. J Agric Food Chem 1992;40(12):2379-83.
31. Miyake Y, Shimoi K, Kumazawa S, Yamamoto K, Kinae N, Osawa T. Identification and antioxidant activity of flavonoid metabolites in plasma and urine of eriocitrin-treated rats. J Agric Food Chem 2000;48:3217-24.
32. Rousseff RL, Martin SF, Youtsey CO. Quantitative survey of narirutin, naringin, hesperidin, and neohesperidin in citrus. J Agric Food Chem 1987;35(6):1027-30.
33. Reinli K, Block G. Phytoestrogen content of foods-a compendium of literature values. Nutr Cancer 1996;26(2):123-48.
34. Thakur VS, Deb G, Babcook MA, Gupta S. Plant phytochemicals as epigenetic modulators: Role in cancer chemoprevention. AAPS J 2014;16(1):151-63.
35. Kunnumakkara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Lett 2008;269(2):199-225.
36. Clarke JD, Dashwood RH, Ho E. Multi-targeted prevention of cancer by sulforaphane. Cancer Lett 2008;269(2):291-304.
37. Banerjee S, Kong D, Wang Z, Bao B, Hillman GG, Sarkar FH. Attenuation of multi-targeted proliferation-linked signalling by 3,30-diindolylmethane (DIM): From bench to clinic. Mutat Res 2011;728:47-66.
38. Banerjee S, Li Y, Wang Z, Sarkar FH. Multi-targeted therapy of cancer by genistein. Cancer Lett 2008;269(2):226-42.
39. Cheung KL, Kong AN. Molecular targets of dietary phenethyl isothiocyanate and sulforaphane for cancer chemoprevention. AAPS J 2010;12(1):87-97.
40. Savouret JF, Quesne M. Resveratrol and cancer: A review. Biomed Pharmacother 2002;56(2):84-7.
41. Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: Review of the epidemiologic literature. J Natl Cancer Inst 1999;91(4):317-31.
42. Hirano T, Gotoh M, Oka K. Natural flavonoids and lignin's are potent cytostatic agents against human leukemic HL-60 cells. Life Sci 1994;55:1061-9.
43. Cushman M, Nagarathnam D. Cytotoxicities of some flavonoid analogues. J Nat Prod 1991;54(6):1656-60.
44. Ohta T, Nakatsugi S, Watanabe K, Kawamori T, Ishikawa F, Morotomi M, *et al.* Inhibitory effects of bifidobacterium-fermented soy milk on 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine-induced rat mammary carcinogenesis, with a partial contribution of its component isoflavones. Carcinogenesis 2000;21(5):937-41.
45. Batra P, Sharma AK. Anti-cancer potential of flavonoids: Recent trends and future perspectives. 3 Biotech 2013;3(6):439-59.
46. Agrawal AD. Pharmacological activities of flavonoids: A review. Int J Pharm Nanotechnol 2011;4(2):1394-7.
47. Sandhar HK, Kumar B, Prasher S, Tiwari P, Salhan M. A review of photochemistry and pharmacology of flavonoids. Int Pharm Sci 2011;1(1):25-41.