ISSN: 2322 - 0902 (P)
ISSN: 2322 - 0910 (O)

International Journal of Ayurveda and Pharma Research

Review Article

IMPORTANT ROLE OF HERBAL EXTRACTS IN THE MANAGEMENT OF BREAST CANCER

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Article info

Article History:

Received: 19-09-2023

Accepted: 11-10-2023

Published: 10-11-2023

KEYWORDS:

Breast Cancer, Global Impact, Herbal Extracts, Cell Signalling Pathways, Anticancer Activity.

ABSTRACT

Cancer recognized as a serious disorder among population worldwide. Breast cancer has been found common in women. Breast cancer diagnosed patients increasing with passage of time, which bringing the attention of researcher to give more potential strategies to irradiate this ailment from the society. Natural remedies from medicinal plants are well acknowledged from primitive time of decade. Modern and advanced analytical tools successfully overcome the burden of this disease by incorporating raw formulations into suitable dosage forms and their efficacy can be determined through experimental and clinical studies. There are numerous medicinal plants present having pharmacological potential to decreases the breast cancer cell viability by involving various mechanisms and significantly overcome the global burden of this disorder. Our presented study motivated from the burden of breast cancer among people and its treatment from natural sources. However, it is much needed to understand etiology of the disease and its associated causes. We also demonstrated the treatment strategies originated from natural sources that conquer the spectrum of this disorder. There are numerous types of natural products that has preventive and curative role in the management of breast cancer. So, accurate method and terminology required to elevating the demand of health care system from natural sources can overcome breast cancer.

INTRODUCTION

According to a report in 2015 about 5.7 million deaths were only because of breast cancer and more than 1 million women were affected with this type of cancer globally. Approximately 2.5 million cases were identified during 2017 in US. Most commonly noticed cancer among women is breast cancer and nearly 12% cases in US were manifested by this disease [1, 2]. It has been found that breast cancer is most frequently occurring disorder after lung cancer in women; majorly manifest Black and Hispanic women. Besides this in US nearly 30% cancer cases are because of overweight, lack of physical activity and diet related factors. According to a report of year 2022, more than 40000 deaths in US were due to breast cancer that makes it a serious disease among women [3].

Method involves in the treatment of non-metastatic cancer based on to remove cancerous growth from affected area of breast and suppresses its further invasion. Commonly applied therapies followed are implementation of surgical procedures, auxiliary lymph nodes cutting, and radiation therapy after completion of operation. Systematic method of treatment considered with incorporation of neo-adjuvant, adjuvant and combination of these for better formulation. Malignant type of breast cancer was found to be very difficult to cure. Therapy concept may run for life long and many cases it has negligible chance to treat [4]. Cancerous cells results in defective cell division that can cause accumulation of cancer cells and give rise to tumor formation. There is five anti-oncogenes attributed the breast cancer; ATM, BRCA 1, BRCA 2, Chk 2, PALB 2, and CDH 1 [5,6].

Access this article online

Quick Response Code

https://doi.org/10.47070/ijapr.v11i10.3003

Different Phases of Breast Cancer

Development of this cancer has been categorized into few stages that lead to the metastasis of cancer. It has been distinguished on the basis of TNM system (here T represents growth of the tumor formation, N represents invasion of tumor forming cells to adjacent lymph nodes, whereas M represents the spread of these tumor cells to concerned body organs).

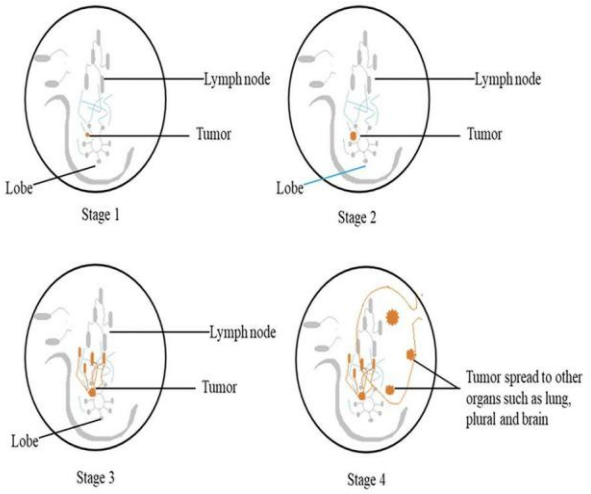

Fig. 1: Different Stages of Breast Cancer [7]

Breast Cancer Types

Invasive lobular carcinoma, invasive duct's carcinoma, medullary carcinoma, mucinous carcinoma, tubular carcinoma, inflammatory breast cancer, glycogen cell carcinoma, acinic cell carcinoma, adenoid cystic carcinoma, lipid carcinoma [8-13].

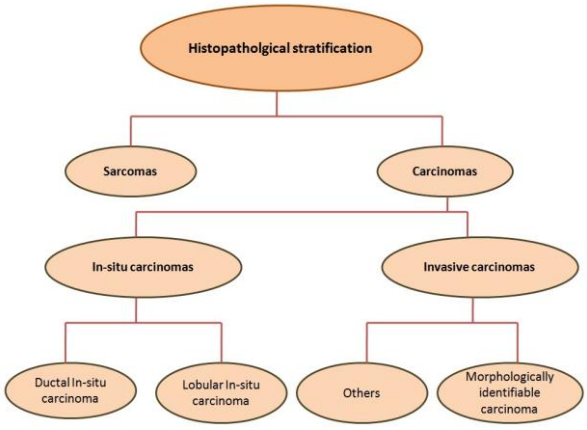

Fig. 2: The visualization of various histo-pathological categorization of breast cancer [8]

Symptoms

Mostly women are well known about the characteristics of breast cancer, but also same numbers are not having better understanding about the subject. Besides environmental factors existing, poor healthy life styles also a major contributor of breast cancer. There is swelling in breasts. It also seems clear or blood containing discharge from nipples. Pain in breasts is characteristics symptoms of breast cancer.

Diagnostic Methods

Many diagnostic methods employed are Mammograms, Breast Ultrasound, Breast MRI Scan, Biopsy, Breast Self-examinations [8, 14-16].

Factors Contributing Breast Cancer

Genetic Factor

Major of the prevalence rate in breast cancer were associated with the mutagenic changes in the responsible genes for this disorder are BRCA 1 and BRCA 2. These genes contributed nearly about half of the cases worldwide. Herein, BRCA1 added the more than 50% of cancer patients, whereas BRCA2 linked with 40-50% of genetically changed genome in these patients. Almost all the patients mentioned above are verified of old age [17,18].

Hormonal Changes

It has been confirmed from previous studies the oral administration of contraceptives elevated the incidence of this cancer, however the incidence rate can be decreased by discontinuation of oral contraceptives. In one of the study the intake of ovulation-stimulating drugs for number of months may raises the development of breast cancer. However hormone replacement therapy does to report any alteration in developing breast cancer [19-21].

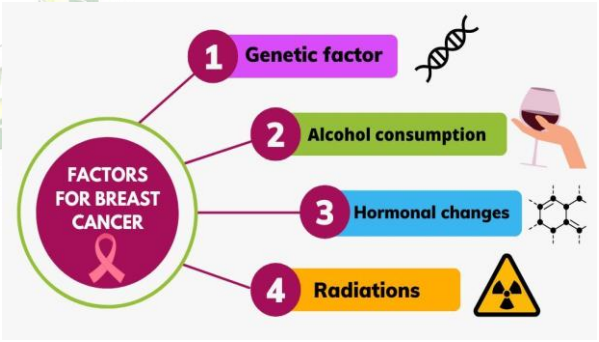

Fig. 3: Factors responsible for breast cancer

Alcohol Consumption

Alcohol consuming individuals is at higher level to develop this disease. Those who were consuming alcohol during their first full term pregnancy was at major risk to develop breast cancer. Therefore, even less than 15gm/day reported to be at higher risk of developing this ailment. Although, this has been found that severity of disease increased who were involve in intake of alcohol during their lifetime [22].

Radiations

Women who were go through radiation therapy and any other screening or monitoring processes during their lifetime are more susceptible to develop this disorder. This include radiations are directly or indirectly involve in damage of DNA, which increase generation of ROS and RNS.

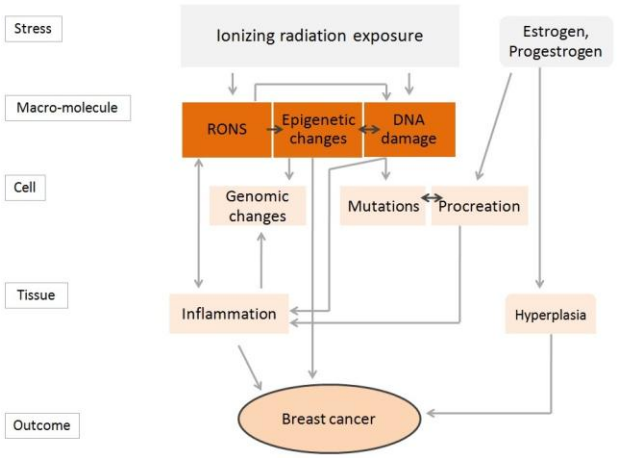

Fig. 4: This has been demonstrated in above about the harmful effect of ionization radiations in the development of breast cancer [23, 24].

Natural Remedies for Management of Breast Cancer

Taraxacum officinale

It has consists of alcoholic extract of whole plant inhibits cell accumulation of breast cancerous cells. It has been act on TNF-ligand (tissue necrosis factor-ligand) induced programmed cell death and ROS (reactive oxygen species) release. Evidence showed that aq. extract of plant parts successfully overcome the growth of cancerous cells and inhibition involves depletion in phosphorylation of focal adhesion kinase, src, MM2 (mitochondrial membrane) and MMP9 (matrix metalloproteinase-9)[25-27]. Aqueous root extract from *Taraxacum officinale,* when studied on adult female rats (albino), which were forced to breast cancer with the help of DMBA (Dimethylbenz-α-anthracene) showed important activity to understand the mechanism of PI3K/AKT (protein kinase). PI3K/AKT pathway involve in the further invasion of breast cancer, they also regulate mutations in PIK3CA gene. It also successfully down regulated the elevated CA15-3 (cancer antigen 15-3) levels in serum. Moreover, this further includes in the normalisation of up-regulated mRNA in affected genes [28]. Breast cancer categorized as the most lethal disease globally. *Taraxacum officinale* plant had showed promising efficacy to limit the growth of cancerous cells. The ethanolic extract exerts cytotoxicity at a concentration of 190.5µg/ml. this strengthen the fact that the plant have bioactive moieties that need to explore [29]. The therapeutic role of silver based nanoparticals has been much effective to counter act the accumulation of MCF-7 cells through programmed cell death by gradually increasing the dose [30].

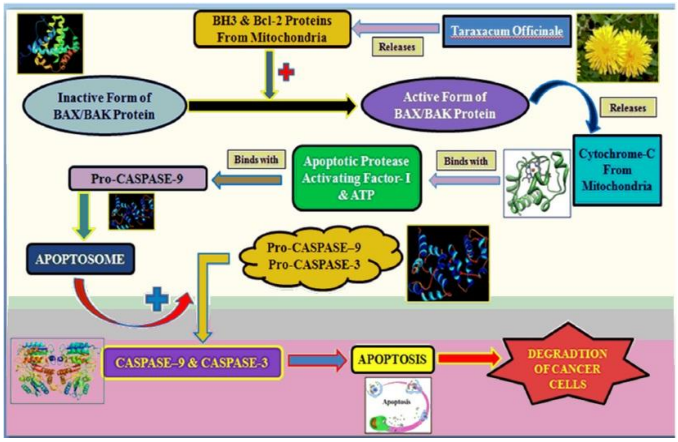

Fig. 5: Mechanism of action *Taraxacum officinale* in controlling breast cancer invasion [26]

Uncaria Tomentosa

Uncaria tomentosa plant extract reported in a study that, it has been significantly reduced the stag II invasive duct carcinoma on human subjects were treated with its aqueous extract at a dose 300mg per day. It successfully reduced neutropenia and also protect the damage to DNA [31]. The ethanolic barks extract when tested on B16-BL6 (murine cell line of melanoma) cell lines successfully decrease the differentiation and accumulation of cells. The cell signalling pathway data analysis reported that, this extract was had significant effect in reducing ERK (extracellular signal-regulated kinases) and Akt phosphorylation from 10 to 20%. There were 50% and 60% decrease in map kinase signalling pathway and Akt/PI3 kinase pathway respectively at 100µg/ml dose concentration of extract. This results in programmed cell death[32]. Mitraphylline obtained through extraction of *Uncaria tomentosa* dried inner bark had inhibitory role against MT-3 (human contaminated breast cancer) cells. The cytotoxicity of the molecule increased on increasing the dose concentration. Therefore, it has been found that the plant loaded with active phytochemicals that needed to treat the ailments [33]. Further studies revealed that the biological effect of the plant in the management of breast cancer has very important because it has been when tested on MCF-7 cells showed much inhibition on cancerous growth and differentiation at concentration of 29.86µg/ml. The extract has potential to irradiate more other type of cancer cell lines at various dose concentrations. These also highlighted the potentiating role of oxindole alkaloids present in the plant [34].

Astragalus membranaceus

Plant extract prepared by treating root with water and ethanol then subjected for in vitro studies. It was reported that extract effective in reduction of breast cells through programmed cell death. There are number of flavonoids and polysaccharides found in the root extract of *Astragalus membranaceus.* The anti-proliferative activity of water extract prepared from

root powder reveals inhibition of cancerous cell lines. MCF-7 cells on treatment with root extract gradually decreases cell viability in dose dependant manner. Same response has been seen in cells like SK-BR-3 as well as in MDA-MB-231 Also, extract manage to decrease the cell signalling pathway like p-PI3K and p-GS3Kβ. The mechanism also derived by down regulating the signalling pathways like p-Akt and p-mTOR [35]. Polysaccharide from *Astragalus membranaceus* has proven to reduce transportation of cancer cells, proliferation and prevent further invasion. This has been indicated in a study, polysaccharide showed potentiating effect by modulation in EMT (epithelial Mesenchymal transition) pathway and related molecules. The polysaccharide from plant reported to decrease the Wnt1/β-catenin cell signalling (Wingless-related integration site 1), this facilitates in down regulation [36]. Astragalus contains polysaccharide that has exerted its cytotoxicity effect by initiating programmed cell death. It has been proved that the efficacy of the extract upon the cancer cells was dependent on alterations in Bax/Bcl-2 ratio [37].

Ocimum sanctum

Oil from fresh leaves of the plant were collected and tested on MCF-7 in various dose concentrations. It has been confirmed from flow cytometry analysis that it act by increase in the apoptotic genes p53 and Bid. It also up regulated the Bax/Bcl-2 (BCL2-associated X protein) ratio [38]. The ethanolic extract, when tested on MCF-7 cell lines, reported the reduction in cell count and produces anti-proliferative activity. T47D cell lines on treatment of above extract showed marked reduction in cell viability and cell proliferation. Apoptosis may occur due to binding capacity at caspase site confirmed by molecular docking. Anti-proliferative activity of the extract was obtained by gradual increase in dose concentration from 50 µg per ml, 100 µg per ml, 150 µg per ml, 200 µg per ml respectively [39]. Moreover, *Ocimum sanctum* extracts alone and in combination with *Piper nigrum* exerts the cell death activity on MCF-7 cells [40]. Irradiating role of *Ocimum sanctum* towards many breast cancer cell lines revealed its effectiveness was much important. The action behind this was through apoptosis and reduction in angiogenesis. Suggestions validated the capacity of the herb to provide a novel molecule that can play significant role to lower the epidemic from disease [41].

Curcuma longa

Curcumin is a secondary metabolite extracted from *Curcuma longa* and continuously reported to decrease breast cancer cells proliferation by preventing the microtubule assembly formation, reduction in NF-κB (nuclear factor-κB), and down regulated the vascular endothelial growth factor [42]. Furthermore, MCF-7 cells showed poor cells growth, reduce cell proliferation as well on treatment with Curcumin and inhibition was very effective at 75µM dose concentration, and also the response gradually increases by addition in dose concentration. MDA-MB-231 cells on treatment with curcumin in same manner results in decrease in cell count and lowered the further differentiation [43]. Curcuma contains many active principles that have potential to conquer many diseases. In-vitro experimental studies found the benefits of the molecules that have been present in it. *Curcuma zedoaria* petroleum extract when tested introduced with MDA-MB-231 cells successfully overcome the cancerous cell growth rate. The extract was successful to decrease the development of cancer cells by variation in dose concentrations and time. It has been proved from the western blotting and other analytical techniques that, cytotoxic activity was due to arrest of cell cycle at G0/G1 phase. It also results in elevation in amount of expression proteins like E-cadherin and it lower the level of SDF-1, CCR7 and CCR4 mRNA [44]. Previous studies reported data lined the role of Curcumin alone to counter act the breast cancer. Major of studies indicated that the action of Curcumin through decreasing the NF-kB, EGFR (estimated glomerular filtration rate), AKT, Nrf2 (Nuclear factor erythroid 2-realted factor 2), ER (estrogen receptor), MMP-1 (matrix metalloprotein-1) and activating the Nrf2, TIMP-1(Tissue inhibitor of metalloproteinases-1). Although, the cell inhibitory activity of the Curcumin covered the number of molecular cell signaling pathways. This also underlines its wide potentiating effect against breast cancer [45].

Ginger Species

Whole experiment was based on testing of alcoholic extract from rhizomes of *Zingiber officinale* on the human cancerous cell lines. It has been observed that with increase in minimum effective dose there were suppression of tissue necrosis factor-*κ*B, Bcl-X, induced myeloid leukemia cell differentiation protein, and Survivin. It reported in the degradation of cell viability and marked cell division. It was therefore suggested has good anti-proliferative activities on breast cancer cells [46]. However, synergistic activity of aqueous extract from plants *Tinospora cordifolia* and *Zingiber officinale* exhibit the potent molecular effects on MCF-7 cell lines. The combined extracts were more effective against cancer cells at 10µg/ml concentration. It was much biologically active when compared with results of standard drug Tamoxifen. The cytotoxicity of the extract were observed and suggested that it has been act by alterations in the cell cycle at G0/G1 phase [47]. Zinger extract tested on MDA-MB-231 cells decreases the cell survival rate and cell accumulation. Methanolic extract prepared from the rhizomes of *Zingiber officinale* had marked action towards

declining the cell proliferation; experimentally gathered information hold the importance of extract to kill the cancer cells, effect of the preparation was at peak in the extract concentration of 12.5µg/mL [48].

Withania somnifera

Ethanolic extract of *Withania somnifera* was involved to decrease the cell viability by reducing vimentin to prevent further invasion. Extract was reported to inhibit the tissue growth factor-β that are responsible for endometrial Mesenchymal transition and prevent metastasis [49]. Root extract of the plant was much effective in the form of nano particles. Zinc oxide nanoparticals of root extract were showed to decrease growth and proliferation by prescribed mechanisms. The effect was dose dependent maximum inhibitory activity was at 13µg/mL dose concentration. It suggested that the extract has been much potent to reduce the proliferation of cancer cells, when incorporated into nanoparticals [50]. Furthermore, it has been observed that *Withania somnifera* root extract contain a protein, this was experimentally established protein from root extract were successfully active against MDA-MB-231 cells. Biological activity was highest at 92µg/mL. The mitochondrial regulated cell death involves production of ROS, blocking of Bax/Bcl-2, caspase-3 activity, decreasing mitochondrial membrane integrity. Furthermore, there has been deregulation in cell differentiation stage at G2/M phase, prevent cell growth and proliferation [51]. *Withania somnifera* have loaded with potent chemical structures, mostly withanolides has reported in many research data. In this scenario we discuss the cytotoxic activity of Withaferin A in the inhibition of MCF-7 and MDA-MB-231 cells. It has been documented that this natural product successfully deregulate the MCF-7 breast cells in the concentration from 722.8nM -1008.0 nM, also effect was very significant against triple negative cancerous cells in the dose concentration from 976.2nM-1164.0 nM. The cytotoxic activity of Withaferin A confirmed through analytical techniques like flow cytometry as well as real-time cell proliferation, that tell us about its action were constitute decline in gene expression and down regulated integrins. Theses tools also showed deregulation of laminins, pro-inflammatory mediators and elevating the suppressor gene BRMS1 [52].

Panax species

Root extract obtained from *Panax ginseng* was reported to exert cytotoxicity when MCF-7 cells and MDA-MB-453 cancer cell lines introduced with it for 48 hours and 72 hours respectively. It has been showed that extract was interfering with cell division phase at G0 and G1; this mechanism reduced the cell count. Moreover, it has produced apoptosis induced cell death by suppression of Bax/Bcl-2, regulated cyt *c*, stimulation in CASP9 that were achieved by degradation of protein involved in reduction in cell viability [53]. The anti cancer activity of ginseng (*Panax quinquefolius*) extract was also tested on MDA-MB-231 cell line; observations suggest its action by blocking cell division at G0/G1 phase. The response of the extract was time dependent and concentration dependent [54]. *Panax ginseng* reported to very effective to inhibit MCF-7, MDA-MB-231 and T-47D breast cell lines in in-vitro studies. The inhibitory response of the isolated moiety Ginsenoside Rp1 was reportedly dependent on dose concentration and time of exposure. The action of chemical entity from *Panax ginseng* was by increasing the Akt cell signaling pathway. The dose concentration at 20µM of phytoactive compound was managed to increase the cell death and cell proliferation. Moreover, it has been interfere with stability of IGF-1R facilitates decrease in its efficiency and promote the activation of Akt pathway [55].

Extract Type	Experimental model	Mechanism of action
Alcoholic extract	Breast cancer stem cells	↑TNF-ligand [26]
Aq. dandelion extract	MCF-7/AZ	↓p-FAK, ↓p-src, ↓MMP2, ↓MMP9 [27]
Aq. root extract	Albino adult female rats	↓PI3K/AKT, ↑PIK3CA, ↑CA15-3 [28]
Aq. extract	Human subjects	↓neutropenia, ↓DNA damage [31]
Ethanolic bark extract	B16-BL6	↓ERK, ↓Akt phosphorylation, ↓map kinase [32]
Aq. extract	MCF-7, SK-BR-3, MDA-MB-231	↓p-PI3K, ↓p-Akt, ↓p-mTOR, ↓Wnt 1/β catenin [35]
Oil extract	MCF-7	↓P53, ↑Bid, ↑Bax/Bcl-23 [38]
Ethanolic extract	MCF-7, T47D	↓Cancerous cells [39]
O. sanctum+ P. nigrum	MCF-7	↑Apoptosis [40]
Curcumin	MCF-7, MDA-MB-231	↓MAF, ↓NF-κB, ↓ VEGF [42]
Alcoholic rhizome extract	MCF-7, MDA-MB-231, MCF-10A	↓TNF-κB, ↓Bcl-X, ↑ Mcl-1, ↓survivin, ↓Bax, ↑CDK-4, ↓ CDK inhibitor [48]

T. cordifolia and *Z. officinale*	MCF-7	↓G_0/G phase [47]
Ethanolic extract	MDA-MB-231, MCF-7, MDA-MB-468	↓vimentin, ↓TGF-β [48]
Root extract + ZnONPs	MCF-7	↓Cancer cell growth [49]
Root extract	MDA-MB-231	↑ ROS, ↑casp-3, ↓Bax/Bcl-2, ↓MMI, ↓ G_2/M phase [51]
Root extract	MCF-7, MDA-MB-453	↓ G_0/G1 phase, ↓Bax/Bcl-2, ↑cytc-C, ↑casp-9 [53]
Root extract	MDA-MB-231	↓ G0/G1 [54]
α-conidendrin	MCF-7, MDA-MB 231	↑ ROS,↓ MP, ↑p53, ↑p21, ↓Bax, ↑Bcl-2, ↑ casp-3, ↑casp-9 [56]

Table 1: Showing biological responses of herbal extracts on in-vitro and in-vivo experimental models with mechanisms

*ROS=reactive oxygen species, NF-kB=necrosis factor-kB, AKT=protein kinase B, MMP-1=Matrix metalloprotein-1, MMP-2=Matrix metalloprotein-2, cyt-*C*=cytochrome-C, CASP9=Caspase-9, p53=tumor protein p53, p21=Cyclin dependent kinase inhibitor 1, CASP3= caspase-3.

Abbreviations

ATM=ataxia telangiectasia mutated, BRCA1=Breast Cancer Gene 1, BRCA2=Breast Cancer Gene 2, Chk 2= checkpoint kinase 2, PALB2=partner and localizer of BRCA2, and CDH1=Cadherin-1, ROS=reactive oxygen species, RONS=reactive oxygen and nitrogen species, SDF-1=stromal cell-derived factor 1, CCR7=C-C chemokine receptor type 7, CCR4 mRNA=C-C chemokine receptor type 4 mRNA, NF-kB=necrosis factor- kB, EGFR=estimated glomerular filtration rate, AKT=protein kinase B, Nrf2=Nuclear factor erythroid 2-realted factor 2, ER=estrogen receptor, MMP-1=matrix metalloprotein-1, TIMP-1=Tissue inhibitor of metalloproteinases-1, cyt *c*=cytochrome-C, CASP9=caspase-9, IGF-1R=insulin-like growth factor-1 receptor, p53=tumor protein p53, p21=cyclin dependent kinase inhibitor 1, CASP3= caspase-3

Taxus yunnanensis

Taxus yunnanensis, contain a polyphenolic compound α-conidendrin, which were managed to kill MCF-7 cells. This chemical entity when treated with MDA-MB 231 cells results in programmed cell death. It has been applied on cells in various dose concentrations, where doxorubicin acts as standard drug at 10μM. The polyphenolic compound was partially reduced the further proliferation and development of cancer cells by production of ROS, loss of mitochondrial protein. It also increases the transcription of p53, p21, Bax and decreases the Bcl-2. The role of α-conidendrin showed to up regulation of the CASP3 and CASP9 activation. However, previous studies reported the inhibitory role of silver nanoparticals of *Taxus yunnanensis* against MCF-7 cells. This showed its efficacy has been altered when incorporated into nano formulation. *Taxus yunnanensis* exert its cytotoxic effects by up regulated the p53 and also p21. It has been found that there were elevated level of Bax to produce activity. In other case it included in response by deregulation of Bcl-2. Furthermore, these particles up regulated the CASP 3 and CASP 9 [56, 57]. The diterpenoid 2-deacetoxytaxinine had isolate from bark of *Taxus baccata* it promoted the breast cancer cell death rate significantly when applied on MCF-7 and MDA-MB-231. In-vivo studies demonstrated the importance of this compound determined by its suppressive role on cure of mammary tumors (virgin female Sprague Dawley) [58].

CONCLUSION

Breast cancer includes many factors which increases burden of the disease globally. It have been proved to be fatal in many cases if were not detected in early stages of manifestation. With increase in causative factors disease has been categorized into many classes. Also, the drugs available in the market for treatment are very costly; with toxicity profiles of these drugs are also very fatal to our bodies. Therefore, natural therapy being the best option to explore, that can provide us a better hope to get ride the ailment. Although, the herbal drugs suggested a rich concept to conquer it and this has been proved by many researchers that they were effectively manage breast cancer. Also, researches that working on biological activity of natural combinations showed very successful results that can provide a baseline for discovery of new treatment. This also strengthen our hope that there are huge number of active molecules in our nature, are still pending to explore, which can give us novel molecule or molecular structure with potential results on breast cancer treatment.

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Cite this article as:
Shiv Kumar, Avneet Gup, Vinod Kumar Gauttam, Karan Sharma, Amar Deepak, Rohit Thakur. Important Role of Herbal Extracts in the Management of Breast Cancer. International Journal of Ayurveda and Pharma Research. 2023;11(10):92-100.
https://doi.org/10.47070/ijapr.v11i10.3003
Source of support: Nil, Conflict of interest: None Declared

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