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Overview of Genetics: Breast Cancer and Herbal Treatment

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Abstract
In recent time, breast cancer has ranked number one cancer among Indian females and became the leading cause of women death. Now a days, there has been an extraordinary progress in the researches related to breast cancer resulting into so many more efficient treatments. The GSTP1 gene polymorphism can increase the risk of breast cancer due to reduced conjugating activity of the gene. Increased expression of the CYP19A1 gene in breast cancer cells leads to higher oestrogen production, making it a good candidate for treatment. The Brca1 and Brca2 genes play vital roles in DNA repair and cell cycle regulation, and any mutation can lead to cell transformation and cancer development. High expression of the STK11 gene has been linked to breast cancer and identified as a potential target for treatment. From ancient times, number of common medications are derived from medicinal plants. There are so many phytoconstituent extracted from plants which are successfully proved for the treatment of severe diseases like cancer, diabetes, heart diseases. If we use herbal plants for treatment of diseases there are fewer toxic effects seen. Turmeric (*Curcuma Longa*), Garlic (*Allium sativum L.*), Curry leaves (Murraya koenigii), Bhumi Amla (*Phyllanthus niruri*), Mushroom (*Agaricus bisporus),* Ashwagandha (*withania somnifera*), Mango (*Mangifera indica L.*) are the phytoconstituents extracted from this herb are used as an effective treatment to treat breast cancer without any side effects. This review paper has covered the epidemiology, types, causes, stages, signs and symptoms, treatments of breast cancer and the use of different types of herbs in treatment and management of breast cancer.

Keywords
Breast Cancer, Types, Genes, Phytoconstituents, Herbal plants.

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INTRODUCTION:
Breast cancer is the most common cancer and the primary cause of mortality due to cancer in females worldwide (Akram M, Dec 2017). The statistics show that approximately 1.7 million women were diagnosed with breast cancer in that year, with an increase in breast cancer incidence and related mortality by nearly 18% from 2008 (Tao Z, Jun 2015). According to the American Cancer Society, one in eight women in the United States will develop breast cancer in continuance. There are several types of breast cancer, such as invasive breast cancer, ductal carcinoma in situ, Infiltrating lobular carcinoma, Medullary carcinoma, Inflammatory breast cancer, etc. The disease begins when estrogens become endogenous carcinogens via the formation of

catechol estrogen quinones. These quinones react with DNA and form specific depurating estrogen-DNA adducts. The adducts can cause mutations that may result in cell transformation and the onset of breast cancer. (Gaikwad NW, May 2008)

Genetic alterations of genes lead to cancer initiation and development. Genes such as: p53, BRCA1, and PTEN proteins have a key role in preventing breast cancer formation and cancer-associated splicing variants of these tumor suppressor genes may lead to disease (OKumura N, sep 2011). In GSTP1 (Glutathione S-Transferase Pi 1) gene, the isoleucine to valine substitution at codon 105 (polymorphism) has been associated with the reduced conjugating activity of the gene (De Jong MM, April 2002). In normal human breast, most of the transcripts of the CYP19A1 gene are derived from the 1.4 distal promoter, however, in the case of breast cancer, transfer of the 14 promoter occurs to the 1.3 promoter, which causes a 3-to-4-fold increase in transcripts of the CYP19A1 gene Increased CYP19A1 gene expression is one of the most significant events for the intratumoral production of estrogens in these malignant tissues. Hence, this enzyme is a molecular target for several therapeutic approaches (Barros-Oliveira MD, 2021).

Growth factors play an important role in the proliferation of cells, and the deregulation of their mechanism and receptors may contribute to cancer development. One of the most important growth factors is Epidermal Growth factors (EGF), whose functional polymorphism at position 61 (AG) is associated with its increased expression, and hence cancer (Araujo AP, May 2009). Research carried out in 2018 has revealed that high expression of the STK11 gene is involved in breast cancer cell lines, as compared to normal breast cell lines. The study was confirmed by reverse and real-time PCR, indicating that the STK 11 gene may act as a promising target for breast cancer treatment (Alkaf A, 2017).

The BRCA1 gene has several roles in the cell cycle-such as repair of several highly specialized types of DNA, targeting of several upstream DNA damages signaling nuclear protein kinases, acting as an important component of several DNA damage-responsive cell cycle checkpoint mechanisms, and the proper replication and functioning of centromeres, etc. (Rosen EM, Jul 2003). BRCA1 binds to BRCA2, TP53, and RAD51. Cells lacking a functional BRCA1 protein cannot undergo arrest in the G2 phase of the cell cycle following DNA damage and are deficient in transcription-coupled repair. BRCA1 also modifies the chromatin structure to allow access to DNA repair proteins at sites of damage, by interacting with yH2AX (Godet I, Feb 2017). Due to such extensive involvement of BRCA1 in cell cycle regulation and DNA repair, the gene is essential, any mutation in which disturbs the normal functioning of cells. The BRCA2 gene is a mediator of homologous recombination. It is involved in the maintenance of chromosome stability and double-strand break repair of DNA (ShampooY., 2003).

EPIDEMIOLOGY:

The breast cancer is one of the most common female cancers worldwide and according to Nation Cancer Registry Program report by National Centre for Disease Informatics and Research which occurred in 2020 estimated that 39.4% of the total cancer cases are from India. According to reports from 2020, more than two lakh women from India were diagnosed with breast cancer and more than 76,000 deaths were estimated (Yadav, March 2024) . It is expected by National Cancer Registry Program Report that the risk of breast cancer will increase up to 3 lakh cases in 2025. Due to lack of inadequate breast cancer screening, unavailability of appropriate medical facilities and diagnosis of disease at advanced stage the hike in mortality is observed (Mallath MK, 2014). To evaluate cancer mortality in relation to incidence Mortality Incidence Ratio is another novel measure. Those people which have prevalent breast cancer family history will have high risk of development of breast cancer. The breast cancer etiological study deals with lots of factors associated with lactational history, marital factors, fertility, and dietary factors etc (Basu P, 2021).

TYPES OF BREAST CANCER:

There are different types of breast cancer based on different factors such as occurrence of cancer tumor and their sites (MacMahon B, 2011).

According to site:

Type of breast cancer	Information
Non-Invasive Breast Cancer	In this the cancer cells do not spread to other parts. The most common form of non-invasive breast cancer is Ductal Carcinoma In situ (DCIS). The DCIS is also known as Intraductal Carcinoma or stage 0 breast cancer.

Invasive Breast Cancer	In this the cancer cells spread to other parts invading connective tissues and surrounding fatty tissues of breast. Invasive Ductal Carcinoma is one of the most common types of this cancer.

According to occurrence:

Frequently occurring Breast Cancer

Types	Information
Lobular Carcinoma	In this condition the abnormal growth of cells occur in the milk glands i.e., lobules in breast.
In Situ Ductal Carcinoma	It is not a cancer but increases the chances of developing breast cancer.
In Situ Infiltrating Lobular Carcinoma	The Ductal Carcinoma in Situ is also known as Intraductal Carcinoma or stage 0 breast cancer. It is non-invasive type of breast cancer. It does not spread out of milk duct.
Infiltrating Ductal carcinoma	It is an invasive type of cancer and has ability to spread to the lymph nodes and to other parts of body. 10% to 15% of breast cancers are included in this type of cancer.
	It is an invasive type of cancer and has ability through the blood and lymph system throughout the body. If prompt treatment is not done then it could be severe. 80% of breast cancers are of Infiltrating Ductal carcinoma.

Less commonly occurring Breast cancer (Topcul, 2022)

Types	Information
Medullary Carcinoma	The medulla is present in thyroid and it consist of parafollicular C cells which produces hormones. In this these C cells becomes cancerous. It is an invasive type of breast cancer. 5% of breast cancer are medullary in nature.
Mucinous Carcinoma	It is one of the rarest types of breast cancer which is present in cells of mucous and can develop anywhere but mainly in breast. It is called as colloidal carcinoma, mucinous carcinoma. It is less aggressive in nature.
Tubular Carcinoma	It is an invasive type of breast cancer. It is formed in milk ducts of breast and then spread to other tissues of breast. Less than 2% of breast cancer are tubular carcinoma.
Inflammatory Breast Cancer	Inflammatory breast cancer is a rare and rapidly developing cancer. Inflamed breasts with thick ridges are caused due to blockage of lymph vessels or channels in the skin over the breast. It causes rashes. Only 1% of breast cancer is inflammatory.
Paget`s Disease of the Nipple	It is also called as Paget`s Disease of Breast. It is a rare condition. It surrounds the nipple and areola invading from the milk ducts. The area of nipple gets darker. About 1% of breast cancer is of Paget's disease.
Phylloides Tumor	It is also called as Phyllodes Tumor. It could be benign or malignant. Initiates from the connective tissues of the breast to the surrounding area of breast. It can be treated by surgery. It is a rare type of cancer.

STAGES OF BREAST CANCER

There are mainly five stages of breast cancer i.e., stage 0, stage I, stage II, stage III, and stage IV The stage 0 cancer comes in the group of in situ carcinoma.

In situ carcinoma

Stages	Description
0	It is a non-invasive type of ductal carcinoma in situ (DCIS). It initiates in the milk duct or milk producing glands. It will not spread to the surrounding breast tissue

The stage I, stage II and stage III cancers come in the group of localized and regional invasive cancer.

Localized and regional invasive cancer

Stage	Description
I	In this stage the cancer is small and the breast tissues can get affected minorly. the cancer can also find in lymph nodes which are closer to breast.
IIA	In this stage, no evidence is observed of tumors in the breast but can be spread to lymph nodes. The lymph nodes may spread in the armpit and near the breast bone on the same side where the tumor is present.

IIB	The tumor size increases to 20 mm till 50mm and can be spread throughout the lymph nodes covering the surrounding area of breast.
IIIA	In this stage the cancer tumor invades to more than nine lymph nodes near the breastbone. It has not spread to other body parts.
IIIB	In this stage, the cancer tumor invades the chest wall and skin of breast which then causes swelling of breast, ulceration, and inflammation on breast. Its lymph nodes spread under the collar bone.
IIIC	In this stage, the cancerous tumor spread to the number of lymph nodes like lymph nodes of mammary glands and nodes under the collar bone.

The stage IV cancer comes in the group of Metastatic cancer (Moran MS, 2014)

Metastatic Cancer	
Stages	**Description**
IV	In this stage, the cancerous tumor spread in surrounding area of breast and to the other body parts like bones, liver, and lungs.

DIAGNOSIS:

The diagnosis of breast cancer is mainly done by Biopsy. Biopsy means removing breast cells for diagnosis. In biopsy, a specialized needle device is used by surgeon with the X-ray imaging or any another imaging test to extract a core of tissue from the affected area. It is most used technique for the diagnosis of breast cancer (Oluwole Adeyemi Babatunde, 2022).

AVAILABLE MANAGEMENT AND TREATMENT OF BREAST CANCER:

For the management and treatment of breast cancer a surgeon must make several approaches. The surgeons specialized in different areas like radiology, pathology, oncology, and surgery works together for the treatment of breast cancer. This team is known as Multidisciplinary team. There is a specialized geriatric oncologist for the patients whose age is above 65. Before the treatment starts the patient must fill the ASCO Treatment Plan Form which is then given to surgeon for the further treatment.

Chemotherapy: Chemotherapy is key treatment for breast cancer. In this the anticancer drugs are used to cure cancer. These drugs are administered via intravenous route or by oral route. This drug causes reduction in tumor size or shrinkage of tumor before the surgery making surgery possible. It avoids the use of mastectomy treatment. To administer chemo into intra venous system a Central Venous Catheters (CVS), Central lines and Central Venous Access Devices are used. They are used to administer blood, drugs or medicines, nutrients, and fluids as well as it is used to take out blood for diagnosis purpose.

Some side effects may occur due to chemotherapy are: Hair loss, Diarrhoea, Nausea and vomiting, Nail changes, Fatigue, Menopause, Vaginal dryness, Fertility issues, Increased chances of infection, Nerve damage, Bleeding may cause low blood platelet count and Anaemia.

Radiation therapy: In radiation therapy, the radiations are used to kill the cancerous cells which were present after the surgery. In this the use of protons and high energy x-rays are used which then target a tumor or post-surgery tumor site (Oluwole Adeyemi Babatunde, 2022). This x-ray particles are painless and invisible. After treatment the person does not become radioactive hence is safe to other people.

The radiation therapy for breast cancer may be given by following:

- External Radiation: The radiations are delivered to the breast from outside of the body. It is one of the most common techniques to deliver radiations.
- Internal Radiation: It is also called as Brachytherapy. In this technique the surgeon puts the radiation delivery device in breast area where the cancer is caused before the surgery. It can cure cancer of every stage.

Surgery:

The surgery in cancer patient is done based on the stage of cancer in the patient. In this the mastectomy can be done means the removal of entire breast can be done (Pinchinat T, 2016). Surgery for breast cancer is done by following options:

- Breast Conserving Surgery: In this the tumor and the tissue surrounding the tumor is removed. It consists of three types:

a. Lumpectomy: In this the minute number of surrounding tissues are removed.
b. Wide excision: In this larger amount of surrounding normal tissues are removed and it is also known as Partial-mastectomy.
c. Quadrantectomy: In this the one fourth of breast is removed.
d. Mastectomy: In this Surgery all the breast tissue are removed (Moo TA, 2018).

Covered Objective:

1. Review on concept and treatment of Breast Cancer by using the plants in Ayurveda
2. Review on Gene Based Breast Cancer Treatment in relation to different plant varieties such as etc.

Genes Based Anticancer Activity of Medicinal Plants to Prevent DNA Damage

Turmeric (*Curcuma Longa*)

Turmeric powder is widely used as a spice and cultivated mainly in Asian countries (Kanjana Singh, 2022). Curcumin is a main constituent of turmeric which is a yellow-coloured substance belonging to the polyphenols, is the active component of turmeric, numerous studies have confirmed that curcumin possesses anti-oxidant, anti-inflammatory and anticancer properties (Natalia G, 2015).The effectiveness of curcuminoids and other chemical components in turmeric has a significant impact on their ability to treat human diseases. For example, curcuminoids, phenolic acid, and flavonoids are the major bioactive properties found in turmeric rhizomes (Thi Sinh, 2021).

The traditional extraction technique (TDE) involves using the Soxhlet extraction method. To obtain turmeric powder, 5 grams of turmeric powder is placed in a Soxhlet apparatus and extracted using 95% v/v ethanol at a temperature of 60 degrees Celsius for a duration of 8 hours. The ethanol is then separated from the extracts using a rotary evaporator under vacuum conditions at 40 degrees Celsius for 1 hour. For another extraction method, ultrasonic-assisted extraction (UAE) is used with an ultrasonic power of 250 watts and a frequency of 22 kHz. In this experiment, 5 grams of turmeric powder is dissolved in 100 millilitres of ethanol and extracted using the ultrasonic machine for 3 hours. The ethanol is again separated from the extracts using a rotary evaporator under vacuum conditions at 40 degrees Celsius for 1 hour. Microwave-Assisted Extraction (MAE) is performed using a Toshiba ER-300C (S) model. In this extraction, 5 grams of turmeric powder is dissolved in 100 millilitres of 95% v/v ethanol and placed in the microwave chamber. The extraction is carried out at a power of 800 watts for 3 minutes. The extraction process is performed in cycles, consisting of 30 seconds of irradiation followed by 5 minutes of cooking time to maintain a temperature of 25 degrees Celsius and prevent solvent boiling (Kanjana Singh, 2022).

Curcumin, a substance derived from turmeric, has been discovered to enhance the effectiveness of mitomycin (mmc)-based chemotherapy. It accomplishes this by making cancer cells more sensitive to mmc while also reducing the side effects associated with the treatment. This leads to increased survival of the cells and a decrease in lipid peroxidation and DNA damage. Researchers have found that the combination of mmc and curcumin helps alleviate the toxicity of mmc by inhibiting the activity of a glucose regulatory protein called grp58. This inhibition prevents the formation of DNA cross-links through a pathway involving the proteins erk and p38 mapk. In addition, curcumin has been shown to enhance the ability of mmc to inhibit the proliferation of breast cancer cells. This effect is achieved through the activation of the p38 mapk pathway, which leads to cell cycle arrest. Specifically, the expression of proteins involved in cell cycle progression, namely cyclin D1, cyclin E, cyclin A, cyclin-dependent kinase 2 (CDK2), and CDK4, is suppressed. On the other hand, the levels of cell cycle inhibitors p21 and p27 are increased in both breast cancer cells and breast cancer xenografts derived from these cells (Dongwu Liu, 2013).

Garlic (*Allium sativum L.*)

Garlic (Allium sativum L.) is one of the oldest plants cultivated for its use as food and medicine. It is a plant with many useful impacts such as antithrombotic, antimicrobial, anticancer, antiarthritic, antitumor, hypoglycemic and hypolipidemic activities [4]. Bulbs of Allium sativum are known to contain numerous phytochemicals, including sulphur-containing compounds like ajoene's (e-ajoene, z-ajoene), thiosulfates (allicin), vinyl dithiins (2-vinyl-(4h)-1,3-dithiin, 3-vinyl-(4h)-1,2-dithiin), and sulphides (diallyl disulfide (DADS), diallyl trisulfide (DATS)), which make up 82% of the total sulphur content in garlic. When garlic is cut and its parenchyma breaks down, the primary cysteine sulfoxide, alliin, is converted into allicin by the alliinase enzyme. Freshly milled garlic homogenates mainly contain s-propyl-cysteine-sulfoxide (PCSO), allicin, and s-methyl cysteine-sulfoxide (MCSO), which are responsible for the characteristic smell of garlic. PCSO can produce more than fifty metabolites depending on the water content, temperature, and the presence of alliinase enzyme. This enzyme can act on a mixture of MCSO, PCSO, and alliin to produce other molecules such as allyl methane, thiosulfates, methyl methanethiosulfonate, and various corresponding thiosulfates (R-S-S-R0), where R and R0 represent allyl, propyl, and methyl groups [(Gaber El-Saber Batiha, March 2020) (Faisal Nouroz, 2015)].

garlic extract was prepared by blending 350 grams of garlic cloves with 40% ethanol in a bench-top blender to activate alliinase. The mixture was then transferred to a glass jar with an air-tight lid, stored in darkness at 4°C for five days, and strained through a cloth or nylon stocking. After discarding the dry

mass, the solution was centrifuged and the supernatant was stored at -20°C (Reticulum Stress Voin Petrovic, 2018). When fresh garlic extract was applied to MCF7 cells, noticeable changes in cell structure occurred within an hour. On the other hand, boiled garlic extract did not have any effect on the cells. The cells treated with garlic extract showed distinct morphological features and lost contact with neighbouring cells after a period of two to four hours. These findings were consistent across different sources of garlic bulbs and two separate sources of MCF7 cells (CellsSuhasini Modem, Feb 2012).

Curry leaves (Murraya koenigii)

Murraya koenigii (m. koenigii), Micromelum minutum (m. minutum), and Clausena indica (c. indica) belong to the Rutaceae family and are three different types of curry leaves. These plants have various parts such as leaves, seeds, flowers, and fruit, which contain active components that can affect multiple biological processes. Previous research has provided strong evidence supporting the powerful medicinal and biological properties of these three curry leaf species, including antioxidant, antidiabetic, anti-inflammatory, and antitumor activities. These findings demonstrate the potential of curry leaves as a valuable source for pharmaceutical applications and their ability to positively impact human health (D. T. Abeysinghe, 2021).

Till date, near about 88 different alkaloids, and several other important metabolites such as terpenoids, phenolic and essential oils have been identified from different plant parts of murraya koenigii. Mahanine and mahanimbine are the important alkaloids which shows the anticancer activity. The medicinal properties of curry leaves have been attributed to several secondary metabolites like alkaloids, flavonoids, essential oils, terpenoids, etc (Suman Kumar Samanta, 2017).A research study has revealed that the extract derived from the leaves of the MK plant, known as polyphenol-rich hydro-methanolic extract (CLE), was found to inhibit the proteolytic activity of the 26S proteasome. Additionally, the CLE extract induced cell death (apoptosis) in breast cancer cells, specifically MCF-7 and MDA-MB-231, by reducing cell viability, altering growth kinetics, and causing a halt in the S phase of the cell cycle. (Aniqa Aniqa, 2021).

A process was carried out to extract the essence from the leaf samples. Initially, a specific quantity of these samples (0.25 g) was put into a container with 20 ml of methanol. The container was then placed on a shaker and left there for two hours at room temperature. The solution was treated with 5 ml of hydrochloric acid (6 m) and refluxed for another 2 hours at 90◦ c. Afterward, the samples were cooled down to the room temperature and then filtered through a 0.45 μm membrane. This aided in hydrolysing the samples and filtering out any unwanted substances (Ali Ghasemzadeh, 2014).

The findings suggest that Murraya koenigii leaves contain potent proteasome inhibitors that may hold promise as a treatment option for various types of cancer. Another study reported that the total alkaloid extract obtained from Murraya koenigii leaves, as well as a compound called mahanine, exhibited anticancer properties as well. These extracts were found to inhibit trypsin-like 26S proteasome activity and induce apoptosis in breast cancer cells (MDA-MB-231) by reducing cell viability, altering growth kinetics, and arresting the cells at the S phase (Aniqa Aniqa, 2021).

Mushroom (*Agaricus bisporus)*

Mushrooms belong to the mushroom kingdom of fungi and have properties entirely different from species of other kingdoms. White button, also known as Agaricus bisporus, is a commonly available mushroom species. Due to the abundance of nutrients in it, it is widely consumed over the globe. Button mushroom and amino acids like alanine, aspartic acid, glutamic acid, and arginine and saccharides like chitin, mannan, and trehalose. It also contains indole and phenolic compounds such as L-tryptophan, melatonin, and gallic acid, and ferulic acid, respectively. In this fungi, vitamin B family and Vitamin D are present too (Muszynska B, 2017).

The extraction process for button mushrooms was done by the method described by Cardoso et. al., with modifications 12.5 g of dry mushroom powder was kept under UV light for one hour after which it was mixed with 20 ml of dimethyl sulfoxide. A mixture of methanol and water was added, followed by 90 ml of hexane. The resulting mixture was kept in a rotary shaker for 8 hours. It was then filtered and the filtrate was kept in a rotary shaker, followed by a heating mantle, till the solvent had evaporated and a dry powder of extract was obtained the powder was re-dissolved in 15 ml methanol and stored in an amber-coloured bottle for further use. The percentage yield of the extract was calculated using Weight of dry extract obtained after evaporation/ Total weight of dry powder taken.

MTT assay is one of the most popular and widely-used assays. It is a sensitive, quantitative, and reliable colorimetric assay, which gives excellent linearity, up to 10° cells per well. It involves the conversion of MTT dye [3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide), which is a water-soluble yellow dye, to an insoluble purple formazan, because of the action of mitochondrial reductase

enzyme. Viable cells can reduce the yellow MTT under tetrazolium ring cleavage to a water-insoluble purple-blue formation which precipitates in the cellular cytosol and can be dissolved after cell lysis, whereas cells being dead following toxic damage, cannot transform MTT. This formation production is proportionate to the viable cell number and inversely proportional to the degree of cytotoxicity (K., 2015) (Kumar P, 2018)

Ashwagandha (*withania somnifera*)

The Withania have been widely used in the indigenous medicine cultivated in India, Pakistan, Afghanistan, Spain, parts of the Middle-East Africa, Canary Islands and South East Asia. It is extensively used as anticancer anti-inflammatory, metabolic, and pro-apoptotic agent (Atteeq, 2022). Withania somnifera is a plant that contains a wealth of beneficial phytocompounds. Roots of this plant alone have been reported to contain over 35 different chemical compounds. These compounds include alkaloids, steroids, flavonoids, phenolics, and glycoproteins. The major active compounds in all parts of the plant belong to the withanolides group, including withaferin A and withanolide D, withaniol, acylsteryl glucoside, and amino acids such as aspartic acid, proline, tyrosine, alanine, glycine, glutamic acid, cystine, tryptophan, and a high content of iron. (Neetu Singh, 2020) (Atteeq, 2022)

Extensive in vivo and in vitro studies have depicted Withaferin-A's interactions with key role players in cancerous activity of the cell to exert its pro-apoptotic effects (Atteeq, 2022). The process involved in obtaining the plant extract was carried out in several steps. Firstly, the plant leaves were dried in the air and then finely grounded to obtain a powder. Next, methanol (60°c) extraction of the powder was carried out using a Soxhlet apparatus for a period of 4-5 days. Further purification was done by subjecting the methanol extract to two more extractions. The first one was with hexane, which was done to eliminate the chlorophyll and pigments present. The second extraction was carried out with diethyl ether, the extract of which was later evaporated to obtain an ether extract out of the plant material (Nashi Widodo, 2007).

A cell line called mcf-7, which has been used for in vitro analysis for many years, is being used to study breast cancer. This cell line is classified as oestrogen and progesterone receptor-positive, meaning that it responds to these hormones. Oestrogen is necessary for the growth of mcf-7 cells. Researchers have studied the potential anticancer effects of ashwagandha leaves by examining their impact on mcf-7 cells both in vitro and in vivo (Ruju Vashi, 2020). As a result, Multiple in vitro and in vivo investigations have depicted promising outcomes for the compounds anticancer effects when administered alone or in combination with other available therapeutics (Atteeq, 2022).

Mango (*Mangifera indica L.*)

Mango is a highly cultivated tropical fruit that has a rich concentration of polyphenolic compounds. These compounds include gallic acid, gallotannins, galloyl glycosides, and flavonoids like quercetin and kaempferol glycosides (Nivedita Banerjee, 2015). Mangifera has been found to possess numerous beneficial pharmacological properties such as pain-relieving, antibacterial, anti-inflammatory, antioxidant, diabetes-fighting, and immune system-regulating activities. It highlights the potential of mangiferin as a powerful and versatile natural compound with a broad range of therapeutic applications (Kah Min Yap, Sept 2022).

The laboratory findings indicate that the use of pomegranate polyphenolics in combination can effectively reduce inflammation and limit the growth of bt474 xenograft tumors in nude mice. In the model of breast cancer, the levels of mir-126 expression are decreased according to studies. The level of proteins such as PPI3K, PAKT, and mTOR decreased when mango extract was used. Moreover, the expression of HIF-1α and VEGF, which are downstream targets of the mTOR pathway, was significantly suppressed by the mango extract. Additionally, the protein level of NF-κB (p65) was reduced in xenograft tumors from the group receiving mango extract compared to the tumors of control animals (Nivedita Banerjee, 2015). The extracts of M. Indica and their phytochemicals activate a process called oxidative stress-induced cell death, which involves the production of reactive oxygen species (ROS). These ROS molecules are normal products of cellular metabolism and play a crucial role in signaling pathways related to processes like cell death, proliferation, and carcinogenesis. The studies have suggested that due to quercetin there was greater production of superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2). As a result, it is speculated that quercetin increases oxidative stress and, thus, induces apoptosis in MCF-7 cells (Kah Min Yap, Sept 2022).

Bhumi Amla (*Phyllanthus niruri*)

The findings suggest that P. niruri shows promising result as a chemo modulatory agent against resistant breast cancer. (Ali El-Halawany, 2023) The findings of the study reveal that hypophyllanthin and phyllanthin, obtained from P. niruri, display a moderate level of antiproliferative/cytotoxic property on resistant breast cancer cells (Ola E. Abdel-Sattar, 2023). Doxorubicin (dox) is widely used as a chemotherapy drug for treating breast cancer.

The chemo modulatory effects of extracts and fractions of P. niruri were investigated in breast cancer cells, alongside different concentrations of dox (Ali El-Halawany, 2023). The process of examining apoptosis was carried out on MCF-7ADR cells by treating them with hypophyllanthin (PN4) and phyllanthin (PN5) individually as well as in combination with doxorubicin for 48 hours. The cells were then trypsinized and washed twice with PBS. To determine the level of apoptosis, the cells were suspended in 0.5 ml of binding buffer, and then 5 µl of annexin V-FITC and 5 µl of PI were added then incubated for upto15 minutes in the dark. Subsequently, the cells were examined using FACS analysis within an hour of staining (Ola E. Abdel-Sattar, 2023).The culture media was supplemented with 10% fetal bovine serum (FBS) and 100 units/ml of penicillin/streptomycin (PS). The cells were then incubated at 37°C in a humid environment with 5% CO2. The viability of MCF-7 cells showed a dose-dependent decrease upon treatment with dox, with a noticeable decline starting at a concentration of 0.1 µg/ml. The IC50 value for dox was determined to be 0.2±0.06 µg/ml (Ali El-Halawany, 2023).

Hypophyllanthin and phyllanthin have been found to overcome the resistance of doxorubicin in MCF-7ADR breast cancer cells by reducing the activity of the Sirt1/Akt pathway. The expressions of Sirt1 and phosphorylated Akt (p-Akt) were then assessed using Western blot analysis. Hypophyllanthin and phyllanthin have been found to have an inhibitory effect on the migration ability of mcf-7adr cells. Additionally, they also decrease the expression of epithelial-mesenchymal transition (EMT) markers. These agents exhibit a significant positive effect on the anticancer qualities of doxorubicin, when used together. This outcome suggests that hypophyllanthin and phyllanthin can be potential candidates for combination therapy to treat breast cancer, particularly for cases where the cancer is resistant to other treatments (Ola E. Abdel-Sattar, 2023). Now, future studies should focus on further understanding its effects on resistant breast cancer and other types of cancer cells that overexpress multidrug resistance (MDR) genes (Ali El-Halawany, 2023).

CONCLUSIONS AND FUTURE PERSPECTIVES:

Researchers are currently exploring the combination of natural products with chemotherapeutic agents, as it has been observed to enhance the effectiveness of conventional chemotherapy drugs and/or protect patients from their adverse effects. It provides an overview of various medicinal plants and their potential in fighting cancer. While not all these plants can completely cure the disease, they do produce active compounds with anti-cancer properties. These compounds work in synergy with chemotherapy drugs to enhance their effectiveness while minimizing side effects. The article also focuses on explaining the mechanisms by which certain native medicinal plants act against tumors.

Phytochemicals hold significant potential in improving the lives of cancer patients. Some phytochemicals can effectively work together with chemotherapy and radiation therapy, providing a beneficial synergy. Therefore, the appropriate use of these compounds, whether in preventing or treating breast cancer, offers an appealing approach to complement traditional treatments. By combining these therapies appropriately, it may be possible to reduce side effects without compromising or even enhancing the therapeutic effects. Additionally, bioactive compounds derived from plants that can regulate the expression of numerous genes associated with uncontrolled growth in hormone-independent cancers could also prove beneficial.

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