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A REVIEW ON THE RELATIONSHIP OF MAST CELLS AND MACROPHAGES IN BREAST CANCER

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Abstract-This article investigated all about breast cancer a different dimensions of breast cancer and its associated factors. It revealed that breast cancer was and continues to be among the most prevalent and growing malignant diseases among Iranian women in the past four decades. Also there are mast cells and their relation between breast cancers is shows. In this article, required information was collected through literature review and keyword (cancer, breast cancer, cell, gene, life quality, women, prevalence, productivity, age, obesity, alcohol, cigarette, menopause, genetic, Cytokine, and mortality) this disease affects all physical, mental, and social aspects of women life. On the other hand, such factors as social and family supports during the illness can reduce its damages.

Index Terms - Cancer, diagnosis, mast cells.

INTRODUCTION:

This article provides a standing report on the worldwide burden of cancer worldwide using the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, with attention on geographic variability across 20 world regions. There'll be an estimated 18.1 million new cancer cases (17.0 million excluding non-melanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding non-melanoma skin cancers) in 2018. In both sexes combined, carcinoma is that the most ordinarily diagnosed cancer (11.6% of the entire cases) and therefore the leading explanation for cancer death (18.4% of the entire cancer deaths), closely followed by female carcinoma (11.6%), prostatic adeno-carcinoma (7.1%), and colorectal cancer (6.1%) for incidence and colorectal cancer (9.2%), stomach cancer (8.2%), and cancer of the liver (8.2%) for mortality. carcinoma is that the most frequent cancer and therefore the leading explanation for cancer death among males, followed by prostate and colorectal cancer (for incidence) and liver and stomach cancer (for mortality). Among females, carcinoma is that the most ordinarily diagnosed cancer and therefore the leading explanation for cancer death, followed by colorectal and carcinoma (for incidence), and the other way around (for mortality); cervical cancer ranks fourth for both incidence and mortality. the foremost frequently diagnosed cancer and therefore the leading explanation for cancer death, however, substantially vary across countries and within each country counting on the degree of economic development and associated social and life style factors. it's noteworthy that high-quality cancer registry data, the idea for planning and implementing evidence-based cancer control programs, aren't available in most low- and middle-income countries. The worldwide Initiative for Cancer Registry Development is a world partnership that supports better estimation, also because the collection and use of local data, to prioritize and evaluate national cancer control efforts.

Against this backdrop, the present article provides a standing report on the cancer burden worldwide in 2018, supported the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer (IARC).6 As in previous reports for 2002, 7 2008, 8 and 2012, 9 the first focus is on an outline of cancer incidence and mortality at the worldwide level and an assessment of the geographic variability observed across 20 predefined world regions. We describe the magnitude and distribution of the disease overall and for the main cancer types, commenting briefly on the associated risk factors and prospects for prevention of the main cancers observed worldwide. We conclude by stating the restrictions of the exercise and therefore the need for population-based national and subnational cancer surveillance data to enhance the accuracy of the GLOBOCAN estimates and inform on-the-ground initiatives in cancer control.Breast cancer is that the commonest sort of cancer in women and therefore the second commonest cancer overall. Over 2 million new cases of carcinoma appeared in 2018, and its incidence and mortality are rapidly growing worldwide. Carcinoma may be a complex and heterogeneous disease in terms of microscopic features, therapeutic response, spreading to distant sites, and patients' outcomes. A possible explanation might be, in part, that we still lack an entire picture of the biological heterogeneity of carcinoma with reference to molecular changes and cellular composition.

Importantly, this complexity isn't entirely reflected by the most clinical parameters (age, lymph gland status, tumor size, histological grade) and molecular markers.

Breast cancer and mast cells:

Mast cells (MCs) represent the foremost controversial non-malignant element of the tumor microenvironment. Our aim was to review how MCs density and distribution (intratumoral-MCit versus peritumoral-MCpt) relate to tumor grade and molecular subtypes. Materials and Methods: MCs tryptase immunohistochemistry was performed on 80 cases of breast carcinomas. Results: For Luminal A tumors, a correlation was detected between MCit and progesterone receptor (PR) (p=0.005). Luminal B tumors showed a big correlation between MCpt and age (p=0.009), estrogen receptor (ER) (p=0.017) and PR (p=0.035). MCit and MCpt were strongly interrelated during this subtype (p=0.002) and in triple-negative breast cancers (p=0.002). In HER2 subtype, MCpt tumors were significantly correlated with HER2 (p=0.044). In G2 tumors, MCpt correlated with ER (p=0.015) and PR (p=0.038) while in G3 tumors ER correlated with both MCit (p=0.009) and MCpt (p=0.000487) tumors. Conclusion: MCs dynamics are strongly influenced by hormone receptors and HER2 status. MCit increased in aggressive tumor types and may be a worse prognostic factor.Mast cells (MCs) were first identified in human tumors and were named intrinsically by Ehrlich. These cells store and release a spread of biologically active substances which will affect various target cells. Although usually related to allergic disorders, MCs are a serious source of pro-tumorigenic (e.g., angiogenic and lymphangiogenic factors) and anti-tumorigenic molecules (e.g., TNF-α and IL-90), thus, their role on carcinoma is controversial. Some scholars believe that mastocyte infiltration suggests an honest prognosis of breast cancer: almost like our results, three other groups have observed high MCs density in luminal A and B sorts of carcinoma, which may be hormonally treated and have a far better prognosis. This means that MCs are related to less aggressive tumors. On the opposite hand, we all know that estrogen acts as a proliferative factor, and may stimulate carcinoma development. this will explain why in our study both MCit and MCpt interrelated with ER in G3 tumors. Positive correlations between ER and MCs suggest that estrogen may be a chemotactic molecule for MCs. We were especially curious about the correlation between MCit and ER+ carcinoma cells, as some studies have proved that estrogen activates mast cells in ovarian endometriosis which human uterine mast cells express ERβ. Others have shown that administration of estrogens results in eosinophilic and MCs infiltrations. MCs play a pro-tumorigenic role in human bladder cancer through stimulating ERβ and it's been demonstrated during a murine model of bladder cancer that a selective ERβ antagonist can inhibit mast cell-promoted tumor growth.

Mast Cells Are Potential Targets for Anticancer Therapy:

Experimental studies in mice have suggested that mastocyte inhibitors could reduce the amount and activity of the cells in certain sorts of cancers improving disease outcomes. as an example , in murine models of prostate adenocarcinoma, treatment with cromolyn (sodium cromoglicate), a well known mastocyte degranulation inhibitor, blocked prostate tumor growth. Paradoxically, treated mice developed highly malignant neuroendocrine cancers, a fatal collateral event that ought to be more deeply studied before proposing the utilization of cromolyn or the targeting of mast cells as therapy. On the opposite hand, during a preclinical study involving carcinoma patients treated with the drug masitinib, a tyrosine-kinase inhibitor that has inhibitory activity against c-Kit compromising mastocyte survival, it had been shown that patients receiving a mixture of masitinib plus standard chemotherapy had an increased survival compared with patients receiving chemotherapy alone. However, it's important to notice that the study didn't distinguish whether the increased survival was directly associated with mastocyte activity.Other in vitro and in vivo studies using mastocyte stabilizers or mast cell-depleting agents have shown controversial results. as an example , depletion of mast cells with imatinib enhanced tumor growth during a murine model of breast carcinoma, supporting an antitumoral role for mast cells. In agreement, mice treated with cromolyn showed mammary tumors with extensive hypoxic hemorrhagic regions and clots, which weren't observed within the control group, suggesting that mast cells play a crucial role in inhibiting blood coagulation and maintaining blood perfusion in carcinoma , probably through secretion of heparin, urokinase , chymase, and tryptase.Histamine, one among the foremost important components of mastocyte granules, has been shown to be critical for development of the traditional rat mamma . Likewise, histamine has been implicated in promoting tumor cell proliferation and enhancing growth of experimental mammary carcinomas, particularly acting through H2 receptors, and treatment with H2 receptor antagonists significantly inhibited tumor cell proliferation and tumor growth. However, a person's clinical test testing the H2 receptor antagonist cimetidine (Tagamet), found no relationship between the preoperative drug administration and carcinoma growth.

Breast Cancer and Macrophages:

Macrophages are critical mediators of inflammation and important regulators of developmental processes. As a key phagocytic cell type, macrophages evolved as a part of the innate system to engulf and process cell debris and pathogens. Macrophages produce factors that act directly on their microenvironment and also bridge innate immune responses to the adaptive system. Resident macrophages are important for acting as sensors for tissue damage and maintaining tissue homeostasis. It’s now well-established that macrophages are an integral component of the breast tumor microenvironment, where they contribute to tumor growth and progression, likely through many of the mechanisms that are utilized during normal wound healing responses. Because macrophages contribute to normal mamma development and carcinoma growth and progression, this review will discuss both resident mamma macrophages and tumor-associated macrophages with a stress on describing how macrophages interact with their surrounding environment during normal development and within the context of cancer. Inflammation may be a complex process that has evolved to resolve damage to the body caused by pathogens or disease within the normal mammalian, tissue-resident macrophages play an important role within the regulation of development and maintenance of tissue homeostasis. Pro- and anti inflammatory factors produced within the microenvironment act not only on epithelial cells, but also on macrophages and cause the further disruption of inflammatory homeostasis and therefore the creation of a protumorigenic niche that's primed for oncogenic initiation. Tumor cells acquire the capacity to harness the functions of inflammatory cells, like macrophages, to assist in their growth and progression. Experimental studies have demonstrated that macrophages interact with cancer cells and their phenotype and performance evolve because the tumor itself evolves. However, recent studies demonstrating the complexity of macrophage polarization and therefore the impact of macrophage localization within the tumor microenvironment

suggest that the contributions of macrophages to carcinoma growth and progression are likely to be quite complex. Therefore, it'll be critical to get a far better understanding of the mechanisms that drive macrophage recruitment, polarization, and performance within the tumor microenvironment at different stages of carcinoma formation and progression.

Herbal Medicine utilized in Breast Cancer:

Breast cancer is among the foremost common sort of cancer in women round the globe. Prevention of carcinoma is best than its treatment due to the molecular variation and complexity underlying carcinoma occurrence, its treatment by using chemotherapy and/or radiotherapy is extremely complicated and sometimes results in undesirable side effects. Plants and their extracts are used for hundreds of years for the treatment of just about every disease and carcinoma isn't an exception. Herbal products are often trusted for cancer treatment due to their low toxicity. Besides, herbal remedies are easily accepted by the bulk of woman affected by carcinoma due to their easy availability and affordability within the last decade, an outsized number of plants and their compounds were reported to point out promising anticancerous effects against carcinoma cells in both in vivo and in vitro models. However, their beneficial effects on carcinoma treatment are still doubtful thanks to the shortage of randomized clinical trials. This chapter is devoted to reporting the potential of some herbal products for the prevention and/or treatment of carcinoma. Besides, it focused on the anticarcinogenic mechanism of these phytocompounds to report their potential chemotherapeutic role. Carcinoma remains to be the leading explanation for cancer death among women worldwide with the speed of reported incidence and mortality increasing annually. within the past decade, women with tumors between stages I and II increased from 41% to 65%, 80% of which are invasive tumors originating from ductal carcinoma and its variants. Current early detection methods allow carcinoma to be diagnosed at an early stage when successful treatment is more likely. Multiple agencies and organizations round the world support mammography because the most reliable thanks to detect carcinoma at an early stage, particularly in women aged 50 years and older. About 70% of breast cancers express estrogen hormone receptor (ER) and/or progesterone receptor (PR), and these markers alongside human epidermal protein receptor 2 (HER-2) and proliferation marker Ki-67 provide information about tumor grade and possible response to different treatments . Although several treatment options are currently available including surgery, radiotherapy, and chemotherapy, specific treatment strategies depend upon characteristics like tumor grade, hormone receptor status, metastatic potential, and molecular and patient profile. Chemotherapy remains the foremost commonly used and recommended treatment option for carcinoma, either by employing a single compound or combination therapy with multiple drugs. However, chemotherapeutic drugs have narrow therapeutic indices leading to nonselective toxic effects on normal tissues, thus increasing the danger of infection. Although chemotherapy and radiotherapy are effective against carcinoma, they're amid varied side effects including vasomotor syndrome (occurring in up to 80% of patients), nausea and vomiting (75%), postmastectomy edema (30–60%), arthralgia (over 40%), neutropenia, cachexia, fatigue, pain, hair loss, hot flushes, and psychological stress, which present major hurdles in increasing the effectiveness of cancer therapy.

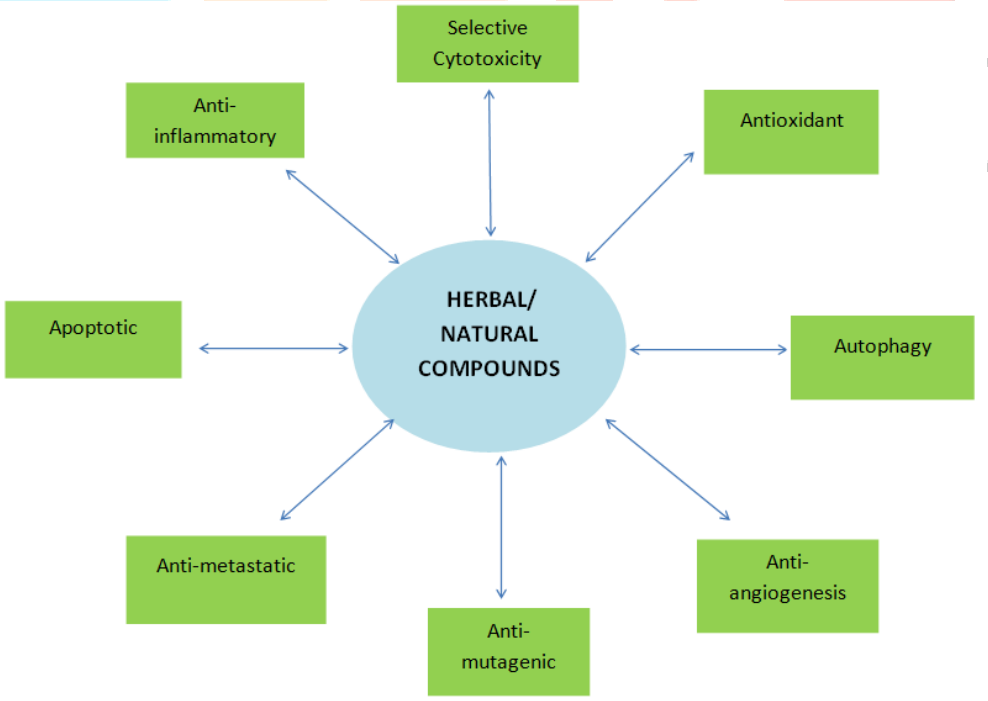

Fig. 1 Diagrammatic representation of Herbal Medicine

Herbal extracts

Apart from natural compounds, rising attention was paid to discoverherbal extracts with anti-inflammatory activity. Here, HMC-1 mast cellline is the most common cell line for such screening. Both black cohoshmethanol extract and buckwheat grain ethanol extract inhibited IL-4, TNF-α mRNA induction. Ethanol extract of Betula platyphylla also inhibited inflammatory cytokines production and the activation of NF-κB and caspase-1 in stimulated HMC-1 cells.Comparing Citrus unshiu peel water extract with hesperidin, a commonconstituent of Citrus unshiu, both inhibited PMA plus A23187-inducedHIF-1α expression and the subsequent production of vascular endothelial growth factor (VEGF), as well as phosphorylation of the extracellularsignal-regulated kinase (ERK). In addition, both suppressed TNF-α, IL-1β and IL-8 levels. Cortex Moutan, one of the major herb in PentaHerbs formula, the levels of suppression produced by its water extractwere not significantly different from those produced by dexamethasone. Besides, Cynanchum atratum extract reduced pro-inflammatorycytokines, such as IL-6, IL-1β and TNF-α, and

Th2 cytokine IL-4. Inaddition, it decreased the expressions of NF-κB, phospho-IκBα and MAP kinase. By examining the effect of extracts of Drosera rotundifolia,Drosera tokaiensis and Drosera spatulataon on activated T cell membrane(aTc-m)-induced inflammatory gene expression in mast cells, extractsfrom Drosera rotundifolia and Drosera tokaiensis suppressed inflammatorygene expression, while Drosera spatulation extract did not. Waterextract of Eriobotrya japonica leaf was proven to correlate negativelywith p38 MAPK, ERK, and NF-κB activation in mast cells. BothForsythia fructus and Forsythia koreana were capable of regulatingproinflammatory and chemotactic cytokines. Significantinhibitory effects of the Fritillaria ussuriensis extract on IL-6, IL-8 andTNF-α, as well as inducing phosphorylation of all three MAPKs were observed. Previous studies demonstrated the inhibitory effects ofGeranium sibiricum extract on MAPK activation, AP-1, COX-2 and iNOSexpression . Furthermore, Houttuynia cordata ethanol extract, Isodon japonicus, Ixeris dentata extract, Lithospermi Radix and motherwortwater extracts all modulated mast cells activation through suppressingsimilar cytokines or proteins.

Genetic predisposition

Young breast cancer patients are more likely to carry pathogenic or likely pathogenic germline mutations, making genetic screening for young breast cancer necessary. Common genetic susceptibility for breast cancer in Chinese population include mutations in BRCA1, BRCA2, PALB2, TP53, ATM, RAD51D, RECQL, CHEK2, and BARD1.10,11 Young breast cancer has a unique spectrum of mutation that confers genetic susceptibility. The frequency of germline mutation in young breast cancer patients reaches 24.0%.9 Pathogenic mutations are usually associated with specific clinical phenotypes and prognosis, and are potential targets for treatment. Patients with BRCA2 mutation are more likely to develop luminal subtype, while triple-negative breast cancer is more common in patients with BRCA1 mutation. Patients with germline mutations display more aggressive clinical features, and studies have confirmed that patients with BRCA 1/2 mutation have worse overall survival and disease-free survival.

Fertility management

The rapid progression in anti-tumor therapies has greatly improved the long-term survival of breast cancer patients, but it also brings short-term and long-term adverse effects including ovarian function damage. The result of a population-based study showed that the pregnancy rate of treated breast cancer patients is only 3%, which is 40% lower than that of the general population. The fertility rate of breast cancer patients depends on the age of diagnosis and treatment plan. During treatment, chemotherapy drugs such as cyclophosphamide can destroy ovarian function, leading to early amenorrhea. Furthermore, endocrine therapy for up to 5–10 years can cause young females to miss their optimal reproductive age. Concerns about fertility issues may lead to patients' reluctance to start or fail to adhere to anti-tumor therapy. Therefore, the issue of fertility protection for patients with malignant tumors, especially young breast cancer patients, has attracted increasing attention worldwide.

HERBS USED FOR THE TREATMENT OF BREAST CANCER:

1. Echinacea

Echinacea belongs to a family Asteraceae. It is uninhabited aromatic plant that cultivates mainly in the Great Plains and eastern regions of North America and also produced in Europe. For herbal remedies three types of species are most commonly found, named as Echinacea purpurea, Echinacea angustifolia, and Echinacea pallida. But for research and treatment E. purpurea is most commonly used. There are some common names that are linked with Echinacea are purple coneflower, Kansas snakeroot and black Sampson. Researchers have revealed that E. purpurea raises the number of natural killer cells in the investigational mice. In future E. purpurea could be a potential therapy for anti-cancer treatment. Flavonoids act as an immune-stimulant, they are present in Echinacea. It was supported by Winston et al., and flavonoids promote the lymphocyte's activity that increases the phagocytosis by macrophages and the action of natural killer cells and prompting interferon assembly, and it has also lessen the harmful consequence of radiotherapy and chemotherapy. It also helps the patients in prolonging the survival time with progressive stage of cancer. Cytokines production by macrophages has shown to increase by Commercial preparations of Echinacea juice. Less clear effects on T-cell and B-cell 7 stimulation and propagation are found. Several ingredients of Echinacea are reflected to show a role in its special sound effects on the immune system.

2. Garlic

Garlic (Allium sativum), for hundreds of years it has been used for treating many illnesses. It involves hundred or more than hundred therapeutically useful secondary metabolites, for example, alliin, alliinase, and allicin. Alliin, an amino acid, is present in garlic oil that is transformed to allicin after its rhizomes are crumpled. An originator of Sulfur comprising compound is allicin, which is responsible for odor and its therapeutic properties. Garlic oil contains another Sulfur holding substance, Ajoene. Ajoene delays the cancer production while selenium as antioxidant. Bioflavonoids, cyanidin and quercetin, are also found in garlic with antioxidant properties. Anti-cancer activity of garlic is due to high amount of organic sulfides and polysulfide's. Mechanism behind anti-tumor activity stimulating the lymphocytes and macrophages is that they kill the cancerous cells and interferes with tumor cells metabolism. The number of suppressor T cells is increased by garlic and converts the lymphocytes in that form which is cytotoxic to cancerous cells. Metastases are prevented by altering the adhesion and attachment of cancerous cells, circulating in the blood vessels. Harmful effects of carcinogens to DNA are prevented by ripened garlic extract; it improves the immune system of the body, increases the removal of carcinogens from the body, and enhances the detoxifying enzyme's activity. Researchers have found that the ripened extract of garlic is also helpful to shield the propagation of several types of cancers such as colon, stomach, breast, lungs and bladder. Complications of chemotherapy and radiotherapy could be lessening with garlic extract.

3. Turmeric

Scientific name of turmeric is Curcuma longa. Turmeric gives dark yellow color to food. Curcumin, the active ingredient of turmeric, is present in its rhizome and rootstock. Curcumin is known to have anticancerous activity due to its phenolic substances. Propagation of lung, breast, skin and stomach cancer is limited by turmeric Eicosanoids, for example prostaglandin E-2 (PGE-2), production is altered by curcumin, an antioxidant agent. It has also anti-inflammatory action in human. Curcumin has been revealed to have inhibitory action in all phases of cancer growth which is initiation, promotion, and propagation. Nitrosamine production is inhibited by turmeric; it results in increase natural antioxidant action of the body. Amount of glutathione and other non-protein sulphahydryls is increased by curcumin, and they act directly on different enzymes.

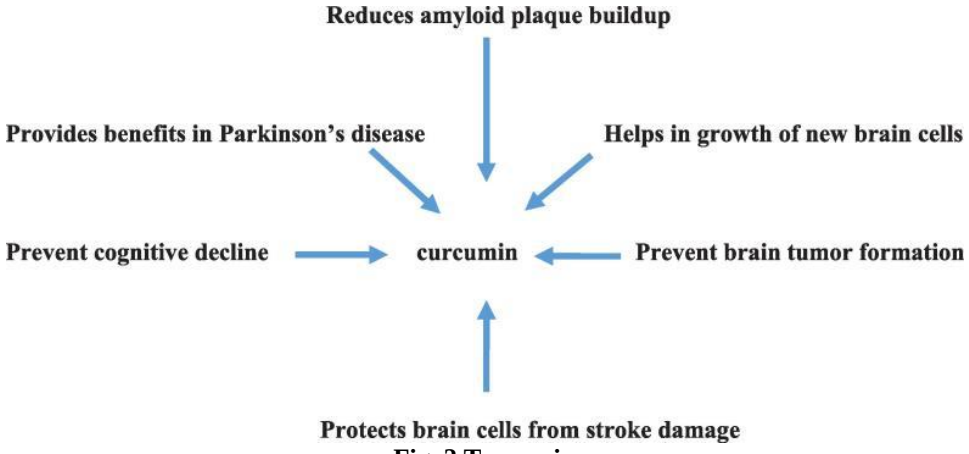

Fig. 2 Turmeric

4. Burdock

Scientific name of Burdock is Arctiumlappa. Its root is found and used in Europe and Asia. There are many therapeutic uses of burdock in herbal remedies. Its root has gummy texture and sweet taste. In old times burdock was useful in arthritis, tonsillitis and measles, but nowadays it has been found that burdock has antitumor activity. It contains some active ingredients that alter the changes in oncogenes. Burdock has been utilized in treatment of breast tumor, ovary, bladder, malignant melanoma, lymphoma and pancreatic cells. It relieves the pain, lessens the tumor size and enhances the survival phase. To withstand the fast propagation and division of cells, a huge amount of nutrients is required during cancer. But cancer cells can live in stressed circumstances for example with low oxygen and less amount of carbohydrates, because tumor cells have high tolerance to stressed conditions. Burdock seeds contain an active ingredient called Arctigenin. Arctigenin, has shown the ability to remove the tumor cells with low nutrients. Burdock root consists of flavonoid type and polyphenol anti-oxidant, and they may have oppressive effect on tumor development. Normal body cells are protected from toxic substances and lessen the cells mutation, by extract of root. Burdock contains the most important active ingredient that is known as, Tannin, a phenolic compound. It stimulates macrophages action, limits cancer propagation and retains immune-modulatory properties.

5. Carotenoids

These aromatic plants are used as dyeing agents for example saffron, annatto and paprika. Consumption of vegetables and fruits has been linked with less expansion of different forms of tumor. Intake of carotenoids through diet also decreases the occurrence of tumor. The carotenoid substances are potent antioxidants and show numerous therapeutic activities, such as searching of free radicals, protecting against oxidative damage to cells, improvement of gap intersections, stimulation of immune system and enzyme's activity regulation contributed in cancer production and encourage the activity of immune system of the body.

6. Green tea

Scientifically green tea is known as *Camellia sinensis*. Anticancer activity is attributed by polyphenolics compounds. Epigallocatechin (EGGG), a polyphenol is present in small amount in *C. sinensis*. Researchers have revealed that green tea possesses antitumor and anti-mutagenic activity. Cells are protected by EGGG from DNA damage produced by oxygen reactive species. Studies on animal were performed resulted that green tea polyphenols restricts the cancer cells division and stimulate the necrosis and apoptosis of tumor cells. While function of immune system is stimulated by tea catechins, they also inhibit the metastases and angiogenesis in tumor cells. Some studies have shown the protective results of green tea in counter o colon and stomach cancer. Tea and their primary catechins reduce the risk of tumor in number of organs of the body. Harmful effects of radiation can be lessened with green tea. All beneficial effects of tea are due to its antioxidant activity.

7. Ginseng

Scientific name of ginseng is Panax ginseng. It is lasting plant mainly grows in China, Korea, Japan and Russia. Part used of this plant is dried root. It has many therapeutic uses including cancer. Active substances of ginseng have shown that it reduces or blocks the development of tumor necrosis factor in the skin of mouse, blocks the propagation and metastases of cancerous cells, stimulate cell differentiation, and level of interferon. Other type of cancerous cells stages may also hindered by ginseng's ingredients. An investigation was also carried out in Korea, recommended that ginseng reduces the cancer risk in human. As related to fresh sliced ginseng, its juice or tea, the most potent and active type of ginseng is its extract and dried powder for prevention of cancer threat. By interrupting the DNA synthesis ginseng retains the tumor development. Beneficial effects of active compound of P. ginseng include restart of natural killer cells impaired during chemotherapy and radiotherapy induces macrophages and enhances antibodies formation.

8. Black cohosh

Scientific name of black cohosh is Cimicifugarecemosa. It is a shrub, found in the eastern forests of North America. Patients of breast cancer most commonly used Black cohosh during radiotherapy and chemotherapy. It has been used by Native American since many centuries for the treatment of menopausal signs, pre-menstrual discomfort and dysmenorrhea. It also induces the abortion-like problems. A patent medicine Lydia Pinkham's Vegetable Compound was famous, and this herb was principle component of this medicine. It was also found in 19th century's pharmacopeia. A large range of preparation of black cohosh is present in drug stores. Herbalists have shown that they are safe and effective therapy for menopausal indications.Females, which have been suggested to escape the Hormonal Replacement Therapy (HRT) by their physician; it has been used by those women. Most of the studies have shown the herb's effects on menopausal indications. Although the vigorous principles of black cohosh have not been known, there is assumption of triterpene glycosides to be a vital component, but trace amount of resins and caffeic,

isoferulic and fukinolic is also present. Ambiguities are found about the estrogenic and anti-estrogenic activity of black cohosh. Various research studies have contradictory results, some studies have shown that it enhances or lesson the cancer cell production in culture. In the literature it is revealed that black cohosh has synergistic effects for breast cancer patients when given in combination with other chemotherapeutic agents.

9. Flax seed

Flax plant has small brown and golden hard-coated seeds. These small seeds contain all active components. Flax seeds are rich source of dietary fiber, omega 3 fat, and lignans. Estrogenic activity is present in flax seeds due to metabolism of lignans to enterodiol and enterolactone, and metabolism occurs in digestive tract. As compared to soy products, flax seeds have more potent phytoestrogens, while intake of flax seeds causes a huge change in the elimination of 2-hydoxyesterone than soy protein. A research group of Lilian Thompson at university of Toronto has shown that ground flax seeds have powerful anti-cancer activity. An experiment was conducted on mice; firstly cancer is induced in mice by administering carcinogens, in one group, anti-cancer activity of flax seed was identified by mixing the lignin in diet of mice. This experiment has results in reducing the tumor load. Recently, this research group induces tumor in mice by injecting human breast cancer cells. While cancer propagates, mice were given with basal diet for 8 weeks after cancer cells' injection. One group was fed with 10% flax seeds while another group continued basal diet. Rate of cancer growth was reduced by 45% by flax seeds. Mammary glands morphogenesis in mice is improved by flax seeds. Researchers examined the female mice fed with 10% flax seeds diet, and they found the improved number of terminal end buds and terminal ducts in their mammary glands. They have extra epithelial cell division. All females show increased differentiation. Relatively low incidence of breast tumor has been shown by female after injection of carcinogens in mammary glands. As a result, increased differentiation mammary tissues of mouse, prevention of malignancies, reduction of tumor development are possible by flax seeds in female offspring, making less vulnerable to carcinogens.

10. Vitamin D

Vitamin D is produced by sun exposure of skin. Large amount of vitamin D is produced by simple contact of hands, arms and face in summer. Even standing in sunshine on the beach until pinkness of the skin is equal to a 20,000 IU oral dose of vitamin D2. Minimal amount of vitamin required by our body is 1000 IU/day, to maintain the sufficient level. Oral uptake of vitamin D is only source to maintain its level in the absence of sunshine. In one day 4000 IU can be taken safely with other benefits. Kidneys are responsible to maintain the active hormonal form of vitamin D in blood. Anti-cancer activity is possessed by this active type of vitamin D. The capability to change the chief circulating form of vitamin D 25(OH) D, into hormonal form, 1, 25(OH) 2D, vital organs of the body performed their functions. All these organs have local mechanism by which they convert the circulating form into hormonal form, and this mechanism is stimulated by exposure to sunshine.

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