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Breaching the Barriers of Chemotherapeutics for Breast Cancer with Alternative Medicine

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Abstract

Breast cancer is one of the most prevalent forms of cancers in women around the world. Owing to its biochemical variation and complexity, treatment with chemotherapy and/or radiotherapy is very complicated and often results in adverse side effects. This article reviews the widely practiced chemotherapeutic drugs, their modes of actions and side effects. The several breast cancer therapeutic approaches based on medicinal plants, hormones, nutritional supplements and/or some advanced drug delivery systems that may lead to faster recovery are also reviewed.

Keywords: Alternative Therapy, Breast Cancer Therapy, Chemotherapeutics

1. Introduction

Breast cancer is the second most leading cancer in women worldwide causing mortality and its incidence increases significantly in developing countries where most cases get diagnosed in the advanced stages. Breast cancer impacts 2.1 million women each year, and causes the most significant number of cancer-related deaths among women. In 2018, an estimated 627,000 women died from breast cancer, approximately 15% of all cancer deaths among women[1]. The fight against cancer has not been successful so far, particularly in developing therapies for rapidly growing tumors. Surgery, chemotherapy and radiation therapy represent the orthodox cancer treatments. Surgical removal of tumor and radiation therapy have shown benefit in many cancer types but mostly restricted to localized tumors. Chemotherapy with cytotoxic compounds involves complications, including severe toxic side effects and development of resistance in cancer cells to chemotherapeutic agents. Treatment of early stages breast cancers in postmenopausal women attempts to inhibit hormone action using aromatase inhibitors (anastrozole, letrozole, and exemestane) or block estrogen action by an antiestrogenic agent (tamoxifen).

Multi-drug approach provides better hope but still leaves much to be anticipated, as the ideal anti-cancer drug must be selective and cytotoxic to cancer cells. Therefore, effective treatment of patients with advanced or metastatic cancer needs a therapeutic strategy which is capable of reaching target tissue, acting specifically on cancer cells without causing any harm to normal tissue. Also, investigation of newer anti-cancer drugs to improve chemotherapy for the inoperable advanced cases is required. It is crucial that such cytotoxic compounds selectively target tumor cells, without toxic side effects but strengthening recovery.

2. Breast Cancer Risk Factors

Several risk factors have been documented. However, it is nearly impossible to evaluate the risk factors for breast cancer for most patients due to heterogeneity[2]. A familial history of breast cancer increases the risk by about three folds. One report shows various modifiable risk factors,

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excluding reproductive factors, to the overall breast cancer burden. It concludes that 21% of all breast cancer deaths worldwide are attributable to alcohol use, overweight and obesity, and physical inactivity. This proportion is higher in developed countries (27%), and the most crucial factors are overweight and obesity. In developing countries, the proportion of breast cancers attributable to these risk factors was 18%, and physical inactivity was the most crucial determinant[3]. The persistent exposure to female reproductive hormones such as estrogens and progesterone also results in issues in reproduction such as early menarche, late menopause, and late-age first childbirth. These are among the most critical risk factors for breast cancer. Those breast cancer patients taking oral contraceptives and hormone replacement therapies face a higher risk of invasiveness. Mutations in well-known proto-oncogenes, particularly BRCA1, BRCA2, TP53, HER2, c-MYC, HRAS, CCND1, Cyclin E, and ER , pose greater risk for breast cancer as they affect cellular pathways including MAPK, RB/E2F, and P13K/AKT/mTOR responsible for cell growth and proliferation[4,5]. The overall mechanism of metastatic progression of normal breast tissue remains unknown until now; however, the expression changes in some genes and target molecules appear during breast carcinogenesis, which play crucial roles in diagnosis, prognosis, and treatment.

3. Recent Chemotherapeutics for Breast Cancer

Chemotherapy for breast cancer is of most frequent use in addition to surgery, radiation and/or hormone therapy. Chemotherapy involves using a specific medication class, either administered intravenously or as a pill which acts as a cytotoxic agent. The drug's primary mechanism of action is to kill the cancer cells characterized by high multiplication and growth rates. It remains a crucial factor of therapy for treating patients with metastatic breast cancer[6]. However, compared to other treatments chemotherapy still poses potentially high risk with many side effects that are difficult to manage. Since these drugs travel throughout the body, they can affect normal, fast-growing healthy cells too leading to side effects by damaging them.

The different types of breast cancers depend on the specific gene expression profile like luminal-a, luminal-b, basal and Her2$^+$. Chemotherapy affects these types of breast cancers differently. One report has shown that the basal-like and Her2$^+$ subtypes of breast cancer are more sensitive to paclitaxel- and doxorubicin-containing preoperative chemotherapy than the luminal and normal-like cancers[7] (Figure 1).

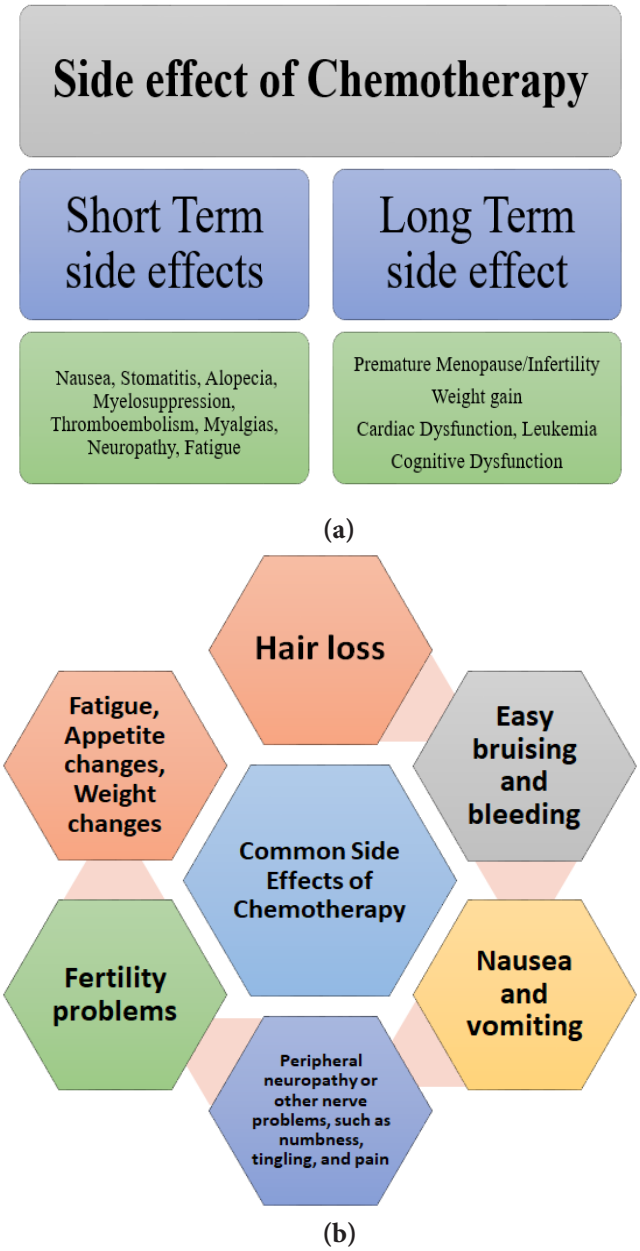

Figure 1. **(a)** Short term and long term side effects of chemotherapy; **(b)** Common side effects of chemotherapy [Adopted from Gegechkori *et al.*[8]].

4. Challenges to Chemotherapy

In cancer therapy, resistance to anti-cancer drugs is a critical problem. Anti-cancer drug resistance is the result of a multifactorial mechanism that arises due to alteration in drug targets. Several factors contribute to the mechanism of chemotherapeutic drug resistance. Cancer cell resistance against the anti-cancer agents can be due to many factors such as the individual's genetic differences, mutations and/or epigenetic changes. Drug resistance gets manifested through other mechanism such as up-regulated drug efflux, cell death inhibition (apoptosis suppression), altered drug metabolism, epigenetic changes in drug targets, enhancement of DNA repair and gene amplification. Although new chemotherapeutic agents are designed fast, effective chemotherapy agents against advanced stage cancers (such as invasion and metastasis) remain elusive. Malignant cells that survive primary treatment continue to evolve with uncontrolled growth of a resistant clone, which leads to progression and death of the patient. In these circumstances, identifying the transforming mechanisms towards resistance developed by tumor cells will help define optimal character, intensity, and/or longevity of primary treatment, which might achieve maximal abolition of tumor cells.

Resistance to cytotoxic agents may occur by several mechanisms. The over-expression of P-glycoprotein efflux pump confers resistance to multiple drug classes, including anthracyclines, taxanes, and vinca alkaloids. Resistance to doxorubicin also may occur by the over-expression of another drug transporter, MRP1 (or ABCC1)[9]. Taxanes stabilise microtubules by binding reversibly to b-tubulin. They bind less effectively to the *b*III-tubulin isoform. Over-expression of *b*III-tubulin can confer taxane resistance[10]. In several metastatic breast cancer cohorts, the higher *b*III-tubulin expression finds an association with disease progression[11]. During paclitaxel therapy, disease progression occurs at higher rates in patients with high versus low tumor *b*III-tubulin levels[12]. Several chemotherapeutic drugs find application in breast cancer treatment worldwide, but patients may suffer from significant life-threatening side effects listed in Table 1.

Table 1. Clinically approved chemotherapeutic drugs for breast cancer, their mode of action and side effects

Sl. No.	Name of chemotherapeutic drug	Source	Generic name	Type of breast cancer	Mode of action	Side effects	Refs.
1.	Doxorubicin	*Streptomyces peucetius var. caesius*	Adriamycin/ Robe	Advanced stage breast cancer	Intercalation into DNA; disruption of topoisomerase-II-mediated DNA repair; generation of free radicals and their damage to cellular membranes, DNA and proteins	Cardiomyopathy, congestive heart failure, arrhythmias	[13]
2.	Pegylated liposomal doxorubicin hydrochloride (PLD)	Semisynthetic	Caelyx/ Doxil	Meta-static Breast Cancer (MBC)	PLD hydrochloride formulation allows the liposomes to circulate in the blood for extended periods.	Myelosuppression, mucositis, alopecia, emesis, tachycardia, arrhythmias	[14]
3.	Liposome-encapsulated doxorubicin citrate (LD)	Semisynthetic	Myocet		LD provides a more prolonged circulating time than conventional doxorubicin; besides, liposome-encapsulation significantly modifies the bio-distribution of doxorubicin, resulting in reduced toxicity.		

Table 1. (Cont)

Sl. No.	Name of chemotherapeutic drug	Source	Generic name	Type of breast cancer	Mode of action	Side effects	Refs.
4.	Epirubicin	A semi-synthetic derivative of doxorubicin	Ellence	Early and advanced stages	Antineoplastic or cytotoxic; induces apoptosis by damaging DNA or RNA	Nausea, vomiting, diarrhoea, mouth sores, hair loss, leukopenia, neutropenia, irregular periods	15
5.	Paclitaxel	Endophytic fungi from the bark of Pacific yew tree (*Taxus-brevifolia*)	Taxol/ Onxol	Meta-static breast cancer	Mitotic arrest, intratumor accumulation of paclitaxel, causing cell death due to chromosome disaggregation on multipolar spindles.	Interstitial pneumonitis, arthralgia, myalgia	16,17
6.	Albumin-bound Paclitaxel	Semisynthetic	Abraxane	Meta-static breast cancer	Effectively inhibits mitosis, motility, and intracellular transport within cancerous cells, leading to apoptotic cell death.	Infusion reactions, neuropathy	18
7.	Docetaxol	A semi-synthetic derivative of paclitaxel	Taxotere	Her2-enriched MBC Solid tumors	Anti-microtubule agent, influences apoptosis, inhibits angiogenesis	Infusion reactions, febrile neutropenia, fatigue, fluid retention, pneumonitis, cutaneous and nail toxicity, epiphora and lacrimal duct stenosis, gastrointestinal complications (perforation, and dehydration as a consequence of enterocolitis, colitis, and neutropenic enterocolitis) and neuropathies.	19,20
8.	5-Fluorouracil (5-FU)	Synthetic	Adrucil	Early and advanced-stage cancer	5-FU is a pyrimidine antimetabolite, an uracil analogue that inhibits thymidylate synthetase activity by converting 5-FU to FdUMP and FUTP, instead of uracil to thymidine conversion. Therefore, 5-FU not only inhibits DNA synthesis in the cell but also inhibits RNA synthesis due to FdUTP incorporation in RNA; leading to highly toxic effects on the growth of rapidly multiplying cells	Diarrhoea, loss of appetite, mouth sores, nausea, taste changes, vision problems, vomiting, leukopenia, neutropenia, hand-foot syndrome, irregular periods	21

Table 1. (Cont)

Sl. No.	Name of chemotherapeutic drug	Source	Generic name	Type of breast cancer	Mode of action	Side effects	Refs.
9.	Cyclo-phosphamide	Synthetic	Cytoxan	Early and advanced-stage cancer	In the liver, cyclophosphamide is converted to active metabolites including phosphoramide mustard, which binds to and cross-links DNA and RNA. It shows the biphasic effect, i.e., at low doses it imparts immuno-suppressive function and at higher doses it functions as an alkylating agent leading to death of tumor as well as lymphoid cells	Cardiotoxicity, neutropenia,	[22,23]
10.	Vincristine	White-flowered periwinkle *Vinca rosea*	Oncovin, Leuro-cristine	Triple-negative breast cancer	Inhibition of microtubules and alteration of tubulin polymerisation equilibrium, which thus causes arrest of cell division in metaphase	Nausea, vomiting, diarrhoea, constipation, hair changes, neuropathy, fatigue, muscle and abdominal cramps, irregular periods	[24]
11.	Vinblastine	White-flowered periwinkle *Vinca rosea*	Velbane	Advanced and MBC	Mitotic inhibitor, arrest G2/M phase cell cycle	Peripheral granulocytopenia and leukopenia	[25]
12.	Vinorelbine	SemisyntheticVinca alkaloid	Navelbine	Meta-static breast cancer	Anti-microtubule agent; arrests cell division in mitosis.	Neutropenia, thrombocytopenia,anaemia, nausea, mucositis, neuropathy, constipation/ motility disorders, phlebitis	[26]
13.	Cisplatin	Synthetic	Platinol	Her2/neu Triple-negative breast cancer	Its interaction with DNA mediates its cytotoxic mode of action to form DNA adducts, primarily intrastrand crosslink adducts, which activate several signal transduction pathways, including those involving ATR, p53, p73, and MAPK, and culminates in activation of apoptosis.	Allergic reactions, decrease immunity to infections, gastrointestinal disorders, haemorrhage, and hearing loss, especially in younger patients.	[27]

Table 1. (Cont)

Sl. No.	Name of chemotherapeutic drug	Source	Generic name	Type of breast cancer	Mode of action	Side effects	Refs.
14.	Carboplatin	Derived from its parent compound -Cisplatin	Paraplatinol	Her2/ neutriple-negative breast cancer	Forms reactive platinum complexes upon activation inside the cell that causes intra- or inter- adducts of DNA; preferentially binds with purines leading to modification of DNA structure and inhibits DNA synthesis.	Less toxic than cisplatin. Neutropenia thrombocytopenia mucositis, hand-foot syndrome, p embolism peripheral sensory neuropathy, pneumonitis, arterial hypertension	[28,29]
15.	Capecitabine	Prodrug of fluorouracil	Xeloda	Meta-static breast cancer	It is activated inside the tumor to its cytotoxic moiety, fluorouracil, by thymidine phosphorylase which is found in higher concentration in the tumor. This interferes with RNA processing and protein synthesis by the production of fraudulent RNA.	Hand-foot syndrome, bilirubin elevation, neutropenia, nausea	[30]

Molecular-level personalized therapy is still not a clinical reality in the case of metastatic cancers. Most of the candidate drugs still have an unanswered mechanism of action. This is also true for the already available drugs. There are (yet) no validated predictive markers based on which one can deduce a therapeutic response and selectively treat individual patients[31].

5. Breast Cancer Therapeutics: A Green Approach

Ayurveda and herbal therapy play crucial roles as cancer therapeutics. Medicinal plants are a rich source of secondary chemicals which provide for discovery of newer drug molecules for various disorders and diseases, including cancer, without showing any toxic effects in the individuals treated. Their non-toxic natureon normal cells and their cytotoxic effects on cancer cells put them in high demand. Many species investigated come from developing countries from Africa and Asia, where herbal therapies are in practice, and medicinal plants are relied upon for primary treatment[32]. *In vitro* study of Brassinosteroids (BRs), steroids extracted from plants, against breast cancer cell lines (MCF-7/MDA-MB-468) has shown anti-cancer, anti-proliferative, and cytotoxic effects without any toxic manifestations. These results support the point that BR compounds are a promising source for anti-cancer drugs[33]. BRs interact or bind with the protein receptors and inhibit the growth of hormone-sensitive and hormone-insensitive cancer cells. Use of natural products and traditional medicines based on Ayurvedic concepts provides excellent scope for cancer research. The less expensive herbal drug treatment could easily be ideal for rural and poor people against various cancers. A large volume of clinical studies has reported the beneficial effects of herbal medicines combined with conventional therapeutics like chemotherapy on survival, immune modulation, and cancer patients' quality of life[34]. The leaf extract of green tea (*Camellia sinensis*) has shown chemo-preventive activity by inhibiting breast cancer cells' proliferation and precancerous polyp formation[35]. The active constituents of Ashwagandha (*Withania somnifera*), withanolides, produced mitigating chemotherapy-induced fatigue and improve quality of life, in a small

study of breast cancer patients[36]. Patients commonly use plant products derived from whole or parts of plants as self-medication against breast cancer. It is common in all civilizations worldwide, including Asia, Africa, Europe, and America. Nevertheless, most phytotherapeutic products/formulations remain unevaluated for scientific validity. Neither are they regulated for purity and potency certification[37].

6. Melatonin, the Novel Anti-breast Cancer Hormone

The research on the relationship between melatonin levels in the body and cancer occurrence is either significant or not at all related. Melatonin also showed the ability to be used as an adjuvant in cancer therapies by improving the therapeutic effects and reducing chemotherapy or radiation-induced side effects[38]. The role of estrogens in the development of mammary cancer is well studied. Estrogens can stimulate mammary cancer cell proliferation acting through their receptors. Cancer cell expansion brought about by estrogens can be hampered by melatonin in three different ways: (i) inhibition of steroid synthesis; (ii) down-regulation of the intermediate enzymes involved in androgen synthesis, e.g., aromatase; and (iii) binding with estrogen receptor and acting as a modulator. Melatonin could be an excellent adjuvant with the drugs currently used for breast cancer prevention (anti-estrogens and anti-aromatase) because of its Selective Estrogen Receptor Modulator (SERM) and Selective Estrogen Enzyme Modulator (SEEM) properties, and the absence of contra-indications.

The antioxidant actions also make melatonin a suitable treatment to reduce oxidative stress associated with chemotherapy, especially with anthracyclines, and radiotherapy. These mechanisms include enhancing the activity of mitochondrial electron transport chain, pro-oxidative enzyme inhibition, augmentation of other antioxidant agents' activity, stimulation of glutathione synthesis and, antioxidant enzyme protection and activation. At the stage of metastasis also melatonin plays a vital role. Melatonin plays an inhibitory function in the viability and invasiveness of mammalian breast cancer. It regulates protein expression associated with EMT in breast cancer stem cells, reflecting its significant anti-metastatic role in breast cancer cell line[39]. One study shows that melatonin is anti-angiogenic in MCF-7 and MDA-MB-231 cells by inhibiting VEGF expression[40-42]. Melatonin, by suppressing endothelin-1 (released by solid tumors to promote proliferation, metastasis and angiogenesis) suppresses angiogenesis[43]. Previous studies have shown a correlation between chronic inflammation and cancer development as inflammation produces reactive oxygen species and reactive nitrogen species which can induce DNA damage and carcinogenesis[44,45]. In MDA-MB-231 cell, melatonin helps down-regulate COX-2 and up-regulate the pro-apoptotic gene[46]. There is a need for further in depth studies to understand its precise onco-static role based on the above-reported melatonin actions.

7. Multivitamin Supplements

7.1 Vitamin B

Plasma concentrations of folate, PLP, and vitamin B12 are not significantly associated with overall risk of breast cancer[47]. One clinical report suggests that females with high serum pyridoxal phosphate levels have a 20% lesser risk of cancer in postmenopausal women. This has greater relevance concerning Estrogen Receptor (ER-positive) and Progesterone Receptor (PR-positive breast tumors[48]. Apparently a positive association between vitamin B and carcinogenesis seems probable. So far, in this broad prospective study, no strong evidence for a therapeutic correlation between plasma folate levels and BC risk has been found. However, potential BC risk interactions between vitamin B12 and folate have been observed.

7.2 Vitamin C

Vitamin C (Vit C) is an essential water-soluble micronutrient that has been considered a canonical antioxidant in the body over many years. A report suggests that loss of 5-hydroxymethylcytosine (5hmC) leads to malignant cellular transformation in breast cancer. The 5hmC is formed from the substrate 5-methylcytosine (5mC) catalysed by Ten-Eleven Translocation (TET) methyl cytosine dioxygenases. Increased of cellular level of 5hmC is correlated with increase in expression of the targeted gene Leucine Zipper, putative Tumour Suppressor 1 (LZTS1) and TET proteins. The catalytic activity of TET enzyme requires Vit C as an additional cofactor. Therefore, the restoration of TET activity by Vit C underlines its role in breast cancer epigenetic

reprogramming. This novel function of Vit C might lead to up-regulation of TET methyl-cytosine dioxygenases resulting in upregulation of 5hmC[49]. The *in-vitro* study has shown that increasing dose of Vit C demonstrates selective apoptosis of cancer cells. Besides, some dose-dependent response studies show that pre-treatment with Vit C on MCF-7 breast cancer cells protects them against lipid peroxidation caused by tamoxifen medication (hormonal therapy).

Vit C alone or in combination with widely used drugs shows remarkable anti-cancer actions. Vit C can potentiate doxorubicin's anti-cancer effect by modulating tumor redox status, which is known to be an important critical parameter for breast cancer therapeutics[50]. In the case of triple-negative breast cancer, preclinical studies show that the combination of Auranofin (antirhumatic agent) and Vit C emphasize selective and effective cancer cell killing through redox-based anti-cancer therapy[51]. Vit C inhibits cell migration and invasion of breast cancer cells and eliminates the cytotoxicity via selective oxidative stress. Selective cancer cell killing mechanism of Vit C is dependent on Sodium-Vitamin C transporter 2 (SVCT2) protein level[52]. The SVCT2 plays a crucial role in the influx of Vit C. The levels of SVCT2 in tumor samples of breast cancer patients were found to be lower than normal tissue. In addition to this, it was found that the influx of Vit C via SVCT2 induces cell death in the case of breast cancer cells, which indicates that Vit C potentially acts as an anti-cancer agent[52]. However further clinical studies are needed to prove the possible strong anti-breast cancer activity of Vit C.

7.3 Vitamin D

Vitamin D deficiency is a potential risk for breast carcinoma. Two forms of Vitamin D that occur naturally are Ergocalciferol (Vitamin D2) from plant sources and Cholecalciferol (Vitamin D3) from animal sources. Vitamin D and its metabolites have been shown in plants such as *Solanum glucophyllum*, *Solanum lycopersicum*, *Cestrum diarnum*, and *Trisetum flavescens* due to exposure to UVB present in sunlight[53]. The Vitamin D Receptor (VDR) expressed on breast epithelium is a nuclear, ligand-dependent transcription factor that regulates the expression of more than 900 genes involved in a wide range of physiological functions in a complex with hormonally active vitamin D, $1,25(OH)_2D3$[54]. Vitamin D is first converted to 25(OH)D, the major circulating metabolite, by 25-hydroxylases within the liver. The 25(OH)D then undergoes a second hydroxylation within the kidney to form 1,25 dihydroxy vitamin D [$1,25(OH)_2D$], by the action of 1-α-hydroxylase (CYP27B). The $1,25(OH)_2D$, also known as Calcitriol, is the biologically active form of vitamin D that binds to VDR and exerts its effects[55]. There is an inverse association between the supply of Vitamin D and breast cancer risk.

Additionally, breast cells also contain 24-hydroxylase (CYP24), which converts $1,25(OH)_2D$ into less active metabolites such as 24, 25-dihydro hydroxyvitamin D3 and 1,24,25-trihydroxyvitamin D3. Therefore, breast cells contain all the components of vitamin D signalling axis that coordinates the local synthesis and metabolism of $1,25(OH)_2D$ and its signal transduction via VDRs. The inhibitory effects of Calcitriol get showcased *via* growth arrest, apoptosis, inhibition of invasion and metastasis and down-regulation of inflammation and estrogen signalling pathways. Calcitriol induces cell cycle arrest by increasing the expression of p21 and p27. The actions of epidermal growth factor, transforming growth factor, Insulin-like growth factor (IGF-1) and expression of oncogenes such as c-myc and c-fos are under the command of Calcitriol. The expression of the crucial mediators of invasion and metastasis such as metalloproteinases, urokinase-type plasminogen activator, and tissue-type plasminogen activator is lowered. In contrast, the expression of plasminogen activator inhibitor and MMP inhibitor 1 is elevated. A high expression level of COX-2 in breast cancer has been shown to correlate with high grade, large tumor size, and poor prognosis. Prostaglandins have a role in the development and progression of breast cancer. Prostaglandins released from breast cancer cells or the surrounding tissues stimulate tumour progression by promoting cell proliferation and resistance to apoptosis and stimulation of tumor cell invasion and angiogenesis. These anti-inflammatory processes are mediated by the down-regulation ofcyclooxygenase-2 (COX-2) and up-regulation of 15-hydroxyprostaglandin dehydrogenase, which catalyses the conversion of prostaglandins to biologically inactive keto-derivatives. The estrogen signalling pathway is taken care of by reducing aromatase expression and down-regulating Estrogen Receptor (ER)-α[56,57]. Despite much research on vitamin D and breast cancer risk and survival, more studies are needed to understand the biological effects of vitamin D in breast cancer. As Vitamin D supplements have less toxicity and low cost, it can be a plausible target for breast cancer prevention and treatment.

8. Emphasizing Drug Availability through Nanotechnology

Administration of new drugs needs to be effective for the compound to be a successful alternative to chemotherapy. Through the field of nanotechnology, the use of nanoparticles as a delivery system for drugs to reach target sites is is making progress. Quercetin has shown a better therapeutic effect against breast cancer (MCF-7) cell using superparamagnetic magnetite nanoparticles. This research demonstrated enhanced activities of the NPs in cytotoxicity of MCF-7 cells compared to free or pure quercetin[58].

9. Immunotherapeutic Agents

The most successful immunotherapeutic agents consist of Immune Checkpoint Inhibitors (ICIs) which block immunosuppressive receptors such as Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) and PD-1, to improve the cytotoxicity and proliferative capacity of Tumor-Infiltrating Lymphocytes (TILs)[59]. These leads indicate that immunotherapy could be a promising strategy for metastatic breast cancer[60]. Many novel immunotherapies like oncolytic viruses, adoptive cell therapies (CAR-TILs, tumor infiltrating lymphocytes), neoantigen vaccines (to target peptides released by metastatic tumors in their microenvironment), and nonspecific immunotherapy (cytokines, immune checkpoint inhibitors, and immunomodulatory drugs) have generated durable response against many tumor types[59,61]. In patients with metastatic breast cancer, single-drug therapies with monoclonal antibodies against Programmed Death-1 (PD-1) and programmed death ligand-1 (PD-L1) have demonstrated little efficacy, perhaps because of the low number of tumor-infiltrating lymphocytes in most breast cancers. However, in developing advanced immunotherapy for breast cancer, it is necessary to understand the response of our immune cells against tumor and the resistance mechanism.

10. RNA-Based Therapy

In the last decade breast cancer therapy based on RNA levels, transport and translation, and mRNA degradation had become a research hotspot for researchers. RNA therapy is classified into several types like Anti-Sense Oligonucleotide (ASO) therapy, RNA interference therapy, and miRNA therapy. ASO therapy was found to be helpful to treat metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) featured breast cancers without leading to any toxicity[62]. Another study found that an ASO therapy designed for TROJAN strongly inhibited the progression of TNBC in humans[63]. When analysing the transcriptome of the entire human endogenous retrovirus genome, researchers discovered that TROJAN gets over-expressed in patients suffering from TNBC, promoting cancer cells reproduction and infiltration, usually associated with poor prognosis. Subsequently, it was further found that TROJAN bound to ZMYND8, which encoded protein kinase C-binding protein with the function of metastasis inhibition, increased the degradation of ZMYND8, and improved the ability of cancer cell metastasis. Therefore, TROJAN and beta-3 integrins are both expected to be new targets of RNA therapy in the treatment of TNBC, and also have a promising prospect. In 2017, researchers constructed c-Met-CAR T cells targeting c-Met, a molecule on the cell surface, expressed in about 50% of breast cancers *via* importing the Chimeric Antigen Receptors (CAR) into the body by mRNA[64].

11. Conclusion

It is proposed that the current lines of research should be enhanced in many ways. The overall incidence of cancer and death from cancer or any particular form of cancer should be registered and documented normatively. Future studies should measure them and the role of the period of intervention and dosage of medication should be taken into account before determining clinical outcomes. The current review evaluates various strategies that combine chemotherapy with additional immunotherapeutic agents, targeted treatment, multivitamin supplements, and local ablative therapies to strengthen the anti-breast cancer strategy. In a nutshell, based on intense preclinical research and acceptable clinical trials for combinational chemotherapy combined with herbal medicine, hormonal therapy and immunotherapy might provide durable and long-lasting therapeutic effect without any complications like chemo-resistance, side effects and cytotoxicity, leading to better prognosis of breast cancer (Figure 2).

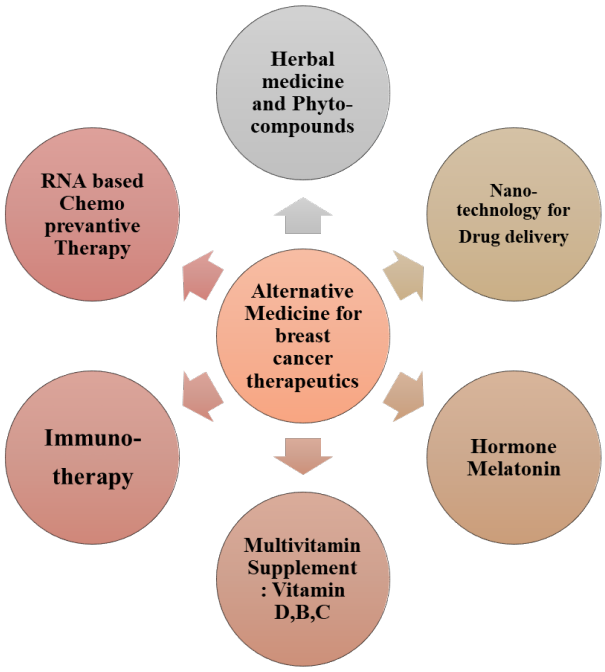

Figure 2. Alternative medicines for breast cancer therapy.

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