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REVIEW ARTICLE **OPEN ACCESS**

Potential Role and Molecular Mechanisms of New and Re-Purposed Synthetic as Well as Natural Bioactive Molecules Against Breast Cancer

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ABSTRACT
Breast cancer is the most frequent type of cancer in women worldwide. Breast cancer deaths have decreased over time, but it is still the second largest cause of cancer mortality among women overall and the top cause of cancer death among women. There have been many strategies developed over the years to control breast cancer, the treatment has been riddled with problems of multi drug resistance (MDR) and cytotoxicity of healthy cells. So, in order to combat the problem some new natural products from the category of ellagitanins (Corilagin, Castalin, Punicalagin) and Triterpenoidsaponins (α-Hederin, D-rhamnose β-hederin, Quillaic acid, Hederagenin) as well as a repurposed contraceptive Ormeloxifene have shown promising results. Thus, the review gives an insight about these new strategies and their mechanism of action for controlling breast cancer.
Keyword: *Breast cancer, Ormeloxifene, Triterpenoidsaponins, ellagitanins, mechanism of action*

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INTRODUCTION

Benign breast disease (BBD) is commonly observed among younger age groups in the second and third decades [1]. Most women experience a lump with or without pain that causes their fear about a malignant tumor and takes the patient to the breast clinic, outside of which 2/3 are benign. 200,000 patients visit annually a doctor with a palpable breast lump, but in most of the cases palpable lump is benign [2]. The common most fear about benign tumors are that it can turn into malignancy. Incidence of breast cancer and mortality rates have shown an increase rate in the last three decades. It has been reported that incidence of breast cancer has doubled in 60/102 countries (e.g., Afghanistan, Philippines, Brazil, Argentina) whereas death in breast cancer has doubled in 43/102 countries (e.g., Yemen, Paraguay, Libya, Saudi Arabia) [3]. Incidence of breast cancer has been reported to increase in low- and medium-income countries because of poor lifestyles (e.g., delayed pregnancies, reduced breastfeeding, low age at menarche, lack of physical activity, and poor diet)[4]. In comparison with men, women have increased risk factors of breast cancer due to enhanced level hormone stimulation (particularly estrogen and progesterone) [5]. Endogenous Hormones and Breast Cancer Collaborative Group reports that the alternation in physiological level of sex hormone may cause higher risk of breast cancer in premenopausal and postmenopausal women. The risk of developing breast cancer increases as follows—the 1.5% risk at age 40, 3% at age 50, and more than 4% at age 70. Mutation of two major genes BRCA1 (located on chromosome 17) and BRCA2 (located on chromosome 13) are associated with an increased risk of breast cancer [6]. Other genes including TP53, CDH1, PTEN, and STK11 can be responsible for breast cancer. A significant interaction of DNA repair genes with BRCA genes (ATM, PALB2, BRIP1, CHEK2) are expected to induce breast cancer. Higher density of breast tissue is found in young age females as well as lower BMI, who are pregnant or during the breastfeeding period, as well as during the intake of hormonal replacement therapy [7]. The higher breast tissue density is associated with the greater breast cancer risk in both premenopausal and postmenopausal females [8]. It has been reported that excessive intake of alcohol and smoking are increasing risk factors in breast cancer [9]. Breast cancer is a heterogeneous as well as complex disease with different biological behavior that is required for different treatment. Much research has been found that treatment for breast cancer initially responds but with time resistance develops to a broad range of drugs.Multidrug resistance (MDR) in breast cancer fails treatment and increases mortality rate in breast cancer. Many researchers developed different strategies to overcome MDR in breast cancer [10]. Many research has reported that

natural products have the ability to overcome MDR in breast cancer by regulating proteins involved in resistance, targeting non-apoptotic cell death, and inducing other types of non-apoptotic cell death. Many natural products including alkaloids, flavonoids, phenylpropanoids, terpenoids and saponin have the ability to reverse drug resistance. Many of these natural products have long been used but very recently bioactive phytochemicals like triterpenoid saponins and ellagitannins have been emphasized upon for their potent action against breast cancer. Another therapeutic strategy that has earned publicity in breast cancer is drug repurposing. Recent pharmaceutical agents that are primarily used for non-cancerous disease are being used for breast cancer, it is called drug repurposing. FDA has approved this strategy for that drug which would have already passed drug safety protocols and has a known pharmacokinetic profile [11]. Ormeloxifene and their derivatives are the drugs that are used for drug repurposing in breast cancer. Here we reviewed the effect of natural products and repurposing drugs in breast cancer treatment to overcome multidrug resistance. This review focuses upon these new strategies and their molecular mechanisms to prevent breast cancer.

PROPERTIES OF ORMELOXIFENE

Ormeloxifene is a centchroman with a non-steroidal selective estrogen receptor modulator (SERM). It is used as an oral contraceptive. Ormeloxifene is a lipophilic in nature with appropriate pharmacokinetic and pharmacodynamic properties. Metabolism of ormeloxifene occurs in the liver and excretion occurs through faces. The active metabolite is found to be 7-desmethylated ormeloxifene. Active metabolite is rapidly produced after administration of ormeloxifene within 1 h **[**12]. It peaks usually between 8–24h. Many researches establish that retention concentration of ormeloxifene in well perfused organs (liver, lungs and spleen) is found to be more than less perfused organs (pancreas and muscle). It has been reported that healthy female volunteers were administered with either a single oral dose of 60 mg or 30 mg ormeloxifene during human clinical trials [13]. The half-life of the drug is observed at 168h. Studies reveal that serum concentration (Cmax) of the drug in humans is found to Cmax of 55.53 ± 15.43 ng/ml for 30 mg dose and Cmax of 122.57 ± 6.25 ng/ml for 60 mg dose and It is reached within 4h–6h. Serum concentration (Cmax) is observed breast cancer patients treated with either 30 mg, twice a week for 12 weeks (Cmax 54.98 ± 14.19 ng/ml) or 60 mg of ormeloxifene on alternate days for 1 month or 1 year (Cmax 135 ± 15.5 ng/ml). It has been demonstrated that the drug has action to inhibit rapid cell proliferation in the endometrium during embryonic implantation along with its favorable bioavailability, stability and safety in humans makes it an attractive repurposing molecule for controlling undesired rapid cell proliferation such as endometriosis and cancerous conditions. It has been observed that it has action for prevention of breast and uterus, probably due to its potent estrogen antagonistic activity. It has weak estrogenic activity in bone that stimulates new bone formation [14].

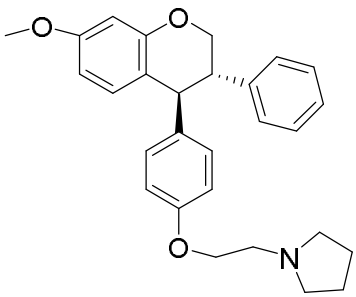

FIGURE 1: Structural properties of Ormeloxifene

Effect of Ormeloxifene in breast cancer

Estrogen mediated signaling acts on two receptors that are ERα and ERβ. After ligand binding, dimerization of receptors occurs to translocate into the nucleus and regulate the expression of a multitude of genes. Protein Kinase C (PKC), AKT pathways are activated by specific estrogen receptor stimulation to regulate various functions within the cell. Initiation and progression of breast cancer depends on dysregulation of ER signaling. Opposite effects on cell proliferation, apoptosis and motility are found in two estrogen receptors (ERα and ERβ) [15]. Proliferation of breast cancer cells as well as poor disease prognosis depends on mitogenic properties of ERα. studies appear that Over expression of ERα is associated with 70% of breast tissue. ERβ mediated signaling has the ability to prevent the proliferative and malignant effect of ERα by modulating the expression of many ERα regulated genes [16,17]. Down regulation of ERβ is significantly responsible for invasion in breast cancer. Compounds that have the ability to selectively regulate expression of ERα signaling to treat breast cancer. Ormeloxifene modulates both estrogen receptor subtypes, illustrating higher selectivity and affinity towards ERα (8.8%) as compared to ERβ (3%) [18].

This is why ormeloxifene is used for the treatment of breast cancers [19,20]. Mishra et al reported the first in vivo use of ormeloxifene as an anti-cancer drug on advanced stage breast cancer patients, non-responsive to conventional therapy. Studies reported that patients having breast cancer were treated with ormeloxifene (60 mg, three times a week) for 4–6 weeks, about 38.5% of breast cancer patients responded to the ormeloxifene therapy [21]. Studies revealed that response of ormeloxifene is better anti-cancer activity in older female patients (peri and postmenopausal) compared to younger (premenopausal) patients. Much research demonstrated that ormeloxifene has the ability to induce caspase and mitochondrial-dependent apoptosis in breast cancer cells. The action of ormeloxifene is to inhibit cell proliferation at concentrations similar to tamoxifen in both In ER+ (MCF-7 cells) and ER– (MDA-MB231) breast cancer cell line models. Ormeloxifene appeared to produce apoptosis by depolarizing the mitochondrial membrane potential as well as arresting G0/G1 cell cycle phase in both above breast cancer cell lines. This above effect corresponded with the enhanced expression of cell cycle regulators like p21Waf1/Cip1and p27Kip1 and down regulation of Cyclin-D1 and Cyclin-E expression. Since p21Waf1/Cip1 expression is usually controlled transcriptionally and post-transcriptionally by the p53-dependent/independent pathway. A research study demonstrated that ormeloxifene can induce apoptosis in combination of resveratrol or curcumin at much lower concentrations. Ashok K.Giri et al. reported that it has ability to partial to complete remission of lesions in 40.5% of breast cancer patients [22].Vandana Bansal et al. reported that Ormeloxifene showed significant efficacy for the treatment of mastalgia and fibrocystic breast disease [23]. Girish T. U et al. reported that ormeloxifene can be used as the first line of treatment in patients with fibroadenosis and mastalgia and used as an alternative to surgery for fibroadenoma [24]. Satish Agrawal et al. reported that pegylated chitosan nanoparticles enhanced anti-breast cancer activity [25].

New natural products in breast cancer

Breast cancer treatment was a bit of a mirage in terms of natural product breakthroughs. Theoretically, however, medicinal plants have the capacity to play a big role in drug development because, if used effectively, they could address the issue of synthetic medications having multidrug resistance, which are mainly out of reach for the impoverished people of developing countries [26,27]. The descriptions of numerous natural product types are provided here.

Numerous studies have focused on phytochemicals, which are non-nutritive plant chemicals that have disease-protective or -preventive properties. Some of these have shown excellent results in breast cancers especially as potential treatment for therapeutics for ER(+) breast cancer [28].

In over 80% of all cases of breast cancer, the ER status is positive. Tamoxifen and aromatase inhibitors are two hormone therapies now utilized to treat ER(+) breast cancer [29]. Although these treatment options have produced notable outcomes, after a few years of treatment, female patients begin to manifest overt signs of resistance to hormonal therapy. As a result, a number of medications with natural origins, such as lignans, isoflavones, ellagitannins, triterpenoidsaponins, prenyl flavonoids, etc., act as selective estrogen receptor modulators to counteract resistance. This paper presents a thorough analysis of many phytochemicals classified as triterpenoid saponins and ellagitannins, along with an explanation of how they work [30,31].

Effect of triterpenoid saponins in breast cancer

Numerous triterpenoid saponins have been demonstrated to be promising treatments and chemo preventatives for breast cancer. The triterpenoids such α-hederin, β-hederin, hederagenin, and quillaic acid as prospective medicines for chemoprevention and therapy of breast cancer were reviewed in a number of outstanding studies.

α-hederin

α-Hederin, a monodesmosidictriterpenoid saponin found in Nigella and Hedera species, exhibits a wide range of biological functions [32]. According to Cheng et al, α-Hederin enhances release of Apaf-1 and cytochrome c from the intermembrane gap into the cytosol, where they enhanced caspase-3 and caspase-9 activation, was caused by α-hederins induction of depolarization of mitochondrial membrane potential. Accordingly, it suggests that triterpenoidsaponin -hederin may be a good choice for chemotherapy of breast cancer [33]. A report by Wang et al, Alpha-hederin induces the apoptosis of cancer cells by regulating PI3K/Akt/mTOR signaling pathway [34].

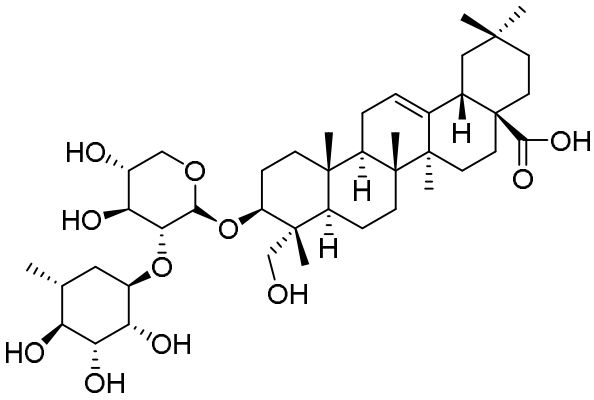

FIGURE 2: Structural properties of α-Hederin

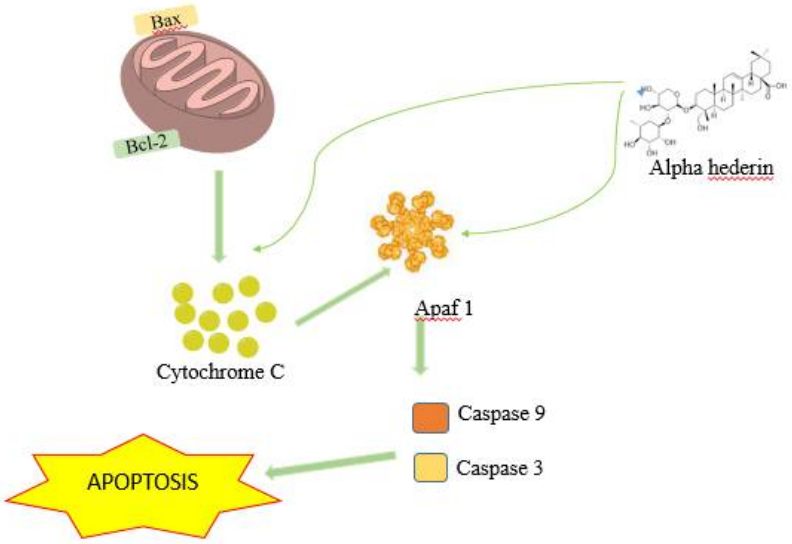

FIGURE 3: Mechanism of action for α-Hederin causing apoptosis.

D-Rhamnose-β-hederin

A novel oleanane-type triterpenoid saponin called D-rhamnose β-hederin (DR- βH), which was discovered in the *Clematis ganpiniana* plant used in traditional Chinese medicine, has been shown to be effective against several tumour types. Exosome production and secretion are regulated by D-rhamnose - β hederin, according to numerous findings [35]. Studies by Chen et al., carried out in vitro revealed that DR- β H has anti-proliferative and pro-apoptotic activities in human breast cancer cells [36].

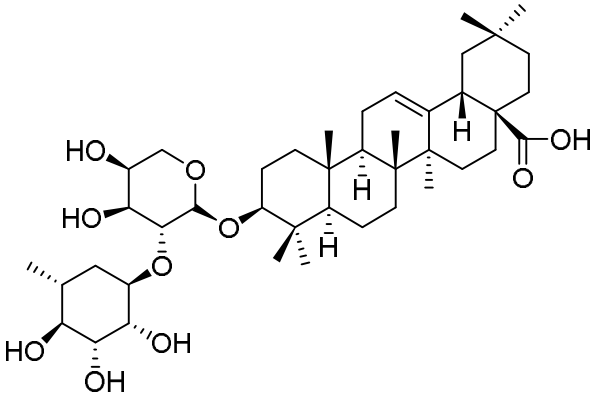

FIGURE 4: Structural properties of D-rhamnose β-hederin

Quillaic acid

Quillaic acid is a pentacyclic triterpenoid that is olean-12-ene substituted by hydroxy groups at positions 3 and 16, an oxo group at position 23 and a carboxy group at position 28 (the 3beta,16alpha stereoisomer) [37]. The native *Quillajasaponaria*Mol tree in Chile is known for its saponins, which are both common and

well investigated. Quillaic acid is highly desired for use in the treatment of breast cancer because it is known to cause cell cycle arrest and apoptosis through regulating NF-κB and MAPK pathways [38].

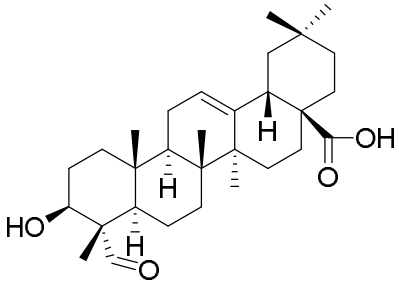

FIGURE 5: Structural properties of Quillaic acid

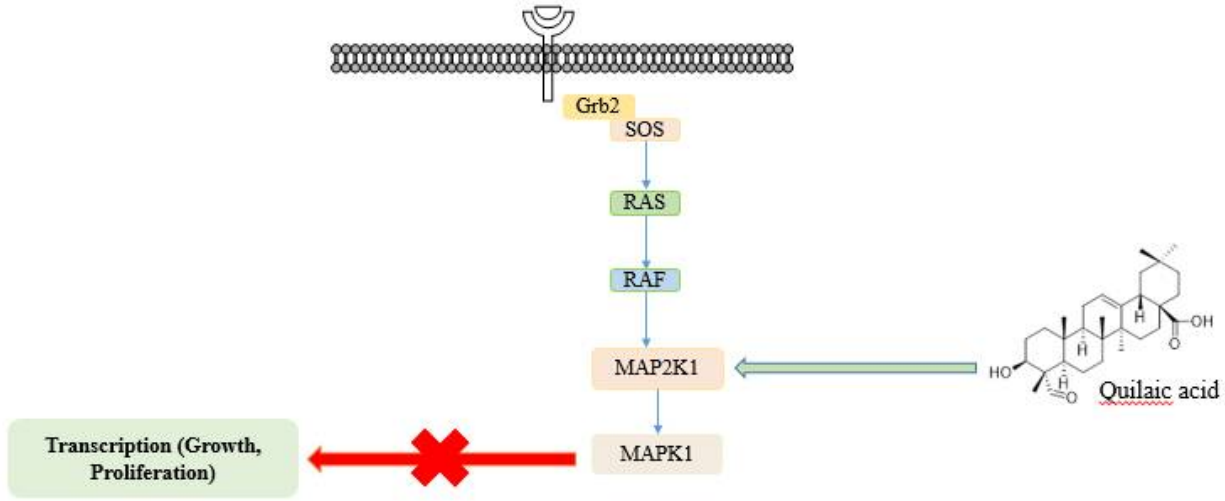

FIGURE 6: Anti cancer mechanism of Quillaic acid

Hederagenin

Hederagenin is a sapogenin that is olean-12-en-28-oic acid substituted by hydroxy groups at positions 3 and 23 (the 3β stereoisomer). Hederagenin selectively induces apoptosis in cancer cells by promoting reactive oxygen species (ROS) production and Glutathione (GSH) depletion via inhibition of the Nrf2-ARE pathway [39-41].

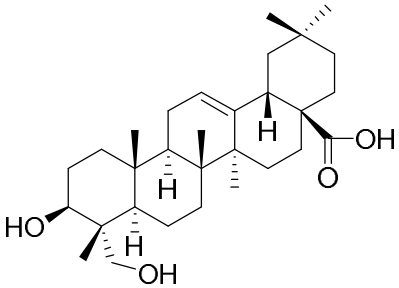

FIGURE 7: Structural properties of Hederagenin

Effect of ellagitannins in breast cancer

Ellagitannins and their hydrolysis product, ellagic acid, inhibit prostate cancer cell growth through cell-cycle arrest and stimulation of apoptosis. Various ellagitannins like Corilagin, Casltalin and Punicalagin.

Corilagin

Corilagin is an ellagitannin with a hexahydroxydiphenoyl group bridging over the 3-O and 6-O of the glucose core. It is an ellagitannin and a gallate ester. Corilagin has shown inhibitory activity against the growth of numerous cancer cells including breast cancer cells by prompting cell cycle arrest at the G2/M phase and augmented apoptosis [42, 43]. As per Tong et al., Corilagin-induced apoptosis and autophagic cell death depends on production of intracellular reactive oxygen species in breast cancer cell line. The potential apoptotic action of corilagin is mediated by altered expression of procaspase-3, procaspase-8,

procaspase-9, poly (ADP ribose) polymerase, and Bcl-2 Bax. In nude mice, corilagin suppressed cholangiocarcinoma growth and downregulated the expression of Notch1 and mammalian target of rapamycin [44].

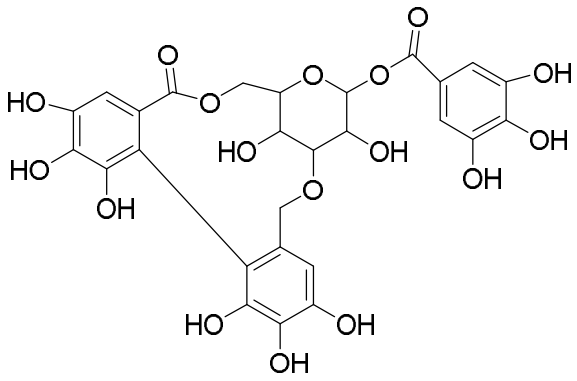

FIGURE 8: Structural properties of Corilagin

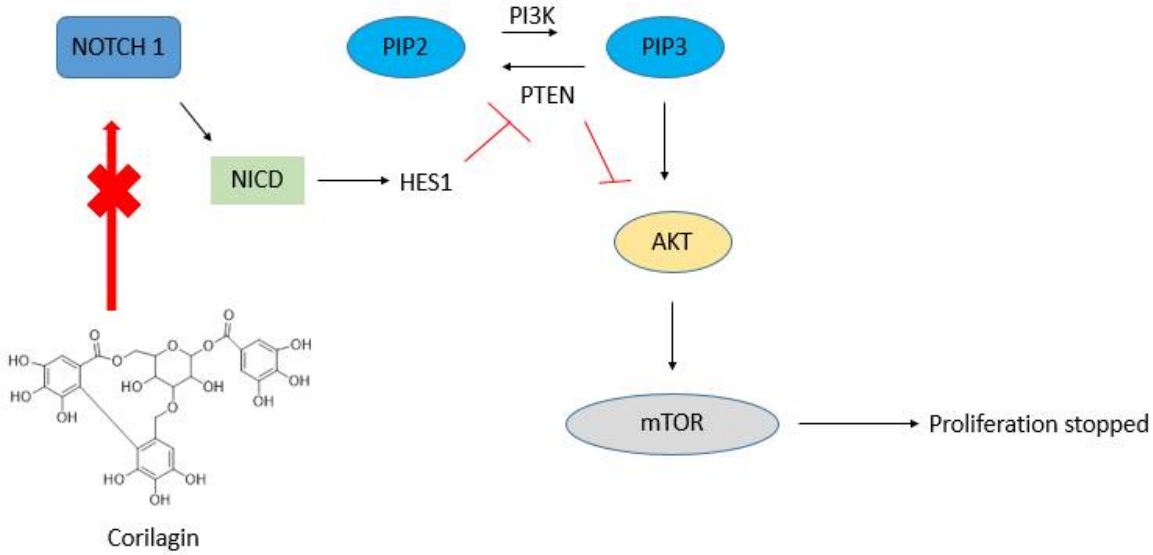

FIGURE 9: Antiproliferative mechanism Corilagin

Castalin

Castalin is an ellagitannin that can be found in oak wood and in *Melaleucaquinquenervia* leaves. Various reports regarding the size-dependent bioactivities of castalin were analyzed by comparing the cytotoxic effects of native castalin and castalin nanoparticles on cancerous cells in vitro and in vivo [45]. In vitro experiments indicated that castalin nanoparticles induced apoptosis of an osteosarcoma cell line more efficiently than native castalin [46].

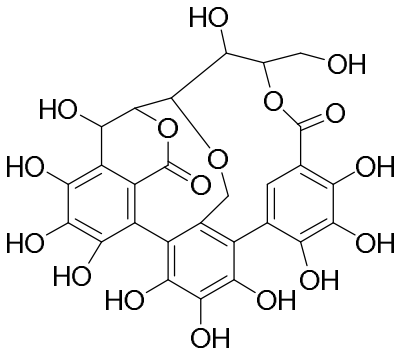

FIGURE 10: Structural properties of Castalin

Punigalacin

Punicalagin is an example of ellagitannin, a phenolic substance. Pomegranates (*Punicagranatum*), *Terminalia catappa*, and *Terminalia myriocarpa* all contain it as alpha and beta isomers [47]. Punicalagin

inhibits proliferation while inducing death and autophagy by activating the caspase cascade, altering Bax and Bcl-2, and controlling autophagy via the mTOR/ULK1 signalling pathway [48,49].

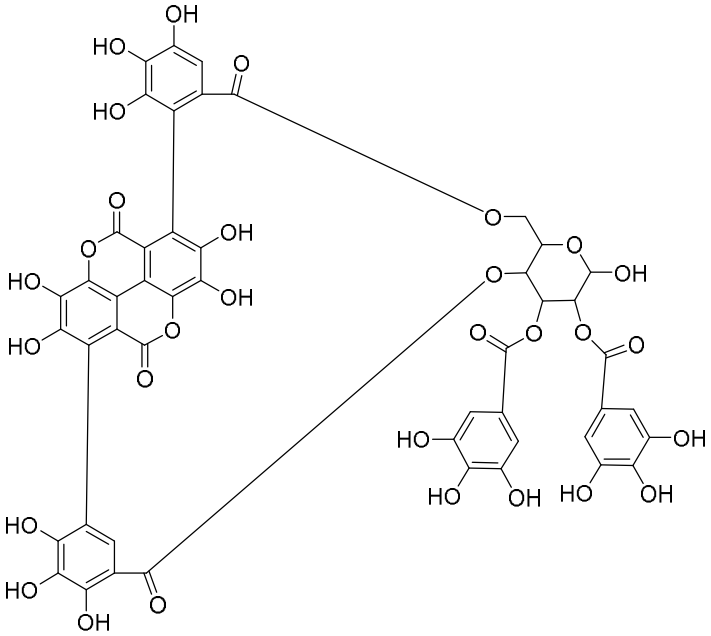

FIGURE 11: Structural properties of Punigalacin

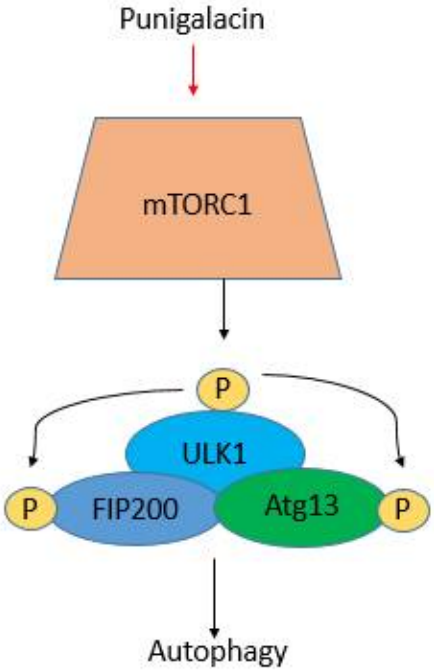

FIGURE 12: Mechanism of action of Punigalacin against breast cancer cells.

Table 1: Molecular mechanisms of new and re-purposed synthetic as well as natural bioactive molecules against breast cancer

COMPOUND NAME	SOURCE	MECHANISM OF ACTION
Ormeloxifene	Synthetic	Selective estrogen receptor modulator [22].
α-Hederin	Natural	α-Hederin enhances release of Apaf-1 and cytochrome c from the intermembrane gap into the cytosol, where they enhanced caspase-3 and caspase-9 activation, was caused by α-hederins induction of depolarization of mitochondrial membrane potential [33].
D-rhamnose β-hederin	Natural	DR- β H has anti-proliferative and pro-apoptotic activities in human breast cancer cells [35].

Quillaic acid	Natural	Quillaic acid is known to cause cell cycle arrest and apoptosis through regulating NF-κB and MAPK pathways [38].
Hederagenin	Natural	Hederagenin selectively induces apoptosis in cancer cells by promoting reactive oxygen species (ROS) production and Glutathione (GSH) depletion via inhibition of the Nrf2-ARE pathway [41].
Corilagin	Natural	Corilagin-induced apoptosis and autophagic cell death depends on production of intracellular reactive oxygen species in breast cancer cell line [44].
Castalin	Natural	Castalin nanoparticles induces apoptosis of an osteosarcoma cell line more efficiently [46].
Punicalagin	Natural	Punicalagin inhibits proliferation while inducing death and autophagy by activating the caspase cascade, altering Bax and Bcl-2, and controlling autophagy via the mTOR/ULK1 signalling pathway [48].

CONCLUSION

Breast cancer is one of the most widely spread cancers in both developed and developing countries worldwide. Many resources and research has been conducted to understand its progression, multiple gene involvement in unregulated growth and proliferation. Abnormal growth by involvement of multiple molecular pathways in breast cancer causes difficulties for designing and developing new anti-cancer drugs with little or no side effects. The invention of new drugs is very time consuming with lots of expensive and also few molecules can pass the final stage. To overcome high mortality and morbidity rate in breast cancer, the more effective and convenient way might be the repurposing of established drugs such as ormeloxifene as anti-cancer agents, using natural product that have potential anticancer effect (α-Hederin, Castalin) and also combination of synthetic and natural product. Here we reviewed molecular mechanisms of repurposing of established drugs and also few natural products that have potential inhibition effects in breast cancer. This information may help in developing a novel therapeutic regimen for the treatment of breast cancer to overcome multidrug resistance and side effects.

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