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Review Article

Therapeutic and pharmacological efficacy of plant-derived bioactive compounds in targeting breast cancer

Heena Saini[1*], Partha Basu[2], Tanuja Nesari[3], Vitthal Govindappa Huddar[4], Koninika Ray[5], Anil Srivastava[5], Subhash Gupta[6], Ravi Mehrotra[7], Richa Tripathi[1*]

[1]Integrated Translational Molecular Biology Unit (ITMBU), Department of Rog Nidan evam Vikriti Vigyan (Pathology), All India Institute of Ayurveda, New Delhi-110076, India; [2]Section of Early Detection and Prevention, International Agency for Research on Cancer, Lyon-69008, France; [3]Department of Dravyaguna (Materia Medica and Pharmacology), All India Institute of Ayurveda, New Delhi-110076, India; [4]Department of Kayachikitsa (Internal Medicine), All India Institute of Ayurveda, New Delhi-110076, India; [5]Open Health Systems Laboratory (OHSL), Los Gatos, California-95032, US; [6]Department of Radiation Oncology, Dr. B. R. Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi-110029, India; [7]Rollins School of Public Health, Emory University, Atlanta, Georgia-30322, US. [*]Equal contributors.

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Abstract: Breast cancer (BC) ranks number one among cancers affecting women globally. Serious concerns include delayed diagnosis, poor prognosis, and adverse side effects of conventional treatment, leading to residual morbidity. Therefore, an alternative treatment approach that is safe and effective has become the need of the hour. In this regard, plant-based medicines via a combination of conventional drugs are gaining increasing acceptance worldwide, playing a pivotal role in cancer management as proven by their efficacy evaluation studies. This review aims to fill the knowledge gaps by providing the preclinical evidence of cellular and molecular mechanisms of Indian phytomedicines in targeting varied pathways of breast cancer progression. A comprehensive search was performed on different platforms, followed by screening of relevant studies for review. In this article, the in-depth of various botanical drugs covering their nomenclature, dosage, toxicity, and modus operandi in BC cells have been extensively discussed. Various signaling pathways like Notch signaling, MAPK signaling, apoptosis, Wnt signaling, etc. regulated by herbal medicine treatment in BC are also highlighted to understand the drug mechanism better. This will guide the researchers to plan future strategies and generate more robust integrated evidence of plant-based drugs or botanical formulations for their potential role in the management of BC.

Keywords: Phytomedicine, Indian herbs, breast cancer, integrative oncology, cancer treatment, anticancer

Introduction

Breast cancer (BC) is the number one female cancer across the globe, both by incidence (2,261,419 cases) and mortality (684,996 cases) [1] with every 1 in 4 women affected in 2020. In India, all population-based cancer registries (PBCRs) reported an annual percentage increase of BC incidence for selected anatomic sites of cancer over time; lowest in Nagpur (0.4%, 2005-2016) and highest in Aurangabad (6.8%, 2005-2016). Further, as reported, 1 in 29 females will develop BC cancer during their lifetime (0-74 years of age) [2].

Although scientific research has made significant progress in unravelling breast cancer and its molecular basis, a gap exists in our understanding of preventive and therapeutic approaches against BC. Currently, depending on the stage and molecular sub-type, treatment for BC requires a multi-modal approach like non-metastatic tumors being removed surgically along with radiation or systemic therapy. For hormone receptor-positive BC subtype, endocrine therapy including Tamoxifen, Letrozole, and Trastuzumab-based receptor-directed antibody with chemotherapy is prescribed. For triple-negative breast cancer (TNBC), mostly

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chemotherapy is given. Along with these, CDK inhibitors, PARP inhibitors, etc. are also given [3, 4]. Even though, the current treatment regime has increased patient survival, it is associated with acquisition of drug resistance, tumor recurrence, lack of specificity towards cancer cells, inhibiting the growth of healthy cells, toxicities, stress, depression, and poor quality of life (QoL), which demands a more effective and better alternative.

Plant-based bioactives with or without conventional medicine demonstrated an improvement in QoL in cancer patients [5, 6], leading to better palliative care management. Indian herbs constituting various bioactives have been claimed to prevent certain cancers or suppress their progression with minimal toxicities [7]. Preclinical studies assessed many herbs to understand their tumoricidal activities against BC. *Withania somnifera, Butea monosperma, Rheum emodi,* and *Piper nigrum* are few among many herbal botanicals which are well known for their anticancer properties [8-11]. Hence, there is an urgent need for continued research to integrate complementary herbal bioactives with the modern system of medicine to improve BC outcomes and palliative care management [12].

Indian herbs have the potential to be used for cancer treatment via their action on various biological and signaling pathways or supporting the body's defense systems. This review summarizes the studies regarding the efficacy of different plant-based bioactives in prevention, treatment, and management (symptom relief) for BC patients. The broad aim of this review is to bring forth various scientific evidence on the cellular and molecular mechanisms of Indian medicinal plants in cancer, for a better understanding of the opportunities to integrate Indian phytomedicines with conventional therapies. This will lead to delivering evidence-based care, filling the knowledge gaps, and guiding to prioritize research to generate more robust clinical evidence addressing the existing deficiencies.

Methodology

A thorough search was performed on platforms like PubMed, Research Gate, and Google Scholar to identify the publications in English language evaluating plant-based bioactives in BC using the keywords: "Ayurveda Bioactives" AND "Breast cancer" or "Indian herbs AND Breast cancer". The search was conducted for all the publications with the last retrieval on 16th December 2023. In addition, a manual search was also performed on the above keywords. An initial screening of all abstracts was done to search for relevant studies related to the field. Further, all the relevant studies were selected and reviewed.

Pathways in breast cancer

Wnt signaling pathway

The Wnt pathway is associated with both normal breast and breast cancer development. The ligand proteins interact with the frizzled receptors and activate the downstream proteins leading to the nuclear translocation of β-catenin, which initiates the transcription of cell proliferation, survival, differentiation, and migration associated genes [13]. Induction of Wnt pathway signaling led to an expansion of progenitor cells and an enhanced breast tumor formation in transgenic mice [14, 15], whereas another report showed that an inhibition of the pathway in mammary alveolar progenitors inhibits pregnancy-induced proliferation and hence, mammary development [16]. Also, dysregulated Wnt signaling is the hallmark of triple negative BC, involved in enhanced tumorigenesis and metastasis [17].

Hippo signaling pathway

Hippo signaling is critically involved in regulating tissue homeostasis and organ development. Upon activation, Yes-associated protein 1 (YAP1) gets phosphorylated, sequestered in cytoplasm, and degraded, while during inactivation of Hippo signaling, unphosphorylated YAP/TAZ along with TEAD enters the nucleus and activates transcription of genes involved in cell proliferation and apoptosis [18]. An enhanced TAZ expression is correlated with breast tumors of higher histological grade and increases invasiveness as observed in invasive BC cell lines and 20% of BC tissues [19]. Also, YAP is reported to inhibit hormone-independent transcription of ERα gene and an enhanced expression of YAP is correlated with good prognosis of ER+ patients [20].

Notch signaling

The Notch signaling is a complex transmembrane signaling pathway. The receptors and ligands of Notch family are involved in cell fate determination, vasculogenesis, and organogenesis by regulating cell growth, proliferation and apoptosis. Overexpression of Notch1 and Notch3 results in the induction of BC in transgenic mice [21], whereas Notch2 is shown to cause inhibition of tumor xenograft growth in vivo [22]. Also, a higher chance of survival in BC patients with overexpression of Notch2 has also been reported [23].

Hedgehog signaling

The hedgehog pathway regulates cell proliferation, cell fate, and cell maintenance. The pathway is crucial for the early development of mammary glands, and sonic-(Shh) and Indian-hedgehog (Ihh) are expressed and needed in mammary epithelium [24]. Also, in half of the BC, Ptch-1 is almost negligible in expression, whereas enhanced Smo expression has been observed in ductal carcinoma as well as invasive BC [25, 26]. Recently, high expression of Smo and Gli-1 is reported to be associated with activation of BC stem cells in triple negative BC patients [27].

JAK-STAT pathway

The JAK-STAT pathway is involved in many cytokines and growth factor signaling that further regulates cellular functions, such as immune response, cell proliferation and growth. The JAK-STAT pathway is known to be dysregulated in various cancers including BC. Single nucleotide polymorphism (SNPs) in the promoter region of IL-6 gene have been found in the BC patients resulting in increased IL-6 levels in the sera [28]. IL-6 SNPs in BC are reported to be associated with ER positivity and a worse disease-free survival [29].

MAPK signaling pathway

The MAPK pathway is one of the crucial and complex signaling pathways that gets frequently involved in oncogenesis, tumor progression, and drug resistance. A plethora of reports have published the role of MAP kinase in BC progression. Approximately half of the BC tissues possess an enhanced level of the activated MAPK than the adjacent benign tissues [30]. Deletion of JNK1 and JNK2 in the mouse mammary epithelium is observed to further promote the genetic instability and initiate tumor development [31]. In BC, p38 inhibits the bone metastasis of BC cells by reducing the expression of RANK while facilitates lung metastasis by upregulating pro-metastatic genes [32, 33]. The p38 activation is also associated with acquisition of resistance to trastuzumab (Herceptin), used to treat HER2+ve BC patients; inhibiting p38 restores the drug sensitivity [34].

Plant-based bioactives in BC treatment

Withania somnifera

Withania somnifera or ashwagandha (smell of horse), an evergreen shrub from *Solanaceae* family mainly grows in India, the Middle East, and different parts of Africa. It has been known as the “King of Ayurvedic medicine” because of its wide role in a variety of ailments including stress and anxiety, cancer, inflammation, etc. [35, 36].

Many phytoconstituents have been isolated from different parts of *Withania somnifera*, for instance, leaves-Withanolide D, N, O, P (Alcoholic extract), Withanoside IV, physagulin, and withanoside VI (Butanol) [37]; roots-withaferin A, withanolide D, 27-hydroxy withanolide B, and withanolide A (methanol) [38]; fruits-linoleic acid, palmitic acid (oil) [39], Withanamides A-I (methanolic) [40]; stem bark-Withasomnilide, somniferanolide (methanolic) [41], Aerial parts-27-acetoxy-4β,6α-dihydroxy-5β-chloro-1-oxowitha-2,24-dienolide, along with diepoxy withanolide (methanolic) [42].

Among all, Withaferin A (WA) has been studied extensively for its efficacy in human BC cells [43]. It has been studied exclusively in different molecular subtypes of BCs like triple-negative BC (TNBC), luminal like (ER+ and/or PR+ but HER2 negative), and HER2 expressing type [44-46]. Samanta et al. [46] have studied the chemo-preventive property of WA, by determining mitotic arrest and apoptosis induction in an N-methyl-N-nitrosourea (MNU) induced BC rat model and/or mouse mammary tumor virus-neu (MMTV-neu) models. In another report, the same group had shown that three times per week treatment with 0.1 mg WA per mouse for

28 weeks inhibited the incidence of ER- BC in MMTV-neu mice [47]. WA-mediated apoptosis was induced by the FOXO3a-Bim pathway by inducing Bim-s (short form of BH-3 only member of the Bcl-2 family) via FOX-3 (Forkhead box O3) in the MDA-MB-231 (estrogen-independent) and MCF-7 (estrogen-responsive) human BC cells [48]. Sehrawat et al. in 2019 [8] has shown that WA-induced apoptosis in BC cells was associated with alterations in mitochondrial fusion (full-length optic atrophy protein 1; OPA1) and mitochondrial fission (dynamin-related protein 1; DRP1) [8] protein expression. WA induced pro-survival autophagy in MCF-7 and MDA-MB-231 cells is also reported [49].

Further reported in MCF-7 and MDA-MB-231 cells, WA-induced apoptosis is mediated by reactive oxygen species (ROS) production via inhibition of mitochondrial respiration. The authors have also shown that WA mediated activation of Bax/Bak results in apoptosis of BC cells [50]. Studies have also highlighted the role of WA in ROS-mediated paraptosis (non-apoptotic alternate programmed cell death) in BC cells. This is due to the gradual fusion of mitochondria and dilation of the endoplasmic reticulum (ER) leading to the formation of large cytoplasmic vacuolar structures along with decreased expression of the actin interacting protein-1 (Alix/AIP-1), an endogenous paraptosis inhibitor [51]. Authors have also depicted the synergistic effect of tumor treating fields and WA to effectively inhibit the proliferation of human breast adenocarcinoma cells [52]. Ashwagandha root (150 mg/kg), when ingested orally for 155 days in mammary carcinogen (metylnitrosourea) treated female rats, reduced the tumor occurrence (23%) and size (21%) [53].

Lee J et al. [54] has demonstrated that WA can activate Notch2 and Notch4 along with a decrease of Notch-1 in human BC cells [54]. The impeding inhibitory effect of WA on MDA-MB-468 and MDA-MB-231 cell migration was shown by RBP-Jk, HEY-1, HES-1A/B luciferase reporter assays [54], which was further validated via knockdown of Notch-2 and Notch-4 protein. Hahm et al. [55] showed WA induced apoptosis through Mcl-1 downregulation and WA mediated apoptosis was found to be further increased by inhibiting ERK and p38 MAPK pharmacologically and decreased by inhibiting JNK. Withaferin A (2.5 μM) induced p53 protein suppresses the estrogen receptor-α (ER-α) and confers partial protection in estrogen responsive BC cells [56]. Lee et al. in 2010 observed that in WA-treated MDA-MB-231 and MCF-7 BC cells, IL6-inducible activation, upstream regulator JAK2 and STAT3 phosphorylation were inhibited [57]. The inhibition of MDA-MB-231 BC cell invasion by WA confers protection by the IL-6-stimulation of STAT3.

It has been reported that the *Withania somnifera* root extract (WSR) causes reduced BC metastasis and epithelial to mesenchymal transition (EMT) by inhibiting vimentin [58]. The role of Ashwagandha/Withaferin identified by various studies has been depicted in **Figure 1**, which concludes its importance in designing therapies and palliative care management of BC.

As per reports, LD50 for 2% pure alkaloids extract of *Withania somnifera* was found to be 465 mg/kg in rats and 432 mg/kg in mice [59], while the LD50 with the alcoholic extract was reported to be 1750 ± 41 mg/kg, and 1564 ± 92 mg/kg for Ashwagandha, and withaferin-A respectively [60]. However, administration of an aqueous extract of *Withania somnifera* at 2,000 mg/kg to rats failed to produce any clinical or biochemical toxicity [61].

Piper nigrum

Piper nigrum or black pepper is a flowering vine belonging to the *Piperaceae* family. Piperine is a well-known bioactive component of *Piper nigrum* Linn, used as a traditional medicine for various ailments including cancer. Piperine is reported to strongly inhibit cell proliferation, downregulate HER2 gene expression, block ERK1/2 signaling, suppresse MMP-9 expression and induce apoptosis through caspase-3 activation, and enhance sensitization to paclitaxel in HER2-overexpressing BC cells [62]. Piperine (20 μM) enhanced apoptosis when given in combination with cisplatin (5 μM) for 24 hours through Bcl-2 reduction and caspase 3, p53, caspase 9, and Bax upregulation (**Figure 2**) [63]. Also, Piperine is known to inhibit growth of 4T1 cells with IC50 values of 105 ± 1.08 and 78.52 ± 1.06 μmol/L, respectively, at 48 and 72 hours and suppress the primary 4T1 tumor growth at a dose of 2.5 mg/kg [64]. Additionally, Piperine is reported to be the most

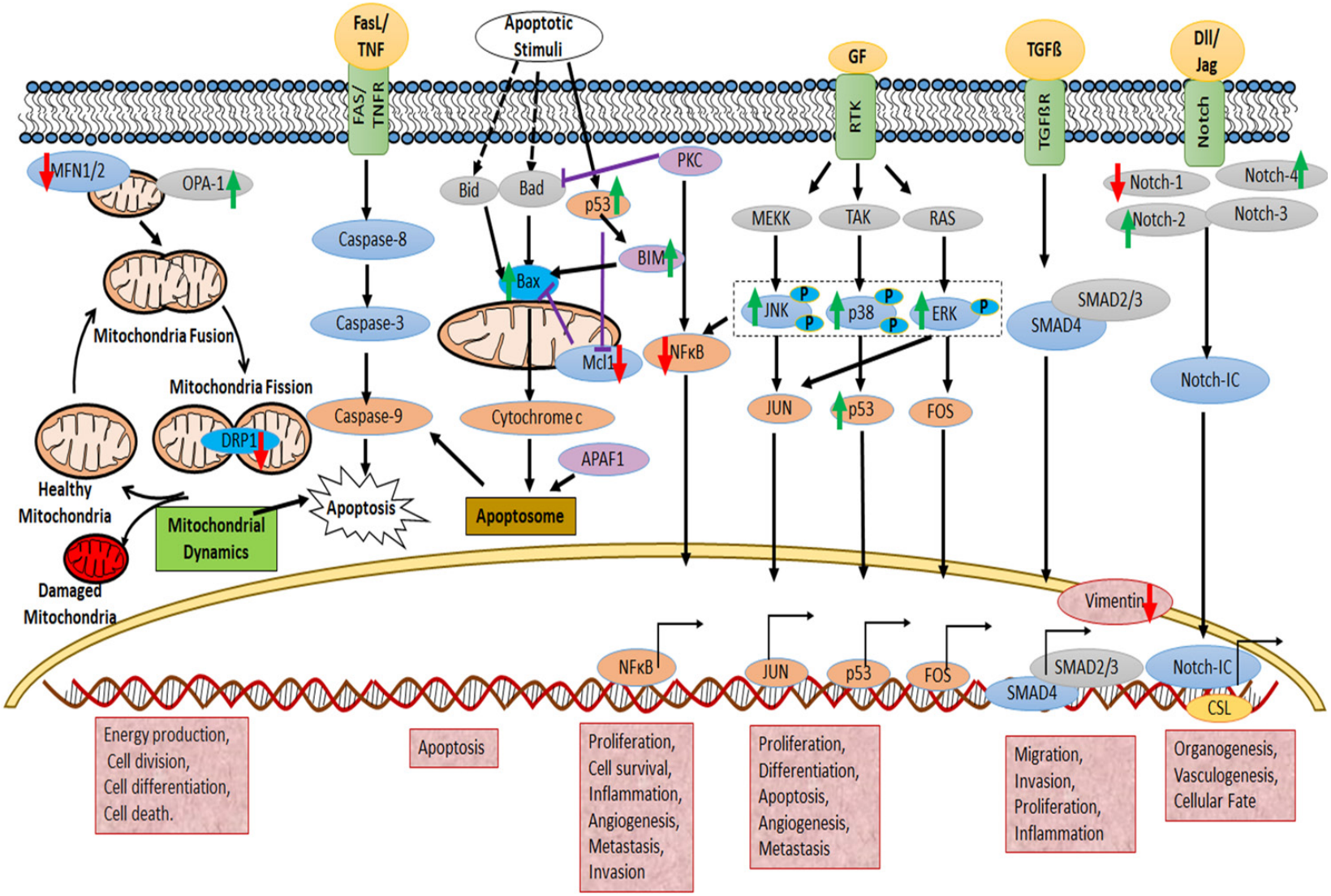

Figure 1. Role of *Withania somnifera* and Withaferin A in regulating various pathways or signaling mechanisms in breast cancer (BC) cells. Here, upright green arrows depict induction or upregulation and inverted red arrow depicts reduction or downregulation.

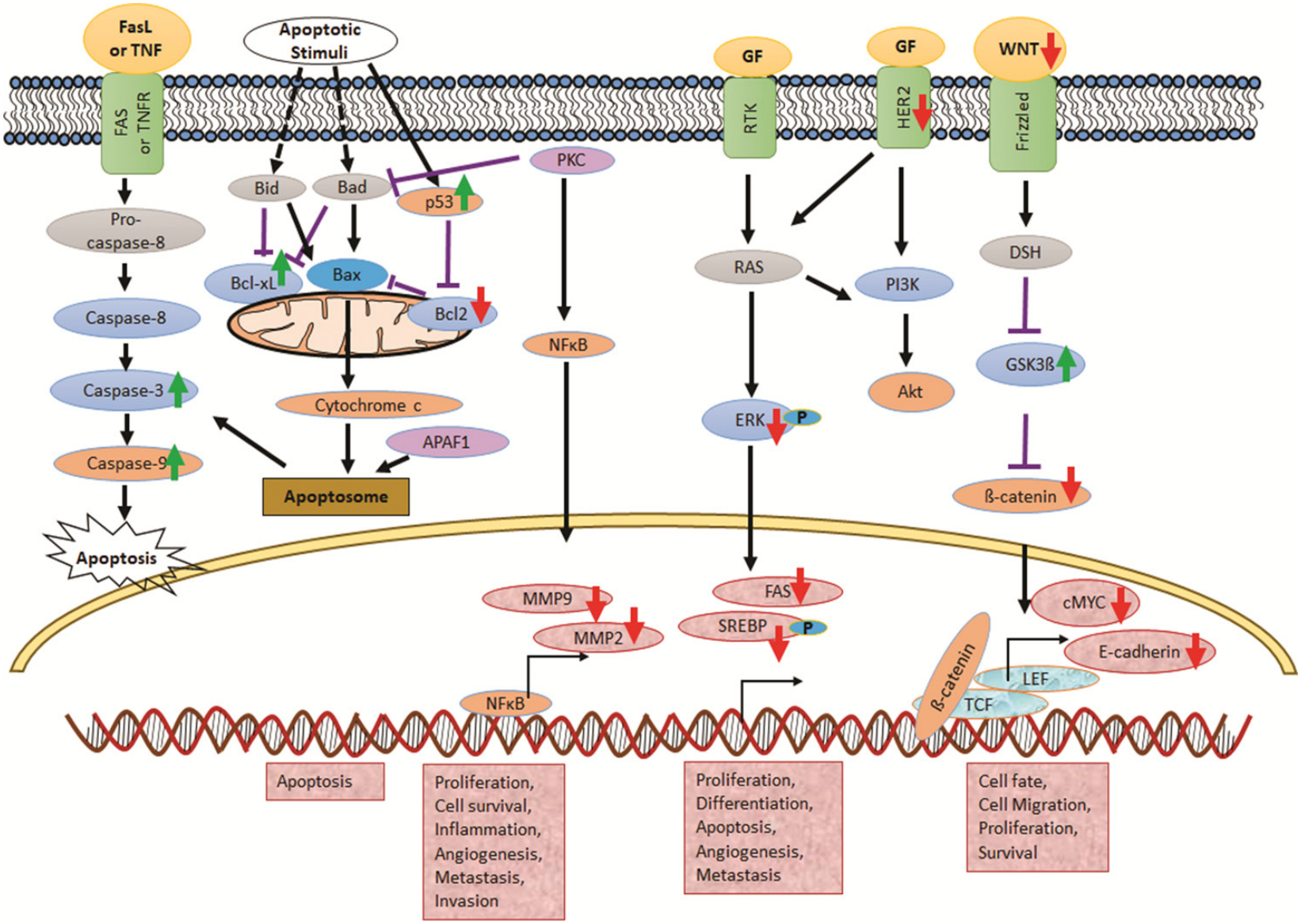

Figure 2. Role of *Piper nigrum* and Piperine in regulating various pathways or signaling mechanisms in breast cancer (BC) cells. Here, upright green arrows depict induction or upregulation and inverted red arrow depicts reduction or downregulation.

potent adjuvant among the 55 compounds derived from natural plants in enhancing the efficacy of TRAIL-based therapies in human and murine triple negative BC cells, probably through inhibiting survivin and p65 phosphorylation [65]. Another study on piperine free *Piper nigrum (PFPE)* revealed the anti-cancer effects of the PFPE via p53 upregulation, and estrogen receptor, E-cadherin, MMP-9, MMP-2, c-Myc, and VEGF downregulation in N-nitroso-N-methylurea (NMU)-induced mammary tumorigenesis rats and in MCF-7 cells [66]. Evidence demonstrated the relationship among anti-tumor activity, the ROS overproduction, and the antiproliferative effect of *Piper nigrum* extract along with apoptosis and DNA fragmentation, leading to altered expression of cell cycle arrest proteins (increased p53 and Bax and inhibited Bcl-xL) in MCF-7 cells [67]. Discussed in an interesting study, nanoparticles (NPs) loaded with black pepper essential oil (BP-EO) were prepared and given to MDA-MB-231 cells. The nanoparticle treatment inhibited BC progression via inhibiting the Wnt/β-Catenin signaling pathway which provides an innovative idea for the treatment of invasive BC in the future [11].

The potential health benefits of piperine could cause harm depending on the dose, time or route of exposure. For instance, piperine is more toxic when administered intravenous than intragastric, subcutaneous, and intramuscular. Piperine is insoluble or instable in the stomach, and hence induces hemorrhagic ulceration in the gastrointestinal lumen. Piperine, when administered through intravenous, intraperitoneal, intragastric, subcutaneous, and intramuscular routes, imparts LD50 values at 15.1, 43, 200, 330, and 400 mg/kg body wt, respectively in adult male mice [68]. Also, piperine's toxicity mainly affects the reproductive system [69].

Berberine

Plants like *Berberis vulgaris* (barberry), *Berberis aristata* (tree turmeric), *Coptis chinensis* (Chinese goldthread), and others contain protoberberine alkaloids like berberine, oxyberberine, epiberberine, palmitine, and bis-isoquinoline [70]. Among all, berberine has gained more attention due to its low toxicity and crucial role in antiviral, anti-inflammatory, and anticancer activities.

According to the literature, berberine is either used at a higher dose of 100 μM or an IC50 values ranging from 0.19 to 16.7 μM to inhibit proliferation and induce death in BC cells either by p53 upregulation, metadherin (MTDH) downregulation, or regulation of AKT/ERK and p38 pathways (**Figure 3**) [71-73]. Authors have also reported that berberine inhibits colony formation and cellular migration by decreasing the c-Jun and c-Fos phosphorylation, downregulating ephrin-B2, TGF-β1, MMP2, MMP9, and NF-κB gene expression levels [73-75]. Recently, berberine and exercise have been used as synergistic therapy to regulate intestinal microbial metabolites via apoptosis induction to reduce the BC progression in 4T1 tumor-bearing rats [76]. Berberine has also been known to downregulate the X-ray cross complementing protein 1 and excision repair cross-complementing group 1 levels involved in the cell DNA repair to sensitize the MDAMB-231 cells to chemotherapeutic drugs [77]. Interestingly, berberine is reported as both chemotherapy sensitizer and chemotherapy drug, as a lower dose of berberine enhances Doxorubicin sensitivity to drug-resistant BC via AMPK-HIF-1α-P-gp pathway while a higher dose of berberine induces apoptosis through AMPK-p53 pathway [78]. Recently, authors have also reported that berberine can reverse multi drug resistance by inhibiting the expression of P-gp/ABCB1 and MRP1/ABCC1 and increasing the uptake of Doxorubicin in tumor tissues when given synergistically in MCF-7/DOX^{Fluc} cells and/or nude mice [79].

Butea monosperma

Butea monosperma (Palash), a deciduous tree belonging to the Fabaceae family, has been widely used to cure various ailments [80-82]. The methanol extract of the flower of *Butea monosperma* (MEBM), has shown a decreased cell proliferation and significantly less IC-50 value in MCF-7 (estrogen receptor-positive BC) cells than in MDA-MB-231 (triple-negative BC) and MDA-MB-453 cells (human epidermal growth factor-2 or HER2 positive BC), showing anti-apoptotic, anti-angiogenesis, and anti-metastatic activity of MEBM via altering the estrogen receptor and progesterone receptor [9]. Varinder et al. [83] have reported that in vitro treatment of butanol fraction from the bark of *Butea monosperma* resulted in sub-G1

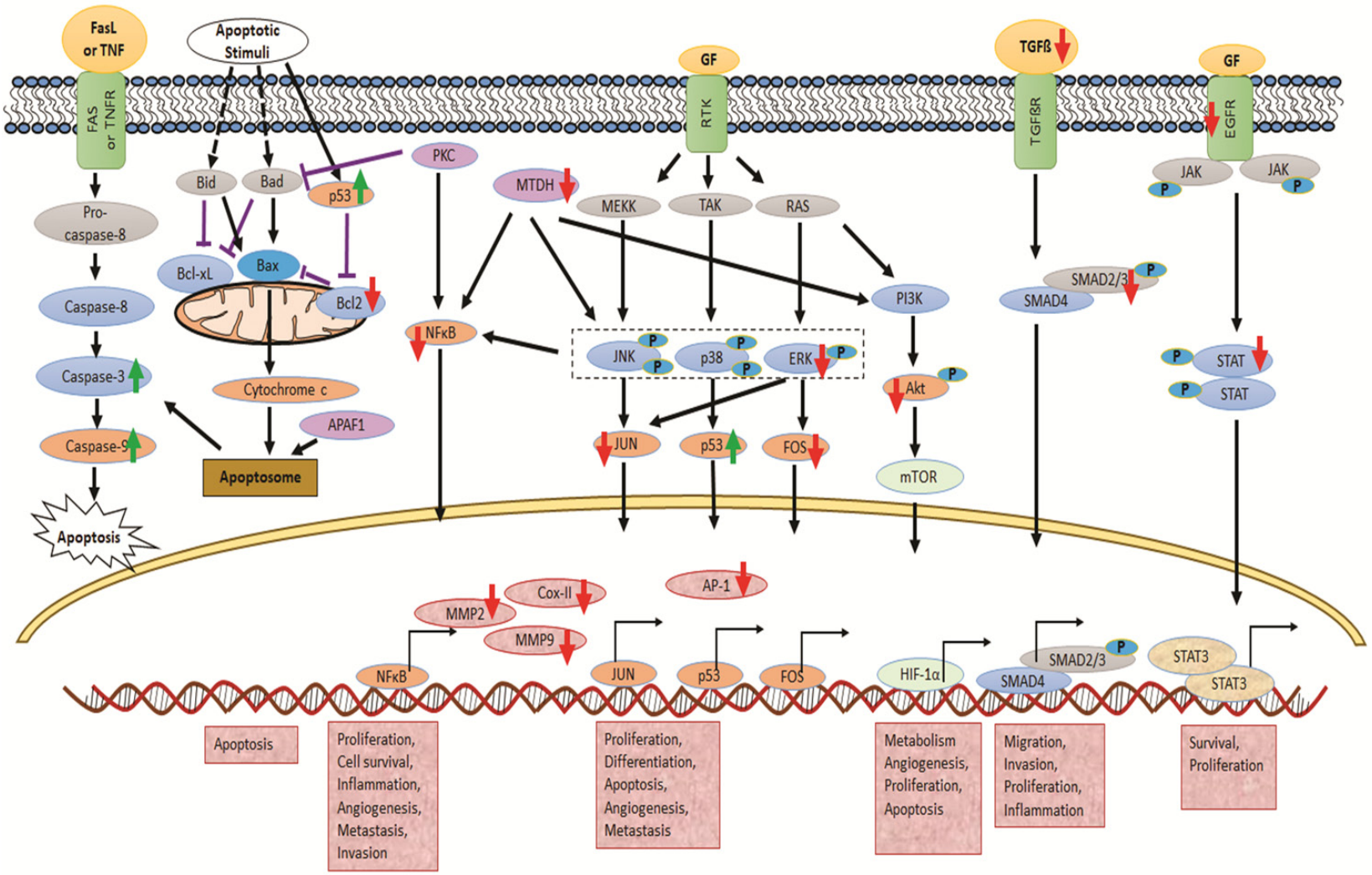

Figure 3. Role of Berberine in regulating various pathways or signaling mechanisms in breast cancer (BC) cells. Here, upright green arrows depict induction or up-regulation and inverted red arrow depicts reduction or downregulation.

cell cycle arrest, ROS generation, and decreased mitochondrial membrane potential in MCF-7 cells indicating its role in apoptosis induction. In another study by the same group, different extracts from the bark of *B. monosperma*, namely, methanol, hexane, chloroform, and ethyl acetate, were prepared and evaluated for anti-proliferative and apoptotic activity in human BC cells with increasing concentrations (50, 100, 200, 400, and 800 µg/mL) for 24 h. Among all extract/fractions, chloroform and ethyl acetate fractions (25-400 µg/mL) exhibited a pronounced anti-oxidant activity. As per HPLC analysis, chloroform constitutes high kaempferol while Beac has high catechin, epicatechin, and gallic acid. They were also observed to induce apoptosis in MCF-7 cells by inducing double-strand DNA breaks [84]. Furthermore, the flowers of *Butea monosperma* produce a flavonoid named Butein which has been reported to significantly inhibit 1 µM PMA-induced COX-2 expression in breast cells along with phospho-MAPK, ERK-1/2, and PKC reduction with a concentration of 0.1, 1 and 10 µM, suggesting its potential role as chemopreventive agent against breast carcinogenesis [85].

Triterpene (TBM) present in the n-hexane:ethyl acetate (1:1) fraction of the petroleum ether extract of dried flowers of *Butea monosperma* was administered intraperitoneally to male mice and found to have an LD50 value at a dose of 500 ± 32 mg/kg. TBM (100 mg/kg) after 60 minutes of administration showed sedative-like side effects [86]. The ethanolic bark extract of *B. monosperma* did not show any apparent clinical toxicity in rats at oral doses up to 2,000 mg/kg [87]. Further, palasonin, isolated from the ethanolic extract of *Butea monosperma* seeds, and its piperazine salt showed low toxicity in mice and rats; specifically piperazine salt was less toxic than palasonin alone [88].

Rheum emodi

Rheum emodi Wall. ex Meissn. is a Himalayan perennial herb belonging to the *Polygonaceae* family of plants. It is commonly known as Rhubarb (Trade name), which has been cultivated over 5000 years for its medicinal properties by rural and tribal people of Himalayas [89]. *R. emodi* has been reported to have antibacterial, antifungal laxative, diuretic, and anticancer activity [89, 90].

Petroleum ether extracts (hot [PHR] and cold [PCR]) of R. emodi, had been reported to show a significant ($P < 0.05$) cancer-cell-specific cytotoxicity in the MDA-MB-231 cells at 100 µg/mL concentration. Further, the authors have performed HPLC and GC-MS analysis to reveal major polyphenolics, 4,7-Dimethyl-(octahydro) indolo[4,3-fg] quinolin-10-one, 5-Oxo-isolongifolene, Valencene-2, and other quinone, quinoline and anthraquinone derivatives as the active constituents of the extract [91]. Later, Kumar et al. [10] demonstrated that the hot and cold ethyl acetate extracts (EHR and ECR respectively) of *R. emodi* rhizome had specific chemo-preventive, anti-oxidant and significant cancer-specific cytotoxic properties towards estrogen receptor-negative BC cells (MDA-MB-231) with IC-50 of 56.59 ± 1.29 µg/ml (EHR) and 152.38 ± 1.45 µg/ml (ECR). The extracts induced more apoptosis in MDA-MB-231 cells in comparison to ER-positive MCF-7 cells.

As reported by Ye BG et al., Sprague Dawley rats were randomly divided into four groups (10 rats/sex/group) and were treated with 0, 1000, 2000, and 4000 mg/kg/d sub-toxic dose of aqueous extract of R. emodi (AERE) rhizome for 90 days. The authors reported 4000 mg/kg/d as no-observed-adverse-effect level (NOAEL) dose for AERE in both male and female rats [92].

Vernonia cinerea (VC)

Vernonia cinerea, is an annual herb belonging to *Asteraceaes,* grows in India and other South-East Asian countries. It is used in curing pain, inflammation, infections, malaria, diuresis, cancer, and various gastro-intestinal diseases. VC has shown anti-cancerous activity in many malignancies including BC. Compounds isolated from the chloroform partition of a methanol extract of VC inhibited the aberrant STAT3 activity when given at 5 µM concentration for a time period of 10 mins to 6 hours. Authors further showed the reduced viability of MDA-MB-231 BC cells upon isolated compound treatment [93]. Also, dichloromethane fraction of ethanolic extract of VC showed increased apoptotic effects, inhibition of multi-drug resistance (MDR) transporters, enhanced drug uptake,

and increased cell sensitization in MCF-7 BC cells [94]. Another report has shown that the 'sesquiterpenoids' enriched fraction of VC induced cell cycle arrest, DNA damage and apoptosis in human adenocarcinoma cells [95].

Amooranin (AMR)

Amooranin, a triterpene acid isolated from the stem bark of *Amoora rohituka,* is used for the treatment of various ailments in India. AMR has shown to decrease cell migration, and induce growth arrest and caspase mediated apoptosis in BC cells [96, 97]. Induced caspase-8 activation and apoptosis was reported in MCF-7 (human mammary carcinoma), MCF-7/TH (multidrug-resistant breast carcinoma), and MCF-10A (breast epithelial cell lines) at 1-8 μg/ml concentrations [98]. AMR-Me, an amooranin-methyl ester, has been reported to possess significant antiproliferative effect against BC cells via decreasing ERα expression, effectively inhibiting Akt phosphorylation, and targeting NFκB-evoked inflammatory cascade to achieve BC chemoprevention [99, 100].

Eclipta alba (AEEA)

Eclipta alba (L.) Hassk, commonly known as Bhringraj, is an annual herb from *Asteraceae* family. It has been used since ages to treat various ailments especially related to the liver and hair. Based on the color of their blossom, it is divided in four main varieties. Lirdprapamongkol et al. [101] reported the potential role of *Eclipta alba* in inhibiting invasion, migration, and adhesion of cancer cells. Although the anticancer activity of *Eclipta alba* is reported almost a decade back, however, many reports have come up showcasing its role in BC management. The chloroform fraction of *Eclipta alba* (CFEA) when given as 100 μg/ml for 24 hours is reported to selectively induce cytotoxicity to MCF-7 and MDA-MB-231 BC cells over MCF 10A. The study revealed that CFEA induced BC cell cytotoxicity is associated with disruption in mitochondrial membrane potential, upregulation of Hsp60 protein expression and downregulation of XIAP protein levels. Additionally, 50 mg/kg of body weight oral dose of CFEA also mitigates tumor associated hepato-renal toxicity in 4T1 syngenic mouse model [102]. Moreover, they found that Luteolin but not Wedelolactone is mainly responsible for the anti-cancerous activity of CFEA. Further, another group reported that Luteolin-Fabricated ZnO nanoparticles showed greater polo-like kinase 1 (PLK1) proteins mediated anticancer activity in MCF-7 cell line as compared to luteolin or ZnO alone [103]. Yadav et al. in 2017 [104] studied the antioxidant, and anticancer role of *Eclipta alba* (AEEA) from its alcoholic extract in varied cancer cell lines including BC. The authors have shown that AEEA significantly induced a dose dependent anti-cancer activity by disrupting mitochondrial membrane potential and inhibiting migration in BC cells.

Curcuma longa

Curcuma longa or turmeric, belonging to *Zingiberaceae* family is a very famous spice of Asian countries. Various curcuminoids, present in turmeric (from roots of *Curcuma longa*) have been associated with wound healing, anti-inflammatory, and anti-carcinogenic properties. Curcumin is one of the most important components of the curcuminoids which can be isolated from the rhizome of *Curcuma longa* L. With an IC50 value of 25.63 μg/mL, curcumin is reported to be more potent in imparting anticancer effects in MCF-7 cells as compared to other active curcuminoids of *Curcuma longa* such as demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) [105]. Various authors have shown the anti-BC activity of curcurmin like reduction in Gli1-overexpressing MDA-MB-231 cell invasion, down-regulation in the expression of Hedgehog, EMT and stemness genes in MDA-MB-231 mammospheres, modulation of epigenetic events that are dysregulated in cancer cells, and promotion of SLC1A5-mediated ferroptosis by enhancing lipid ROS [106-108]. Authors have also reported the inhibitory effect of curcuminoids on cytochrome P450 CYP17A1 and CYP19A1 enzymes used for steroidal metabolism pathway in a dose-dependent manner for designing effective potential drugs against BC [109]. As per reports, 6000 mg/day is the recommended dose of curcumin along with a standard dose of docetaxel for seven consecutive days every 3 weeks in advanced and metastatic BC patients. Further, a clinical trial reported a reduction in the severity of radiation dermatitis in BC patients upon recommended curcumin dose during radiotherapy [110, 111].

Garcinia mangostana Linn

Garcinia mangostana Linn (GM), family *Guttiferae*, is known as 'the queen of fruits' due to its taste. It is cultivated in the tropical rainforest of South-East Asian countries. Its pericarp contains various phytochemicals, primarily xanthones, and has been used for the treatment of dysentery, infected wound, chronic ulcer, leucorrhoea, inflammation and tumor in many Asian countries [112]. α-mangostin is the most found xanthone present in mangosteen pericarp that has been reported to have anti-proliferative and apoptotic function in various malignancies including BC. α-mangostin induced anti cancerous activity in BC cells is known to be associated with decreased fatty acid synthase (FAS) expression and activity, reduced phosphorylation of FAK, increased phosphorylation of ERα, HER2, PI3K, Akt, mitochondria-mediated apoptosis, G1-phase arrest, increased p21cip1 expression, decreased cyclins, cdc(s), CDKs, PCNA, ERK1/2 expression, enhanced p-JNK1/2 and p-p38 expression, and activation of MOAP-1 tumor suppressor [113-115]. Additionally, the crude methanolic extract (CME) from the pericarp of *Garcinia mangostana* induced a dose-dependent reduction in cell proliferation with ED50 of 9.25 ± 0.64 μg/mL for 48 hours in human BC (SKBR3) cell line. CME was found to inhibit ROS production in a dose and time dependent manner [112]. Recently α-mangostin encapsulated chitosan/pluronic F127@MRGO nanocomposites has been shown to induce a significant reduction in BC cell proliferation at a varied concentration of 78.125 μg/mL to 5000 μg/mL. The authors showed that α-mangostin-loaded PF127-Chi@MRGO exhibit high toxicity in human BC cells (MCF-7) at 2500 and 5000 μg/mL [116]. Further, α-mangostin has been suggested as adjuvant therapy for the treatment of BC due to its anti-metastatic activity along with the reduced tumor growth and chemo-preventive benefits in the p53 mutant metastatic mammary cancer immunocompetent xenograft model [117].

Cyathocline purpurea

Cyathocline purpurea belonging to *Asteraceae* family of plant kingdom is found in Indo-China region. Studies showed that in HER-2 positive BC cells, sesquiterpene lacton of *Cyathocline purpurea,* SRCP1 can induce mitotic arrest and apoptosis, inhibit the cancer growth, reduce cell migration and alter TNF-α and Wnt signaling pathways in MDA-MB-453 cells [118]. Further, three main constituents of Cyathocline *purpurea,* santamarine, 9β-acetoxycostunolide and 9β-acetoxyparthenolide have shown growth inhibition activity in human breast adenocarcinoma cells in vitro, with IC50 of 0.53 ± 0.10 μg/mL, 0.63 ± 0.0.7 μg/mL, and 0.50 ± 0.03 μg/mL respectively at 72 hours exposure [29].

Pterocarpus santalinus

Pterocarpus santalinus Linn. f. ('Red-sander' or 'Rakt-Chandan') from family *Fabaceae* is mainly found in the Eastern Ghats of South India and has been used to exhibit cytotoxic properties in various cancer cell lines [119]. The three new sesquiterpenes, canusesnol K, canusesnol L, and 12,15-dihydroxycurcumene, along with five known compounds, isopterocarpolone, ent-4(15)-eudesmen-1α, 11-diol, hamahasal A, pterocarpol, and (3β)-eudesm-4(14)-ene-3,11-diol, were isolated from the heartwood extract of *P santalinus* and were looked for their inhibitory activity in cancer cells. Among all, canusesnol K (50 μmol/L) showed the maximum Inhibitory effect (35.07 ± 4.9%) in MDA-MB-231 cell lines after 48 hours of exposure [120]. For the first time, the seeds of *P santalinus* were studied in an animal model by Akhouri et al. [121] who showed the anti-cancerous, antioxidant and hypoglycemic properties of their ethanolic seeds extract after developing BC by oral induction of DMBA in rats. Oral administration of *P* santalinus extract showed a 49.5% tumor growth inhibition in *P santalinus* treated group as compared with the only DMBA treated control group. *P santalinus* administration also significantly reduced ($P < .0001$) the serum malondialdehyde level, serum tumor necrosis factor-α level, and blood serum glucose level in the *P santalinus* treated group. This further resulted in the improved histology of breast tissues and hence, highlighted the chemotherapeutic property of *P santalinus*.

Others

Besides all above medicinal plants/herbs, Avemar is the only patented fermented wheatgerm extract, which has been studied as an adjunct to conventional anticancer therapy. It is

reported to have a role in apoptosis, arresting disease progression, starving the sugar supply required by cancer cells to survive, unmasking cancer cells, and preventing repair of abnormal cells [122]. Rasa Manikya nanoparticle (RMNP), a herbometallic nano-drug, has been investigated for its antimicrobial and anticancer activity, and proved synergistically for combating drug-resistant microbial strains and impairing redox balance (GSH/NADPH) in cells along with initiation of apoptosis in BC [123]. Recently, researchers [124] have also shown the RMNP induced metastatic growth inhibition due to exhaustion in fatty acid uptake and energy metabolism in BC. Electrical pulse (EP)-mediated turmeric silver nanoparticles (TurNP) therapy has been developed as alternate therapeutics for TNBC, leading to reduced viability of BC cells, alterations in various proteins and pathways, which redirect the TNBC metabolism to mitochondria [125]. Panchakola, a combination of five herbs i.e., Pippali (*Piper longum*), Pippalimoola (*Piper longum*), Chavya (*Piper retrofractum*), Chitraka (*Plumbago zeylanica*) and Shunthi (*Zingiber officinale*) has increased cytotoxicity and antioxidant activity in MCF-7 cells, suggesting its antineoplastic potential against BC [126]. Triphala (TPL) is a polyherbal combination of three herbs - Haritaki (*Terminalia chebula*), Bibhitaki (*Terminalia bellirica*) and Amla (*Phyllanthus emblica*). In vitro studies showed that TPL acts effectively on wild type p53 harboring MCF 7 cells than p53 mutant T 47 D cells [127] and induces a significant upregulation in intracellular ROS. The gallic acid - a major polyphenol observed in Triphala was found to be responsible for its cytotoxicity [128, 129]. Maharishi Amrit Kalash (MAK) is prepared as a mixture of several herbs. MAK-4 (paste) and MAK-5 (Tablet) are two forms; MAK-4 is made up of thirty-eight herbs lyophilized in ghee (a class of clarified butter frequently used in India) and MAK-5 contains thirteen herbs [130]. Studies have demonstrated anti-neoplastic properties, reduction in metastasis, and regression in mammary tumors after application of both MAK-4 and MAK-5 in an animal model [131, 132]. MAK has shown to reduce the common chemotherapy induced side effects (reduced appetite, stomatitis, nausea, vomiting, weight loss, fatigue, leukopenia, etc.) in clinical studies [133, 134]. HC9 (herbal composition-9) is a polyherbal formulation which contains matairesinol as an active constituent. Recently, *in vitro* studies have shown anti-HDAC8 (histone deacetylase-8 activity) and anti-neoplastic activity of HC-9 in BC via regulating modulators of chromatin, inflammation as well as cell proliferation, metastasis, viability, migration, invasion, and cell cycle arrest [135].

Additionally, Psoralens (in plants, e.g., lemons, limes) [136], extract of *Withania coagulans* (Indian cheese maker, Rishyagandha/*Paneer phool)* [137], bark of *Mangifera zeylanica Hook.f.* [138], Guggulu (*Commiphora mukul*) [139], fruits of *Embelia* ribes (false black pepper or white-flowered embelia) [140], *Murraya koenigii* leaf (curry leaf) [141], agarwood essential oil [142], *Cinnamomum zeylanicum* (CZ) [143], *Njavara,* a distinct rice variety in Kerela, India [144], Genistein, a natural isoflavone and a phytoestrogen [145], root of *Tiliacora racemosa* and oil of *Semecarpus anacardium* [146], Swarna sindoor, hirak bhasma and Suvarna bhasma [147], and *Pueraria tuberosa* (Roxb. ex-Wild.) *DC*. (Indian Kudz) [148] have also shown antitumor, apoptotic, anti-metastatic, cell cycle arrest and regulatory activities in BC cell lines influencing various enzymes, pathways, and cell cycle pathways, preventing anorexia, cachexia and hence, playing significant role in palliative care management of BC by improving QoL.

Discussion

With advancements in pharmacological technology, an increasing number of natural products with certain chemical structures have been identified and studied to exert a myriad of pharmacological effects in pre-clinical and clinical studies. The successful events reported have shown the potential of these natural products to become new drugs which can be used to treat various diseases.

As per reports, complementary and alternative traditional medicines are used to treat cancer patients worldwide along with regular cancer-directed treatment [149]. Hence, it is possible to design a tailored treatment for BC patients by using plant-based bioactives along with conventional medicine for the treatment, management of side-effects, and improvement of the state of mental wellbeing in cancer patients.

Various aspects of phytomedicine can be combined with modern treatment as an integrated approach. A large number of cell line studies have shown that Indian herbal extracts can induce apoptosis, inhibit proteasome leading to cancer cell death, possess anti-metastatic activity, anti-oxidant properties, cytotoxic activity, capacity for mitotic arrest, and potential for activating tumor suppressor genes in cancer. They are also known to enhance chemo-sensitivity and radio-sensitivity in the context of BC [150]. Several botanical drugs described in this article can alleviate the common side effects associated with radiation or chemotherapy and can be helpful in palliative care management and improving QoL.

Our review provides evidences of cellular and molecular mechanisms of medicinal herbs including *Withania somnifera, Butea monosperma, Eclipta alba, Piper nigrum,* or drugs like WA, Berberine Panchkola, MAK, and Triphala, which have been studied for their efficacy in BC. The details of these herbs/extracts and various mechanisms by which they act or mediate their mode of action have been described in Supplementary Table 1. Various Signaling pathways were also observed to be altered by botanical drugs, for instance leptin, Notch [54], AKT/ERK and p38 pathways by Berberine [71-73], Hedgehog pathway, EMT and stemness by *Curcuma longa* [106-108], TNF-α, Wnt/β-catenin signaling by *Cyathocline purpurea* [118], MAPK, IL-6, STAT-3 [151] by *Withania somnifera*, and metastatic signaling [140] by Embelin. **Figure 4** depicts the different pathways affecting various neoplastic processes by some of the most effective traditional drugs (*Butea monosperma, Garcinia mangostana, Vernonia cinerea, Curcuma longa*) in BC, which depict their future role in targeted therapies.

Various polyherbal formulations like Panchkola [126], Triphala [118], MAK (*Maharishi Amrit Kalash*), and *Pueraria tuberosa* have also shown cytotoxic, apoptotic, antioxidant, anti-neoplastic potential to diminish BC. Recently, HC9 [135] and turmeric-based electrochemotherapy [125] have been explored, showing promising results for the treatment of BC and TNBC respectively. Literature showed that the Indian herbs with their anti-cancer properties have the potential to be an integrative medicine in BC and can be used for their add-on effects to cancer treatment via diminishing clinical side-effects of chemo/radiotherapy and refining the patient's QoL (**Figure 5**). However, very few clinical studies have evaluated such synergy. More robust evidence supporting well designed clinical intervention trials are needed in humans to determine their efficacy and safety for BC treatment and palliative care. The botanical drugs of Indian medicine can fill in several existing gaps rather than being an 'alternative' to the conventional oncology treatment.

Current challenges and future perspectives

Although modern medicine has moved towards the advancement in therapeutics of BC, yet the problems related to the adverse effects of the treatment modalities, especially worsening of QoL with anticancer treatment and development of tumor resistance remain as unresolved issues. Integration with natural plant based bioactive compounds may lead to the development of alternate novel therapies and better palliative care. However, there are various pitfalls in the field of integration with plant based bioactives. There is a shortage of studies on herbal drug interaction, pharmacokinetic and pharmacodynamic. Additional studies should be designed to gain more information on the dosing, side effects, toxicities, interaction with other drugs, and efficacy in disease models. Quality control (QC) of herbal drug must be properly maintained for the assurance of safety and global acceptability.

Conclusion

The botanical drugs have been known to regulate cytotoxicity, apoptosis, angiogenesis, metastasis, and target multiple cell cycle signaling pathways in BC. Additionally, they can also be used for improved QoL, treatment and management of BC. To the best of our knowledge, this is the first review article that has discussed such an in-depth knowledge of various Indian herbs including nomenclature, dosage, toxicity, and modus operandi in BC cells. Taken together, this review will pave the way to deciphering novel strategies integrating Indian phytomedicine in translational research to overcome the current existing serious challenges of BC treatment.

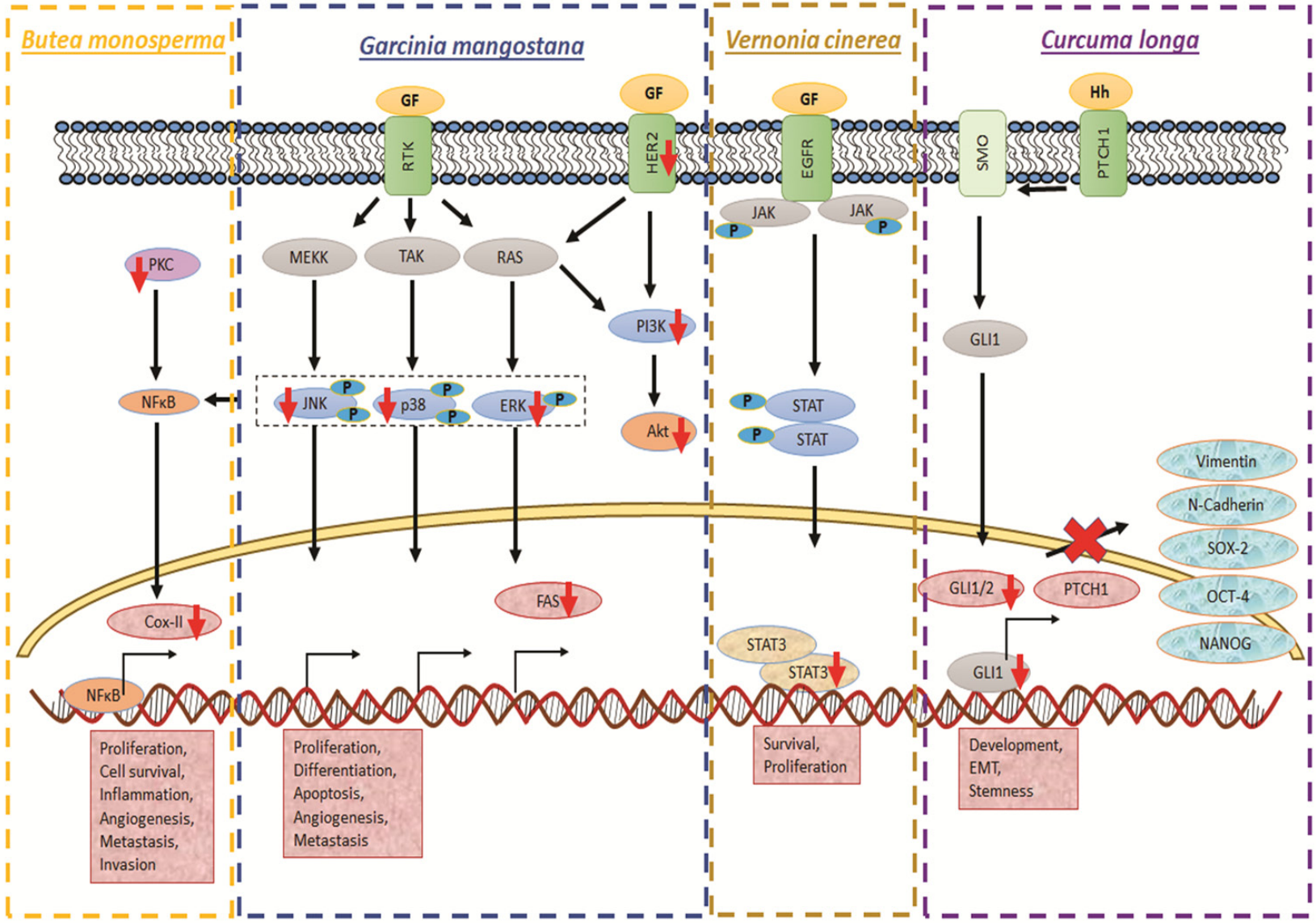

Figure 4. Varied herbal drugs modulating different pathways regulating the neoplastic activity in breast cancer (BC) cells. Here, upright green arrows depict induction or upregulation and inverted red arrow depicts reduction or downregulation.

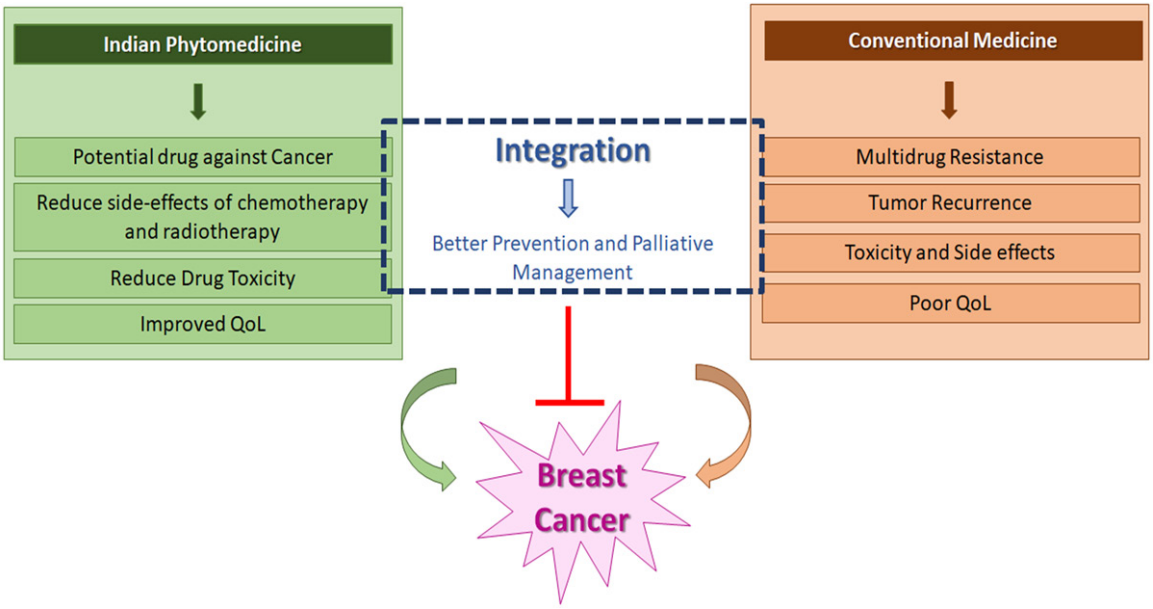

Figure 5. The figure depicts the integrative role of Indian phytomedicine and conventional medicine in breast cancer.

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None.

Authors' contribution

Conceptualization: P.B., R.M., R.T.; Methodology: H.S. and R.T.; Writing-original draft: H.S., R.T and PB; Writing-review and editing: H.S., P.B., T.N., V.H., K.R., A.S., S.G., R.T., and R.M.; Visualization: H.S.; Funding acquisition: T.N, V.H., S.G., R.T.; Supervision: T.N. and R.M.

Address correspondence to: Tanuja Nesari and Dr. Richa Tripathi, All India Institute of Ayurveda (AIIA), Mathura Road, Gautam Puri, Sarita Vihar, New Delhi-110076, India. E-mail: director@aiia.gov.in (TN); richa.trpths@gmail.com (RT); Ravi Mehrotra, Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia-30322, US. E-mail: ravi.mehrotra@emory.edu

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Supplementary Table 1. Ayurvedic drugs/medicinal plants for potential use in breast cancer treatment

Sr. No.	Ayurvedic Drugs/Medicinal Plants (Scientific name)	Chemo Prevention	Cytotoxic	Anti-oxidant	Anti-metastatic	Apoptosis	Increased Chemo/Radio sensitivity	Reduce treatment toxicity	Anti-estrogenic	Anti-angiogenic	Role in Others	Reference
1.	*Withania somnifera* (Ashwagandha)	+	+	+	+	+	+	+	+	+	EMT, ROS induction; the role in paraptosis, anti-proliferative, mitotic arrest, inhibition of Mcl-1 protein, Role in Notch, MAPK p53, insulin/IGF. STAT-3, IL-6 signaling	[8, 44, 46, 50, 51]
2.	*Piper nigrum* (Black pepper)	+	+	+	+	+	+	-	-	-	Anti-tumor activity, Antiproliferative effect, Reactive oxygen species (ROS) overproduction, DNA fragmentation, cell-cycle arrest	[11, 63-67]
3.	Berberine	+	+	+	-	+	+	-	-	-	Anti-proliferative	[72-74, 76-78]
4.	*Butea monosperma* (Palash)	+	+	-	+	+	-	-	+	+	G1 cell cycle arrest, double-strand DNA breaks, increased ROS levels, reduced mitochondrial membrane potential	[9, 81, 84]
5.	*Rheum emodi*	+	+	+	+	+	-	-	-	-	-	[10, 90, 91]
6.	*Vernonia cinerea*	-	+	+	-	-	+	-	-	-	Inhibited multi-drug resistance (MDR) transporters	[94, 95]
7.	Amooranin (*Amoora rohituka)*	-	+	-	-	+	+	-	-	-	-	[97, 98, 100]
8.	*Eclipta alba* (Bhringraj)	+	+	+	+	+	-	-	-	+	Antioxidant, and anti-cancerous activity, obstruct cell migration and induce apoptosis	[101, 102, 104]
9.	Curcuma longa	+	+	+	+	+	+	-	-	-	Inhibitory effect on cytochrome P450 CYP17A1 and CYP19A1, Epigenetic regulation	[105-111]
10.	*Garcinia mangostana* Linn	+	+	+	+	+	-	-	-	-	Reduced tumor growth	[112-115, 117]
11.	Cyathocline purpurea	+	+	+	+	+	-	-	-	-	Mitotic arrest at G2/M phase, inhibition of DNA synthesis, reduce migration by reducing EMT levels and altering TNF-α, and Wnt/β-catenin signaling pathways	[118]
12.	*Pterocarpus santalinus* Linn. f.	+	+	+	-	+	-	-	-	-	Chemotherapeutic, improved breast tissues histology	[119, 121]
13.	Panchakola A polyherbal (five) ayurvedic formulation of Pippali (*Piper longum*), Pippalimoola (*Piper longum*), Chavya (*Piper retrofractum*), Chitraka (*Plumbagozeylanica*) and Shunthi (*Zingiber officinale*)	-	+	+	-	-	-	-	-	-	Nitric oxide scavenger, superoxide dismutase, glutathione S-transferase, and glutathione peroxidase	[126]
14.	Triphala (TPL)	-	+	+	-	+	-	-	-	-	Anti-proliferative	[127-129]
15.	Maharishi Amrit Kalash (MAK)	-	+	+	+	+	+	+	-	-	Metastasis reduction, regressed breast tumor	[130-132]
16.	*Commiphora wightii* (Guggul)	-	+	-	-	+	-	-	-	-	Chemotherapeutic agent	[139]
17.	*Embelia ribes* (False black pepper)	+	+	+	+	+	-	-	-	-	Anti-cancerous effects-by targeting mortalin and inhibiting mortalin-p53 interactions	[140]

Note: '+' means positive effect; '-' means no effect/not studied.