Phytoestrogen a combat kit against cancer

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Abstract

Worldwide cancer is now becoming leading cause of death. Main aim of therapy is to stop progression of disease. Disease fighting aspect is major concern in all fields of health. Now we are trying to cure all these with help of natural things. Food items containing Phytoestrogens are now considered important in treatment of cancer. Either with chemotherapy that involve use of chemicals to suppress cancer growth and invasion. These natural products are part of our everyday life like grains, nuts, vegetables, herbs. Phytoestrogens and its related products have benefits of no side effects in fact will protect our body from various types of cancers like breast, liver, prostate, colorectal and bladder cancer.

Key words: Phytoestrogen, cancer risk, cancer, hormones, diet.

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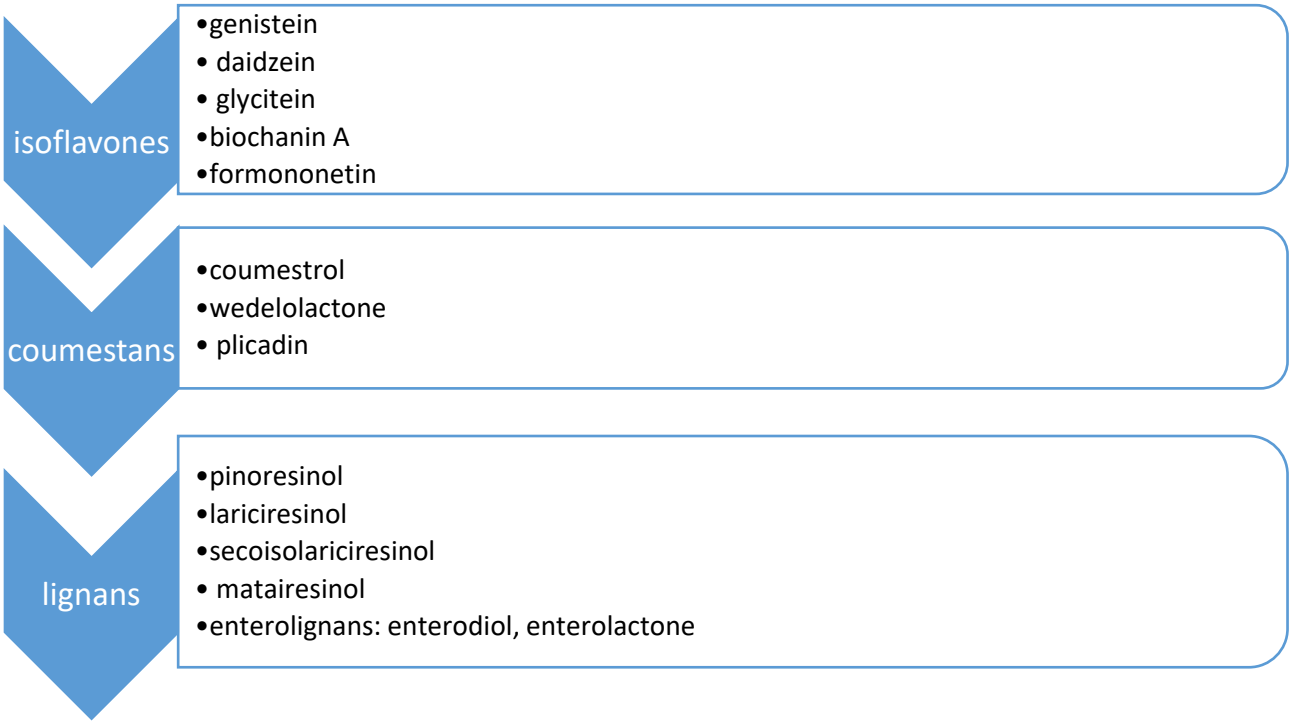
Introduction

Estrogen is steroidal hormone in body that is basically derived via cholesterol having 18 atoms of carbon in it. Female ovaries naturally produce estrogen with help of gonadotrophins (FSH, LH). Phytoestrogens are plant based dietary compounds that are present in various food items. (2). Plants contain various compounds having estrogenic or anti-estrogenic properties.

Some of them show weak properties towards in female body Isoflavone and lignans are well studied phytoestrogens (4). Phytoestrogens act as antioxidant as well as anti-inflammatory, anti-allergic, anti-tumor and anti-thrombotic compound. Phytoestrogen and cancer link was created after observing soy, ginseng and its products on various types of cancers (5). They are basically similar structure to female hormones estrogen that is present in form of 17-β-oestradiol E2. This enables them to bind estrogen receptors. (3). Estrogen has alpha and beta receptors that have different functions and phytoestrogen has ability to bind them. Alpha receptors do cell proliferation and beta cell do apoptosis (natural cell death). Phytoestrogen after binding to ligand move to nucleus where gene expressions are controlled by DNA and RNA via transcription (36). Enterodiol are plant-based act by intestinal bacteria to show phytoestrogenic activity (19). Phytoestrogens after digestion than metabolized by intestinal bacteria and are conjugated via liver. They keep on circulating in plasma till these are excreted in urine (36).

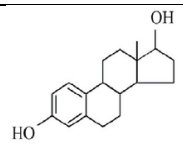
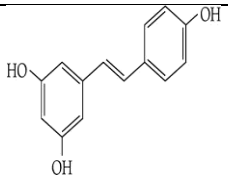
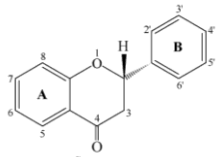
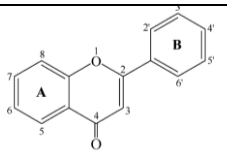
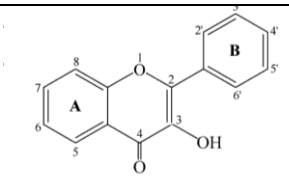
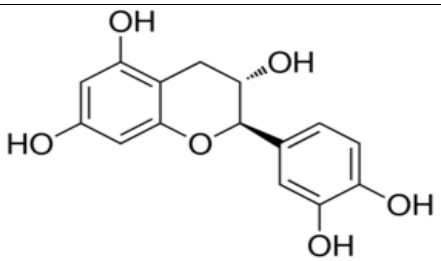
Types of phytoestrogens

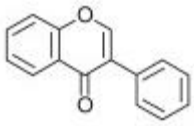
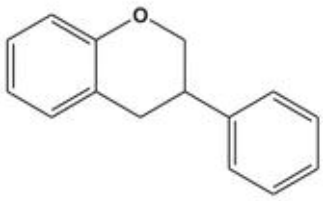
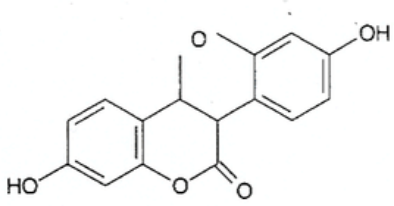


(9).

Food sources

Main sources for phytoestrogen are nuts, seeds vegetables and fruits. In foods we can say phytoestrogen are present in soy and its products, garlic, celery, carrots, rice, potatoes, wheat and certain fruits like apple, grapes, berries, pomegranates and dried fruits like dates, prunes, raisins (17).

Group	Sub group	Dietary source	Structure
17-β-oestradiol	Endogenous Estrogen		 17-beta-estradiol
Polyphenol		Grape skin	
Flavonoids	Flavanones	Citrus fruits and juice	 flavanone
	Flavones	Parsley, celery, capsicum	 flavone
	Flavonols	Kale, broccoli, onion, apple, tomato, lettuce	 flavonol
	Catechins	Green tea, beans, chocolate, apricots, cherries, berries	

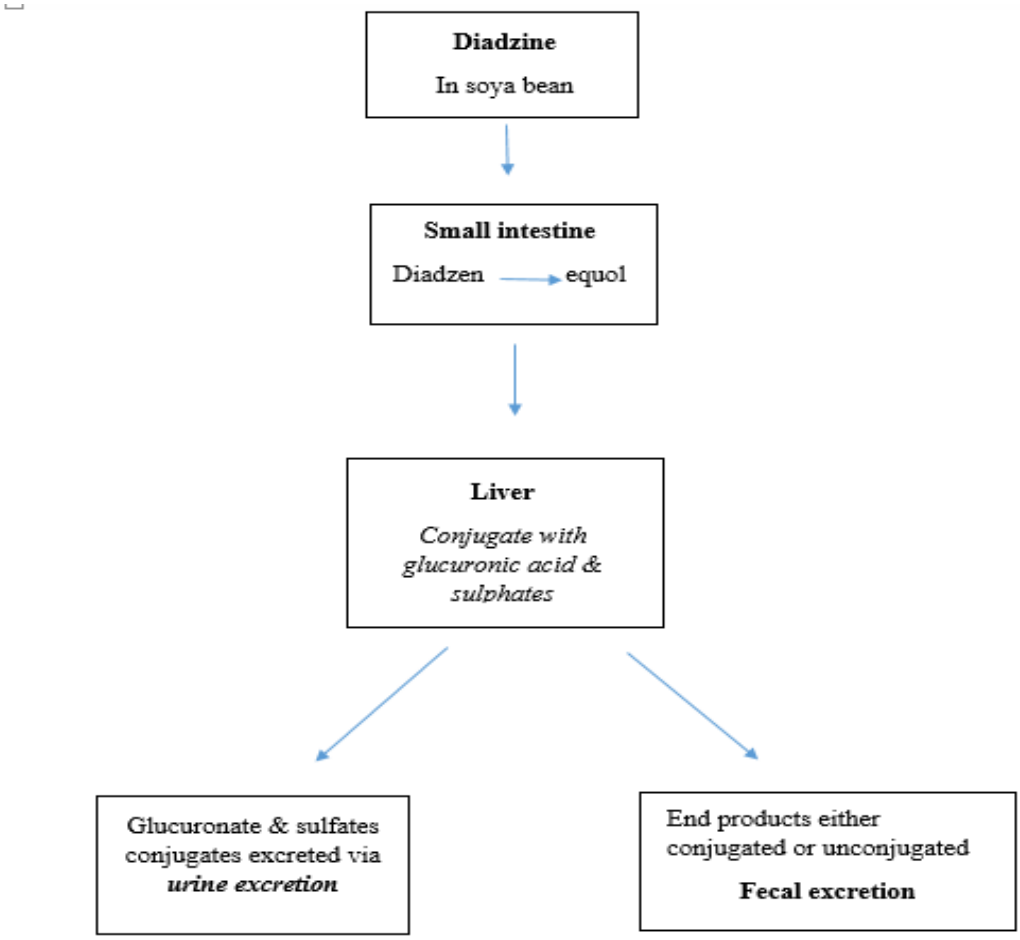
isoflavonoids	Isoflavones	Soy bean, legumes	 Isoflavone
	Isoflavans	Metabolites of daidzens	 Isoflavans
	Coumestans	Clover, alfalfa, spinach	 Coumestans

(7).

Human Estrogens versus Phytoestrogens

Estrogen hormone produce in body are in three main forms that are estradiol, estrone, estriol basically produced in ovaries or placenta and in minute amount in testes. Human body estrogen has its metabolites in blood known as steroids. Although phytoestrogens are similar to estrogen but they don't produce steroidal metabolites in blood. Phytoestrogens just mimic action of estrogen by binding its receptors (11).

Intestinal Absorption and Metabolism of Phytoestrogens

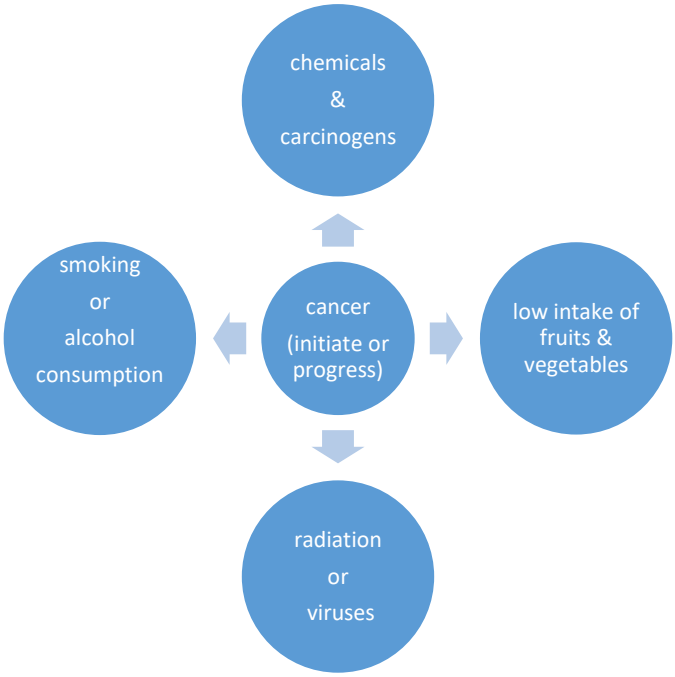


Daidzein is main active ingredient present in soya bean that are in inactive form known as glycoside conjugates. After ingestion they are hydrolyzed via small intestine bacteria's and are converted to aglycones. This is primary metabolites that are lipid soluble and absorb in intestinal mucosa. So, it shows intestinal bacteria like species of lactobacilli, bacteroids and bifidous bacteria help in hydrolysis to a form similar to human estrogen. So easily attached to estrogen receptors and waste products are excreted via urine and feces (8).

Cancer

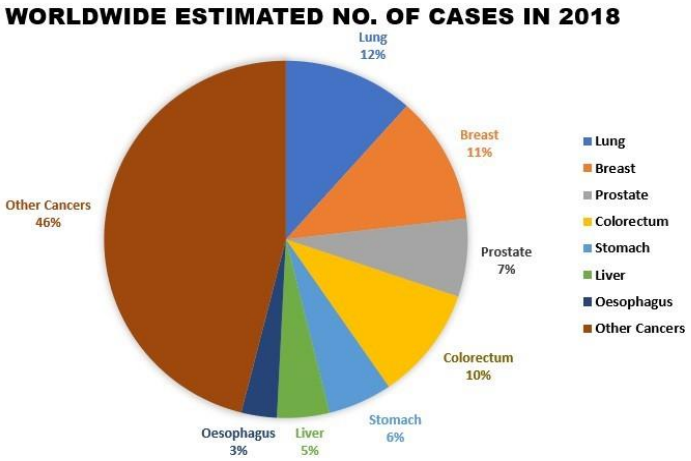
Cancer is uncontrolled division of cell towards surroundings. More abnormal cells are produced these damaged cells are replicated despite of fact they are not needed. These unstoppable cells are called tumors (12). Cancer is genetic defect. Mortality rate is higher in any sort of cancer because of disease progression. Over past few years reduction in smoking decline mortality from cancer because of early treatment and less damage because of smoking cessation (13).

Cancer is caused by Oxidative stress, Inflammation, Metastasis, Apoptosis and Angiogenesis (17). Now use of herbal or natural products are used along with medicine. Herbal medicines or natural products have least side effects. These are known as co drugs (9). Cancer of various types are being studied. Major categories are carcinomas, lymphomas, sarcoma, leukemia, myeloma and tumors of brain and spinal cord (16). Cancer basically spread via tissues by growing rapidly, lymph via vessels and blood via blood vessels to whole body (17).



(17).

Prevalence



(World Health Organization et al, 2018).

Phytoestrogen and cancer

Structurally estrogen 17-β-estradiol and phytoestrogen are similar (29). In human body phytoestrogens has various health benefits like heart disease, cancer, and bone health and menopause symptoms prevention (36).

For the identifcation of breast cancer, breast cancer tissues are investigated for estrogen and progesterone receptors including HER2 antigen. These tests give information regarding the aggressiveness of cancer and response of certain drugs used for treatment of breast cancer. (29). High levels of estrogen might be a risk factor for breast cancer in women by overgrowing cancer cell and disturb apoptosis. Some endocrine disturbers have same structure like E2 so interfere signaling of estrogen.

Mechanism of cancer prevention

Soy products mainly contain genistein (a phytoestrogen). ERβ is in higher concentration than ERα. ERβ protect against tumors so we can say ratio of ERα/ERβ is important in determining chemo preventive properties (45). Estrogen assay is developed which act as missing receptors are compensated. Deficiency of these receptors is major cause of mortality from cancers (29).

Mode of action of phytoestrogens

Estrogen receptors have different subtypes that play role in gene regulation. ERα maintain tissue proliferation, growth and maintenance. ERβ shows response to ERα by

multiplication of cells (27). Reverse role of both of these is way by which phytoestrogen work similar to E2 and bind them.

They have different role in gene regulation so in cancer progression and treatment (28). ERα act on breast and uterus via cell division that is need for maintaining and regrowth of body tissues. T47D–ERβ cell line is used for the treatment of breast cancer to create constant level of ERα which work with E2 and increase cell division. Whereas, ERβ with E2 will not divide cells. This shows that ERβ respond to ERα divide cell (3). Phytoestrogens bind especially with ERβ that help inhibiting activity of ERα (2).

Breast cancer and phytoestrogen

In female all over the globe breast cancer is one of the most common cancer-causing mortalities (29).

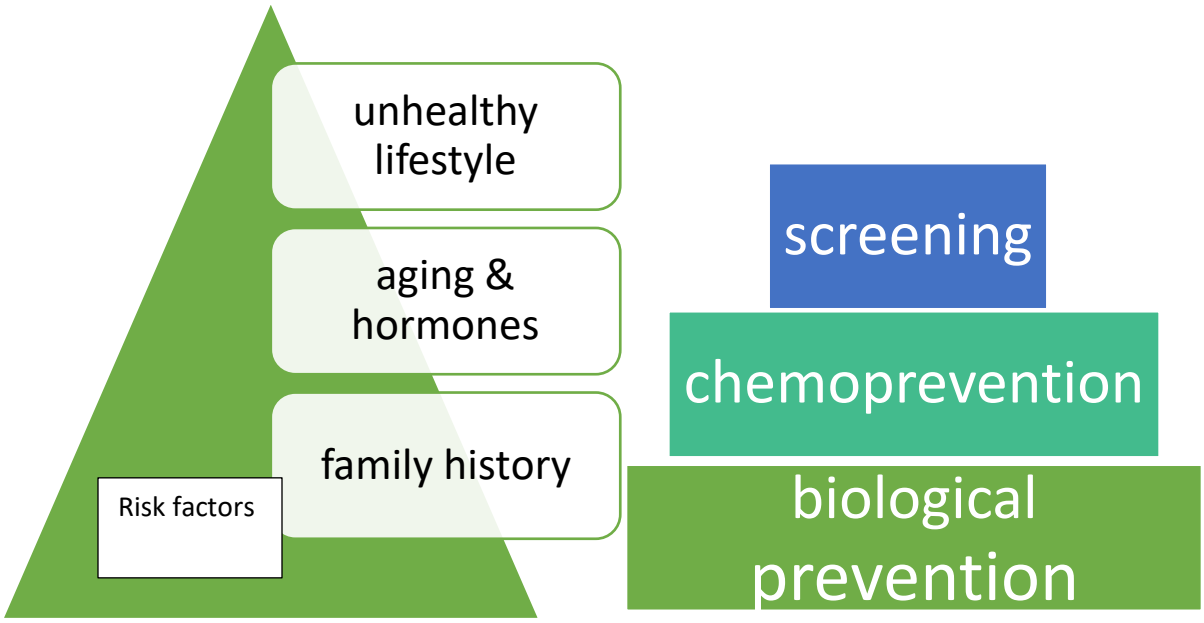
With new trends it is seen that phytoestrogens are acing well against treatment of breast cancer by doing apoptosis, cell mediated death and cell cycle arrest. Recent clinical trials have shown that these natural compounds can be used for treatment (27). For treatment of breast cancer most commonly used words are estrogen and progesterone receptors and HER2 all these collectively provides therapy against breast cancer (28). It is seen that Asian and American women consume soy products have lower cancer risk as compare to those who are not consuming soy. Minute quantity of soy was consumed by American and slightly larger amount by Asians. Reason of its action was similar structure to estrogen (31). Estrogen in large amount cause pain and edema in breast whereas no such symptoms see while using phytoestrogen (29). However, placebo effect shows no changes in isoflavones and placebo group which shows more research is needed (21). Another study suggests that soy intake in early life will help you in protection

(26). Any sort of cancer treatment is done to remove tumor or avoid its spread to surroundings and ultimately improving quality of life (10).

Natural products are now being used as medicine main reason is that it has least side effects along with this it also inhibits metastasis or epithelial division (29). Breast cancer starts from abnormal cell division that lead to tumor development with other cancer-causing factors like macrophages and stromal effects (11). Role of phytoestrogens as anti-cancer agent depends on cyclin D1 and its

related kinase inhibitors or tumor suppressor genes like P21, 27,57 and APC, PTEN, ATM respectively (34).

When estrogen is present in large amount it will bind to ERβ whereas, Phytoestrogens bind with ERβ when they are in low amount. This shows a low number of Phytoestrogens will work for breast cancer prevention (35).



(55).

Liver cancer

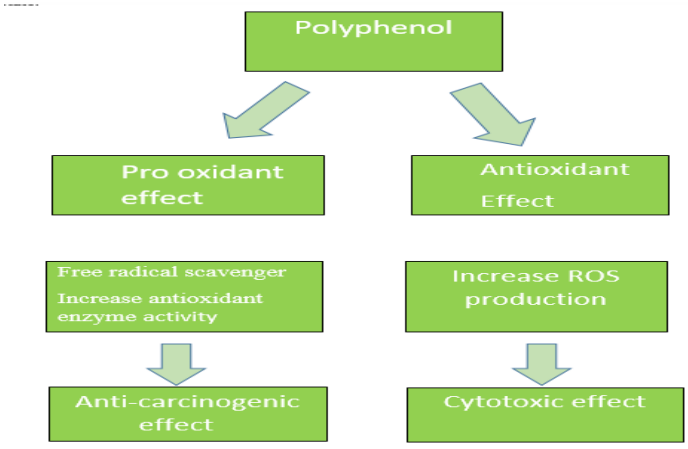
In worldwide 6th common cause of cancer is liver cancer not only this mortality rate is very high due to this cancer. Reason is it is mostly diagnosed when this tumor is at advance stage so no therapeutic option is left behind (37). Liver carcinomas are malignant tumors arising from parenchymal cells of liver. Between malignant tumors Hepatocellular carcinoma and cancer of bile duct is most important (36). Now it is seen that phytoestrogens along with treatment drugs of hepatic carcinoma will minimize medication side effects (38). Combination of biochanin-A along with sorafenib increase apoptosis which help to kill cancer cells (40).

Prostate cancer

Like females are facing issue of breast cancer worldwide men are facing abnormal and uncontrolled production of cell of prostate, main gland in reproductive system of males. This might be due to genetic variation,

inflammation which help tumor to grow and development of abnormal blood vessel to support tumor or either abnormal cell doesn't undergo apoptosis (41)

Polyphenol a potent phytoestrogen act as both anti-inflammatory and pro inflammatory agent by increasing ROS activity via free radicals. Moreover, it also increases antioxidants enzymes in prostate.



Bladder cancer

Bladder cancer is at ninth number and men are affected more than women. The reason

why men are more effected as smoking is main cause. Beside this arsenic present in drinking water is main

risk factor. Isoflavone in soy consumed on daily basis are excreted via urine so we can say that its lining is more exposed with these protecting agents will save from bladder cancer (42).

Colorectal Cancer (CRC)

Colorectal cancer is combination of both colon and rectum which are basically lower parts of our digestive system. When polyps and adenomas are formed in these areas risk of converting in colon cancer will increase. Firstly, noncancerous polyps or adenomas are formed. Adenomas might be conventional or sessile in form of polyp which then convert to cancer (Strum et al, 2016). Phytoestrogens found in various food items are used as cure for cancer (43).

Chemotherapy

Alkylating agents or chemotherapeutic agents are used in cancer treatment but its effects are seen depending on type of cancer. In treatment of gastric cancer genistein used to overcome resistance caused by cisplatin used for cure of pancreatic cancer by activation of NF-κB.

Phytoestrogens also show the potential to increase the efficacy of alkylating agents in several studies. The combination of cisplatin

with apigenin seems to inhibit cell proliferation in breast cancer cell lines and decreases telomerase activity, limiting one of the mechanisms to escape apoptosis and induce metastasis. Chemo preventive properties of phytoestrogens have emerged from epidemiological observations. In recent clinical research studies, phytoestrogens are safe and may even protect against breast cancer (44).

In vivo and in vitro models show good effect of chemo therapeutic agents along with clinical studies that show improvements. Another study of genistein with chemotherapy drugs show improvement for some pancreatic cancer patients. This led to development of drug based on phytoestrogens along with chemo agents to minimize side effects and maximize benefits (45).

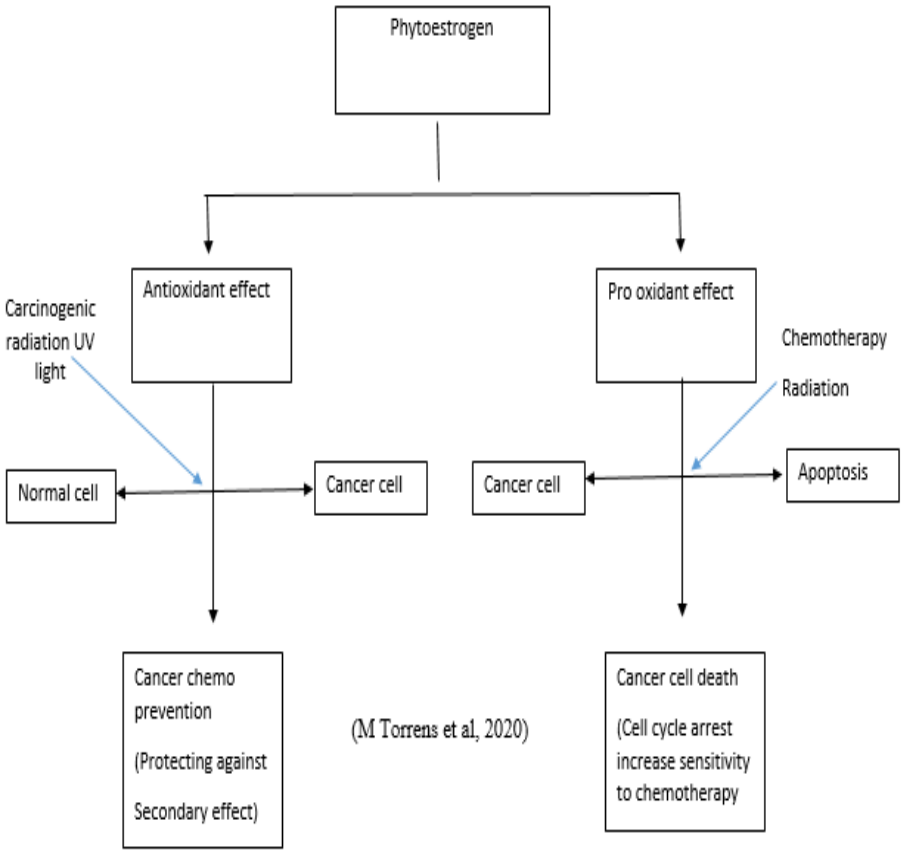
One of the side effects of chemo therapy is excess free radicals in body which means increase in oxidative stress which cause hindrance in positive effect of chemo on body by apoptosis and disturb cell cycle in which cell is not moved to G1 phase from G0 phase or S phase which result in inhibition of DNA synthesis. Both these points are checking point in cell division (46). Alkylating chemo drugs like platin family adducts DNA as a result interfere with DNA repair process which protect cell from division. As a result, cancer cell won't replicate so this is widely used in various cancer treatment like lung, breast and ovarian cancer (45).

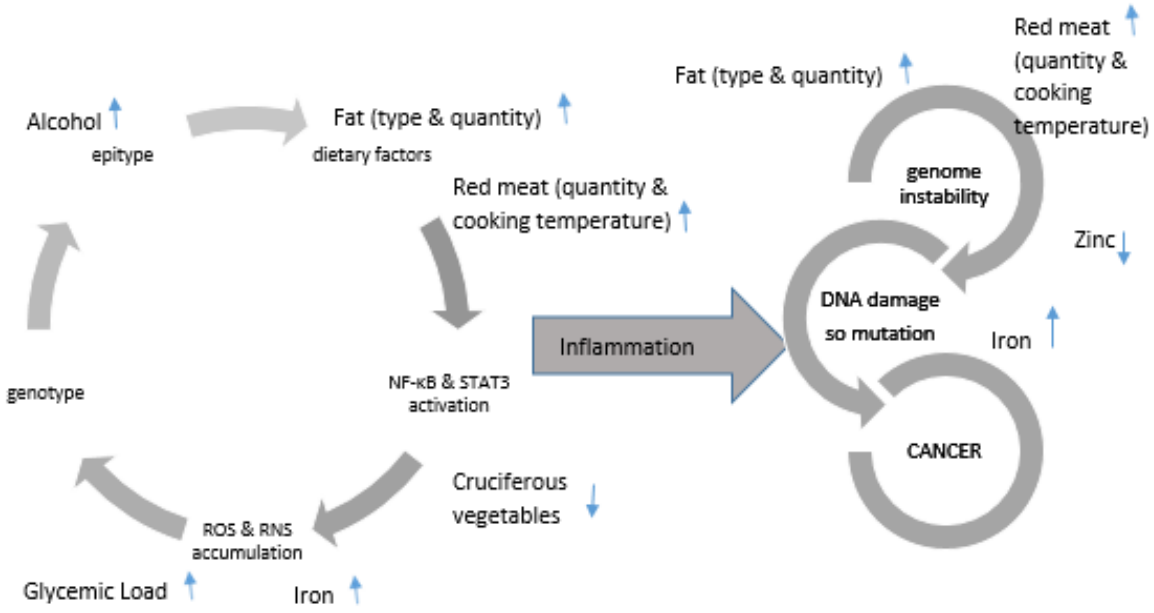
Nutrition therapy

Diet plays an important role in progression and treatment of cancer. Worldwide diet related to cancer is most common (46).

Before going to any diet therapy Subjective global assessment SGA form is used that has 3 major categories to check nutritional status like well nourished, moderate malnourished or severely

malnourished. After this classification follow up is set. Reason for setting follow up is to check nutritional status routinely. It is usually broad-spectrum approach clinical or personalized might vary because of tolerance and cultural values. Different studies suggest that 5-9 fruits 3-4 vegetables are needed per day for antioxidant properties in cancer patient (47).



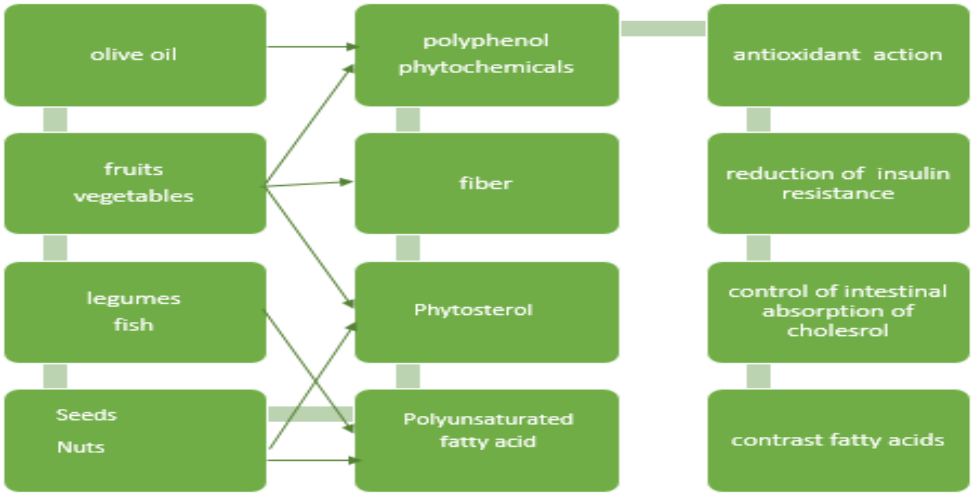


(A Al Shaikh et al, 2019)

Mediterranean Diet

It arises from different cultures collectively to call it Mediterranean introduced by UNESCO in 2010. As it shares cultural diversity so a greater number of people follow it and is beneficial. This diet protects from heart disease by lowering level of cholesterol along with fighting cancer cells as it is rich in antioxidants along with other minerals and vitamins. Following this diet also prevent from DNA damage so help in cancer prevention (50). Now this diet is no more a life style rather become a part of culture so in result in improving quality of life (51).

High fiber, rich in antioxidants and carotenoids play role in decreasing risk of breast cancer. This will decrease level of estrogen that is basically cause of cancer. Not only this being rich in antioxidant free load of free radicals from body along with protecting DNA damage (52). Following Mediterranean diet lower the risk of all sort of cancers and its related mortilities. High intake of fiber in this diet along with β-glucans found in food lower low-density lipoprotein cholesterol is good for colorectal cancer (53).



(F Turati et al, 2018)

Combination Effects of Soy Isoflavones and Other Types of Phytoestrogens

Phytoestrogens are part of our daily life. Combination of these produce more beneficial effects. Kumar et al. observed the combine effects of different phytoestrogens like biochanin A, quercetin, and genistein on PCa cell lines. This shows that all three combinedly inhibit growth of prostate cancer as compare to alone effect of any of phytoestrogen. So, we can say that phytoestrogens are protective against cancer when work together (54). Another phytoestrogen resveratrol helps our body to fight with oral cancer it will also involve cancer of esophagus. It

suppresses growth rate of any sort of cancer. In spite of chemotherapeutic effect of different phytoestrogen like resveratrol will inhibit tumor replication not only this it reverts back already present tumor in any part like ovaries, bladder, head and neck or stomach. It also suppresses growth of tumor cells by inducing apoptosis via direct action on mitochondria by activating it (55).

Future Prospects

To prevent cancer in human body Phytoestrogens, exhibit both hormonal and non-hormonal mechanisms. With increase modernization and rapid change in diet and life style cancer cases are

increasing worldwide. For cure of any sort of cancer whether breast, prostate, liver colon or lungs cancer medicines being used for treatment have various toxic effects on body which might lead to drug resistance which

lead to low response or poor outcomes. Chemotherapy or radiotherapy done to cure cancer is also casing many adverse effects which are long lasting. Natural compounds like Phytoestrogens are easy to obtain via diet and have helpful affect in control and treatment of cancer (56).

Conclusion

It is seen that phytoestrogens have protective effect against various cancers. However, exact chemotherapeutic effect is not studied yet so we can say that it will minimize harmful effects. Moreover, phytoestrogens are present in every day to day used item so we can easily consume it to get benefits. Diet rich in plant-based foods are high in phytoestrogens so help in various pharmacological therapy. At age of menopause women mainly suffer from estrogen related issues like heart issues, bones related issues and cognitive issues along with poor quality of life. Future research should focus on specific soy components, variability in phytoestrogen metabolism and effects of phytoestrogens on specific target tissues.

References

1. Qadir, M. I., & Cheema, B. N. (2017). Phytoestrogens and related food components in the prevention of cancer. Critical Reviews in Eukaryotic Gene Expression, 27(2), 99–112.
2. Rietjens, I. M. C. M., Louisse, J., & Beekmann, K. (2017). The potential health effects of dietary phytoestrogens: Potential health effects of dietary phytoestrogens. British Journal of Pharmacology, 174(11), 1263–1280.
3. Mohd Siddique, M. U., Barbhuiya, T. K., Sinha, B. N., & Jayaprakash, V. (2019a). Phytoestrogens and their synthetic analogues as substrate mimic inhibitors of CYP1B1. European Journal of Medicinal Chemistry, 163, 28–36.
4. Dixon, R. A. (2004). Phytoestrogens. Annual Review of Plant Biology, 55(1), 225–261.

5. Torrens-Mas, M., & Roca, P. (2020). Phytoestrogens for cancer prevention and treatment. Biology, 9(12), 427.
6. Desmawati, D., & Sulastri, D. (2019). Phytoestrogens and their health effect. Open Access Macedonian Journal of Medical Sciences, 7(3), 495–499.
7. Stojanov, S., & Kreft, S. (2020). Gut Microbiota and the metabolism of phytoestrogens. Revista Brasileira de Farmacognosia: Orgao Oficial Da Sociedade Brasileira de Farmacognosia, 30(2), 145–154.
8. Viggiani, M. T., Polimeno, L., Di Leo, A., & Barone, M. (2019). Phytoestrogens: Dietary intake, bioavailability, and protective mechanisms against colorectal neoproliferative lesions. Nutrients, 11(8), 1709.
9. Research journal of life sciences, bioinformatics, pharmaceutical and chemical sciences (Vol. 2). (2017). Life Science Informatics Publications.
10. Dhan, P., & Charu, G. (2014). Role of phytoestrogens as nutraceuticals in human health. In Phytochemicals of nutraceutical importance (pp. 148–172). Wallingford: CABI.
11. M. Saljoughian, PharmD, PhD Department of Pharmacy, Alta Bates Summit Medical Center, HS-27HS-32. Berkeley, California. (2007, December 20). Focus on Phytoestrogens. Retrieved January 4, 2021, from Uspharmacist.com
12. What Is Cancer? (2007). Retrieved January 4, 2021, from Cancer.gov website: https://www.cancer.gov/about-cancer/understanding/what-is-cancer
13. Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019: Cancer statistics, 2019. CA: A Cancer Journal for Clinicians, 69(1), 7–34.
14. Maruca, A., Catalano, R., Bagetta, D., Mesiti, F., Ambrosio, F. A., Romeo, I,

Lupia, A. (2019). The Mediterranean Diet as source of bioactive compounds with multi-targeting anti-cancer profile. European Journal of Medicinal Chemistry, 181(111579), 111579.

15. (N.d.). Retrieved January 4, 2021, from Cell.com website: https://www.cell.com/cancer-cell/pdf/S1535-6108(17)30253-2.pdf
16. National Cancer Institute (NCI). (2015, July 7). Retrieved January 4, 2021,
17. Mahan, L. K., Escott-Stump, S., & Raymond, J. L. (2014). Krause's food & the nutrition care process (13th ed.). London, England: W B Saunders.
18. Lee, G.-A., Hwang, K.-A., & Choi, K.-C. (2016). Roles of dietary phytoestrogens on the regulation of epithelial-mesenchymal transition in diverse cancer metastasis. Toxins, 8(6), 162.
19. Stojanov, S., & Kreft, S. (2020). Gut Microbiota and the metabolism of phytoestrogens. Revista Brasileira de Farmacognosia: Orgao Oficial Da Sociedade Brasileira de Farmacognosia, 30(2), 145–154.
20. Desmawati, D., & Sulastri, D. (2019). Phytoestrogens and their health effect. Open Access Macedonian Journal of Medical Sciences, 7(3), 495–499.
21. Hasan, M., Kumolosasi, E., Jasamai, M., Jamal, J. A., Azmi, N., & Rajab, N. F. (2020). Evaluation of phytoestrogens in inducing cell death mediated by decreasing Annexin A1 in Annexin A1-knockdown leukemia cells. Daru: Journal of Faculty of Pharmacy, Tehran University of Medical Sciences, 28(1), 97–108.
22. Akram, M., Iqbal, M., Daniyal, M., & Khan, A. U. (2017). Awareness and current knowledge
23. of breast cancer. Biological Research, 50(1), 33.

24. Torrens-Mas, M., & Roca, P. (2020). Phytoestrogens for cancer prevention and treatment. Biology, 9(12), 427.
25. Rietjens, I. M. C. M., Louisse, J., & Beekmann, K. (2017). The potential health effects of dietary phytoestrogens: Potential health effects of dietary phytoestrogens. British Journal of Pharmacology, 174(11), 1263–1280.
26. Ali, S., & Coombes, R. C. (2000). Estrogen receptor alpha in human breast cancer: occurrence and significance. Journal of Mammary Gland Biology and Neoplasia, 5(3), 271–281.
27. Rietjens, I. M. C. M., Louisse, J., & Beekmann, K. (2017). The potential health effects of dietary phytoestrogens: Potential health effects of dietary phytoestrogens. British Journal of Pharmacology, 174(11), 1263–1280.
28. Hapangama, D. K., Kamal, A. M., & Bulmer, J. N. (2015). Estrogen receptor β: the guardian of the endometrium. Human Reproduction Update, 21(2), 174–193.
29. Akram, M., Iqbal, M., Daniyal, M., & Khan, A. U. (2017). Awareness and current knowledge of breast cancer. Biological Research, 50(1), 33.
30. M, A. S., P, A. K., & Narayanankutty, A. (2020). Natural bioactive compounds as emerging therapeutic molecules against breast cancer: Emphasis on the role of phytoestrogens. Current Drug Targets, 21.
31. Momenimovahed, Z., & Salehiniya, H. (2019). Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Cancer (Dove Medical Press), 11, 151–164.
32. Zuljevic, G., & O'Brien, S. (2016). Phytoestrogens in soy: a tentative protective factor against breast cancer.
33. Moghadas-Dastjerdi, H., Sha-E-Tallat, H. R., Sannachi, L., Sadeghi-Naini, A., &

Czarnota, G. J. (2020). A priori prediction of tumour response to neoadjuvant chemotherapy in breast cancer patients using quantitative CT and machine learning. Scientific Reports, 10(1), 10936.

34. Ström, A., Hartman, J., Foster, J. S., Kietz, S., Wimalasena, J., & Gustafsson, J.-A. (2004). Estrogen receptor beta inhibits 17beta-estradiol stimulated proliferation of the breast cancer cell line T47D. Proceedings of the National Academy of Sciences of the United States of America, 101(6), 1566–1571.
35. Basu, P., & Maier, C. (2018). Phytoestrogens and breast cancer: In vitro anticancer activities of isoflavones, lignans, coumestans, stilbenes and their analogs and derivatives. Biomedecine & Pharmacotherapie [Biomedicine & Pharmacotherapy], 107, 1648–1666.
36. Desmawati, D., & Sulastri, D. (2019). Phytoestrogens and their health effect. Open Access Macedonian Journal of Medical Sciences, 7(3), 495–499
37. Llovet, J. M., & Beaugrand, M. (2003). Hepatocellular carcinoma: present status and future prospects. Journal of Hepatology, 38 Suppl 1, S136-49.
38. Research journal of life sciences, bioinformatics, pharmaceutical and chemical sciences (Vol. 2). (2017). Life Science Informatics Publications.
39. Youssef, M. M., Tolba, M. F., Badawy, N. N., Liu, A. W., El-Ahwany, E., Khalifa, A. E., … Abdel-Naim, A. B. (2016). Novel combination of sorafenib and biochanin-A synergistically enhances the anti-proliferative and pro-apoptotic effects on hepatocellular carcinoma cells. Scientific Reports, 6(1), 30717.
40. Li, H., Jia, E., & Jiao, J. (2020). Phytoestrogens in NAFLD: Potential mechanisms of action. Hormone and Metabolic Research, 52(2), 77–84.

41. Costea, T., Nagy, P., Ganea, C., Szöllősi, J., & Mocanu, M.-M. (2019). Molecular mechanisms and bioavailability of polyphenols in prostate cancer. International Journal of Molecular Sciences, 20(5), 1062.

42. Wada, K., Tsuji, M., Tamura, T., Konishi, K., Goto, Y., Mizuta, F., Nagata, C. (2018). Soy isoflavone intake and bladder cancer risk in Japan: From the Takayama study. Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 27(11), 1371–1375.

43. Rossi, M., Mirbagheri, S. E. Y. E. D. S., Keshavarzian, A., & Bishehsari, F. (2018). Nutraceuticals in colorectal cancer: A mechanistic approach. European Journal of Pharmacology, 833, 396–402.

44. Domínguez-López, I., Yago-Aragón, M., Salas-Huetos, A., Tresserra-Rimbau, A., & Hurtado-Barroso, S. (2020). Effects of dietary phytoestrogens on hormones throughout a human lifespan: A review. Nutrients, 12(8), 2456.

45. Torrens-Mas, M., & Roca, P. (2020). Phytoestrogens for cancer prevention and treatment. Biology, 9(12), 427.

46. Sahin, I., Bilir, B., Ali, S., Sahin, K., & Kucuk, O. (2019). Soy isoflavones in integrative oncology: Increased efficacy and decreased toxicity of cancer therapy. Integrative Cancer Therapies, 18, 1534735419835310.

47. Ana Teresa Limon-Miro, Veronica Lopez-Teros, Humberto Astiazaran-Garcia, Dietary Guidelines for Breast Cancer Patients: A Critical Review, Advances in Nutrition, Volume 8, Issue 4, July 2017, Pages 613–623.

48. Ziaei, S., & Halaby, R. (2017). Dietary isoflavones and breast cancer

risk. Medicines (Basel, Switzerland), 4(2), 18.

49. A Keys, Mediterranean diet and public health: personal reflections, The American Journal of Clinical Nutrition, Volume 61, Issue 6, June 1995, Pages 1321S–1323S
50. Mentella, M. C., Scaldaferri, F., Ricci, C., Gasbarrini, A., & Miggiano, G. A. D. (2019). Cancer and Mediterranean diet: A review. Nutrients, 11(9), 2059.
51. Divella, R., Daniele, A., Savino, E., & Paradiso, A. (2020). Anticancer effects of nutraceuticals in the Mediterranean diet: An epigenetic diet model. Cancer Genomics & Proteomics, 17(4), 335–350.
52. Turati, F., Carioli, G., Bravi, F., Ferraroni, M., Serraino, D., Montella, M., La Vecchia, C. (2018). Mediterranean diet and breast cancer risk. Nutrients, 10(3), 326.
53. Hernáez, Á., & Estruch, R. (2019). The Mediterranean diet and cancer: What do human and molecular studies have to say about it? Nutrients, 11(9), 2155.
54. Zhang, H.-Y., Cui, J., Zhang, Y., Wang, Z.-L., Chong, T., & Wang, Z.-M. (2016). Isoflavones and prostate cancer: A review of some critical issues: A review of some critical issues. Chinese Medical Journal, 129(3), 341–347.
55. Ko, J.-H., Sethi, G., Um, J.-Y., Shanmugam, M. K., Arfuso, F., Kumar, A. P., Ahn, K. S. (2017). The role of resveratrol in cancer therapy. International Journal of Molecular Sciences, 18(12).
56. Mitra, S., & Dash, R. (2018). Natural products for the management and prevention of breast cancer. Evidence-Based Complementary and Alternative Medicine: ECAM, 2018, 1–23.