

Biomarkers, Critical Disease Pathways, Drug Targets, and Alternative Medicine in Male Breast Cancer

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Abstract: While breast cancer (BC) is commonest malignancy among female with highest death rate, male breast cancer (MBC) is very rare but exhibits highest cancer specific death in men and the incidences of MBCs are rising rapidly. Due to rarity of the disease, no detail information about biomarkers and drug targets available and because of late diagnosis and rarely understood the pathogenesis at molecular level, the treatment of MBC is also not yet standardized. Though the MBC biology, pathogenesis, and the clinical outcomes resembles with female breast cancer (FBC), they are quite unique in many aspects. Therefore, the uses of FBC specific drugs for treatment of MBC are not only dissatisfactory but also increases mortality rate due to severe side effects of these conventional drugs. To avoid side effects of usual therapeutic drugs, new drugs and their targets should be identified and evaluated, where the dietary phytochemicals may be the alternative of currently used drugs. Similarly, an integrated strategy and pharmacogenomics approach is now essential to fight against this malady. This article will deal with different aspects of MBC including biomarkers, pathways, drug targets, and common dietary phytochemicals as effective alternatives of conventional chemotherapeutic drugs for targeted therapy without any side effect.

Key Words: Biomarkers, Drug Targets, Critical Pathway, Female Breast Cancer, Male Breast Cancer, Phytochemical.

INTRODUCTION

MBC-Epidemiology

Cancer is uncommon in vestigial organs [1]. Being male breast a vestigial part, the incidences of MBCs are very rare that accounts for less than 1% of all cancers in men but this lower incidences show highest cancer specific death rate in men [2]. It accounts for 0.1% of cancer mortality in men in US [3, 4]. Occurrences vary with geographic locations, higher in USA and UK, where even the FBC incidences are also high, and lower in Japan, where frequencies of FBCs are low [5]. Zambia and Egypt show respectively 15 and 12 times higher incidences than that of the USA [6, 7]. Incidences vary from 0.08 to 6.4% of total breast cancers in the western countries and 0.06 to 4.06% in India [8]. In India the incidences have been reported 0.9 to 1.9% [9], 1.8% [10], 2.6% [11], 4.7% [12], 5.3% [8], and 4.76% [13]. The trend is increasing over years [14]. Little is known about the etiology of MBC due to its rare occurrence but it apparently looks similar to FBC in biology and the clinical outcomes [15, 16].

Signs and Symptoms

MBCs are most common in men between the ages of 60 and 70. Most common sign of breast cancer for both men and women is a lump or thickening in the breast those are often painless. Other signs are skin dimpling or puckering, development of a new retraction or indentation of the nipple, redness of scaling of the nipple or breast skin, and a spontaneous clear or bloody discharge from the nipple. 96% MBCs

are carcinoma and remaining 4% are sarcomas. The most common form is invasive ductal carcinoma and lobular cancer is very rare [17]. In general MBCs are painless, show unilateral breast mass, most often eccentric, slightly irregular, quite firm, occasionally associated with nipple discharge, and serious discharge have been found in ~15% of patients [15]. Bloody discharge is associated in 75% of cases with malignancy [18]. More than 75% MBC cases are positive for estrogen and progesterone receptors (ER and PR), nodal metastasis is common, and is likely older and advance stage disease than FBC [19]. Though the biology, pathogenesis, and clinical outcomes of MBCs apparently looks similar to FBCs [15, 16, 20-22], however, they differ in several aspects [23-25].

Risk Factors

The risk of MBC increases with age in males but lacks the early pre-menopausal peak seen in females that is why the greatest incidence occurs with the peak at 60 years of age in male. A family back ground of FBC has a 2- to 3-fold increased risk of developing MBC [26]. Onset of MBC correlates with marital status, gynaecomastia, and relative hyperoestrogeny [27]. Other risk factors include **Genetic predisposition:** 5 to 10 % cases are inherited. Career mutations in especially BRCA2, BRCA1, CHEK2, PTEN, P53, AR, ESR, and CYP17A1 gene are associated with increased risk of MBC. **Radiation exposure:** radiation treatments to chest at child or young age make it susceptible to develop BC at later age in life. **Exposure to estrogen:** use of estrogen-related drugs for treatment of prostate cancer or other hormone related disorders can higher the risk of MBC. **Liver disease:** liver cirrhosis condition where body's androgen activity is reduced and estrogen activity increases can in-

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crease risk of gynecomastia and MBC. **Excess weight:** obesity is also a risk factor. Obesity increases the number of fat cells and those fat cells convert androgen into estrogen, thus increases the risk of MBC. **Excessive use of alcohol:** amount of alcohol consumption directly proportionate to the risk of MBC.

Associated Diseases

Occurrence of MBC associates with aneuploidy [28], gynecomastia [29], paraneoplastic syndromes [30], and prostate cancer hormone therapy [31]. The extra X chromosome in Klinefelter's syndrome causes abnormal development of the testicles, lowers male hormone secretion, and produces more estrogens, which can cause noncancerous breast growth (gynecomastia) and increases the risk of MBC [32].

Screening and Diagnosis Methods

Available diagnosis tests include- **a) Clinical breast examination:** to check the lumps or other changes, sensitivity of pain and metastatic symptoms like enlarged liver or lymph nodes. **b) Mammogram:** though generally not recommended because of lack of dense breast tissue in men that can make it difficult to distinguish abnormal cells from normal tissue or breast cysts, yet can be performed if required. **c) Breast ultrasonography:** used to evaluate an abnormality seen on a mammogram or abnormalities found during a clinical examination. **d) Nipple discharge examination:** nipple discharge can be used to examine for presence of cancerous cells. **e) Biopsy:** core needle biopsy is more preferable to get cells from breast lump and their subsequent analysis for presence of malignant cells and also to determine the cancer type. **f) Estrogen and progesterone receptor tests:** a biopsy positive for malignant cells can be tested for ER and PR positivity and MBCs positive for ER or PR can be treated with tamoxifen. **g) HER2 testing:** a biopsy positive for malignant cells also requires HER2 test that can be carried out by immunohistochemistry or FISH or by PCR method. About 30% MBCs show overexpression or amplification of HER2 and are usually more aggressive and metastatic. HER2 overexpressing MBCs can be treated with trastuzumab and lapatinib. **h) Ploidy level and cell proliferation rate test:** although these tests are not usually recommended, they may help to determine prognosis. Flow cytometry and image cytometry can be used to measure ploidy level. Flow cytometry measures the S-phase fraction thus helps in disease prognosis. The rate of cancer cell division can also be estimated by a Ki-67 test. A high S-phase fraction or a high Ki-67 labeling index is an indication of rapidly dividing cancer cells and a more aggressive cancer. **i) Tests for gene expression patterns:** MBC specific microarray chip can also be used to get gene expression patterns for biomarkers, prognosis, and treatment efficacy. Oncotype DXTM and Mamma Print® for FBC are now available with different gene sets but MBC specific chip is not yet introduced in market. **j) Imaging tests:** chest X-ray, mammogram, bone scan, CT scan, MRI, and PET may be practiced depending on disease condition and to confirm metastasis and aggressiveness. While grading can be done based on how closely the biopsy sample resembles to normal breast

tissue, staging can be practiced based on tumor node metastasis (TNM) staging system.

Available Treatments

Despite the biological differences, clinical outcomes of FBCs and MBCs are apparently similar for age, treatment, and stage of cancer [20-22]. In both cases HER2 is overexpressed. While germ line BRCA1 mutation confers a 60-80% risk for breast cancer in female, mutations in BRCA1 do not increase the risk in men instead, BRCA 2 mutations correlate with the risk [33-35]. Androgen deficiency may be one of the causes [36]. Simultaneous overexpression of HER2, c-MYC, and P53 shows high-risk with a shorter survival in MBC [37]. P21/WAF1 is expressed in 70.3% primary MBCs [38]. In most cases no fixed treatment exists and the treatment depends on grade, stage, age, and the genetic makeup of the cancer. Treatment options include breast-conserving surgery (lumpectomy, mastectomy, and lymph node dissection), radiation therapy, chemotherapy, hormonal therapy, targeted therapy, combinational therapy, and stage specific treatments. Drugs generally used in treatment of MBC are listed in Table 1 and 2.

Drugs used in MBC treatment mainly consist of selective estrogen-receptor modulators (SERMs), aromatase inhibitors, anthracyclines, and microtubule dynamics modulator etc. As more than 75% MBCs are ER or PR positive, SERMs and anti-estrogen drug tamoxifen are most commonly used [39]. Doxorubicin is generally used in ER (-) MBCs [40]. Aromatase inhibitors along with luteinizing hormone-releasing hormone (LHRH) analogs such as leuprolide and goserelin are in trial now. Orchiectomy, the surgical removal of the testicles to lower the level of testosterone and other androgens can be practiced for androgen receptors positive MBCs. Orchiectomy shrinks most male breast cancers but recently this process is substituted by LHRH analogs and anti-androgens (flutamide and bicalutamide) treatments. Hormonal therapy is beneficial for non-invasive ductal carcinoma in situ and it lowers the risk of recurrence and metastasis, prevents early-stage invasiveness and secondary tumors, and helps to shrink the size of the cancer.

Some targeted therapeutics such as herceptin (trastuzumab) and tykerb (lapatinib) can be used in case of HER2-positive MBCs. Avastin (bevacizumab) is used to check angiogenesis and metastasis in combination with taxol (paclitaxel) and to target VEGF. Adjuvant and several combinational chemotherapies are in practice for many cases. Preferred combinations include drugs such as doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, methotrexate, fluorouracil etc. Preferred single agents for recurrent and metastatic cases are doxorubicin, epirubicin, pegylated liposomal doxorubicin, paclitaxel, docetaxel, capecitabine, vinorelbine, gemcitabine, and albumin-bound paclitaxel etc.

BIOMARKERS IN MBC

Till the date there is no microarray or other kind of high throughput screening data available for MBC. Hence, the identified biomarkers for drug targets are not yet available. An extensive literature database search reveals that at least 25 genes are involved in the MBC pathogenesis.

Table 1. Classes of Drugs Used to Treat Breast Cancer

| Classes of Drugs | Action | Examples |
|-----------------------------|--|---|
| SERMs | Bind to estrogen receptors in breast cancer cells, block the effects of estrogen, starving cancer cells, block (or selectively inhibit) estrogen receptors in breast cells | Tamoxifen, Evista (Raloxifene), Fareston (Toremifene) |
| Aromatase Inhibitors | Prevent production of estrogen in adrenal glands, lower the amount of estrogen in post-menopausal women | Aromasin (Exemestane), Femara (Letrozole), Arimidex (Anastrozole), Megace (Megestrol) |
| Biologic Response Modifiers | Bind with certain proteins on breast cancer cells preventing their growth | Herceptin (Trastuzumab) |
| Other Hormonal Therapies | Block and break down estrogen receptors. Treat breast cancers that are dependent on estrogen for survival | Zoladex (Goserelin acetate), Faslodex (Fulvestrant) |

Table 2. Chemotherapy Drugs

| Classes of Drugs | Action | Examples |
|-------------------------------|--|--|
| Anthracyclines | Inhibit topoisomerase II and prevent DNA replication also deform DNA structure of cancer cells | Adriamycin (Doxorubicin), Ellence (Epirubicin) |
| Taxanes | Prevent cancer cells from dividing disrupting the normal microtubule dynamics | Taxol (Paclitaxel), Taxotere (Docetaxel) |
| Alkylating Agents | Interfere with DNA synthesis and replication | Cytosan (Cyclophosphamide) |
| Antimetabolite | Nucleoside analog, damaging the RNA or DNA brings apoptosis | Gemzar (Gemcitabine), Xeloda (Capecitabine) |
| Semi-synthetic vinca alkaloid | Binds to tubulin, thereby inhibiting tubulin polymerization into microtubules and spindle formation and resulting in apoptosis | Navelbine (Vinorelbine) |

BRCA1 and BRCA2

14% of MBCs are associated with BRCA2 mutations [41]. Sporadic [42-44] and germ-line mutations [41, 45, 46] in BRCA2 have also been reported to be associated with MBCs. Familial form of MBCs generally correlates with BRCA2 mutation [42, 43]. Loss of BRCA1 protein is associated with increased cell proliferation in MBC similar to FBC [47]. Mutations in the BRCA1 have also been observed [31, 44]. 16% Central Italy MCB population have been reported to exhibit BRCA1 (3345delAG) and BRCA2 (6696delTC) mutations accompanied with ERBB2 overexpression and BRCA2 LOH [48]. BRCA2 founder mutations (9346(-2) A>G, 4075 delGT, 5808 del5, and 999 del5) are observed in 6.5% of MBCs in Finnish population [49]. BRCA1 and BRCA2 are reported to upregulate in MBC and estrogen regulates this upregulation [50]. At mRNA level, a higher BRCA2 than the BRCA1 have been reported in sporadic cases and that the higher BRCA2 mRNA expression associates with ER or PR negativity or high histological grade. High proliferation and genomic instability in high histological grade tumors may be the cause of higher level of BRCA2 expression [51].

Androgen Receptor

Lack of expression [52], loss of function, and decreased DNA binding and transcriptional activator activity [53] of

androgen receptor (AR) also correlates with MBC. G2185A point mutation that causes decrease in androgen protection action to breast tissue can lead to the development of MBC [54] but in certain cases AR does not account for MBC [55] and that the somatic mutations in AR are not necessary for the development of male breast cancer [56]. CAG repeat mutation in AR also has been observed in certain cases [57]. Downregulation of AR has been reported to cause early onset of the disease [58].

Other Markers

Mutations in the TP53 [16] and CHEK2 [59] are associated with several MBC cases. Gly12Lys and Gly12Arg mutation in KRAS along with mutation in P53 also have been reported [60]. Whereas, decreased expression of ESR1 has been noticed in familial MBC [61], polymorphism in the CYP17A1 gene correlates with disease susceptibility [62]. Upregulation or overexpression of PCNA [63], ERBB2/HER2 [17, 37], MYC [37], and TP53 [37, 64] are associated with increased occurrence of death. PGR [58], MMP2 and MMP9 [65] have been found to overexpress in few cases.

Overexpression of P53 and HER2 have been reported respectively in 46% and 39% cases with 81% case of ER positivity [66]. Similarly, overexpression of ERBB2, P53 and c-MYC (62.5, 16.7 and 20.8% cases), and 75% and 69% cases respectively ER and PR positivity in MBCs have been observed [67]. Though CYP17A1 polymorphism is not asso-

ciated with risk of MBC, it plays a significant role in carriers of a BRCA2 mutation [68]. According to Bärlund *et al.* (2004) [69] 1-2% of MBCs show overexpression of ERBB2, MYC, PPM1D and ZNF217 that indicates a lower amplification frequency of these genes in MBC than that of FBC but CCND1 amplification was observed in 12% cases. 63% CCND1 overexpression was associated with ER positivity. HER2 gene amplification is associated with 11.5% of MBCs [70] and Fonseca *et al.* (2006) [71] reported respectively 14% and 8% cases of HER2 overexpression and amplification in MBC with poor survival. ER (89%), PR (73%), and intratumoral aromatase (ITA, CYP19A1) (27%) positive cases, and HER2 overexpression in 10% of MBCs are also in report [72]. Other mutations associated with MBCs are HFE, MSH2, MLH1, PMS1, and PMS2 [73].

Pathways and Drug Targets

In our recent analysis, we identified 3 critical pathways (ER signaling, EGFR signaling, and DNA repair) (Fig. 1) involving all these genes with 30 possible drug targets in MBC. It has also been found that estrogen and in some ex-

tent cAMP is key regulator of all critical paths. CYP19A1, ESR1 and NF-κB are found to be key regulators thus probably are good drug targets in ER signaling critical path. Whereas ERBB2/EGFR, AKT, and β-catenin seems to be good drug targets in EGFR signaling critical pathway, restoration of specific genes functions or targeting their downstream molecules for regulation of cell cycle or DNA repair will be a strategy for DNA repair pathways. Pathways may crosstalk with each other and in advanced metastatic cases more than one pathway have been found to involve [74].

DIETARY PHYTOCHEMICALS AS ALTERNATIVE MEDICINE

Treatments generally practiced for FBC are also in some extent applicable to MBC. But all these treatments evoke severe deadly side effects [75, 76] and frequently affect cognitive abilities. Due to late diagnosis and yet unknown biology and molecular events [77], when fixed treatments of FBC are applied to MBC cases, they do not work satisfactorily [78]. Again, severe side effects of conventional chemotherapeutic drugs used for FBC [79, 80] and the impact of

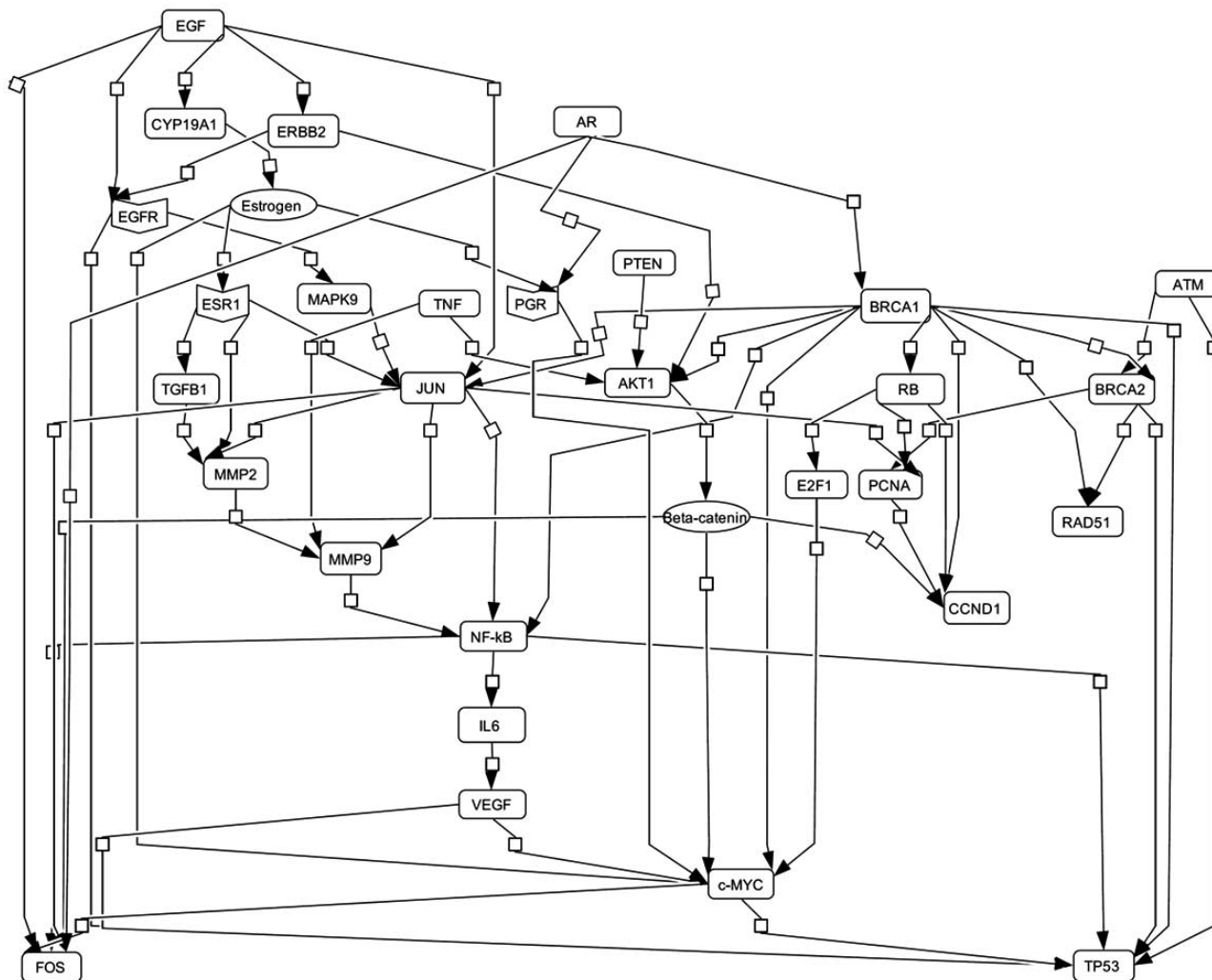


Fig. (1). Biomarkers and critical disease pathways in male breast cancer.

comorbidities and secondary neoplasm in MBC; the mortality rate is increasing [81]. Strategy of induced apoptosis [82] and cell cycle arrest in the cancer cells without affecting the normal cells with chemopreventive dietary and safer phytochemicals [83, 84] are showing promising results for FBC.

Our study predicted that at least thirteen phytochemicals can cover all drug targets in MBC. Among them, genistein, curcumin, resveratrol, ATRA, and EGCG have the potentiality of simultaneous induction of apoptosis and growth inhibition in both ER (+) and ER (-) MBCs targeting all three critical pathways covering all drug targets. These five phytochemicals also have the ability to inhibit metastasis, thus they might be potential alternative sources of conventional drugs for MBCs [74] (Table 3).

Resveratrol

Resveratrol of red grape skin acts as an antiestrogen in combination with 17 β -estradiol [85]. It also can act as an aromatase (CYP19A1) inhibitor to suppress ER- α expression [86] and estrogen biosynthesis [87]. Resveratrol upregulates BRCA1 and BRCA2 mRNAs [88], and downregulates TP53 [85, 89, 90] and VEGF to inhibit angiogenesis in ER (-) BCs [91].

In ER (+) cases, it inhibits COX2, MMP9, and NF- κ B expression and brings S-G2-M arrest [92]. Resveratrol induces apoptosis through FAS/FAS ligand [93], through AKT-Caspase-9 pathway [94] and by downregulating telomerase activity [95]. It exerts its apoptotic effects in ER (+) BCs by inhibiting Cyclin-D/CDK4, TP53, and P21, activating Caspase-9 and BAX, and by downregulating BCL2 and BCLXL [96]. By inhibiting PI3K signaling, BCL2, and NF- κ B it induces caspase-independent apoptosis in ER (+) BCs [97].

Rretinoic Acid

Rretinoic acid inhibits expression of the estrogen responsive genes PR and PS2 [98], IRS1, and AKT to inhibit breast cancer cell proliferation [99] and downregulates BCL2 to induce apoptosis in metastatic ER (+) BCs [100, 101]. Rretinoic acid inactivates EGFR, inhibites PKC α , prevents

growth factor signaling, and induces cell cycle arrest in hormone dependent breast cancers [102].

Curcumin

Curcumin from *Curcuma longa* inhibits IkappaB, NF- κ B, and COX2, downregulates metastatic proteins VEGF, MMP9, and ICAM1, and restrains anti-apoptotic XIAP, IAP1, IAP2, BCL2, and BCLXL [103, 104]. It inhibits ER downstream genes, PS2, TGF- β , and MMP2 and upregulates TIMP1 in estrogen-dependent breast cancers [105]. Curcumin downregulates Cyclin-E [106], Cyclin-D1, and blocks its association with CDK4 and 6 to inhibit breast cancer proliferation [107]. It induces apoptosis by inhibiting MAPK activation [108] and by upregulating TP53 followed by BAX level increase in ER (+) BC [109].

EGCG

EGCG of green tea inhibits TGF- β induced EGFR autophosphorylation, upregulates P21/WAF1 and P27 in both ER (-) and estrogen-dependent BCs [110, 111]. It inhibits ER-dependent transcription and MAPK activation [112], HGF-induced MET phosphorylation and subsequent AKT and ERK activation [113], and Wnt signaling in invasive breast cancers [114]. In mouse model of metastatic BC, EGCG induces apoptosis by upregulating BAX/BCL2 ratio and by activating Caspase-3 [115].

Genistein

Genistein from soy derivatives is a potent estrogen agonist that binds to ER and induces dose dependent growth-inhibition similar to tamoxifen treatment [116]. It inactivates NF- κ B and downregulates AKT [117], inhibits angiogenesis and metastasis by downregulating VEGF, TGFb1, MMP9, and upregulating TIMP1 in both ER (+) and ER (-) BCs [118, 119]. It inhibits growth of HER2 overexpressing BC by downregulating survivin, EGFR, HER2, and ER [120]. Genistein inactivates AP1/JUN and ERK, downregulates FOS [121], MET, JUN, and EGR1 binding to SP1 transcription factor, and upregulates breast tumor suppressor EGR1 [122]. It causes ATM dependent upregulation and activation

Table 3. Phytochemicals Those can Target Both Growth Factor Signaling and Apoptosis

| Phytochemicals | Apoptotic Targets | Cell Proliferation and Metastasis Inhibitory Targets | Breast Cancer Types |
|---------------------------------|---|--|-------------------------------|
| Genistein (Soy derivatives) | PTEN, BCLXL, and BAK | VEGF, NF- κ B, TGFb1, AKT, MMP2, MMP9, EGFR, HER2, AP1, ERK, FOS, TP53, CHK2, ATM, BRCA1, BRCA2, and ESR1 | ER(-), ER (+), and Metastatic |
| Resveratrol (Red grape skin) | Akt-caspase-9 pathway, FasL, P53, PI3K, NF- κ B, and hTERT | VEGF, NF- κ B, MMP9, CYP19A1, Cyclin-D/CDK 4, P53, P21, BRCA1, BRCA2, ESR1, | ER(-), ER (+), and Metastatic |
| Ratinoic Acid | BCL2 | EGFR, PKC, IRS1, AKT, and ESR1 | ER (+) and Metastatic |
| Curcumin (Turmeric) | XIAP, IAP1, IAP2, TP53, BAX, BCL2, and BCLXL | VEGF, MMP2, MMP9, TGF β , NF- κ B, MAPK, Cyclin-D1, Cyclin-E, CDK-4 and -6. | ER(-), ER (+), and Metastatic |
| EGCG (Green tea) | BAX and Caspase-3 | TGF- β , MAPK, AKT and ERK, P21/WAF1, and P27 | ER(-), ER (+), and Metastatic |

of TP53 and CHK2 [123] and inhibition of CYP1A1-mediated EROD and TPA-induced COX2 activities [124]. Genistein has been found to act on BAK and BCLXL mediated apoptosis [125] and in ER (+) BC it induces cell death by upregulating PTEN [126].

CONCLUSION

MBCs are rare but accounts for highest cancer specific death in men and the incidences are increasing rapidly. Lack of proper identification of biomarkers and disease characterization, subsequent appropriate treatment is yet to be standardized. Due to the apparent similarities between FBC and MBC, general treatments of FBC when applied for MBC do not give expected result. Again, severe side effects of FBC specific drugs increasing death tolls in case of MBC. Thus understanding of molecular pathology and biomarkers for effective drug targets is essential for better treatment of MBC.

25 genes namely BRCA1, BRCA2, HER2/ERBB2, P21/WAF1, P53, MYC, AR, CYP19A1, ESR1, PGR, PPM1D, ZNF217, CCND1, KRAS, CHEK2, MMP2, MMP9, CYP17A1, PCNA, PTEN, HFE, MSH2, MLH1, PMS1, and PMS2 are involved in MBCs pathogenesis. Mutations have been found in BRCA1, BRCA2, CHEK2, P53, PTEN, CYP17A1, HFE, MSH2, MLH1, PMS1, PMS2, AR, KRAS, and CYP17A1. HER2/neu, ESR1, PGR, MYC, PPM1D, ZNF217, CCND1, P53, MYC, CYP19A1, MMP2, MMP9, P21, and PCNA are upregulated in many cases individually or in small groups in different population. AR and BRCA1 are found to be downregulated in few cases. Therefore, all genes are not involved in a single pathogenesis instead, single or a group of them are involved in specific MBC cases and in a particular population group.

30 possible drug targets (EGF, EGFR, ERBB2, JUN, FOS, AKT, β -catenin CYP19A1, ESR1, NF- κ B, MYC, TNF, IL6, VEGF, MMP2, MMP9, BRCA1, BRCA2, P53, CHK2, PCNA, PPM1D, PKAc, PI3K, MAPK, JNK1, PTEN, KRAS, and CyclinD-CDK4) have been reported those can be targeted with 13 different dietary phytochemicals among them Curcumin, Resveratrol, ATRA, Genistein, and EGCG have potentiality to act on all maximum targets even in ER (+), ER (-), and metastatic breast cancers [74].

The most essential thing is the biomarker specific characterization of MBC cases as the evidences shows that there are several biomarkers and at least three critical pathways are in action those can interplay. Identification of unique marker in specific MBC case and subsequent marker specific treatment is important for affective treatment of male breast cancer. Development of early stage detection, screening, and diagnosis method is also essential. A gene chip comprising of all markers can be used for the purpose. Specific tests to determine the expression levels of EGF, EGFR, ESR1, ERBB2, estrogen, JUN, NF- κ B, and β -catenin can give better understanding of involved pathways so that targeted treatment can be easier. Mutation screening of BRCA1 and 2 and CHK2 will be helpful in determining the hereditary risk of MBC. Identified five phytochemicals need *in vitro* study for their specificity to MBC. If these phytochemicals show promising result, multi-targating formulation combining all five phytochemicals can be taken into consideration for its

general application to any MBC cases regardless of their molecular profile.

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