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Phytoconstituents in Breast Cancer Prevention

Shreya Sood[1], Sushma Devi[1*], Thakur Gurjeet Singh[1], Amarjot Kaur[1], Vinita Singh[2] and Prinsi Sahpuriya[2]

[1]*Chitkara College of Pharmacy, Chitkara University, Punjab - 140401, India*
[2]*Department of Pharmacy, IITM, IES University Campus, Kalkheda, Ratibad Main Road, Bhopal, Madhya Pradesh - 462044, India*

[*]devi.sushma@chitkara.edu.in (Corresponding Author)

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ABSTRACT

Background: In today's developing nations, breast cancer (BC) is among the foremost risk factor for women. The causes of mortality are still unclear, yet they are frequently related to socioeconomic level and way of life. Numerous clinical therapies have been employed up to this point, i.e., radiotherapy, hormonal treatment, targeted treatment, mastectomy, and treatment with drugs etc.

Purpose: However, resistance development to chemotherapeutic drugs, radiation and hormonal therapy is one of the common problems for many of the patients with BC. Numerous studies have looked at the anti-cancer potential of natural products due to the fact that they are generally safe. Researchers' interest is being drawn by phytochemicals from plants that are thought to be bioactive. In this review the formation and progression of breast cancer were also studied, along with the mode's of activity and regulatory function of these phytoconstituents in major signalling networks within the cell.

Conclusion: Phytoconstituents in Breast Cancer Prevention have potential future as well as the difficulties. So, need more study and instructions for experimental animals, medical research, and experimental in vitro and in vivo methods are critically evaluated.

1. Introduction

Cancer is major disease of concern and the leading cause of death. Although, surgery, anti-hormone therapy, radiotherapy and chemotherapy are the current treatment regimens available to treat cancer but the side effects associated with them force researchers to develop newer molecules. Extensive literature reports suggested that more than 1000 species of plants are available with anticancer activities. In the 1960s, when vincristine, vinblastine, camptothecin, and taxol were discovered (Torre et al., 2015, Iqbal et al., 2017), initiated the discovery of natural anticancer substances from plants and herbs was initiated. Around the world, it was predicted that there would be 8 million fatalities and 14 million additional cases per year (Torre et al., 2015). Based on the BC statistics from GLOBOCAN 2012 (Stewart and Wild, 2014), it was projected that there were 1.7 million new cases and 0.5 million deaths from the disease. In the US, BC is recognized as most repeatedly recognized in females, affecting one in eight women (Ahmad et al., 2019). According to studies from developing countries, around 50 percent of instances of BC and 58 percent of fatalities have been recorded, indicating that BC is the most concerning disease (Ferlay et al., 2015). According to the 2017 BC statistics report in the US, there have been documented cases of 600,920 fatalities and 1,688,780 fresh cases of breast cancer (Ferlay et al., 2015, Ferlay et al., 2014). The country that has the greatest prevalence of BC in Europe is Belgium, which is followed by Denmark and France (Uramova et al., 2018, Santis et al., 2014).

BC is widely detected by the growth of lumpy mass in the tissues of breast. The ducts and lobules that deliver milk to the ducts are lined with the cells, these cells are the source of BC as shown in figure 1 (Zainurin et al., 2018). The most prevalent threats for BC are endocrine and reproductive variables, obesity, activity level, and alcohol use (Ge et al., 2019, Zainurin et al., 2018). However, due to advancement in technology, screening and early detection reduces the mortality rate in breast cancer. Despite these developments, BC continues to be the major reason for mortality in females since it has a lifetime diagnosis rate of one in eight(Chavez et al., 2010, Maughan et al., 2010). As a reason for the efficacy and safety of natural plant derivatives, it is predicted that more than 60% of anti-cancer compounds are medicinal plant derivatives in comparison to conventional treatment methods (Tamrat et al., 2018).

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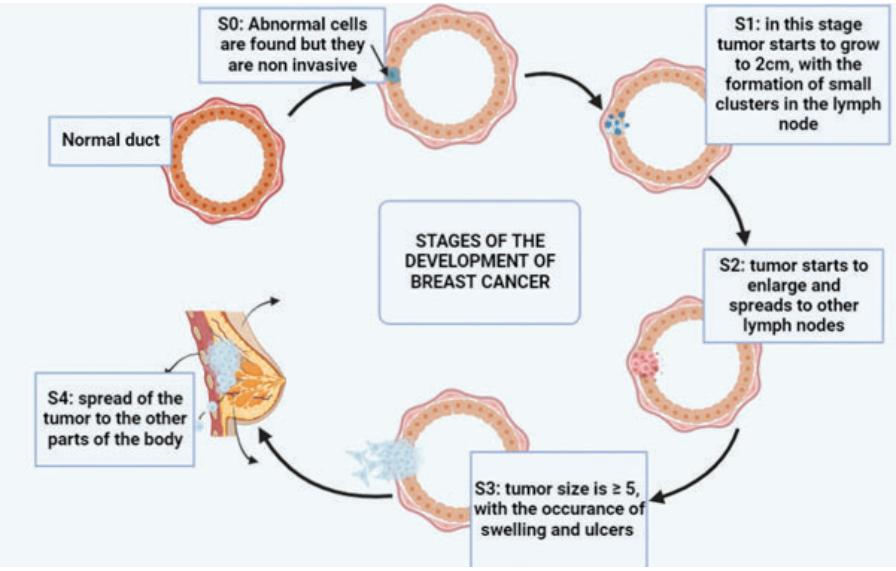

Figure 1: illustration of stages involved in the progression of BC.

There are four distinct phases that breast cancer goes through as it develops. In stage 0 the abnormal cells are observed but tumor is non-invasive, in stage 1 the tumor starts to grow in diameter and the small clusters starts to form, in stage 3, the tumor enlarges and starts spreading to other lymph nodes such as axillary lymph nodes and breast bone lymph nodes. Finally in stage 4 tumor spreads to the other parts of the body through the process known as metastasis.

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BC is an illness of major concern therefore it is vital to diagnose the disease and to provide proper treatment. An earlier diagnosis decreases mortality in the future. over the decade, mortality has been decreased to around 20%, due to high-quality selection methods, early finding, and high value treatment (Wang et al., 2017). To decrease the mortality rate due to BC, researchers have developed numerous diagnostic methods like magnetic resonance imaging (MRI), breast self-analysis of Breast cells, ultrasound, mammogram, ductogram, etc. However, the advanced technology has severe demerits such as elevated charge, time consumption, and in-appropriacy for juvenile women. These demerits emerge the need to develop newer diagnostic aids with high sensitivity and rapid early detection.

In the renaissance era, myriad of treatment methods is available for breast cancer treatment such as radiotherapy, hormonal therapy, and chemotherapy, (Moulder et al., 2008). However, the potential demerits and problem of drug resistance, decreased the potential of existing methods for the treatment of cancer cells (Santis et al., 2014, Nidhi et al., 2019). Additionally, the majority of treatment plans have caused the body to become resistant to them. (Reddy et al., 2011). Therefore, the designing of a successful medication regimen for cancer treatment is urgently needed. These lacking are forcing the researchers towards the development of newer derivatives from plants having a potential role in cancer treatment (Zheng et al., 2016). Literature from the last 5 years was systematically reviewed. This review mainly focuseds on the summarization of phytochemicals from natural medicinal plants in the avoidance, diagnosis and treatment of BC.

2. Herbal Plants and their Constituents in the Alleviation of BC

As anti-tumor and anti-cancer medicines, naturally derived compounds have demonstrated encouraging effects. Their usefulness is also indicated by reports of decreased usage, toxicity and fewer repeated resistances to hormone-targeting anti-cancer medications (multi-drug resistances as seen with several anti-neoplastic agents) (Santis et al., 2014, Reddy et al., 2011). Due to their anti-inflammatory, antioxidant, and immunomodulatory qualities as well as their capacity to limit the growth and apoptosis of these tumor cells, phyto-

compounds are used for these purposes. They are performed in a way that offers a chemo-preventative characteristic that can be utilised both prophylactically and therapeutically and is secure for long-term usage (Zheng et al., 2016, Ishan et al., 2018). Flavonoids, terpenoids, alkaloids, coumarins, and other naturally occurring components of plant products are known because of their capacity to reduce inflammation, function as antioxidants, and stimulate lymphocytes (arctigenin, ajoene, curcumin, glabridin etc). These are potent immunoregulatory characteristics required to inhibit or compete against cancer cells (Torre et al., 2015). Endocrine disorders, which are typically the foundation for the development of these cancer outcomes, might be made worse by phytochemical components acting as endocrine disruptors. Examples of such molecules include isoflavonoids and phytoestrogens, which are non-steroidal phenolic compounds with structural similarities to steroids like oestrogen. According to reports, these botanical flavonoids have chemopreventive, anti-estrogenic, and estrogenic activities (Iqbal et al., 2017). In addition to being able to suppress oestrogen receptor-dependent (cell expansion and proliferation) and autonomous (production of reactive oxygen species and mutagenic substances) connections, they also have the ability to enhance peroxidation and cancer promotion via oestrogen receptor signalling (Torre et al., 2015).

2.1. Tacca Integrifolia

The phytoconstituents isolated from the rhizomes of *Tacca integrifolia* has a greater impact on antiproliferative activity of breast cancer cell having their lethal concentration 50 (LC_{50}) = 114.46 μg/mL as predicted by post-authorisation safety study (PASS) analysis. Among the isolated phytoconstituents of *Tacca integrifolia*, quercetin-3-α-arabinoside depicted the finest fitness score and betulinic acid displayed better absorption upon oral administration (Ahmed et al., 2019).

2.2. Calendula Officinalis

A recent study depicted the molecular effect of *Calendula officinalis* extracts on breast cancer cells. For the first time in *Calendula officinalis* formulations, phenolic and volatile classes of compounds were identified. The extracts of both leaf and flower were found to acquire selective cytotoxicity against tumor cell lines of breast cells, whereas the extract of flowers was found to possess superior cytotoxicity in comparison to leaf extracts. Both extracts were competent to change the appearance of several proliferation- and apoptosis-related genes (Cruceriu et al., 2020).

2.3. Withania Somnifera

A new protein fraction that was extracted from the root component of the *Withania somnifera* plant was shown in a recent research to have antiproliferative action against a variety of tumor cell lines. This activity was shown by the plant's root. With an IC50 of 92 g/ml, this protein fraction demonstrated negligible activity MDA-MB-231 cell lines. The formation of reactive oxygen species, altered BAX/Bcl-2 protein regulation, reduction in the potential of membrane of mitochondria, induction of caspase-3, and mitochondrial-mediated death in MDA-MB-231 cells were likely causes of this considerable cytotoxic action. These interpretations clearly specify that the isolated portion of protein from the rhizome of *Withania somnifera* can be considered as a budding therapeutic agent for BC management (Dar et al., 2019).

2.4. Cuminum Cyminum

In the prevention of cancer, *Cuminum cyminum* fruits plays a significant role. Four constituents namely luteolin, luteolin-7-O-glucoside, apigenin, apigenin-7-O-glucoside were isolated. Among these constituents, Luteolin-7-O-glucoside displayed significant anticancer activity with IC_{50} = 3.98 mg/ml against MCF-7 cells and non-toxic towards normal cells with selectivity index of 8.0. To recapitulate, Luteolin-7-O-glucoside demonstrated significant anticancer profile and could be used as a candidate for chemotherapeutic drugs (Goodarzi et al., 2020).

2.5. Rheum undulatum

From the roots of *Rheum undulatum*, several constituents i.e., aloe emodin, chrysophanol-1-O-β-D-glucopyranoside, and rhapontigenin were extracted to display a significant antitumor profile. In addition to showing a substantial anticancer impact against MCF-7 cells, these extracts from the rhizome of *Rheum undulatum* demonstrated significant antitumor activity against two breast carcinoma cells. These isolated compounds also have the capability to reduce the feasibility of MCF-7 cells in comparison to standard drug fulvestrant. Aloe-emodin and rhapontigenin are responsible to induce of apoptosis by caspase-8 activation and chrysophanol 1-O-β-D-glucopyranoside exert its cytotoxic effect by inducing mitochondria-independent apoptosis. Three extracted components work as potential therapeutic agents due to its antiestrogenic and anti-Breast cancer activities (Lee et al., 2018).

2.6. Cimicifuga Dahurica

Isolated phytoconstituents from the *Cimicifuga dahurica* plant showed substantial growth inhibition activity against the MCF-7 cell line with BC. The ethanolic extract of *Cimicifuga dahurica* significant inducer of apoptosis and arrest the cell cycle growth through the caspase-dependent pathway at G0/G1-S phase (Huyen et al., 2018).

2.7. Allium Sativum

Allium sativum most commonly known as garlic has been used by the people to treat a range of illnesses from centuries. It consists of more than hundred varieties, with more medicinally effective secondary metabolites i.e. allicin, allinase and alliin. In the process of crushing the rhizomes, the amino acid alliin, which is already abundant in garlic extract, is converted into allicin. Allicin is the chemical that is essential for the production of sulfur-containing compounds, as well as the smell of those compounds and the medicinal characteristics they possess. (Wu et al., 2002). Garlic's high concentration of organic sulphides and polysulfides is what gives it its anti-cancer characteristics. White blood cells and macrophages increase anti-tumor activity by targeting cancerous cells and impairing the metabolic activity of tumour cells (Craig et al., 1999).

2.8. Flax Seed

The flax plant produces tiny, hard-shelled seeds that are brown and golden in appearance. All the active ingredients are contained in these tiny seeds. Omega 3-fatty acids, lignans, and dietary fibres are all found in abundance in flax seeds (Brooks et al., 2004). In contrast to soy products, flax seeds have stronger phytochemicals and significantly alter 2-hydroxyesterone clearance after consumption. Lignans are transformed into enterodiol and enterolactone in the gastrointestinal tract, which is what gives flax seeds their estrogenic impact.

3. Role of Phytoconstituents in the Modulation of Major Signaling Pathways Involved in BC

The pathways such as Extracellular signal regulated kinase (ERK) and Mitogen activated protein kinase acts as a major regulator of cellular development and survival. It has been shown that phytochemicals that target this pathway may be useful in inhibiting the proliferation of tumour cells, which can eventually lead to the death of the tumour cells. (Cohen et al., 2011, Burotto et al., 2014). Beside this Akt/PI3 signalling pathway is another essential pathway involved in regulation and development of breast cancer. Epidermal growth factor (EGF) levels drive a cascade of molecular pathways that ultimately result in resistance to apoptosis and unchecked cell proliferation, like Nuclear Factor kappa B (NF-κB) activation and Akt phosphorylation, while downstream of EGF can regulate, caspases Glycogen Synthase Kinase 3 beta (GSK3β), and mammalian Target of Rapamycin (mTOR) (Sun et al., 2010). Phytoconstituents such as, alkaloids and phenolics can considerably regulate the activation of these factors. They were shown to decrease Akt/PI3K signalling, cause cell cycle arrest and death, activate forkhead box O_3 ($FOXO_3a$), and suppress growth and migration of cancer cells (George et al., 2021). In addition to this, Janus kinases, also known as JAKs, have been shown to phosphorylate signal transducer and activator of transcriptions, also known as STATs. This causes the STATs to move through the membrane towards nucleus, where they regulate the gene transcription such as p53, Bcl-2, cyclin D, and interleukin-6 (IL-6), all of which are essential in the processes of growth, and cell death. (Yu et al., 2014). Compounds derived from plants have been shown to drastically increase the rate of induction of apoptosis in a variety of cancers by downregulating JAK/STAT signalling and activating apoptotic pathways. (Kim et al., 2016). Next is the Wnt/β-Catenin signaling Pathway, in this Wnt-protein binds to frizzled group transmenbrane receptors, along with this there is accumulation of catenin inside the nucleus and activates transcriptional factors that control cell proliferation, survival, and migration (Figure 2).

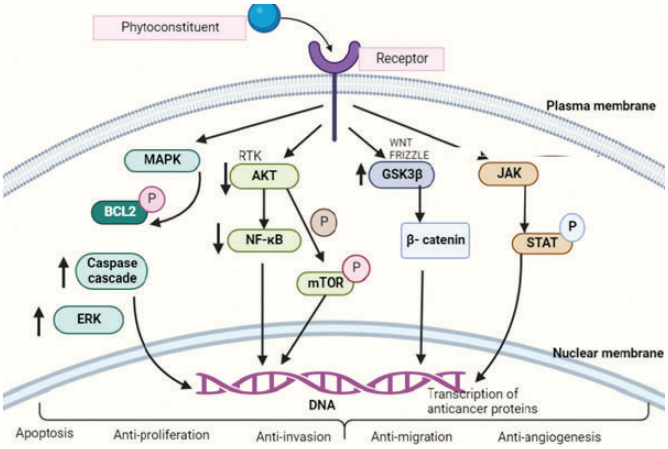

Figure 2: This is diagramatic illustration of mechanisms that contributes to the progression and development of BC and discussing the role of phytoconstituents in their inhibition.

By stimulating glycogen synthase kinase 3(GSK3), phytochemicals including curcumin, resveratrol, and epigallocatechin-3-gallate (EGCG) prevent the nuclear translocation and buildup of catenin (George et al., 2014).

During breast cancer signalling pathways such as MAPK, ERK, Akt/PI3, JAK-STAT, Wnt/β-Catenin, etc, are activated and can lead to the cellular differentiation, proliferation and survivability during tumor. In cancer cells, phytoconstituents that act on certain receptors may be useful in suppressing their growth, development, angiogenesis, and invasion, which can eventually lead to the death of cancer cells via a process known as apoptosis. ERK: Extracellular Signal Regulated Kinase, MAPK: Mitogen Activated Protein Kinase, BCL2: B-Cell Lymphoma2, NF-κB: Nuclear Factor kappa B, mTOR: mammalian Target of Rapamycin, Janus kinase (JAK)-signal transducer and activator of transcription (STAT), DNA: Deoxyribonucleic acid. GSK-3β: Glycogen Synthase Kinase-3 beta.

Table 1. In-vivo and in-vitro studies conducted to determine the effect of natural phytoconstituents on BC cell line.

Phytoconstituents	BC Cell line	Observation
Curcumin (Liu et al., 2017)	MCF-7 cells	Curcumin was able to inhibit MCF-7 cellular growth and promote apoptotic cell death, most likely through altering the NF-kB signalling pathway.
Sulforaphane (Pledgie at al., 2007)	SK-BR 3, MDA-MB-231, MCF 7 cell-lines	In the MDA-MB-231 cells, the apoptosis that was induced by sulforaphane seemed to start with the activation of Fas ligand, which subsequently activated Caspase 3, Caspase 8, and poly(ADP ribose)polymerase. A reduction in B-Cell Lymphoma 2 expression, the liberation of Cytochrome-C into the cytoplasm, and the activation of Caspase 9 as well as Caspase 3 were the first steps in the process of apoptosis in the other BC cell lines.
Withaferin A (Hahm et al., 2011)	MCF 7, MDA-MB-231 cell-line	Apoptosis may be triggered by WA by the generation of ROS and the activation of Bax/Bak.
aza-2'-deoxycytidine with green tea polyphenols (Tyagi et al., 2015)	MCF-7 and MDA-MB-231 cell-lines	Epigenetic therapy with the DNA demethylating chemical 5-aza-2'deoxyctidine (5-aza-2'dc) is clinically beneficial in the treatment of acute myeloid leukaemia. However, it has demonstrated very moderate success in the therapy of BC and has a large detrimental impact on normal cells.
Genistein (Pons et al., 2014)	MCF-7 T47D, MDA-MB-231 cells	In contrast to MCF-7 cells, which have an elevated ER/ER proportion and MDA-MB-231 cells, which have an ER-negative status, T47D cells, which have a low ER/ER ratio, respond well to genistein therapy, which results in a halt of the cell cycle and an increase in the functioning of mitochondria. This is in contrast to MCF 7 cells, which have a increased ER/ER ratio.
Wild thyme (Bozkurt et al., 2012)	MDA MB 231 and MCF-7 cells	It was shown that BC cells lines were much more susceptible to the cytotoxic effects of wild thyme than normal cells. Additionally, it reduced the activities of DNA Methyltransferase (DNMT) and Histone Deacetylase (HDAC) in MDA-MB 231, which led to the induction of apoptosis.
Isoliquiritigenin (Wang et al., 2014)	Mouse BC model	A growing body of research demonstrates that β-catenin signalling in BC stem cells (CSCs) is linked to cancer cell resistance and Adenosinetriphosphate-binding cassette subfamily G2 (ABCG2) expression. Isoliquiritigenin targets aberrant β-catenin signalling in CSCs which results in improving cancer chemosensitivity.
Clove buds (Kubatka et al., 2017)	MCF-7 cell line	In vitro tests on cytotoxicity, Brdu, cell cycle, annexin V/PI, caspase-7, Bcl-2, and mitochondrial membrane potential found that CLO extracts, which are made from dried flower buds of cloves, suppressed cell growth and accelerated apoptosis in MCF-7 cells.
Flax Seed (Di et al., 2018)	MDA-MB 231, MCF-7 cells, SKBR3	When flaxseed lignans were added to the treatment regimen, BC cells of both the SKBR3 and MDA-MB-231 subtypes were shown to be much more receptive to the lethal effects of the chemotherapeutic medicines.

4. Challenges Arose in the use of Phytoconstituents as Treatment of Breast Cancer

Before phytochemical anticancer treatments is be approved for use in patients, considerable proof of the agents' effectiveness, generated from proper clinical studies, is required to prove that they are effective against cancer. In spite of the fact that the aforementioned compounds exhibit promising anticancer properties, they too have drawbacks that need to be discussed either in order to improve the characteristics of (currently used) cancer treatment drugs or prior to their further clinical application (in the case of constituents that are already in the clinical stage). Because of their low therapeutic potential and harmful side effects, phytochemical substances

are still mostly avoided in cancer therapy. Other issues include poor aqueous solubility, poor penetration to enter in targeted cells, absorption by normal cells, and poor toxicity (Choudhari et al., 2020, Jafri, et al., 2020). In addition to these difficulties, the extraction, synthesis, optimization, and characterization of phytochemicals anticancer substances are obstacles to overcome in the identification and development of prospective phytochemical compounds applied therapeutically. Because of this, developments in analytical technology and computational approaches are anticipated to help in the discovery of novel phytochemicals, optimization of their extraction, and the selection of chemical synthesis or alterations (Garcia et al., 2021).

Conclusion

Overall, phytochemicals from natural plants have shown important role in suppressing tumor growth in breast cells. In the future, the extensive research should be concerned towards the search of more medicinal plants. In order to offer people suffering from breast cancer the most successful therapy possible, the newly discovered chemicals need to be both affordable and free of the harmful consequences that are often associated with chemotherapy. Overall, the literature survey identified that phytochemicals isolated from the medicinal plant could serve as the promising lead for BC treatment, therefore further research studies need to be implemented.

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Conflict of interest

There are no conflict of interest.

Declaration

It is an original data and has neither been sent elsewhere nor published anywhere.

Reference

Ahmad, A. (2019). Breast cancer statistics: Recent trends. *Advances in Experimental Medicine and Biology*, *1152*, 1–7. https://doi.org/10.1007/978-3-030-20301-6_1

Bozkurt, E., Atmaca, H., Kisim, A., Uzunoglu, S., Uslu, R., & Karaca, B. (2012). Effects of Thymus serpyllum extract on cell proliferation, apoptosis and epigenetic events in human breast cancer cells. *Nutrition and Cancer*, *64*(8), 1245–1250. https://doi.org/10.1080/01635581.2012.719658

Brooks, J. D., Ward, W. E., Lewis, J. E., Hilditch, J., Nickell, L., Wong, E., & Thompson, L. U. (2004). Supplementation with flaxseed alters estrogen metabolism in postmenopausal women to a greater extent than does supplementation with an equal amount of soy. *American Journal of Clinical Nutrition*, *79*(2), 318–325. https://doi.org/10.1093/ajcn/79.2.318

Burotto, M., Chiou, V. L., Lee, J. M., & Kohn, E. C. (2014). The MAPK pathway across different malignancies: A new perspective. *Cancer*, *120*(22), 3446–3456. https://doi.org/10.1002/cncr.28864

Chavez, K. J., Garimella, S. V., & Lipkowitz, S. (2010). Triple negative breast cancer cell lines: One tool in the search for better treatment of triple negative breast cancer. *Breast Disease*, *32*(1–2), 35–48. https://doi.org/10.3233/BD-2010-0307

Choudhari, A. S., Mandave, P. C., Deshpande, M., Ranjekar, P., & Prakash, O. (2019). Phytochemicals in cancer treatment: From preclinical studies to clinical practice. *Frontiers in Pharmacology*, *10*, 1614. https://doi.org/10.3389/fphar.2019.01614

Cohen, S. M., & Arnold, L. L. (2011). Chemical carcinogenesis. Toxicological Sciences, 120 Suppl. 1(suppl_1), S76–S92. https://doi.org/10.1093/toxsci/kfq365

Craig, W. J. (1999). Health-promoting properties of common herbs. *American Journal of Clinical Nutrition*, *70*(3) Suppl., 491S–499S. https://doi.org/10.1093/ajcn/70.3.491s

Cruceriu, D., Diaconeasa, Z., Socaci, S., Socaciu, C., Rakosy-Tican, E., & Balacescu, O. (2020). Biochemical profile, selective cytotoxicity and molecular effects of Calendula officinalis extracts on breast cancer cell lines. *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*, *48*(1), 24-39. https://doi.org/10.15835/nbha48111778

Dar, P. A., Mir, S. A., Bhat, J. A., Hamid, A., Singh, L. R., Malik, F., & Dar, T. A. (2019). An anti-cancerous protein fraction from Withania somnifera induces ROS-dependent mitochondria-mediated apoptosis in human MDA-MB-231 breast cancer cells. International

Journal of Biological Macromolecules, *135*, 77–87. https://doi.org/10.1016/j.ijbiomac.2019.05.120

Di, Y., De Silva, F., Krol, E. S., & Alcorn, J. (2018). Flaxseed lignans enhance the cytotoxicity of chemotherapeutic agents against breast cancer cell lines MDA-MB-231 and SKBR3. *Nutrition and Cancer*, *70*(2), 306–315. https://doi.org/10.1080/01635581.2018.1421677

Dubey, I., Saluja, M. S., Gilhotra, R. M., & Chhajed, M. (2018). Evaluation of polyherbal anticancer tablets: A review. *Journal of Pharmaceutical Technology*, *6*(1), 67–79. https://doi.org/10.15415/jptrm.2018.61006

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., & Bray, F. (2015). Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer*, *136*(5), E359–E386. https://doi.org/10.1002/ijc.29210

Garcia-Oliveira, P., Otero, P., Pereira, A. G., Chamorro, F., Carpena, M., Echave, J., and Prieto, M. A. (2021). Status and challenges of plant-anticancer compounds in cancer treatment. *Pharmaceuticals*, *14*(2), 157. https://doi.org/10.3390/ph14020157

Garg, N., Baishnab, S., Das, R., Kaur, K., Gupta, S., & Arora, S. (2019). Insights of breast cancer and barriers to its therapy. *Journal of Pharmaceutical Technology*, *7*(2), 73–86. https://doi.org/10.15415/jptrm.2019.72010

Ge, X., Chen, S., Liu, X., Wang, Q., Gao, L., Zhao, C., & Liu, Z. (2019). Ferrocene-appended iridium (III) complexes: Configuration regulation, anticancer application, and mechanism research. *Inorganic Chemistry*, *58*(20), 14175–14184. https://doi.org/10.1021/acs.inorgchem.9b02227

George, B. P., Chandran, R., & Abrahamse, H. (2021). Role of phytochemicals in cancer chemoprevention: Insights. *Antioxidants*, *10*(9), 1455. https://doi.org/10.3390/antiox10091455

Goodarzi, S., Tabatabaei, M. J., Mohammad Jafari, R., Shemirani, F., Tavakoli, S., Mofasseri, M., & Tofighi, Z. (2020). Cuminum cyminum fruits as source of luteolin-7-O-glucoside, potent cytotoxic flavonoid against breast cancer cell lines. *Natural Product Research*, *34*(11), 1602–1606. https://doi.org/10.1080/14786419.2018.1519824

Hahm, E. R., Moura, M. B., Kelley, E. E., Van Houten, B., Shiva, S., & Singh, S. V. (2011). Withaferin A-induced apoptosis in human breast cancer cells is mediated by reactive oxygen species. *PLOS ONE*, *6*(8), e23354. https://doi.org/10.1371/journal.pone.0023354

Huyen, C. T. T., Luyen, B. T. T., Khan, G. J., Oanh, H. V., Hung, T. M., Li, H. J., & Li, P. (2018). Chemical constituents from Cimicifuga dahurica and their anti-proliferative effects on MCF-7 breast cancer cells. *Molecules*, *23*(5), 1083. https://doi.org/10.3390/molecules23051083

Iqbal, J., Abbasi, B. A., Mahmood, T., Kanwal, S., Ali, B., Shah, S. A., & Khalil, A. T. (2017). Plant-derived anticancer agents: A green anticancer approach. *Asian Pacific Journal of Tropical Biomedicine*, *7*(12), 1129–1150. https://doi.org/10.1016/j.apjtb.2017.10.016

Iqbal, J., Ginsburg, O., Giannakeas, V., Rochon, P. A., Semple, J. L., & Narod, S. A. (2017). The impact of nodal micrometastasis on mortality among women with early-stage breast cancer. *Breast Cancer Research and Treatment*, *161*(1), 103–115. https://doi.org/10.1007/s10549-016-4015-5

Jafri, A., Amjad, S., Bano, S., Kumar, S., Serajuddin, M., & Arshad, M. (2020). Efficacy of nano-phytochemicals over pure phytochemicals against various cancers: Current trends and future prospects. In. Nanotechnology in the Life Sciences. *Cham, Germany: Springer*, 407–424. https://doi.org/10.1007/978-3-030-34544-0_20

Kim, D. H., Park, K. W., Chae, I. G., Kundu, J., Kim, E. H., Kundu, J. K., & Chun, K. S. (2016). Carnosic acid inhibits STAT3 signaling and induces apoptosis through generation of ROS in human colon cancer HCT116 cells. *Molecular Carcinogenesis*, *55*(6), 1096–1110. https://doi.org/10.1002/mc.22353

Kubatka, P., Uramova, S., Kello, M., Kajo, K., Kruzliak, P., Mojzis, J., & Busselberg, D. (2017). Antineoplastic effects of clove buds (Syzygium aromaticum L.) in the model of breast carcinoma. *Journal of Cellular and Molecular Medicine*, *21*(11), 2837–2851. https://doi.org/10.1111/jcmm.13197

Lee, D., Park, S., Choi, S., Kim, S. H., & Kang, K. S. (2018). In vitro estrogenic and breast cancer inhibitory activities of chemical constituents isolated from Rheum undulatum L. *Molecules*, *23*(5), 1215. https://doi.org/10.3390/molecules23051215

Liu, J. L., Pan, Y. Y., Chen, O., Luan, Y., Xue, X., Zhao, J. J., & Jia, H. Y. (2017). Curcumin inhibits MCF7 cells by modulating the NF-κB signaling pathway. *Oncology Letters*, *14*(5), 5581–5584. https://doi.org/10.3892/ol.2017.6860

Maughan, K. L., Lutterbie, M. A., & Ham, P. S. (2010). Treatment of breast cancer. *American Family Physician*, *81*(11), 1339–1346.

Moulder, S., & Hortobagyi, G. N. (2008). Advances in the treatment of breast cancer. *Clinical Pharmacology and Therapeutics*, *83*(1), 26–36. https://doi.org/10.1038/sj.clpt.6100449

Pledgie-Tracy, A., Sobolewski, M. D., & Davidson, N. E. (2007). Sulforaphane induces cell type–specific apoptosis in human breast cancer cell lines. *Molecular Cancer Therapeutics*, *6*(3), 1013–1021. https://doi.org/10.1158/1535-7163.MCT-06-0494

Pons, D. G., Nadal-Serrano, M., Blanquer-Rossello, M. M., Sastre-Serra, J., Oliver, J., & Roca, P. (2014). Genistein modulates proliferation and mitochondrial functionality in breast cancer cells depending on ERalpha/ERbeta ratio. *Journal of Cellular Biochemistry*, *115*(5), 949–958. https://doi.org/10.1002/jcb.24737

Reddy, K. B. (2011). Triple-negative breast cancers: An updated review on treatment options. *Current Oncology*, *18*(4), e173–e179. https://doi.org/10.3747/co.v18i4.738

Santis, C., De, C., Bryan, L., Ma, J., & Jemal, A. (2014). Cancer. *Journal of Clinical Medicine*, *64*(1), 52–62. https://doi.org/10.3322/caac.21203

Sun, Z. J., Chen, G., Hu, X., Zhang, W., Liu, Y., Zhu, L. X., . . . and Zhao, Y. F. (2010). Activation of PI3K/Akt/IKK-α/NF-κB signaling pathway is required for the apoptosis-evasion in human salivary adenoid cystic carcinoma: Its inhibition by quercetin. *Apoptosis*, *15*(7), 850–863. https://doi.org/10.1007/s10495-010-0497-5

Tesfaye, T., & Ravichadran, Y. D. (2018). Traditional Uses, Pharmacological Action and Phytochemical Analysis of Carissa carandas Linn: A Review. *Natural Products Chemistry and Research*, *06*(5), 334. https://doi.org/10.4172/2329-6836.1000334

Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal., Iqbal, J., Abbasi, B. A., Mahmood, T., Kanwal,,A. (2015). *Global cancer statistics*, 2012. *CA: a Cancer Journal for Clinicians*, *65*(2), 87–108. https://doi.org/10.3322/caac.21492

Tyagi, T., Treas, J. N., Mahalingaiah, P. K. S., & Singh, K. P. (2015). Potentiation of growth inhibition and epigenetic modulation by combination of green tea polyphenol and 5-aza-2′-deoxycytidine in human breast cancer cells. *Breast Cancer Research and Treatment*, *149*(3), 655–668. https://doi.org/10.1007/s10549-015-3295-5

Uramova, S., Kubatka, P., Dankova, Z., Kapinova, A., Zolakova, B., Samec, M., & Danko, J. (2018). Plant natural modulators in breast cancer prevention: Status quo and future perspectives reinforced by predictive, preventive, and personalized medical approach. *EPMA Journal*, *9*(4), 403–419. https://doi.org/10.1007/s13167-018-0154-6

Wang, B., Xing, Z., Wang, F., Yuan, X., & Zhang, Y. (2017). Fangchinoline inhibits migration and causes apoptosis of human breast cancer MDA-MB-231 cells. *Oncology Letters*, *14*(5), 5307–5312. https://doi.org/10.3892/ol.2017.6831

Wang, N., Wang, Z., Peng, C., You, J., Shen, J., Han, S., & Chen, J. (2014). Dietary compound isoliquiritigenin targets GRP78 to chemosensitize breast cancer stem cells via β-catenin/ABCG2 signaling. *Carcinogenesis*, *35*(11), 2544–2554. https//doi.org/10.1093/carcin/bgu187

Wu, X. C., Hotes, J. L., Fulton, J. P., Chen, V. W., Howe, H. L., & Correa, C. (2002). Cancer in North America, 1995–1999. NAACCR Combined Cancer Incidence Rates. Springfield, IL: North American Publishing Association of Central Cancer Registries. https://doi.org/10.3390/molecules23051083

Yu, H., Lee, H., Herrmann, A., Buettner, R., & Jove, R. (2014). Revisiting STAT3 signalling in cancer: New and unexpected biological functions. *Nature Reviews Cancer*, *14*(11), 736-746. https://doi.org/10.1038/nrc3818

Zainurin, N. A. A., Hashim, Y. Z. H. Y., Azmin, N. F. M., & Abbas, P. (2018). Agarwood Leaf essential oil characterization and effects on MCF-7 breast cancer cells. International Journal on Advanced Science, *Engineering and Information Technology*, *8*(4–2), 1604–1609. https://doi.org/10.18517/ijaseit.8.4-2.7034

Zheng, J., Zhou, Y., Li, Y., Xu, D. P., Li, S., & Li, H. B. (2016). Spices for prevention and treatment of cancers. *Nutrients*, *8*(8), 495. https://doi.org/10.3390/nu8080495

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