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Novel potential herbal drugs to treat 7,12-dimethylbenz[a]anthraceneinduced Breast Cancer: A review on the 2021 – 2022 pre-clinical studies

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ABSTRACT:

Treatment with herbal medicine is said to be very beneficial for cancer patients, which has shown dramatically increased survival rates. Numerous phytochemical classes are being used therapeutically in herbal medicine. This review article was carried out by examining clinical trial studies between the period of 2021 and 2022. This review aims to give an overview of the recent development of herbal medicine in the prevention and treatment of cancer. Examples of promising bioactive chemicals with medicinal and other therapeutic uses that were derived from diverse plants are included in this review. The results of the study showed that the medicinal plants, which include *Agaricus bisporus, Cynanchum paniculatum, Dacryodes edulis, Senecio rhizomatus Rusby, Eurycoma longifolia Jack, FDY003, Maranta arundinacea L., Salvadora persica and Zingiberene* were effective in the treatment of breast cancer. The investigation of these herbs' photochemical properties has made some progress in the search for novel anticancer medications. People now choose to use natural plant products to treat cancer since they are afraid of the adverse effects. In a conclusion, this article gives information on medicinal plants utilized by people all around the world as anticancer treatments using new anticancer medications derived from medicinal plants.

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INTRODUCTION:

According to cancer epidemiological research, breast cancer (BC), lung cancer, and colorectal cancer account for more than 50% of all cancer cases in women and have a high prevalence in the population as a whole. BC is the most frequent kind of cancer in women and the second most common primary cause of death, accounting for 30 % of all new cancer diagnoses [1]. Alternative and Complementary Medicine (ACM) is becoming more popular globally since it is ingrained in many nations' folklore and has been shown via research to be useful in medical care. ACM integration into

national health systems is advised by the World Health Organization [2]. In addition to surgery, chemotherapy, and pharmacogenomics therapy, traditional and complementary medicine has been proposed as an alternate treatment to lower the incidence of breast cancer [3]. Additionally, because most molecular targeted medicines have a limited ability to therapeutically modify the malignant activities of different oncogenic cellular components, their pharmacological efficacy frequently falls short of expectations [4].

These problems highlight the requirement for anticancer drugs that can safely pharmacologically regulate a variety of oncogenes and pathways. Herbal medicines are multi-component treatments that target several genes, proteins, and pathways associated with various diseases to produce their desired pharmacological effects [5]. Medicinal plants are one of the promising chemopreventive options that have a long history in both breast cancer prevention and treatment since medicinal plants have anticarcinogen components. According to a literature survey, plant-derived compounds constitute more than 50% of anticancer agents [6]. Additionally, prior clinical research studies have demonstrated how using herbal medicines might enhance the tumor response, survival, health status, and quality of life for patients receiving cancer therapy [7].

BC is a disorder that affects women more often than males, thus it's important to keep looking for natural remedies as therapeutic alternatives. Environmental elements such as exposure to polycyclic aromatic hydrocarbons produced by the burning of coal, manufacturing, and automotive gasoline might raise the risk of breast cancer in addition to hereditary and aging-related variables. 7,12-dimethylbenz(a)anthracene (DMBA), one of the polycyclic aromatic hydrocarbons known to cause cancer, is used to induce breast cancer in laboratory rats. Since breast cancer grows in rats similarly to how it does in people, this model of breast cancer in rats is the one that is most frequently utilized [8].

Herbal drug in breast cancer:

For a very long time, the usage of herbs was forgotten due to the development of the industrial sector and industrial medicine [9]. Herbal therapy has developed into a very secure, non-toxic, and widely accessible source of chemicals that treat cancer. Because of a variety of properties, herbs are thought to counteract the effects of illnesses in the body [10]. The development of new procedures has lowered obstacles relating to natural substances, and interest in using such natural constituents in the pharmaceutical business has grown [11].

However, there is a misconception that there are no safety or side effect concerns with herbal components when they are used as pharmaceuticals. There are numerous plant species that are harmful to human health. Similarly to this, some substances found in otherwise beneficial plants can be harmful to cells. It has been demonstrated through experimentation that even anticancer plants have cytotoxic effects [12].

Herbal remedies can help with symptom management, but harnessing their anticancer characteristics also tends to bring out the best in them. Numerous researches are being conducted to confirm the effects of the co-administration of herbal medicines and anticancer treatments to further understand the anticancer effects of herbal medicines [13].

This review article aims to give researchers a glimpse of the most recent developments and pre-clinical studies in the use of herbal medicines for breast cancer prevention and treatment, including ethnopharmacology, natural product chemistry, effectiveness, safety, dosage, and toxicity, in vitro and in vivo preclinical trials, herb-drug relationships, and potential biochemical and molecular pathways. This page includes a number of thoroughly screened and accepted for publishing papers. They are briefly described as follows.

Agaricus bisporus [14]**:**

The goal of the study was to examine if the white button mushroom (*Agaricus bisporus*) can prevent breast cancer that has been caused by the chemical 7,12-dimethylbenz[a]anthracene (DMBA). According to the experiment the rats were given a single gavage dosage of 50 mg/kg DMBA to cause breast cancer. Four groups of rats were created: G1 (negative control group), G2 (positive control group), G3 (rats receiving mushroom extract), and G4 (rats getting no treatment) (rats administered with doxorubicin).

In carcinogenic rats, the mushroom extract considerably ($p < 0.001$) increased the activity of antioxidant enzymes. Additionally, the mushroom extract protected the rats used in the trial from a rise in the levels of the tumor biomarkers CEA, CA 15.3, and CRP. Enzymes involved in liver function increased in G2 and G4 compared to G3. RBCs and Hb levels were likewise considerably lower in G4 compared to G3, as well.

According to the results mushroom significantly reduced the levels of antioxidant enzymes, increased lipid peroxidation, and increased tumor biomarkers. Further investigation can be done to learn more about the mushroom's anticancer activities and use it as a potential source to avoid breast cancer.

Cynanchum paniculatum [15]**:**

Cynanchum paniculatum (Bge.) Kitag. (CP) is a significant medicinal plant used in Chinese herbal medicine? It has a number of biological activities, including anticancer properties [16].

In this study, the researcher investigated the anticancer properties of CP water extract against breast cancer cells with various mutation types. Cells were divided into four groups: untreated (Control), directly treated with CP (dir-CP), treated with CP in conditional media (sup-CP), and untreated cells (sup-Control).

In a 24 h scratch assay, sup-CP administration prevented the migration of MDA-MB-231 and MCF-7 (Her2) cells. The findings suggested that ER (+) PR (+) cells are more susceptible to the CP's direct cytotoxicity which is not controlled by caspase-3than other cell types. The two Her2(+) cells' migration was decreased by CP, and this was associated with the control of MMP-2. The migration of ER (+) PR (+) cells is not controlled by MMP-2, but was more susceptible to conditioned media with CP treatment compared to straight CP. The findings indicated that CP is particularly efficient at preventing the triple-negative MDA-MB-231 breast cancer cell migration through a variety of methods [17-19].

The findings offer an understanding of how CP prevents the spread of breast cancer and will aid medical professionals in better CP administration.

Dacryodes edulis [20]**:**

In ovariectomized rats, an aqueous extract of the leaves of *Dacryodes edulis (Burseraceae)*, a plant used as a cancer remedy in Cameroon, was discovered to have antiproliferative effects [21]. This plant's extracted compounds showed in vitro antitumor action [22]. The effects of AE were studied in rats with breast cancer to see if it has the potential to be an anticancer agent [23].

The finding suggests that one subcutaneous administration of 7,12-dimethylbenz[a] anthracene (DMBA; 50 mg/kg BW) to immature female rats resulted in the development of mammary tumours under the mammary gland [24]. Further, Weekly breast tumour volume measurements were made using a calliper. Animals were sacrificed on day 22. Then the researcher measured the levels of cholesterol and oestrogen in serum, breast tumours, mammary glands, and ovaries. Tumour oxidative status was assessed. Mammary glands and breast cancers underwent histological investigation. According to the findings, AE decreased tumour volume and weight (p 0.05). Reduced cholesterol (p 0.001) and oestrogen (p 0.01) levels in breast tumours, blood, ovaries, and mammary glands were linked to this impact. Malondialdehyde and antioxidant enzyme levels were also elevated by AE in tumours (p 0.05 and p 0.01, respectively).

Based on the finding these effects influenced the number of cancer cells in breast tumours, the size of breast alveoli, and the penetration of these cells into the connective tissue of the tumour (p 0.01). In conclusion, the aqueous extract of *D. edulis* leaves may offer an alternative to the neoadjuvant therapy of estrogen-dependent breast cancer because of its capacity to prevent tumour growth.

Senecio rhizomatus Rusby [25]:

Senecio rhizomatus Rusby (SrR), a member of the Asteraceae family, is a traditional Andean infusion used to treat inflammatory conditions [26]. This investigation sought to identify the histopathological alterations facilitated by SrR in rat models of breast cancer (BC) brought on by 7, 12-dimethylbenz[a]anthracene (DMBA) [27].

Based on the finding of macerating SrR aerial parts with 96% ethanol, an ethanolic extract of the material was created. The chemical components were then identified by gas chromatography-mass spectrometry [28], the antioxidant activity was assessed using the 1,1-diphenyl-2-picril-hidrazil (DPPH) assay, and the acute toxicity was evaluated in accordance with OCED 423 standards. In a pharmacological investigation, 30 female Holtzman rats were randomly assigned to the following five groups. Group I is the negative control (2 mL/kg of physiological serum); Group II is DMBA (80 mg/kg body weight); and Groups III, IV, and V are, respectively, DMBA plus an ethanol extract of SrR at doses of 10, 100, and 200 mg/kg [29].

The researcher stated that at 200 g/ml, the SrR extract's antioxidant activity against DPPH was 92.50 %. SrR was administered orally at doses of 50, 300, 2000, and 5000 mg/kg without producing any clinically significant toxicity or fatalities. Comparing the groups that got SrR to the DMBA group, the groups that received SrR showed a lower frequency of tumours and a cumulative

tumour volume (p 0.05); the DMBA group also showed a greater incidence of necrosis and moderate mitosis, up to 66.67 and 100.00 %, respectively. Finally, significant tumour necrosis and infiltrating cancer were found [30].

Eurycoma longifolia Jack [31]**:**

The goal of the reported study was to compare the cytotoxic effects of *Eurycoma longifolia* (Jack) leaf extracts on the hormone-independent MDA-MB-231 and the non-hormone-dependent MCF-7 breast cancer cell lines. *E. longifolia* leaves were divided into batches that were fermented and unfermented, then dried using freeze and microwave oven methods [32].

Based on the experiment MTT assay was used to examine the cytotoxicity of the obtained extracts, and the HPLC-DAD technique was used to determine the phenolic content [33]**.** Using the flow cytometry approach, the most toxic sample's apoptotic cell count, cell cycle distribution, and expression of caspases and apoptotic proteins were examined [34].

A technique for analysing agarose gel electrophoresis was used to analyse DNA fragmentation. The findings showed that, in a dose-dependent way, the unfermented freeze-dried leaf extract was the most lethal to MDA-MB-231 and MCF-7 cells. The maximum concentration of gallic acid, chlorogenic acid, ECG, and EGCG phenolics is found in this extract.

The cell cycle was halted at the G2/M phase in MCF-7 cells and the S phase in MDA-MB-231 cells, where DNA fragmentation was seen in both cell lines. MDA-MB-231 cells saw an increase in the number of apoptotic cells when the treatment was extended from 24 to 48 hours, but a minor drop at 72 hours, whereas MCF-7 cells experienced time-dependent apoptosis. These findings show that *E. longifolia's* unfermented freeze-dried leaf extract can cause MDA-MB-231 and MCF-7 cells to undergo apoptosis, as well as concrete proof of the sample preparation's influence on the level of cytotoxicity.

FDY003 [35]**:**

Herbal remedies have received a lot of interest in relation to their possible uses in the treatment of breast cancer (BC), a malignancy that is commonly identified, due to their anticancer effects and very low side effects [36]. But a thorough understanding of their mechanisms of systemic action is lacking. In this experiment, the researcher attempted to identify the systemic mechanisms of FDY003, a herbal remedy made of *Lonicera japonica, unberg, Artemisia capillaris, unberg,* and *Cordyceps militaris*, based on network pharmacology techniques [37].

On human BC cells, the researcher discovered that FDY003 had pharmacological actions. Then, thorough databases on herbal medicine, such as TCMSP and Cancer HSP, were used to gain precise information about the biochemical components found in FDY003 [38-39]. 18 chemical compounds in FDY003 were shown to be potentially active ingredients interacting with 140 BC-associated therapeutic targets to provide pharmacological activity by assessing their pharmacokinetic properties. The modulation of biological processes, including cell proliferation, cell cycle, and cell apoptosis, was implicated in the modulation of the FDY003 targets, according to a gene ontology enrichment study carried out using g: Profiler [40].

Based on the finding it was also discovered that a number of oncogenic pathways, including PI3K-Akt, MAPK, focal adhesion, FoxO, TNF, and oestrogen signalling pathways, which are important in the pathogenesis of BC, were considerably enriched with the therapeutic targets of FDY003. Here, we discuss the molecular processes by which herbal medicines treat BC from a network approach.

Maranta arundinacea L. [41]**:**

There is still room for improvement in breast cancer prevention. Through the stimulation of autophagy, calorie restriction is suggested to prevent breast cancer [42-43].

Due to its high fibre content, *Maranta arundinacea L.* (MA) has the ability to reduce calorie intake. This study sought to determine how dietary MA affected autophagy and its relationship to DMBA-induced mammary cancer in Sprague Dawley rats.

In the given experiment twenty-five Sprague Dawley rats were divided into five groups at random: 1) A control group without DMBA induced with a conventional diet; 2) 20 mg/kg BW of DMBA twice weekly for five weeks; 3) DMBA and diet modification with 30% of MA; 4) DMBA and diet modification with 45 % of MA; and 5) DMBA and diet modification with 60 % of MA. For 22 weeks, the nodule was examined once a week. Breast tissue and tumours were examined histologically using hematoxylin-eosin. To identify autophagy, immunohistochemistry staining against Beclin1, LC3B, and SQSTM1 was investigated. Using a one-way ANOVA with a 95 % confidence level and

significance set at p = 0.05, the difference in autophagy protein expression was examined.

Four rats on the conventional DMBA diet, two on the 30 % MA diet, and one on the 45 % MA diet all had cancer. Both the control group and the 60 % MA group of rats did not have any signs of malignancy. According to the Beclin1 expressions, 60 % of the MA group had the highest score (2.50.52), followed by the 45 % of the MA group (1.870.49), the control group (1.770.11), the 30 % of the MA group (1.280.75), and the lowest scoring group, DMBA with a standard diet (1.280.91). Beclin1 expression differences were statistically different (p-value = 0.03). However, the difference between the LC3B expressions and the SQSTM1 expressions (p-value=0.11 and p-value=0.225, respectively) was not statistically significant.

It was found that dietary changes containing MA may lower breast cancer risk and trigger the start of autophagy.

Salvadora persica [44]**:**

A growing body of research has focused on naturally occurring phytochemicals, particularly polyphenolic compounds, as chemopreventive agents. This study looked into the chemopreventive potential of *Salvadora persica L.* fruits SP, also known as the arak tree or miswak [45], on 7,12-dimethylbenz (a) anthracene (DMBA)-induced breast carcinogenesis in female albino rats. For 22 weeks, the experimental groups received ethanol extract of SP fruits at a dosage of 500 mg/kg body weight. According to histological analysis, administration of SP extract prevented DMBA-induced breast carcinogenesis from occurring. In the mammary tissue of mice treated with SP, there was a downregulation of oestrogen receptor expression, which resulted in an increase in apoptosis and a considerable reduction in cell proliferation.

Additionally, rats treated with DMBA had their breast tissues' oxidative damage reduced by SP extract. The SP treatment also caused early and late apoptosis, S cell cycle arrest, and lowered the viability of MCF-7 breast cancer cells. Findings suggest that the anti-oxidative and highly concentrated phenolic chemicals and esters found in SP's fruit extract may be responsible for its chemopreventive and anticancer benefits [46].

Zingiberene:

The ginger plant contains *zingiberene*, a monocyclic sesquiterpene with a wide range of therapeutic uses. In this investigation, the researcher evaluated the anticancer properties of ginger against DMBA-stimulated mammary carcinogenesis in rats and MDA-MB-231 cells. Female Sprague-Dawley rats were exposed to 25 mg/kg of DMBA in 0.5 ml of maize oil, which was used to cause breast cancer. The rats were then treated with 20 and 40 mg/kg of zingiberene, respectively. Animal body weight and tumour volume were weighed. Using industry-standard methods, haematological parameters, transaminases, lipid profile, lipid peroxidation, and antioxidant status were examined.

Using corresponding test kits, the oestrogen receptor- and inflammatory-related markers were examined. Scores of histological damages were established. Examining *Zingiberene's* impact on cell viability and apoptotic cell death in MDA-MB-231 cells required the use of in vitro research. In the DMBA-stimulated animals, *zingiberene* significantly reduced transaminases, lipid peroxidation, and DMBA-stimulated physiological and haematological alterations. Additionally, zingiberene increased antioxidant levels and decreased inflammatory indicators. *Zingiberene* has been shown to be protective in a histological examination. *Zingiberene* significantly reduced the viability of MDA-MB231 cells, leading to apoptotic cell death. Overall, the obtained results convincingly demonstrated *Zingiberene's* anticancer potential against DMBA-stimulated mammary tumorigenesis and suggested that it may be a suitable chemotherapeutic drug [47].

CONCLUSION

In addition to preserving a person's health and vigour, medicinal plants also effectively treat cancer and other ailments without harming the patient. The development of natural cancer treatments from medicinal plants has been significant. A malignant tumour or malignancy is a cancerous development. A benign tumour is a development that is not malignant. Each of the sequential, interconnected processes that make up the cancer metastasis process is rate-limiting. Clinical trials are being conducted on plants that are laden with chemicals that have chemoprotective properties of them. an innovative method of cancer therapy is the inhibition of angiogenesis. This plant may be used carefully and selectively in anti-angiogenic therapy and afterwards in the management of cancer.

Human health has benefited greatly from medicinal plants. The bioactive chemicals found in plant extracts that are responsible for their anticancer activity must be

evaluated for their useful information. Several anti-cancer plants have been introduced in this review. These plants have potent antioxidant and immunomodulatory characteristics that promote anticancer activity.

In a conclusion, this article gives information on medicinal plants utilised by people all around the world as anticancer treatments. Using new anticancer medications derived from medicinal plants is important as well.

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