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Role of Natural Products in Breast Cancer Management – An Overview

Mythili Srinivasan[a], Sathiyanarayanan Lohidasan[b]*

[a]Department of Quality Assurance Techniques, Poona College of Pharmacy, Bharti Vidyapeeth Deemed University, Pune 411038,

[b]Assistant professor, Department of Pharmaceutical Chemistry, Poona College of Pharmacy, Bharti Vidyapeeth deemed University, Pune 411038, India

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ABSTRACT

Background Breast cancer is the most frequently diagnosed neoplastic disease in women. Breast cancer is the second leading cause of cancer-related deaths worldwide. More attention and sophisticated preventive measures are needed for the management of cancer. **Purpose** This review aimed to search for possible measures in the prevention and management of breast cancer. **Methods** In search of several epidemiological studies suggested the inverse correlation between the intake of fruits, spices and vegetables and the incidence of breast cancer. **Results** Substantial experimental studies indicated that many natural dietary products could affect the development and progression of breast cancer, such as cruciferous vegetables, fruits, spices, edible macro-fungi, and cereals. Their anti-breast cancer effects involve various mechanisms of action, such as inhibiting proliferation, migration, metastasis, angiogenesis, down regulating ER-expression and activity on breast tumour cells. Some of them will be inducing apoptosis and cell cycle arrest. Some phytochemicals will be sensitizing breast tumour cells to radiotherapy and chemotherapy. **Conclusion** From a systematic review, it is found that nutrients are giving a genomic level impact known as nutrigenomics in the prevention and management of various types of breast cancer. The nutrigenomic impact is proven to be beneficial in some of the studies.

Abbreviations

ER, Estrogen; PR, Progesterone; HER 1, Human epidermal growth factor receptor-2 positive 1; TNBC, triple-negative breast cancer; BRCA 1, breast cancer 1; SEER, Surveillance, Epidemiology, and End Results; HBC-SS , Hereditary Breast Cancer Site Specific syndrome; HBOC, Hereditary Breast Ovarian Cancer; PE, pomegranate extract; MCF7, Michigan Cancer Foundation-7; MDA-MB-231, M.D. Anderson Metastasis Breast cancer; STAT3, signal transducer and activator of transcription 3; NF-kB, Necrotic factor-kB; MMP2, matrix metalloproteinase-2; MMP3, matrix metalloproteinase-3; SKBR3, Sloan–Kettering Cancer Centre ; DIM, diindolylmethane; MAPK, Mitogen-activated protein kinase; DADS, Diallyl disulphide; TQ, Thymoquinone; NMU, N-methyl-N-nitrosourea; MAA, Methyl anticipate A; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; CTC50, Circulating tumour cells; Bcl-2 , B-cell lymphoma 2; ROS, Reactive oxygen species; mTOR, mammalian targeting function of rapamycin; MMPs, matrix metalloproteinase; NF-κB, nuclear factor-kappa B; VEGF, vascular endothelial growth factor; EMT, epithelial-to-mesenchyme transition; SNP, Single nucleotide polymorphisms; P-gp, P-glycoprotein; GNT, Genistein ; PXR, Pregnane-X-Receptor; EGCG, Epigallocatechin-3-gallate.

1. INTRODUCTION

In the United States, there are 255,180 new cases of breast cancer found to date and 41,070 people died out of this disease in 2017. [87]. Despite scientific advancements and novel treatment options, the occurrence and mortality continue to increase. It is predicted that the number of people affected by this deadly disease will touch 20 million by 2025. [87]. Breast cancer is usually associated with the uncontrolled growth of carcinogenic cells in the milk-producing glands of the breast or the passages (ducts). [10] The most promising preventive measure is consuming natural products, such as cereals, fruits, and vegetables. Numerous dietary natural products have shown a significant role in the prevention and treatment of cancers. [25]. Numerous phyto studies have proven that the consumption of soy products, fruits, and vegetables (specifically cruciferous vegetables) are correlated with a substantial reduction in the risk of breast cancer , Furthermore, uptake of some dietary natural products might dramatically reduce the recurrence and increase in life span. [64]. Number of experimental studies indicated that many dietary natural products and their bioactive components showed inhibitory effects on breast cancer (Figure 1), by obstructing the process of angiogenesis and metastasis and breast tumour cells, down regulation of ER- expression and activity, inducing cell death and cell cycle arrest, inhibiting increment, and sensitizing breast tumour cells to radiotherapy and chemotherapy [60]. Almost 25,000 different phytochemicals have been identified in fruits and vegetables that have beneficial anticancer properties so far. [65]. All these phytochemicals are generally targeting multiple signalling pathways, non-toxic and safe to consume. [74].

Fig. 1. Dietary natural products that showed inhibitory effects on breast cancer.

2. Types of breast cancers

Gene expression studies have revealed several breast cancer subtypes, including

- **Basal-like** (ER-, PR-, HER2- cytokeratin 5/6 positive, and/or HER1+)
- **Human epidermal growth factor receptor-2 positive / estrogen receptor-negative** (HER2+/ER-)
- **Luminal A** (ER+ and/or progesterone receptor-positive [PR+], HER2-)
- **Luminal B** (ER+ and/or PR+, HER2+)
- **Triple-negative breast cancer** (HER2-/PR-/ER-)

The **basal-like** type is more prevalent among premenopausal African- American women (39%) when comparing with postmenopausal African-American women (14%) and non- African American women (16%) of any age ($P<0.001$).

The **luminal a** subtype is less prevalent (36%, 59%, and 54%, respectively). The HER2+/ER- subtype did not vary with race or menopausal status (6%-9%). [2]

TNBC, which is the reason for an estimated 15–20% of invasive breast cancers, has been connected with distant metastasis, fast growth, and Reoccurrence-free survival when compared to other breast cancer subtypes. [38]

The proportion of TNBC is considerably higher in African American and Asian patients when comparing to patients with non-TNBC. Both BRCA1 and BRCA2 genes play a vital role in carriers to TNBC. In recent reports, the association diagnosis of breast cancer at a younger age is seen with TNBC sub-type (below35). [38]

Further, Asian ancestry and a family history of breast cancer, and BRCA1 or BRCA2 genes are all connected positively with TNBC. [72]

Table.1. Anti-cancer properties of phytochemicals present in dietary natural products. [19]

S.NO	Phytochemicals from natural products	Anti-cancer properties
1	Phenolic Compounds	Substantial reduction of neoplasia induced by chemical carcinogens. Preventing nitrosation of susceptible secondary amines and amides to form highly potent carcinogenic nitrosamines and nitrosamides in our foods. Potent chemical nucleophiles. Inhibitors of promotion processes. Inhibitors of kinases by reducing the hyper proliferation of epithelial cells. Induction of carcinogen detoxification. Inhibition of tumour cell proliferation.
2	Organosulfur compounds	Antimicrobial effect. Free radical scavenging. Inhibition of DNA adduct formation. Induction of cell cycle arrest. Induction of apoptosis Modification of carcinogen metabolism.
3	Alkaloids	Modification of tumour metabolism. Inhibition of tumour cell growth.
4	Carotenoids	Inducers of differentiation
5	Nitrogen-containing compounds	Inhibit metabolic activation and carcinogenicity

3. Intrinsic factors conditioning breast cancer occurrence

3.1.AGE

The occurrence of breast cancer is quite common around the age of menopause. It is significantly less frequently found in women below 45 years of age.

Breast neoplasm's showing estrogen receptor overexpression ER (+) is characterized by a frequency that is increasing with age as opposed to ER (–) tumours. ER (-) occurs more frequently below 45 years of age and then reaches a plateau. This phenomenon explains an increased percentage of ER (+) tumours diagnosed in women after menopause. [25]

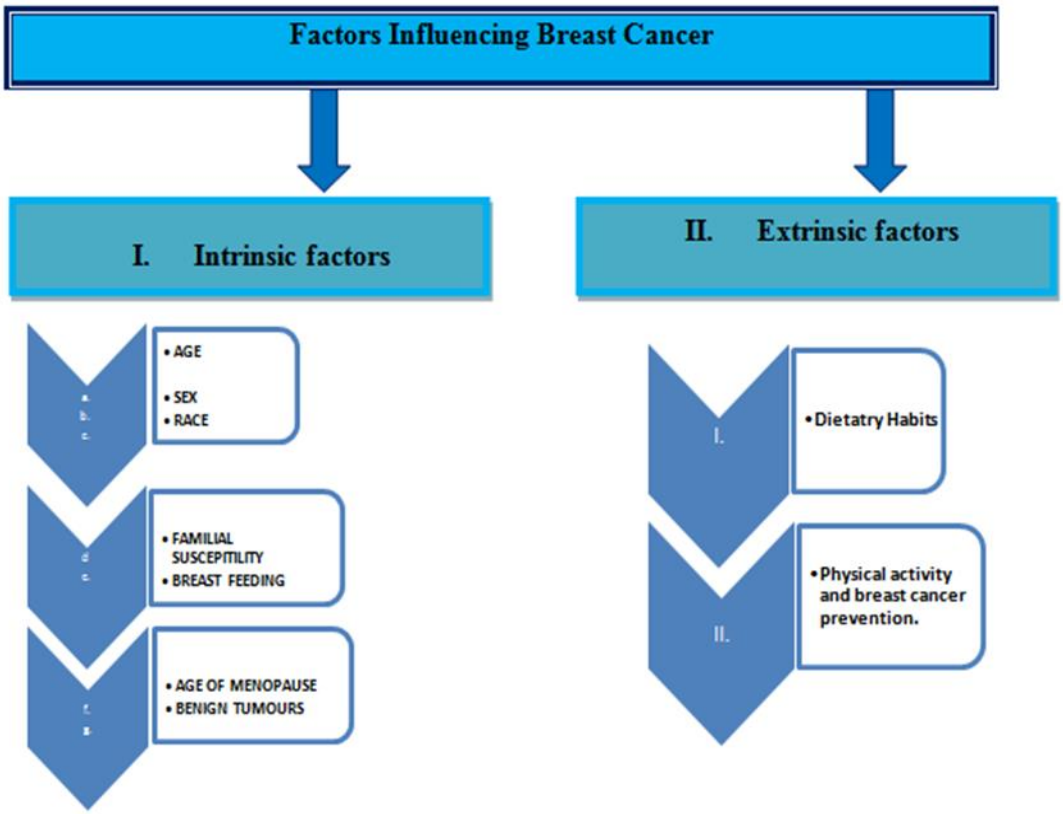

Fig.2. Factors affecting breast cancer occurrence.

3.2.SEX

The disease occurrence is maximum in women (99%) when compared with men. In men, it constitutes less than 1% of all types of breast cancers. [39]

3.3.RACE

The race is a significant factor elevating the risk of occurrence of breast cancer. It was demonstrated in a study done by Ban et al who analysed data included in the SEER (Surveillance, Epidemiology, and End Results) database, the frequency of occurrence in Caucasian women is about 127.4 in 100 000 individuals. The indicators of mortality and 5-year survival are 12.3% and 90.4%, respectively. [39]

On the contrary, the frequency of occurrence in blacks of the neoplasm is about 121.4 in 100 000 individuals and the indicators of mortality and 5-year survival are 18.2% and 78.6%, respectively. [10].

The least incidence of breast cancer is seen in Hispanics, however, in their case, the disease is diagnosed at an early age and often shows a lack of expression of the estrogen or progesterone receptors but super-expression of HER2 receptors. [67]

3.4.FAMILIAL SUSCEPITILITY

A systematic prediction of genes whose disorder is associated with an increased risk of occurrence of malignant breast cancer i**n BRCA1** and **BRCA2** (breast cancer susceptibility 1 and 2). [72]. Modifications in the coding sequence will give way to the occurrence of hereditary syndromes called **HBC-SS (Hereditary Breast Cancer Site Specific) syndrome, HBOC (Hereditary Breast Ovarian Cancer) syndrome,** which will lead themselves in the form of breast and/or ovarian cancer. A thorough complex molecular analysis is needed in the case of hereditary syndromes caused by BRCA1 or BRCA2 gene mutations. [72].The prime most criterion in evaluation is disease detection at a younger age (Below 45). Followed by analysing the pedigree of first and second-generation relatives.

3.5.BREASTFEEDING

Breastfeeding is associated with a 32% breast cancer risk reduction in BRCA1 mutation carriers. Longer duration of breastfeeding is proven to more effective in disease control. On the contrary, this is not the case with BRCA2 gene mutation. Breastfeeding facilitates will make the epithelial cells very less susceptible to the disease by making differentiation of epithelial cells of the lactiferous ducts. Thus, the mutagenicity of DNA (deoxyribonucleic acid) can be prevented. [39].

3.6.AGE OF MENOPAUSE

Women attaining menopause at an early age are more susceptible to breast cancer risk. [26]

3.7.BENIGN TUMOURS

Benign tumours cannot be neglected, as this will significantly increase the risk of getting converted into malignant ones. [10] Based on the previous data, women with benign proliferative tumours of their mammary glands and heredity of breast neoplasms in the pedigree are shown an almost 11-fold increase in breast cancer risk. [75]

4. Extrinsic factors conditioning Breast cancer Occurrence

4.1.DIETARY HABITS

Dietary habits are playing a significant role in breast cancer. Improper diet leading to obesity is quite common in developed countries. [19]. Fat and processed foods containing a variety of chemical substances leading to excess weight or obesity. Long-standing and untreated obesity will lead to carcinogenic alterations of the cells of mammary glands. [30, 43].

Rich in vitamin D diet may lead to a 20% reduction in the relative risk of breast cancer. [39] Even a little amount of alcohol will make a drastic impact by affecting the estrogen metabolism in the liver leading to carcinomas. [67].

4.2.PHYSICAL ACTIVITY AND BREAST CANCER PREVENTION.

Breast cancer risk is reduced predominantly (25%) by doing physical activity. The role of physical activity in cancer prevention is studied by the various researcher and the most influencing factors include chronic inflammation**,** insulin resistance, adiposity, and sex hormones. [30, 43].

5. Carotenoids and Breast Cancer

Carotenoids are micronutrients that are found abundantly in fruits and vegetables, may reduce breast cancer risk. Women with higher circulating levels of lutein+zeaxanthin, lycopene, α-carotene, β-carotene, and total carotenoids may be at reduced risk of breast cancer. [9]. Carotenoids are natural pigments with a colour ranging from yellow to red, are important for photosynthesis in plants. There are almost 600 carotenoids that have been identified to date, among which α-Carotene, β-carotene, zeaxanthin, β-cryptoxanthin, lutein, and lycopene are the most prevalent, comprising 90% of circulating carotenoids. These micronutrients are showing more anti-carcinogenic activities with possible biologic activities including [42].

Antioxidation,

Inhibition of tumorigenesis and malignant transformation,

Enhanced gap-junction intercellular communication,

Immunoenhancement, and

Metabolism to retinoids, which, in turn, contribute to cellular differentiation.

Several experimental studies suggest that carotenoids inhibit tumour progression and reduce proliferation in both estrogen receptor-positive (ER+) and ER− breast cancers. The uptake of α-Carotene, β-carotene, and lutein/zeaxanthin were inversely relating to the risk of ER-negative (ER−) breast cancers. [9]. But these were not inversely associated with the risk of ER-positive (ER+) breast cancer. There is no significant association observed for lycopene intake.

5.1.MECHANISM OF ACTION

The intake of the diet with rich α-carotene, β-carotene, and lutein/zeaxanthin were inversely associated with the risk of ER−, but not ER+ type of breast cancer. Carotenoids have been hypothesized to prevent carcinogenesis by inhibiting the ability of reactive oxygen species to induce DNA damage. This is the most vital step in carcinogenesis and neoplastic transformation. Most of the provitamin carotenoids (including α-carotene, β-carotene, and β-cryptoxanthin) can be metabolized to retinol, which is highly mandatory for the control of cellular differentiation and proliferation and immunologic functions. [10, 43] Other types of mechanisms have been identified for some carotenoids. For example, β-carotene and lycopene might inhibit estrogen receptor-mediated signalling of 17β-estradiol and attenuate its deleterious effect on breast cancer and lutein/zeaxanthin might reduce cell proliferation and helps in the prevention of breast cancer. [9, 10].

6. Antioxidants

Antioxidant supplementation was noted after diagnosis in almost 81% of women in a recent study. Among antioxidant users, frequent use of vitamin C and vitamin E was associated with decreased risk of breast cancer recurrence when compared to non-users. Frequent users of vitamin C are having a lower risk of all-cause mortality. [36].Similarly, Vitamin E users are having more life span compared with non-users. It is found that women who used any form of antioxidants (vitamin E, vitamin C, multivitamins) had a 22% reduced risk of recurrence and an 18% reduced risk of death and 22% decreased the risk of all-cause death when compared with non-users of antioxidants. [37].The mechanisms which are involved by which vitamins C and E could reduce breast cancer recurrence and mortality is through oxidative stress pathways related to cancer and cardiovascular diseases, but precise mechanisms are unclear. [92].

Prevention of Recurrence

Frequent use of vitamin C and vitamin E was associated with a lower risk of recurrence. [39].

7. Dietary Natural Products for Prevention and management of Breast Cancer

Substantial experimental studies indicated that many dietary natural products could alter the development and progression of breast cancer, such as **cruciferous vegetables, ginger, garlic, black cumin, edible macro-fungi, soy, pomegranate, mangosteen, citrus fruits, apple, grape, mango, and cereals.** Their anti-breast cancer effects involve various mechanisms of action, such as metastasis and angiogenesis of breast tumour cells, down regulation of ER-α expression and activity, inhibition of proliferation and migration, inducing apoptosis and cell cycle arrest, and sensitizing breast tumour cells to radiotherapy and chemotherapy. [89].

7.1. SOY

Soy products have been widely consumed in Asian regions. There are so many potential health benefits have been linked with intake of soy products, such as lower incidences of coronary heart diseases, type 2 diabetes, and breast cancer. [6, 13]. Soy products are rich in isoflavones, and a prospective study for the meta-analysis indicated that the intake of isoflavones is closely associated with the decreased risk of breast cancer. [14, 21]

7.1.1. Epidemiological evidence

The amount of soy isoflavone consumption, estrogen receptor status of the tumour, the menopausal status of patients and timing of dietary exposure, are all influencing the soy-breast cancer association [62]. A recent study found an inverse correlation between soy intake and breast cancer risk (HR for fifth versus first quintile soy protein intake = 0.78; 95%CI = 0.63–0.97) of the population-based in Shanghai Women's Health Study, with predominance observed in premenopausal women (HR = 0.46; 95% CI: 0.29–0.74).[44] Further in-depth analyses found that soy intake during adulthood was significantly associated with decreased risk of ER-/PR- breast cancer in premenopausal women (HR = 0.46; 95% CI = 0.22–0.97) and decreased risk of ER+/PR+breast cancer in postmenopausal women (HR = 0.72; 95% CI = 0.53–0.96). But the HER2 status did not show a significant influence on the association of soy consumption. [61, 62].

7.2. FRUITS

Fruits are very rich in polyphenols, those have great antioxidant activity and helps in the reduction of breast cancer risk. [30]

7.2.1. Pomegranate

Pomegranate (Punica granatum L.) has been utilized for medicinal purposes all over the world and is described as “nature’s power fruit”. [18] Pomegranate fruit contains a very high content of polyphenols, among which ellagitannins predominates, and showed great antioxidant activity and anti-inflammatory properties. [56]. In a recent study pomegranate extract (PE) inhibited MCF-7 breast cancer cell growth by inducing cell cycle arrest in the G2/M phase and inducing apoptosis, and the effects might be associated with down regulation of homologous recombination, which could sensitize cancer cells to double-strand breaks.[81].

Another study found that pomegranate extract consisting of fermented juice and seed oil could inhibit invasion and motility of human breast cancer by inhibiting RhoC and RhoA protein expression. [70]. The most predominant bioactive components were identified as ellagitannins and phenolic acids in the aqueous extract and conjugated octadecatrienoic acids in the lipid extract of seed.

7.2.2. Mangosteen

Mangosteen (Garcinia mangostana L.) known as “queen of fruits” is a common tropical fruit. [7] .Crude methanolic extract of mangosteen pericarp had shown inhibition of proliferation and induction of apoptosis on the SKBR3 human breast cancer cell line. [24, 60] Furthermore, phenolics from mangosteen fruit pericarp induced great cytotoxic activity against MCF-7 human breast cancer cells. [45, 58]. Mangosteen pericarp is a rich source of xanthones, such as α- and γ-mangosteen, which have a variety of bioactivities, such as antioxidant, anti-inflammatory, and anticancer activities.[7, 46] In a study, twelve xanthone constituents were isolated from the pericarp of mangosteen, among which α-mangostin, γ-mangostin, garcinone D, and garcinone E, were showing dose-dependent anti-aromatase activity in SK-BR-3 breast cancer cells, among which γ-mangostin being the most potent among all the others. [53, 59].

7.2.3. Citrus Fruits

Citrus fruits consisting of a large variety of fruits, such as grapefruit, pomelo orange, lemon, and lime. In recent studies the anti-breast cancer activity of citrus fruits has been gathering more attention. A meta-analysis of observational studies proving an inverse relation between citrus fruits intake and the risk of breast cancer. Extracts from a citrus fruit named Phalsak induced apoptosis in anoikis-resistant breast cancer stem cell line MCF-7-SC. [75, 83].

In another study, lemon citrus extract induced apoptosis in MCF-7 breast cancer cells through up regulating the expression of Bax and caspase-3 genes and down regulating the expression of bcl-2 genes. More interestingly, naringin, a flavonoid that is present abundantly in citrus fruits, inhibited cell proliferation and promotes cell apoptosis and G1 cycle arrest in TNBC cell lines based *in vivo* and *in vitro* models through modulating catenin pathway. [51, 91].

7.2.4. Apple

Apple is the most consumed fruit worldwide for centuries. Flavonoids which are extracted from the peel and flesh of Pink Lady apples had shown inhibition of MCF-7 breast cancer cell growth, with IC50 of 58.42 ± 1.39 mg/mL and 296.06 ± 3.71 mg/mL, respectively. [90].

In another study, Pelingo apple juice containing tremendous amounts of polyphenols and they are exerting an antiproliferative effect on MCF-7 and MDA-MB-231 cells had been identified. Pelingo juice also inhibited 12-o-tetra-decanoyl-phorbol-13-acetate (TPA) induced tumorigenesis of the pre-neoplastic cells. This activity is achieved by inhibiting colony formation and TPA-induced ERK1/2 phosphorylation. [78].

Apple extract showed a significant antiproliferative effect on MCF-7 and MDA-MB-231 cells at concentrations of 10–80 mg/mL with ($p < 0.05$). The extract also significantly induced cell cycle arrest at the G1 phase in MCF-7 cells by drastically decreasing cyclin D1 and Cdk4 proteins. [80].

7.2.5. Grape

Bergamottin, the furanocoumarin obtained from the grape is derived from psoralen, has been reported to show tremendous inhibitory effects on breast cancer cell growth. [20, 88]. A recent study showed that treatment with bergamottin drastically suppresses the MDA-MB-231 breast cancer proliferation by inhibiting signal transducers and activators of transcription 3 (STAT3) expression [33]. When MDA-MB-231 cells were treated with bergamottin, phosphorylation and nuclear translocation of STAT3 were not only significantly reduced, but also the binding ability of the STAT3 protein to the corresponding DNA sequence was also suppressed. STAT3 signalling is an important intrinsic pathway for cancer development because of its frequent activation in malignant cells, and this also plays a vital role in regulating several genes which are highly crucial for cancer-related inflammation [33].

Another study revealed that grape seed extract reduced migration of the highly metastatic MDA-MB231 cells, this is achieved by inhibiting β-catenin expression and localization, and decreasing fascin and NF-κB expression and the activities of urokinase-type plasminogen activator (uPA), MMP-2 and MMP-9. [84]

7.2.6. Mango

Mango (*Mangifera indica* L.) is the abundantly cultivated tropical fruit which is rich in polyphenolic compounds (gallic acid and gallotannins). A study found that mango polyphenolics exhibited cytotoxic effects on BT474 cells in vitro, and decreased tumour volume by 73% in mice bearing BT474 xenograft compared with the control group. These effects were partially regulated through the PI3K/AKT pathway and miR-126. [1].Three genetically diverse mango varieties were investigated in a study where it is found that the peel extract of Nam Doc Mai mango contained the highest amounts of polyphenols, had very high rate of inhibition cell viability of MCF-7 cells with an IC50 value of 56 µg/mL, and most significantly ($p < 0.01$) stimulated cell death in MDA-MB-231 cells. [8]. Furthermore, mango which is extracted using ethanol (ethanolic extract) induced apoptosis in MCF-7 and MDA-MB-231 cells, by increasing pro-apoptotic proteins [35] (Box, caspase-7, 8, 9 Cytochrome c) and decreasing anti-apoptotic proteins (glutathione, p53, and Bcl-2). These effects are achieved by the association with the activation of oxidative stress in breast cancer cells. [66].

7.2.7. Jujube

Jujube *(Ziziphus jujube*) fruit has shown numerous beneficial medicinal effects, such as antioxidant and anti-inflammatory activities. [3] A study revealed that *Ziziphus jujube* extracts produced anti-breast cancer activity by inducing cell death by apoptosis in MCF-7 and SKBR3 cells, without decreasing cell viability of non-malignant breast epithelial MCF-10A cells or normal human fibroblasts BJ1-hTERT. [3, 28] Betulinic acid which was isolated from sour jujube fruit, and microencapsulated betulinic acid had shown to induce apoptosis in MCF-7 cells, by acting through the mitochondria transduction pathway.[69, 85].Additionally, jujube aqueous extract treatment on MCF-7 cells exhibited pro-apoptotic and antiproliferative effects, through up-regulating the expression of Bax and down regulating Bcl2 genes. These genes are responsible for breast cancer progression. [85].

7.2.8. Berries

Methanolic extract of **strawberry** produced cytotoxicity in T47D breast cancer cells in vitro, and it was also exerting inhibition of the proliferation of tumour cells in mice bearing breast adenocarcinoma by inducing apoptosis. **The blueberry** extract inhibited the proliferation of MCF-7 cells in a concentration-dependent manner (IC50 = 0.3–0.4 mg/mL), this is accompanied by stimulation of apoptotic cell death. [82].

7.3. Cruciferous Vegetables

Cruciferous vegetables such as (cauliflower, broccoli, Brussels sprout, and watercress) are grown and consumed all over the world. According to a meta-analysis with 13 epidemiologic studies exhibited the intake of cruciferous vegetables in the daily diet was inversely correlating with the risk of breast cancer (RR = 0.85, 95% CI = 0.77–0.94). [56]. Cruciferous vegetables have shown anti-breast cancer effects on several experimental models, which might be attributed to its high contents of glucosinolates. When these vegetables are cut or chewed, the enzyme myrosinase is released, and glucosinolates would be degraded to form isothiocyanates. Isothiocyanates include a variety of compounds such as phenethyl isothiocyanate, benzyl isothiocyanate, and sulforaphane, and those were known for their chemopreventive activities for various neoplasms including breast cancer. [41]. Other than this the indole-3-carbinol in cruciferous vegetables and its metabolite 3, 30-diindolylmethane (DIM) are also responsible for anti-breast cancer activities. [11]. DIM is also a promising anticancer agent. Multiple targets and the underlying mechanisms of DIM-induced inhibition on breast cancer cells have been found. For instance, DIM induced apoptosis in MCF-7 and MDA-MB-231 breast cancer cells (Figure 2), by decreasing total transcript and protein levels of Bcl-2 and increasing Bax protein levels. In addition to this, Apoptosis induced by DIM in MCF10CA1a breast cancer cells was also modulated by the inactivation of Akt and NF-κB. [86].

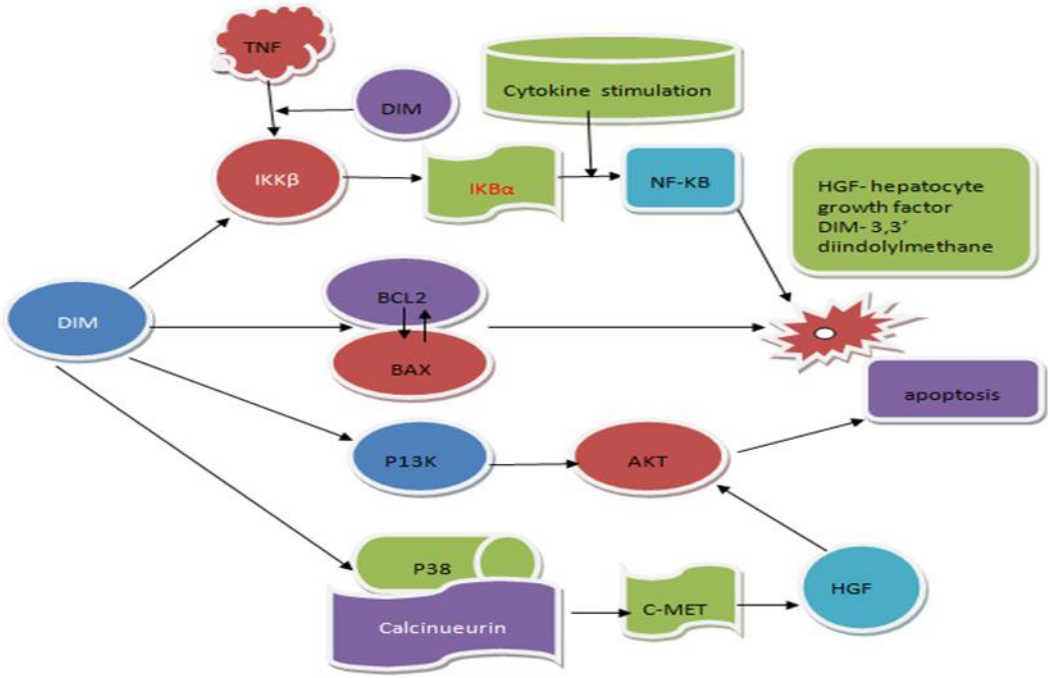

Fig.3. Signalling pathways involved in DIM-induced apoptosis in breast cancer cells.

7.4. Spices

Spices have been widely used for centuries in folk medicine and as food flavouring agents throughout the world. [4] In recent years, several spices and their bioactive constituents, such as organosulfur components in curcumin in turmeric, garlic, gingerols, and shogaols in ginger, and thymoquinone in black cumin, have been suggested to possess a significant amount of anti-breast cancer activity. [27, 93]

7.4.1. Ginger

Ginger (*Zingiber Officinale*) is the most commonly used spice around the world for medicinal and dietary purposes since the ancient period. Ginger has shown the most prominent anti-breast cancer effect in recent researches. [5] The methanolic extract of ginger exhibited an inhibitory effect on the proliferation and colony formation in MDA-MB-231 cells in a dose and time-dependent manner. [5]. The ginger extract also induced apoptosis in MCF-7 and MDA-MB-231 cells, through up-regulation of Bax, and down-regulation of Bcl-X, Mcl-1, survivin, cyclin D1, Bcl-2 proteins, NF-κB, and CDK-4. Besides, the expression of c-Myc and hTERT, the two prominent molecular targets of cancer, was inhibited by the ginger extract. [22]. Gingerols and shogaols are the two bioactive constituents in ginger responsible for the anti-breast cancer property. [49]. In a study **Gingerols** has shown inhibition on the proliferation and metastasis of breast cancer cells. This inhibition in the proliferation of MDA-MB-231cells is achieved by inhibiting cyclin-dependent kinases and cyclins, leading to a G1 phase arrest. The invasion of breast cancer cells was also inhibited by 10-gingerol by the suppression of Akt and p38 (MAPK) activity. [40].

Shogaols also inhibited metastasis of breast cancer cells via different mechanisms, 6-Shogaol reduced expression of MMP-9 through blockade of NF-κB activation, leading to an inhibited invasion of MDA-MB-231 cells. [42].

7.4.2. Garlic

Garlic (*Allium sativum*) is a spice has been used worldwide for its medicinal effects. It has been used in folk medicine to treat a variety of ailments for centuries. [32]. A recent case-control study proved that high consumption of certain Allium vegetables, especially garlic, is associated with a decreased risk of breast cancer, with adjusted ORs of 0.41 (95% CI = 0.20–0.83). [48]. some of the studies indicated that the anti-breast cancer property of garlic might be attributed to diallyl disulfide, diallyl trisulfide, S-allyl mercapto cysteine, and allicin (organosulfur components). [71]. Diallyl disulfide (DADS) is one of the major organosulfur compounds isolated from garlic oil, and this could induce apoptosis in MCF-7 breast cancer cells. The pro-apoptotic effect might be through inhibition of histone deacetylation, activation of the SAPK/JNK, inhibition of ERK through p38 pathways. [63].

7.4.3. Black Cumin

Black cumin (*Nigella sativa*) is the most abundantly used spice and has been used in folk medicine for over 1400 years. Recently, the anticancer effect of black cumin has attracted more amount of attention. In a study, a supercritical CO_2 extract of black cumin exhibited a pro-apoptotic and anti-metastatic effect on MCF-7 cells in vitro.[93] In another study, it has been proved that the antiproliferative (IC_{50} = 62.8 µL/mL) and pro-apoptotic effects of black cumin extract were through mediating both the p53 and caspase pathways.[4].

Thymoquinone (**TQ**) is the major bioactive component isolated from the seeds of Nigella *sativa*, and it has shown potent chemo preventive and chemotherapeutic activities. Firstly, studies indicated that TQ might be an Akt suppressor. Akt could be activated (phosphorylated) by PI3K, and promote cell survival by inhibiting apoptosis through inactivating downstream targets, such as Bcl-2 family member BAD and GSK-3β. [79].

Other Spices

7.4.4. Red chilli peppers

Red chilli belongs to the genus *Capsicum* is a popular spice worldwide. It is containing a certain amount of capsaicin (8-methyl-*N*-vanillyl-6-nonenamide), which has shown an antiproliferative effect on breast cancer cells. Treatment with Capsaicin for 24 hours induced apoptosis in MCF-7 cells dose-dependently in vitro through a caspase-independent pathway. [16]. Other than this, capsaicin-induced apoptosis in MCF-7 breast cancer cells was identified, the reason being this activity is the induction of mitochondrial dysfunction. [16].

7.4.5. Piperine

Piperine is an alkaloid isolated from black pepper (*Piper nigrum*), is possessing most promising anti-breast activities. In a study, piperine has shown growth, motility and metastasis inhibitory effects on TNBC cells in vitro. Furthermore, it suppressed the growth of TNBC xenografts in immune-deficient mice. [29].

7.4.6. Saffron

Saffron (*Crocus sativus*), a well-known spice, is widely used in the Indian, Mediterranean, and Chinese diet. Saffron has shown anticancer effects in several studies. [14]. This activity is attributed to its bioactive compounds, such as crocin and crocetin. According to an in vitro study, incubating the highly invasive MDA-MB-231 cells with crocetin (1 and 10 μM) significantly inhibited proliferation and invasion of cancer cells, and the effect was achieved by the down regulation of MMP expression. [31]. In addition to this, one more study has shown that crocin and crocetin both inhibited the incidence of *N*-methyl-*N*-nitrosourea (**NMU**)-induced breast tumours in rats. Results showed that crocetin was found to be a more effective chemopreventive agent than crocin at both the initiation and promotion stages. [76].

Collectively, ginger, garlic, and black cumin have shown the most promising anti-breast cancer effects among various spices. More attention has been paid to the effects of bioactive components in spices, such as diallyl disulfide and diallyl trisulfide in garlic, gingerols, and shogaols in ginger. [93].

7.5.Edible Macro-Fungi

Various types of edible macro-fungi have shown inhibitory effects on breast cancer, such as oyster mushroom (*Pleutoruseous*), *Antrodia camphorate*, and lingzhi mushroom (*Ganoderma lucidum*).[34] In a case-control study which is conducted among Korean women, a significant inverse correlation between mushroom consumption and breast cancer incidence was found in postmenopausal women. But there is no significant association was found in premenopausal women. [36]. *Antrodia camphorate* is a medicinal mushroom widely used in Taiwan. Methyl anticipates A (MAA) is an ergostane-type triterpenoid isolated from the fruiting bodies of *A. camphorate*. MAA suppressed the population of cancer stem-like cells in the MCF-7 cell line by inhibiting Hsp27 expression and by increasing expression of p53 and IκBα. [52].

7.6. Cereals

Cereals are consumed worldwide as an everyday diet, and they are rich in dietary fiber. A systematic review and meta-analysis of the evidence from prospective studies showed an inverse association between cereal fiber intake and breast cancer risk. [47]

7.6.1. Sorghum

Sorghum (Sorghum bicolor) is a cereal consumed in some parts of the world. A study showed that sorghum suppressed the induction of cell cycle arrest, tumour growth and inhibition of metastasis through the Jak2/STAT pathway in nude mice bearing breast cancer xenografts. [15].

Furthermore, 3-deoxyanthocyanin obtained from red sorghum bran extract exhibited cytotoxicity on MCF-7 cells with a CTC50 value of 300 µg/mL, and also induced apoptosis achieved by up-regulating the p53 gene and down regulating the Bcl-2 gene. [17].

7.6.2. Wheat

Wheat (Triticum aestivum) is the most common kind of cereal consumed worldwide. Wheat contains rich nutritional constituents, such as starches and proteins, vitamins, minerals, phytochemicals and fibers (mainly in the wheat grain). A study showed that germinated wheat flour inhibited the growth of MCF-7 and MDA-MB-231 cells and induced apoptosis in vitro. [15].

7.6.3. Barley

Barley (Hordeum vulgare L.) is widely consumed in western countries. Whole grain barley contains phytochemicals such as phenolic acids, flavonoids, lignans, tocols, phytosterols, and folates. These phytochemicals exhibit strong antiproliferative, antioxidant, and cholesterol-lowering abilities, which are very much useful in lowering the risk of a certain type of cancers. Therefore, the high proportion of phytochemicals in Barley is responsible for its health benefits like preventing nutrition-related diseases including cancer, cardiovascular disease, diabetes, and obesity. [23].

Barley grass extract (*Hordeum vulgare* L.; Bex) is used to prevent or ameliorate various types of disease. Especially in breast cancer, Barley has been revealed to inhibit tumour growth. The role of Barley (Bex) in cancer prevention is attributed by inhibiting the viabilities of breast and prostate cancer cells according to the results of MTT assays. [23]. Apoptosis caused by barley was confirmed by Annexin V staining and western blot analysis for poly (ADP-ribose) polymerase and caspases. Moreover, Barley increased the intracellular levels of reactive oxygen species (ROS). [77]. Collectively, sorghum, barley, and wheat have shown the potential to inhibit the growth of breast cancer cells, mainly through cell cycle arrest, inducing apoptosis and inhibiting metastasis. Some of the effects of dietary natural products against breast cancer and their possible mechanisms are shown in Figure 4.

7.7.The possible Mechanisms involved with phytochemicals present in Dietary natural products

Polyphenols that are obtained from fruits block migration and invasion of breast cancer cells by regulating and inhibition of series of transcription factors viz. mammalian targeting function of rapamycin (mTOR), matrix metalloproteinase (MMPs), nuclear factor-kappa B (NF-κB), vascular endothelial growth factor (VEGF), epithelial-to-mesenchyme transition (EMT), and other signalling pathways.[30]. High exposure of estrogen on estrogen receptor (ER) is significantly playing a role in breast cancer cell proliferation. Numerous phytoestrogens having a more or less similar structure of non-steroidal compounds binds to the estrogen receptor and thereby inhibit the action. Moreover, these phytoestrogens inhibit the production or interference of estrogens. Flavonoid compounds which are abundantly distributed in fruits and nuts involved in the recognition of ER receptors predominantly reduced cancer size with decreased Cytochrome P450 enzyme (Enzyme inhibition). [31].

Table No 2. Possible Mechanism involved with Natural phytoconstituents

1	Antioxidant activity Scavenge free radicals and reduce oxidative stress.
2	Inhibition of Cell proliferation, cell differentiation, Oncogene expression, Signal transduction pathways.
3	Induction of Tumour suppress gene expression, cell-cycle arrest.
4	Enzyme induction and enhancing detoxification Phase II enzyme, Glutathione peroxidase, Catalase, Superoxide dismutase.
5	Enzyme inhibition Phase I enzyme (block activation of carcinogens), Cyclooxygenase-2, Inducible nitric oxide synthase, Xanthine oxide.
6	Enhancement of immune functions and surveillance.
7	Ant angiogenesis.
8	Inhibition of cell adhesion and invasion.

9	Inhibition of nitrosation and nitration.
10	Prevention of DNA binding.
11	Regulation of steroid hormone metabolism.
12	Regulation of estrogen metabolism.
13	Antibacterial and antiviral effects.

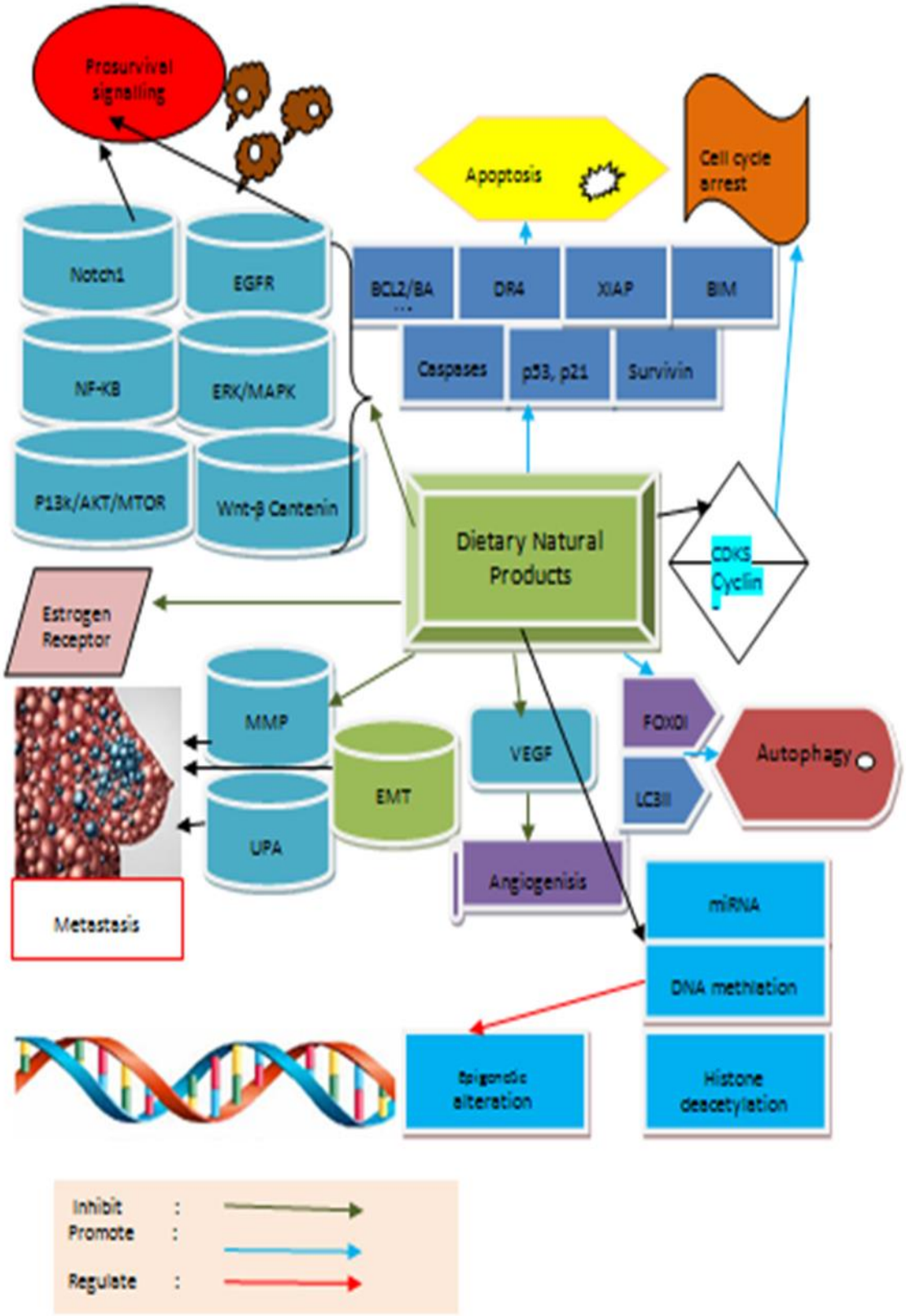

Fig.4. Possible mechanisms involved in the anti-breast cancer activity of dietary natural products.

8. Nutrigenomics (Genomic Effects)

The most growing research field referred to as nutrigenomics summarizes the vital role of natural products in disease prevention, treatment, and management. Nutrition makes an impact not only on health but also on the genome level. [12]. Nutrigenomics has some degrees of similarity with pharmacogenomics, but the predominant difference is that pharmacogenomics uses synthetic chemicals whereas Nutrigenomics applies to natural phytochemicals, where the transcriptomic profile is the key element. Nutrigenomics will give perfect clarification of genetic variations (for example, SNP) and epigenetic alterations (i.e. modifications at the gene level unrelated to changes in DNA sequence). This both control gene expression; influence the requirements for nutrients as well as the response to nutrients. This type of understanding will be particularly useful for several types of cancers that appear to be influenced by nutrition for their occurrence, progression, and recurrence. [68]. Breast cancer is one such nutrition-dependent cancer mainly occurs because of the risk brought by an overweight status in postmenopausal women. However, it is a very long way to go to predict the influence of foods on the mammary gland before and after breast cancer development according to a plethora of reports. Numerous nutrients have been possessing a high potential impact on the mammary gland and its tumorigenesis properties proved by various *In vivo* and *In vitro* studies. [17]. Overall, nutrition is possessing a high degree of association in genetic alterations which are achieved by various phytochemicals and exerting more beneficial effects in the prevention and management of certain nutrition-related diseases like breast cancer, diabetes, obesity, and cardiac diseases.[92].

P-glycoprotein (P-gp), multidrug resistance-associated proteins 2 and 3 (MRP2 and 3) and breast cancer resistance protein (BCRP) are efflux pumps that exert a significant impact on cancer chemo resistance and were proved to be modulated by polyphenols. Genistein (GNT) is the most important estrogen mimetic and was proved to exert its genomic properties through Estrogen-Receptors and Pregnane-X-Receptor (PXR) a key protein related to multidrug resistance genes. [37]. GNT in the concentration range of 1.0 and 10 μM was able to inhibit PXR and activate P-gp. The activation of MRP2 was observed only at 10 μM in Hepato carcinoma and breast cancer. [73, 94]. Therefore, phytochemicals can increase or decrease cancer chemo resistance, the effect depending on the cell type and exposure dose.

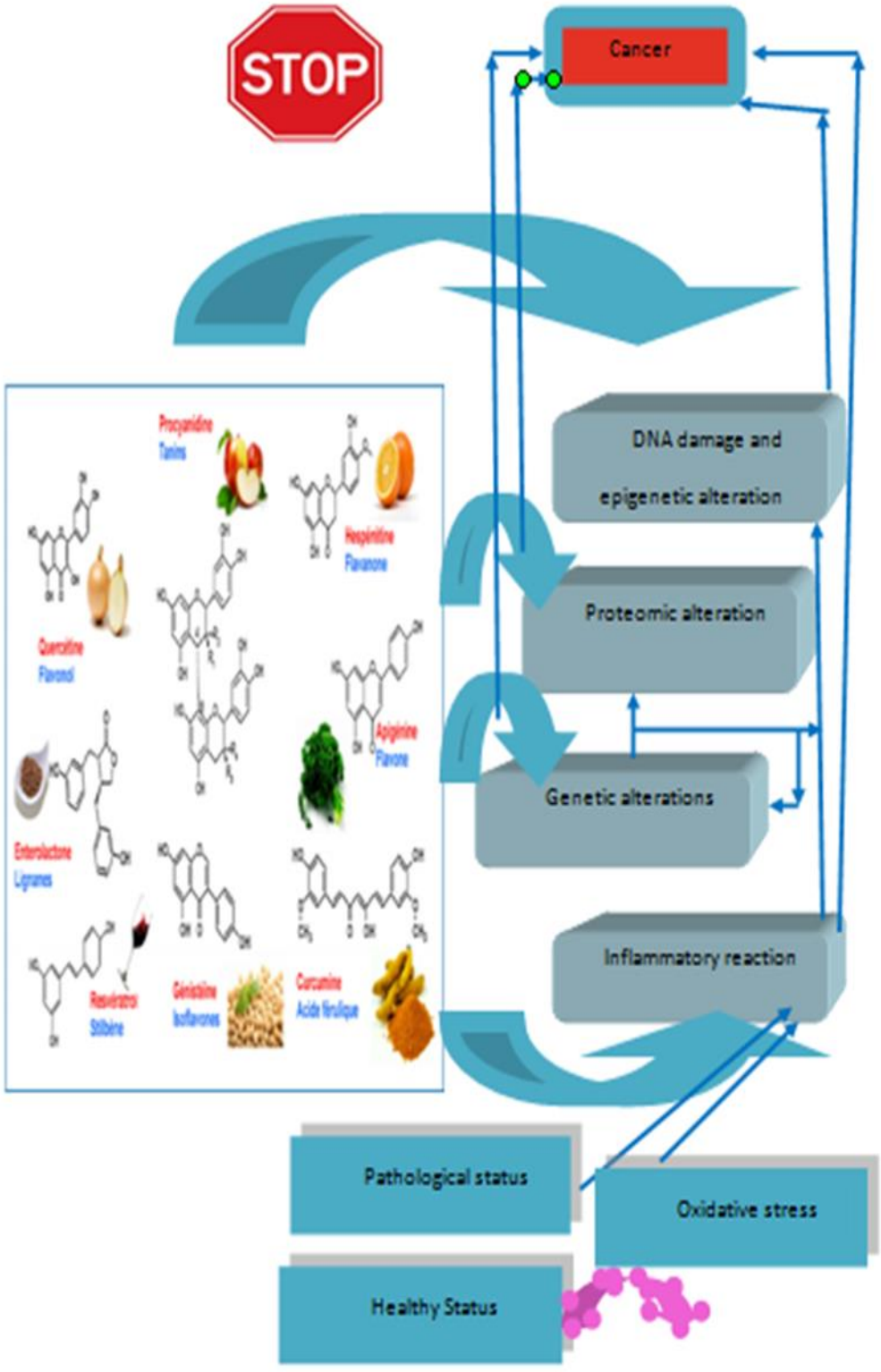

Fig.5. Nutrigenomic impact of natural products

9. DISCUSSION

The latest discoveries in cancer therapy, particularly in preclinical models include a wide range of combinations of low doses of natural phytochemicals with conventional therapies. Predominantly, combination therapy has proven to have an additive or even a synergistic effect. The most significant one to mention is the reduced toxicity caused particularly by chemotherapy or radiotherapy when used in combination with a natural bioactive agent. Genistein a phytoconstituent obtained from soy when taken with gentamicin will lead to inhibition of miR-223 could reverse EMT phenotype and increase chemotherapeutic drug sensitivity to gentamicin in pancreatic cancer models [37]. Epigallocatechin-3-gallate (EGCG) which is obtained from green tea, is a chemopreventive agent. When used in combination with standard chemotherapies, this inhibits sphere formation, a particular phenotype responsible for drug resistance caused by the presence of cancer stem cells [57].

The biological activity of these compounds was relatively reduced. That is the case of the EGCG effect that induces a very low reduction of cell proliferation in a resistant HCC (hepatocell carcinoma) cell line, but when administered with Doxorubicine the antitumor effect is much higher even at lower doses. [94]. Natural phytochemicals act as key signalling molecules as one might see from the nutrigenomics pattern of these molecules. In spite of the increased number of investigations, the results remain inconclusive, and there are only a few cases that are implemented into clinical trials. These preclinical data are useful and can serve as a base for developing novel antitumor agents and antineoplastic drugs with greater pharmacologically and biologically active effects. There is no doubt about the benefit of these natural compounds in human health but at the same time, it is quite difficult to ignore the controversial data due to the extensive range of experimental and preclinical models used for the evaluation of the biological effect. These discrepancies can be reduced with the development of a natural product database and standardization of the protocols. The process of novel drug discovery or drug design from natural products is based on the integration of nutrigenetics and nutrigenomics data. The natural compounds have multifaceted properties due to the heterogeneity of the different molecular structures that are retrieved from natural sources. [93]. In spite of all these difficulties, it is highly mandatory to introduce the concept of a personalized diet that supports the chemotherapeutic treatment.

CONCLUSIONS

In the current scenario, cancer prevention through dietary agents and phytochemicals is quite a promising arena of oncology that has drawn a highly significant amount of attention from researchers as well as medical practitioners. The entire process of carcinogenesis is complex and heterogeneous with several combinations of genetic and epigenetic processes that occur in a particular cell to create a neoplastic deformation. While considering the stages of cancer, initiation, promotion, and progression, the second step is playing a vital role and is considered for cancer chemoprevention. As per research predictions, almost two-third of human cancers could be prevented through proper lifestyle management. [20]

Natural phytochemicals present in the diet play an important role in the prevention of breast cancer through a broad spectrum of mechanistic actions. Extensive studies have shown that natural phytochemicals inhibit cell proliferation, migration, invasion and inhibit metastasis formation. These phytoconstituents down-regulate or inhibit many transcription factors that are responsible for breast cancer. Natural phytochemicals which are possessing anti-breast cancer properties might be used as a chemotherapy agent that may help to obstruct the progression of breast cancer. [92].

Phytochemicals are mainly present in fruits and vegetables and their regular intake would be beneficial in cancer prevention. Furthermore, the highly promising beneficial effects of phytochemicals engulfing the general masses due to their less amount of side effects and cost-efficiency. In some cases, phytochemicals are used along with conventional chemotherapeutic agents for its highly beneficial additive and synergistic effects. More in-depth studies are going on in more promising phytochemicals for their significant role in breast cancer prevention, management, cost efficiency, and abundance. [95]

Conflict of interest

The authors have declared that there is no conflict of interest.

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