International Journal of Science and Research Archive

eISSN: 2582-8185

Cross Ref DOI: 10.30574/ijsra

Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

Check for updates

A comprehensive study on: Allopathy and herbal therapy on breast cancer

Mainak Khan *, Deeparani Urolagin, Ansari Aashif Raza Mohd Imtiyaz, Samir Panda and Maneswari Boro

Department of Pharmacology, R R College of Pharmacy, Bangalore India.

International Journal of Science and Research Archive, 2024, 12(01), 2863–2873

Publication history: Received on 09 April 2024; revised on 18 May 2024; accepted on 21 May 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.12.1.0873

Abstract

Without a question, the two most significant biological targets for breast cancer are HER2 and CDK4/6. Anti-HER2 therapies improve overall survival, progression-free/disease-free survival, and objective response. Overall survival statistics are still pending, but three CDK4/6 inhibitors regularly increase progression-free survival and objective response. There is still a need for better endocrine therapies and chemotherapy optimisation. Particularly for triple-negative breast cancer, check point inhibitor-based immunotherapy in conjunction with chemotherapy is a promising area.

Keywords: Herbal medicines; Anti-tumor; Anti-oxidant; Immune-suppressive; Flavonoids; Cancer; Phytochemicals; Camptothecin; Ixora; Anticancer activity

1. Introduction

Breast tumours are the second most common cause of death worldwide. In the United Kingdom, one in nine women will develop this illness during the course of their lifetime. Breast cancer is linked to a number of variables, including gender, food, alcohol consumption, physical activity, family history, way of life, and endocrine factors, both endogenous and exogenous. Mammographic density and prior benign breast cancer are two more significant risk factors for breast cancer. Therefore, breast cancer is now the second most common cause of death for women. The chemotherapeutic chemicals that are employed in its therapy are primarily derived from plants, specifically lichens, fungus, fruits, leaves, and flowers. In botany, "herb" refers to plants that bear fruits, seeds, and nonwoody stems. The maintenance of human health has been greatly aided by these plants and herbs [1].

2. Inhibitors of CDK4/6

2.1. Ribociclib

An oral bioavailable, highly selective CDK4/6 inhibitor in the later stages of clinical testing is called ribociclib (LEE011) [2]. In preclinical investigations, ribociclib dose-dependently inhibited the growth of tumours and arrested the cell cycle in a number of Rb-positive cell lines. Numerous xenograft tumour models, such as neuroblastoma, melanoma with NRAS and BRAF mutations, and breast cancer with PIK3CA mutation, validate the anticancer efficacy [3].

In postmenopausal patients with newly diagnosed, resectable, HR+, HER2−early breast cancer, MONALEESA-1 (NCT01919229) is a phase II study designed to evaluate the biological activity of 14 days of neoadjuvant treatment with ribociclib (400 or 600 mg, daily) plus letrozole (2.5 mg, daily), compared with single agent letrozole (2.5 mg, daily). The findings indicated that ribociclib and letrozole did not interact with one another and that ribociclib and letrozole together significantly decreased Ki-67 expression in HR+, HER2− breast cancer.

* Corresponding author: Mainak Khan

A phase III trial called MONALEESA-2 (NCT01958021) aims to assess ribociclib as a first-line treatment for HR+/HER2− advanced breast cancer. In contrast to letrozole alone, the study group receives ribociclib (600 mg/day, three weeks on and one week off) in addition to letrozole. Investigator-assessed progression-free survival was the main outcome. In comparison to the placebo group, the ribociclib group's progression-free survival time was considerably longer (hazard ratio, 0.56; 95% CI, 0.43 to 0.72; p = 3.29× 10−6 for superiority). On August 3, 2016, the FDA designated ribociclib as a breakthrough therapy when combined with letrozole, and on March 13, 2017, the drug was eventually approved. Furthermore, there are two active phases MONALEESA-3 (NCT02422615) and MONALEESA-7 (NCT02278120) are the III trials. For the treatment of postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2) advanced breast cancer who have had no or only one line of prior endocrine treatment, MONALEESA-3 is a randomised, double-blind, placebo-controlled study combining ribociclib and fluvastatin. In premenopausal women with HR+/HER2− advanced breast cancer, the phase III MONALEESA-7 research is examining the combination of ribociclib with goserelin and tamoxifen or nonsteroidal aromatase inhibitor (NSAI). A 1:1 random assignment will be used to place patients into one of two treatment groups: either ribociclib or a placebo + goserelin and tamoxifen/NSAID. Moreover, ribociclib is currently undergoing clinical trials in conjunction with hormonal and/or targeted treatments. The initial findings from a phase II experiment served as the basis for phase I trial demonstrating enhanced efficacy and controllable toxicity when ribociclib is coupled with exemestane and everolimus [4].

2.2. PD1 and PD-L1 antibodies

Immunotherapy has emerged as the new standard of care in the last several years, showing impressive results and the ability to cure patients with a wide variety of tumour types. Antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death-1 (PD-1), and programmed death-ligand 1 (PD-L1) have been shown to have higher response rates and overall survival (OS) in melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, urothelial carcinoma, and squamous cell carcinoma of the head and neck. These antibodies work by increasing the immune response against the tumour by blocking immune-regulating proteins that downregulate the immune system. Although the precise function of immunotherapy in breast cancer treatment is unknown, accumulating data suggests that triple negative breast cancer (TNBC) may respond differently to immunotherapy due to certain differences in inhibition if checkpoint. Because TNBC has a higher mutational burden and genomic instability, it is more likely to produce neoantigens, which the adaptive immune system can identify as "nonself." Compared to other breast cancer subtypes, TNBC exhibit higher levels of messenger RNA (mRNA) expression and a higher number of tumour-infiltrating lymphocytes (TILs). Elevated TIL levels are typically linked to poor-prognostic clinicopathologic characteristics, such as lymph node positivity, greater grade, higher proliferative rate, and ER negativity. Higher TIL levels, independent of systemic therapy, are linked to better DFS and OS even in the face of worse clinical characteristics [5].

Long recognised is the correlation between increased tumour infiltrative lymphocytes (TILs) and improved prognosis in breast cancer; more recent research has demonstrated the particular significance in TNBC, whereby has demonstrated a significant TIL invasion. This seeming contradiction implies that TILs could act as a stand-in for an adaptive immune response in certain malignancies and draws attention to the possible involvement of the immune system in a subgroup of TNBC. Six different subtypes were found in a more recent examination of the gene expression profiles of 587 TNBC samples. Among these subtypes was the immunomodulatory (IM) subtype, which is characterised by elevated expression of immune-related genes. This subtype has been linked to better relapse-free survival when compared to other subtypes because it is rich in immune-activated and related signalling components that are provided by both the tumour and the infiltrating lymphocytes. Moreover, RNA sequencing revealed that this subtype expresses PD-L1, PD-1, and CTLA-4 at significantly higher levels. These and more data show that IM subset is mostly likely to benefit from checkpoint inhibition [6,7].

2.3. Other potential agents/therapies

Chimeric antigen receptor (CAR) is a modular fusion protein that contains an extracellular target-binding domain, typically derived from an antibody single-chain variable fragment (scFv), an intermediate domain, a transmembrane domain. , and an intracellular signaling domain. CAR-engineered T cells (CAR-T cells) have yielded unprecedented efficacy in B-cell malignancies, particularly anti-CD19 CAR-T cells in B-cell acute lymphoblastic leukemia (B-ALL), up to 90% complete. remission rate in However, this success encountered significant obstacles in moving to solid tumors.

Specific inhibition of miR-20b in a nude mouse model of breast cancer has been shown to inhibit tumor growth in vivo. Systemic administration of polyglycolic acid-based miR-21 and miR-10b antagonists in a breast cancer model had a dramatic effect on tumor regression. Further biological studies on the ability of new agents to regulate miRNA expression are warranted, and miRNA should become a therapeutic target in breast cancer therapy [8].

2.3.1. Utidelone

The invention of anthracyclines and taxanes remains an important cause of metastatic breast cancer progression. Epothilones are a class of naturally occurring microtubule inhibitors produced by the myxobacterium Sorangium cellulosum. The molecular structure and mechanism of action of epothilones differ from the molecular structure and mechanism of action of taxanes. Thus, patients with taxane-resistant tumors remain sensitive to epothilones. Utidelon is a genetically engineered epothilone analog designed to achieve better efficacy, a more favorable safety profile, and a more affordable price than ixabepilone, a semisynthetic epothilone analog that is the only US FDA-approved drug in its class. Several studies have shown that utidelone is a potential therapy for heavily pretreated, drug-resistant, advanced breast cancer. The Pivot trial is a phase III, open-label, superior, randomized trial that enrolled patients with metastatic breast cancer refractory to anthracycline and taxane chemotherapy regimens.

Four hundred and five patients were randomized 2:1 to receive treatment with utidel (30 mg/m2 once daily on days 1-5) plus capecitabine (1000 mg/m2 twice daily on days 1-14) or capecitabine alone (1250 mg/m2). m2). m2 twice a day on days 1–14). The primary end point, assessed centrally by a blinded independent radiological review committee, showed a superior ORR in the uterus plus capecitabine group compared to the capecitabine group alone (40.4 vs 21.5%; $p = 0.0002$). Median PFS was 8.44 months versus 4.27 months (HR 0.46; $p < 0.0001$). Analysis of OS is immature and analysis with available data up to the end date showed longer survival in the utidelone plus capecitabine group compared to the capecitabine alone group (16.13 vs. 12.78 months; HR0.63 $p = 0.0059$). There were no significant differences in safety outcomes between groups, except for peripheral neuropathy, which was significantly higher with utidelone and capecitabine compared to capecitabine alone [9].

2.3.2. Eribulin

Eribulin mesylate (E7389) is a structurally simplified synthetic analogue of halichondrin B, which was first isolated more than 20 years ago from two different related species, Halichondria okadai Kadota and Aninella sp. It is a non-taxane inhibitor of microtubule dynamics and the only cytotoxic agent in the last decade that has improved overall survival in heavily pretreated MBC patients. Eribulin inhibits microtubule polymerization (or growth) through the eribulin-specific binding site of β-tubulin without affecting microtubule depolymerization (or shortening), unlike conventional antitubulin agents such as taxanes, epothilones, and vinca alkaloids. It may have an additional antitumor mechanism through epithelial-mesenchymal transition and tumor vascular remodeling. The first phase III trial reported was EMBRACE (Eisai Metastatic Breast Cancer Study Evaluating Physician's Choice versus E7389), a pivotal phase III trial that led to regulatory approval of eribulin for the treatment of MBC. In this study, 762 women were randomized (2:1) to either eribulin (n = 508) or physician's choice (TPC; n = 254). OS and PFS were the primary endpoints.

Median overall survival was significantly improved in women receiving eribulin compared to TPC (13.1 vs 10.6 months, $p = 0.041$). In early-line MBC, eribulin did not improve PFS or OS compared with capecitabine. A subgroup analysis of two studies suggested that patients with TNBC may benefit more from it. A recent study directly comparing eribulin with vinorelbine in a Chinese population showed that it improved progression-free survival. Eribulin is currently being studied in several clinical trials. A phase III trial comparing eribulin and paclitaxel in the first- and second-line treatment of HER2-negative MBC is currently enrolling patients in the United States.

A phase II trial of eribulin in combination with trastuzumab and pertuzumab (NCT01912963) is currently recruiting. PD-L1 is expressed in approximately 60% of TNBC tumors, suggesting that PD-L1 may be a therapeutic target for this disease. The combination of pembrolizumab and eribulin showed an ORR of 33.3% in patients with metastatic triple-negative breast cancer (TNBC) who had received 0-2 prior courses; another confirmatory phase III study is warranted. Future studies are needed to optimize the role of eribulin in the treatment of MBC, both in terms of patient selection and its position in the therapeutic sequence. Eribulin should also be further tested as first-line therapy in advanced breast cancer as adjuvant and neoadjuvant therapy alone and in combination with multiple agents, especially biologics one [10].

3. Innovative chemotherapies

3.1. NAB-PACLITAXEL

Taxones are widely used as antitumor agents. Albumin-bound paclitaxel (nab-paclitaxel; Abraxane) is a second-generation taxane developed to improve the therapeutic index of paclitaxel by reducing the toxicities associated with taxol and CrEL and the ethanol vehicle. Nab-paclitaxel is a good candidate because it can be administered without steroid or antihistamine pretreatment. For safety reasons, nab-paclitaxel can be administered at higher doses with a shorter infusion time, allowing higher drug Cmax and plasma area under the curve (AUC). After intravenous infusion,

nab-paclitaxel dissociates into albumin and paclitaxel in small particles with a width of 8-30 nm, and then rapidly distributes to the extravascular compartment and selectively transports larger amounts of nab-paclitaxel to tumors via endogenous albumin transport pathways. Nab-paclitaxel was approved by the FDA for the treatment of metastatic breast cancer in 2005. Since then, it has been studied in different populations of breast cancer patients at different doses and schedules.

The GeparSepto study (GBG 69) evaluated the improvement in pathologic complete response of weekly nab-paclitaxel compared with weekly solution-based paclitaxel followed by neoadjuvant epirubicin and cyclophosphamide. Results showed that 12 continuous weekly doses of nabpaclitaxel 125 mg/m2 in neoadjuvant therapy are well tolerated and associated with significantly better pCR rates (38%) compared to weekly paclitaxel 80 mg/m2 (29%).

This result is consistent with another phase III ETNA study. Results of the phase II tnAcity trial in the metastatic setting were presented at the 2016 SABCS meeting. One hundred ninety-one women with mTNBC were randomized to one of three weekly regimens: nab-paclitaxel + carboplatin (nab-P/C), nab-paclitaxel + gemcitabine (nab-P/G), or gemcitabine + carboplatin (G). /C) as first-line treatment. The study found that weekly nab-P/C combination therapy had a significantly longer PFS (7.4 months) compared with either nab-P/G (5.4 months; p = 0.02) or G/C (6.0 months) for weekly treatment programs; p = 0.03). The MBC approval was based on a randomized phase III trial of nab-paclitaxel 260 mg/m2 versus paclitaxel 175 mg/m2 every 3 weeks. Nab-paclitaxel showed a significantly higher overall response rate (ORR 33 vs 19%; p = 0.001) and longer time to tumor progression (23 vs 17 weeks; HR 0.75; p = 0.006) compared to paclitaxel in the treatment-in-treatment. (ITT) population [11].

The systematic review discussed recent studies and ongoing studies of nab-paclitaxel in the treatment of breast cancer and provides an outlook on the future role of nab-paclitaxel in breast cancer. We analyzed 63 studies on nab-paclitaxel in the treatment of breast cancer between 2013 and 2015, including 23 studies in the early stage and 30 in the metastatic setting.Phase II and III trials of neoadjuvant nabpaclitaxel (at most given once weekly) in which no specific disease subtype was selected, pCR rate ranged from 22% to 40%. And for HER2-negative breast cancer or TNBC, the overall pCR rate ranged from 5.7 to 53%, with the highest pCR rate achieved in TNBC treated with nabpaclitaxel + carboplatin. Four studies of nab-paclitaxel in unselected subtype MBC showed a median survival of 10.8 months for nab-paclitaxel 260 mg/m2 q3d to 26.9 months for nab-paclitaxel 125 mg/m2 qw ¾ in combination with cisplatin. Subgroup response rates showed a higher response rate in TNBC. Nab-paclitaxel is continuously being studied in different stages and settings of aggressive breast cancer. Immune checkpoints and their optimal combination partners are hot topics [12].

3.2. Nivolumab

As the first anti-PD-1 antibody approved for clinical practice worldwide, nivolumab is approved for use in unresectable or metastatic melanoma, metastatic non-small cell lung cancer, advanced renal cell carcinoma, classic Hodgkin lymphoma, and recurrent/ metastatic squamous cell carcinoma of the head and elsewhere unclassified. However, clinical data on breast cancer are rare. To date, no clinically significant results have been published in breast cancer treated with nivolumab, but many studies are ongoing to evaluate the safety and efficacy of nivolumab as monotherapy or as combination therapy for this disease. Phase I/II open-label study of nivolumab as monotherapy or in combination with ipilimumab in advanced or metastatic solid tumors with TNBC cohort [13].

The main objective is to analyze safety and efficacy (ORR, PFS). In addition, the expression of putative biomarkers such as PD-1 and PDL1 will be evaluated. The study uses a modified Simon 2-stage design. In phase 1, 36 patients of each tumor type will be assigned 1:1 to either nivolumab (N) or nivolumab + ipilimumab (N + I) for 4 doses, followed by nivolumab maintenance until progression or toxicity. Treatment arms will advance independently to stage 2 if ≥ 2 patients of each tumor type have an OR in a given arm. In Phase 2, an additional 22 patients per tumor type will be assigned to each arm (N or N + I) and assigned the Phase 1 dosing schedule.Expected completion date is December 2018. Another phase I trial is testing nivolumab (nivo) in combination with nab-paclitaxel (nab-P) in HER2-negative MBC. MBC patients are treated in two arms: nab-P 100 mg/m2 on days 1, 8 and 15 of each 28-day cycle plus 3 mg/kg on days 1 and 15 of cycle 3 or nab-P 260 mg/ m2 each on day 1 of a 21-day cycle plus a level of 5 mg/kg on day 15 of cycle 3. The primary endpoint is DLTs. Secondary study endpoints include treatment-emergent adverse events (TEAEs), PFS, OS, disease control rate, ORR, and duration of response. The research endpoints are tumor-associated PD-L1 expression, modulation of immune activation in tumor and peripheral blood in response to nivo therapy, serum nivo levels, and antiglobulin antibody development. The expected completion date is October 2017. This calls into question the antibodies used in PD-L1 testing and possible differences in efficacy between different subgroups of breast cancer. A phase III randomized trial is underway to test the adjuvant treatment of avelumab (A-Brave, NCT02926196) in high-risk TNBC patients. Patients with high-risk primary TNBC (all patients, PD-L1-positive or unselected for PD-L1 status) who have undergone curative treatment, including resection of the primary tumour, neo- or adjuvant chemotherapy

and radiotherapy (if appropriate). were recruited and randomized to the experimental group (avelumab for 1 year) or no further intervention group. The primary endpoint is DFS [14].

3.3. PARP inhibitors

Healthy cells protect against the harmful effects of DNA damage through several interconnected molecular pathways, the DNA damage response (DDR), which recognize DNA damage, arrest the cell cycle, and mediate DNA repair. Poly (ADP-ribose) polymerase (PARP) are nuclear enzymes that catalyse the transfer of ADP-ribose from NAD+ to target proteins and facilitate DNA repair. At sites of DNA damage, PARP1 binds damaged DNA at DNA single-strand breaks (SSBs) and other types of DNA damage. This event induces a series of allosteric changes in PARP1 structure that activate its catalytic activity as PARP and activate intracellular signalling pathways that modulate DNA repair and cell survival through poly (ADP)-ribosylation of several nuclear proteins involved in chromatin architecture and DNA metabolism. Inhibition of PARP causes double-strand breaks in replicating cells. In wild-type BRCA1/2 cells, double-strand breaks are repaired by homologous recombination, but in BRCA1/2-deficient cells with homologous recombination deficiency (HRD), DNA strand breaks depend on PARP1 functionality. Therefore, inhibition of PARP1 by RNA interference or chemical inhibitors [15,16].

Schematic diagram representing normal and carcinomic breast tissues:

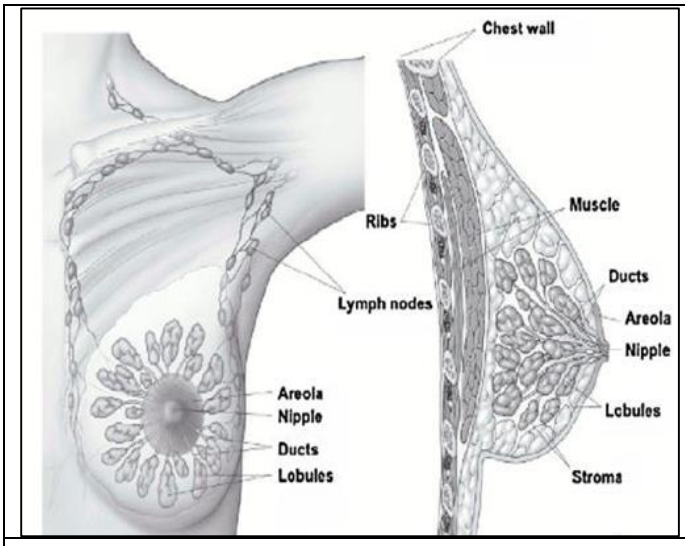

Figure 1 Non-Cancerous Breast Tissue

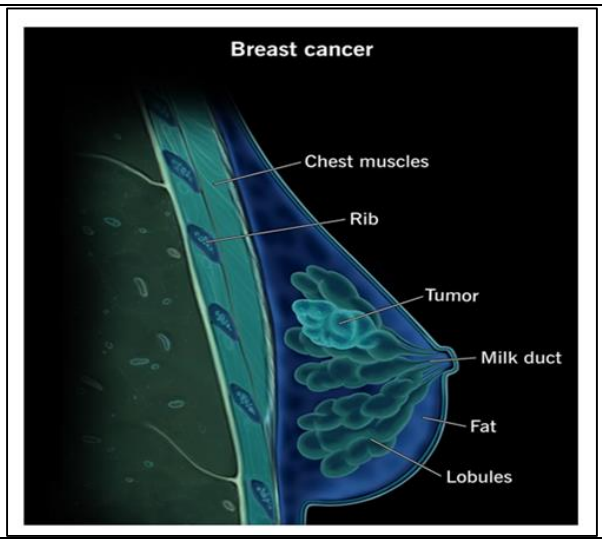

Figure 2 Cancerous Breast Tissue

4. Some herbal anticancer agents

4.1. Garlic

Garlic (Allium sativum) has been used for hundreds of years to treat many ailments. It contains a hundred or more therapeutically useful secondary metabolites such as allin, allinase and allicin. The amino acid alline is found in garlic oil, which turns into allicin after the rhizomes are wrinkled. The sulfur-containing compound element is allicin, which is responsible for the smell and its medicinal properties. Garlic oil contains another sulfur-containing substance called Ajoene. Ajoene slows down the development of cancer, while selenium acts as an antioxidant. Bioflavonoids, cyanidin and quercetin, are also found in garlic, which have antioxidant properties. The anticancer effect of garlic is due to the large number of organic sulfides and polysulfides [17].

The antitumor effect of stimulating lymphocytes and macrophages is that they kill cancer cells and disrupt the metabolism of tumor cells. Studies have shown that garlic increases the number of suppressive T cells and transforms lymphocytes into a cytotoxic form for cancer cells. Metastasis is prevented by changing the adhesion and attachment of cancer cells circulating in blood vessels. Aged garlic extract prevents the harmful effects of carcinogens on DNA; it improves the immune system of the body, increases the removal of carcinogens from the body and improves the activity of the detoxification enzyme. Researchers have found that aged garlic extract also helps protect against the spread of several different types of cancer, including colon, stomach, breast, lung and bladder cancer. Garlic extract can reduce the complications of chemotherapy and radiotherapy [18,19].

4.2. Turmeric

The scientific name of turmeric is Curcuma longa. Turmeric gives food a dark yellow color. The active ingredient in turmeric is found in the rhizomes and root of turmeric. Curcumin is known to have anti-cancer effects due to its phenols. Turmeric limits the spread of lung, breast, skin and stomach cancer. The production of eicosanoids such as prostaglandin E-2 (PGE-2) is altered by curcumin, an antioxidant. It also has anti-inflammatory effects in humans. Curcumin has an inhibitory effect on all stages of cancer growth, which are the stages of initiation, promotion and dissemination. Turmeric inhibits the production of nitrosamine; it increases the body's natural antioxidant activity. Curcumin increases glutathione and other non-protein sulfhydryls and directly affects various enzymes [20].

4.3. Burdock

The scientific name of attraction is Arctium lappa. Its roots are found and used in Europe and Asia. Albush has many therapeutic uses in herbal preparations. Its root has a gummy texture and a sweet taste. While in the past Burdock was useful for arthritis, rheumatism and measles, today it has been found that Burdock has an antitumor effect. It contains a number of active ingredients that cause changes in oncogenes. Buckdock has been used in the treatment of breast, ovarian, bladder, malignant melanoma, lymphoma and pancreatic cancer. It relieves pain, reduces tumor size and improves survival. During cancer, huge amounts of nutrients are needed to sustain the rapid reproduction and division of cells. However, cancer cells can live in stressful conditions, such as low oxygen and less carbohydrates, because tumor cells have a high tolerance to stress. Burdock seeds contain an active ingredient called Arctigenin. Arctigenin has demonstrated its ability to eliminate tumor cells with minimal nutrients. Burdock root is composed of flavonoid-type and polyphenolic antioxidants and may have an inhibitory effect on tumor development. Normal body cells are protected from toxic substances and cell mutation is reduced by root extract. Burdock contains the main active ingredient known as tannin, a phenolic compound. It stimulates the activity of macrophages, limits the spread of cancer and maintains immune response modulating properties [21,22].

4.4. Anogeissus latifolia

Human breast cancer cell lines provide an excellent platform for breast cancer research in tumor progression and treatment. T47D and MCF7 are two human hormone-dependent breast cancer cell lines which are widely used as experimental models for breast cancer studies. The two cell lines were generally used for both the in vitro (in cell culture) and in vivo (tumor xenograft in nude mice) analyses of gene and protein function and inhibitor efficacy assessment. They were both originally derived from a metastatic site of pleural effusion (ATCC) and express oestrogen receptors. Several proteins and enzymes that are involved in cell proliferation and in cancer development were identified in these cell lines by proteomic studies. Although these studies reported the proteomic profiles of each of these cell lines, until now, no study had established their differential protein expression profile. Using a proteomic approach including two-dimensional (2-D) gel electrophoresis and mass spectrometry (MS) analyses, we establish here the proteomic differences between the T47D and MCF7 cell lines [23].

4.5. Ixora coccinea

Ixora coccinea, a small shrub with vibrant red flowers, has been used in traditional Indian medicine, Ayurveda, and folk medicines to treat various ailments, including cancer. The anticancer activity of the leaves of Ixora coccinia (Rubiaceae) was found to be due principally to the known alkaloid, camptothecin. The presence of camptothecin was confirmed by RP-HPLC analysis. The average content of camptothecin both in mature and young leaves was 2.8% and it paves way for new findings. Camptothecin (CPT), isoquinoline alkaloid is one of the most promising anti-cancer drugs of the twenty-first century (Lorence and Craig, 2004). Several water-soluble derivatives of CPT are currently being used for treating colorectal and ovarian cancer (Romanelli et al.,1998). The projected global demand for CPT in 2002 was valued at US$ 4045 million.CPT was first discovered in the Chinese deciduous tree, Camptotheca acuminate (Nyssaceae) (Wall and Wani, 1968). Later, the alkaloid has been reported from several plant species, with by far the highest concentration (about 0.3% on a dry weight basis) from Northupites nimmoniana. N. nimmoniana, formerly known as Northupites foetida Sleumer and Mappia foetida Meirs, is a small tree, naturally distributed in many parts of the Western Ghats, South India, some parts of Assam, the Himalayan foothills, Sri Lanka, Myanmar and Thailand. Members of the Icacinaceae, Olacaceae, Rubiaceae, and Apocynaceae families are also reported to produce camptothecin [24].

4.6. Piper longum

Piper Longum was also shown to inhibit radio resistance and chemoresistance and sensitize the cancer cells to the standard chemotherapeutic agents. Therefore, this compound has high potential as a drug candidate for the prevention and treatment of different cancers. The current review briefly reiterates the anti-cancer properties of Piper Longum against different types of cancer, which permits further investigation by conducting clinical studies. Regardless of the

notable progress achieved in cancer diagnosis and treatment, it is still considered as one of the most dreadful and prevalent diseases having very high morbidity and mortality rate. There are diverse types of cancer, all of which are associated with atypical growth and proliferation of cells leading to approximately 10 million deaths per year. The majority of cancers occur due to genetic mutations associated with lifestyle and environmental-related factors, although some of the cancer types are caused because of inherited genetic makeup. A considerable proportion of the global cancer burden can be relieved by evading the risk factors, such as consumption of carcinogenic products, poor diet, and absence of physical activity leading to obesity, sexually transmitted diseases, and pollution, to name a few. A diverse range of drugs have been discovered and screened with the aim to cure this disease in the last few decades [25].

4.7. Grape seed

Grape seeds extract (GSE) is a famous health food supplement for its antioxidant property. Different concentrations of GSE may have different impacts on cellular oxidative/reduction homeostasis. As a potential anticancer agent, grape seed procyanidins (GSPs) have been shown to inhibit the proliferation of various cancer cells in vitro and in vivo. In this study, it was shown that GSPs significantly inhibit MCF-7 cell proliferation in a concentration/time-dependent manner. The flow cytometric data clearly demonstrated that GSPs cause cell cycle arrest in the G2/M phase, followed by cell apoptosis. Moreover, it also confirmed that growth inhibition mediated by treatment with GSPs is related to the induction of apoptosis due to p53 elevation, purportedly by inhibition of the epidermal growth factor receptor (EGFR)/vascular endothelial growth factor (VEGF)/matrix metalloproteinase 9 (MMP9) pathway. Taken together, these findings suggest that GSPs inhibit MCF-7 cells proliferation and induce cell apoptosis by suppressing EGFR/VEGF/MMP9 pathway.

In the present study, we provided the evidence that GSPs inhibit cell proliferation in human cancer cells through cell cycle arrest at the G2/M phase and induction of apoptosis. Mechanistic studies revealed that interruption of the epidermal growth factor receptor (EGFR)/vascular endothelial growth factor (VEGF)/matrix metalloproteinase 9 (MMP9) signaling pathway plays a critical role in these GSPs-mediated cell cycle arrest and induction of apoptosis via activating p53 expression. Our results provide a novel explanation for GSPs as an angiopreventive agent against breast cancer [26].

4.8. Green tea

Green tea is scientifically known as Camellia sinensis. The anticancer effect is due to polyphenol compounds. Epigallocatechin (EGGG), a polyphenol, is present in C. sinensis in small amounts. Scientists have discovered that green tea has antitumor and mutagenic effects. EGGG protects cells from DNA damage caused by reactive oxygen species. Animal studies have shown that green tea polyphenols limit cancer cell division and stimulate tumor cell necrosis and apoptosis. Although thecatechins stimulate immune function, they also inhibit metastasis and angiogenesis in tumor cells. Some studies have shown that green tea has protective effects against colon and stomach cancer. Tea and its primary catechins reduce the risk of tumors in several body organs. The harmful effects of radiation can be reduced with green tea. All the beneficial effects of tea are due to its antioxidant effect [27,28].

4.9. Ginseng

The scientific name of ginseng is Panax ginseng. It is a hardy plant that grows mainly in China, Korea, Japan and Russia. Part of this plant is the dried root. It has many therapeutic uses, including for cancer. It has been shown that the active ingredients of ginseng reduce or prevent the formation of tumor necrosis factor in mouse skin, prevent the proliferation and metastasis of cancer cells, stimulate cell differentiation and interferon levels. Ingredients in ginseng can also block other types of cancer cell stages. There was also a study done in Korea that suggested that ginseng reduces the risk of cancer in humans. For fresh cut ginseng, its juice or tea, the most effective and active type of ginseng is its extract and dried powder to prevent the risk of cancer. By interrupting DNA synthesis, ginseng supports tumor development. P.beneficial effects of the active compound. ginseng contains reactivation of natural killer cells that have been weakened by chemotherapy and radiation, induces macrophages and increases production of antibodies [29,30].

4.10. Flax seeds

The flax plant has small brown and golden-brown seeds with a hard shell. These tiny seeds contain all the active components. Flax seeds are a rich source of fiber, omega-3 fats and lignans. Flax seeds have an estrogenic effect because the lignans are metabolized into enterodiol and enterolactone, and the metabolism takes place in the digestive tract. Compared to soy products, flaxseeds have stronger phytoestrogens, while flax consumption causes a greater change in 2-hydroxysterone elimination than soy protein. Lilian Thompson's research group from the University of Toronto has shown that ground flaxseed has strong anti-cancer effects. The experiment was performed on mice; First, cancer is

induced in mice by administering carcinogens, one group found the anti-cancer effect of flax seed by mixing lignin into the mice's diet. The results of this study reduce the burden of tumors [31,32].

Flaxseed and secoisolariciresinol diglucoside reduced malignant tumors.Recently, this research group induced tumors in mice by injecting human breast cancer cells. During cancer propagation, mice were fed basic food for 8 weeks after injection of cancer cells. One group was fed with 10% flax, the other group continued the basic diet. Flax seeds reduced cancer growth by 45%. Flax seeds improve mammary gland morphogenesis in mice. Researchers studied female mice fed a 10% flax diet and found that their mammary glands had a better number of buds and ducts. They have excessive epithelial cell division. All females show increased differentiation. A relatively low incidence of breast tumors was found in women after the injection of carcinogens into the mammary glands. Thanks to this, flax can increase the differentiation of mammary tissue in mice, prevent malignant tumors and reduce the formation of tumours in female offspring, making them less sensitive to carcinogens [33,34,35].

5. Resveratrol effects in oral carcinogenesis

Until now, little thought has been given to characterizing the effects of resveratrol using in vivo experimental models to confirm its antitumor activity. Oral cancerwas initially demonstrated in mice with dimethylbenzanthracene as an oral mucosal carcinogen, and it was found that resveratrol reduced the number and diversity of oral tumors. When 4-nitroquinoline-1-oxide(4NQO) was combined to induce exploratory oral carcinogenesis in mice, resveratrol showed significant differences in the selection, grading and severity of lesions compared to 4NQO alone. This was associated with decreased expression of BrdU-labeled cells in resveratrol-treated oral epithelium. Expression of mTOR, a central controller of the cellular digestive system, was hyperactivated in head and neck cancer and was proposed as a potential beneficial target. AMPK activation can limit mTOR signaling. In this setting, immunohistochemical data showed an increased expression of phospho-AMPK (Thr 172) in the resveratrol group. AMPK is produced by phosphorylation when ATP mixing is reducedand/or ATP use is expanded, and such cellular metabolic conditions additionally trigger autophagy. Here, the accumulation of resveratrol showed a decrease in p62 immunoreactivity. When carrier mice were treated with resveratrol by oral gavage for 20 days, tumorwww.wjpr.net | Vol 13, Issue 7, 2024 developed. | ISO 9001:2015 Certified Journal |Imtiyaz et al. World Journal of Pharmaceutical Research1202order has been reduced. Histopathological examination of these tumors showed increased expression of nestin and vimentin in the resveratrol-treated tumor after high expression of E-cadherin in oral mucosal cells compared to the control tumor group. These data suggest that resveratrol treatment inhibited tumorigenesis in vivo. Finally, Pradhan et al. used in vivo mouse xenotransplantation to demonstrate the use of Balb/c mice.After 10 days of implantation of H-357-CSCs, tumor localization was considered.25 days of treatment with resveratrol reduced tumor volume. By extension, resveratrol decreased CD44 expression in liver, CXCR4 and Nanog expression in kidney, and CXCR4 and VEGF-A expression in brain tissue [36].

6. Nyctanthes arbor-tristis

Until now, little thought has been given to characterizing the effects of resveratrol using in vivo experimental models to confirm its antitumor activity. Oral cancerwas initially demonstrated in mice with dimethylbenzanthracene as an oral mucosal carcinogen, and it was found that resveratrolreduced the number and diversity of oral tumors. When 4-nitroquinoline-1-oxide(4NQO) was combined to induce exploratory oral carcinogenesis in mice, resveratrol showed significant differences in the selection, grading and severity of lesions compared to 4NQO alone. This was associated with decreased expression of BrdU-labeled cells in resveratrol-treated oral epithelium. Expression of mTOR, a central controller of the cellular digestive system, was hyperactivated in head and neck cancer and was proposed as a potential beneficial target. AMPK activation can limit mTOR signaling. In this setting, immunohistochemical data showed an increased expression of phospho-AMPK (Thr 172) in the resveratrol group. AMPK is produced by phosphorylation when ATP mixing is reducedand/or ATP use is expanded, and such cellular metabolic conditions additionally trigger autophagy. Here, the accumulation of resveratrol showed a decrease in p62 immunoreactivity. When carrier mice were treated with resveratrol by oral gavage for 20 days, tumorwww.wjpr.net | Vol 13, Issue 7, 2024 developed. | ISO 9001:2015 Certified Journal |Imtiyaz et al. World Journal of Pharmaceutical Research1202order has been reduced. Histopathological examination of these tumors showed increased expression of nestin and vimentin in the resveratrol-treated tumor after high expression of E-cadherin in oral mucosal cells compared to the control tumor group. These data suggest that resveratrol treatment inhibited tumorigenesis in vivo. Finally, Pradhan et al. used in vivo mouse xenotransplantation to demonstrate the use of Balb/c mice.After 10 days of implantation of H-357-CSCs, tumor localization was considered.25 days of treatment with resveratrol reduced tumor volume. By extension, resveratrol decreased CD44 expression in liver, CXCR4 and Nanog expression in kidney, and CXCR4 and VEGF-A expression in brain tissue [37].

7. Mangifera indica

Many pharmacological studies have been conducted on mango fruits to confirm the traditional use of Mangifera indica in the treatment of various diseases. These studies have shown that mango fruit has antioxidant, anti-cancer and anti-diabetic effects. There have been some studies that have proven the non-toxicity of mango ingredients. Although there are many individual studies investigating the anticancer effects of various components of the mango tree, to our knowledge, an up-to-date, comprehensive and critical review of the available research data has not been conducted. The purpose of this review is to provide a comprehensive and critical assessment of M. indica [38].

8. Conclusion

Breast cancer is associated with many factors; many factors act independently or may act together, especially in high-risk individuals. It is important to know the pathogenesis of this common disease with high mortality and morbidity, especially if it is not detected early. Thus, the role of early screening for high-risk individuals and appropriate follow-up of the treated case to detect recurrence at an early stage was recommended.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Abdulkareem I.H. A review on aetio-pathogenesis of breast cancer. *J. Genet. Syndr. Gene Ther.* 2013; 4:1–5.

[2] Atkinson H.G. Alcohol's "darker side." A drink a day may raise a woman's risk of breast cancer. *Health News.* 2003; 9:1–4.

[3] Barreto A.M., Schwartz G.G., Woodruff R., Cramer S.D. 25-Hydroxyvitamin D3, the prohormone of 1, 25-dihydroxyvitamin D3, inhibits the proliferation of primary prostatic epithelial cells. *Cancer Epidemiol. Biomarkers Prev.* 2000; 9:265–270.

[4] Brooks J.D., Ward W.E., Lewis J.E., Hilditch J., Nickell L., Wong E., Thompson L.U. Supplementation with flaxseed alters estrogen metabolism in postmenopausal women to a greater extent than does supplementation with an equal amount of soy. *Am. J. Clin. Nutr.* 2004; 79:318–325.

[5] Brown P., Allen A.R. Obesity linked to some forms of cancer. *W. Va. Med. J.* 2002;98(6):271–272.

[6] Chen J., Stavro P.M., Thompson L.U. Dietary flaxseed inhibits human breast cancer growth and metastasis and downregulates expression of insulin-like growth factor and epidermal growth factor receptor. *Nutr. Cancer.* 2002; 43:187–192.

[7] Chen J., Tan K.P., Ward W.E., Thompson L.U. Exposure to flaxseed or its purified lignan during suckling inhibits chemically induced rat mammary tumorigenesis. *Exp. Biol. Med. (Maywood)* 2003; 228:951–958.

[8] Leung BS, Potter AH. Mode of estrogen action on cell proliferation in CAMA-1 cells: II. Sensitivity of G1 phase population. J Cell Biochem. 1987;34(3):213–25.

[9] Sutherland RL, Hall RE, Taylor IW. Cell proliferation kinetics of MCF-7 human mammary carcinoma cells in culture and effects of tamoxifen on exponentially growing and plateau-phase cells. Cancer Res. 1983; 43:3998–4006.

[10] Sherr CJ. Cancer cell cycles. Science. 1996;274(5293):1672–7.

[11] Roussel MF, Theodoras AM, Pagano M, Sherr CJ. Rescue of defective mitogenic signaling by D-type cyclins. Proc Natl Acad Sci U S A. 1995;92(15):6837–41.

[12] Jiang H, Chou HS, Zhu L. Requirement of cyclin E-Cdk2 inhibition in p16(INK4a)-mediated growth suppression. Mol Cell Biol. 1998;18(9):5284–90.

[13] Weinberg RA. The retinoblastoma protein and cell cycle control. Cell. 1995;81(3):323–30.

[14] Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. J Clin Oncol. 2006;24(11):1770–83.

[15] Fry DW, Harvey PJ, Keller PR, Elliott WL, Meade M, Trachet E, Albassam M, Zheng X, Leopold WR, Pryer NK, Toogood PL. Specific inhibition of cyclindependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Cancer Ther. 2004; 3:1427–38.

[16] Altenburg JD, Farag SS. The potential role of PD0332991 (palbociclib) in the treatment of multiple myeloma. Expert Opin Investig Drugs. 2015;24(2):261–71.

[17] Finn RS, Dering J, Conklin D, Kalous O, Cohen DJ, Desai AJ, Ginther C, Atefi M, Chen I, Fowst C, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res. 2009;11(5): R77.

[18] Wardell SE, Ellis MJ, Alley HM, Eisele K, VanArsdale T, Dann SG, Arndt KT, Primeau T, Griffin E, Shao J, et al. Efficacy of SERD/SERM hybrid-CDK4/6 inhibitor combinations in models of endocrine therapy-resistant breast cancer. Clin Cancer Res. 2015;21(22):5121–30.

[19] Hosford SR, Miller TW. Clinical potential of novel therapeutic targets in breast cancer: CDK4/6, Src, JAK/STAT, PARP, HDAC, and PI3K/AKT/mTOR pathways. Pharmgenomics Pers Med. 2014; 7:203–15.

[20] Qin G, Xu F, Qin T, Zheng Q, Shi D, Xia W, Tian Y, Tang Y, Wang J, Xiao X, et al. Palbociclib inhibits epithelial-mesenchymal transition and metastasis in breast cancer via c-Jun/COX-2 signaling pathway. Oncotarget. 2015; 6:41794–808.

[21] Anders L, Ke N, Hydbring P, Choi YJ, Widlund HR, Chick JM, Zhai H, Vidal M, Gygi SP, Braun P, et al. A systematic screen for CDK4/6 substrates links FOXM1 phosphorylation to senescence suppression in cancer cells. Cancer Cell. 2011;20(5):620–34.

[22] Morikawa A, Henry NL. Palbociclib for the treatment of estrogen receptor positive, HER2-negative metastatic breast cancer. Clin Cancer Res. 2015; 21(16):3591–6.

[23] Hishobkar SM*,Urolagin DK ,Ashish C,Sivarupa M.S.Evaluation of Synergestic Antimicrobial Effect of Anogeissus latifolia and glycerrhiza glabra extract. International Journal of Pharmaceutical Sciences 2010;2(2):570-573.

[24] Deeparani K. Urolagin, S. Jayakumari.In-vitro Anti-Cancer Study of Vitis Viniferae, Ixora Coccinea and Piper Longum Ethanolic extracts on Human Breast Carcinoma Cells.Research J. Pharm. and Tech 2018;11(12):5345-5347.

[25] U. Deeparani, S. Jayakumari.In vitro Anti-Cancer Study of Vitis viniferae, Ixora coccinea and Piper longum Extract on Human Prostate Carcinoma Cells.Research J. Pharma and Tech 2019;12(9):4485-88.

[26] Deeparani Urolagin.Pharmacological screening on Effect of grape seed extract on wound healing in rats.Annals of Pharma Research 2021;09(12):594-603.

[27] Schroder LB, McDonald KL. CDK4/6 inhibitor PD0332991 in glioblastoma treatment: does it have a future? Front Oncol. 2015; 5:259.

[28] Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61–70.

[29] Geradts J, Wilson PA. High frequency of aberrant p16(INK4A) expression in human breast cancer. Am J Pathol. 1996; 149:15–20.

[30] Tamura K. Development of cell-cycle checkpoint therapy for solid tumors. Jpn J Clin Oncol. 2015; 45:1097–102.

[31] Shah PD, Dickler MN. Endocrine therapy for advanced breast cancer. Clin Adv Hematol Oncol. 2014; 12:214–23.

[32] Johnston SR. New strategies in estrogen receptor-positive breast cancer.Clin Cancer Res. 2010;16(7):1979–87.

[33] Chen W.Y., Colditz G.A., Rosner B., Hankinson S.E., Hunter D.J., Manson J.E., Stampfer M.J., Willett W.C., Speizer F.E. Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. *Ann. Intern. Med.* 2002; 137:798–804.

[34] Claus E.B., Stowe M., Carter D. Family history of breast and ovarian cancer and the risk of breast carcinoma in situ. *Breast Cancer Res. Treat.* 2003; 78:7–15.

[35] Coleman M.P., Gatta G., Verdecchia A., Esteve J., Sant M., Storm H., Allemani C., Ciccolallo L., Santaquilani M., Berrino F. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. *Ann. Oncol.* 2003; 14:128–149.

[36] Imtiyaz* AARM, Urolagin D. WJPR - Abstract. World Journal of Pharmaceutical Research . 2024 May 16; Available from:https://wjpr.net/abstract_show/25203.

[37] Panda S. "A Systematic Review Of : Nyctanthes Arbor-Tristis: A Conventional Herbal Remedy With Remarkable Medicinal Potential." IJNRD - International Journal of Novel Research and Development (IJNRD). 2024 Feb 26 cited 2024 May 16;9(2):c737–50 .

[38] Khan Mainak. A comprehensive study on Mangifera indica plant. www.jetir.org. vol 11,2, c864-c870;2024 May 16.