Review Article

Lupeol Impact on Breast Cancer Management

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ABSTRACT

Conventional therapies for the management of breast cancer are lacking in outcomes and also cause several adverse effects that prompted the acquisition of new therapeutic approaches for combating breast cancer without any of these pitfalls. Moreover, fostering a holistic therapeutic strategy might be a significant solution to this issue, because it is evident that products obtained via dietary sources have a great number of anti-breast cancer capacities with fewer side effects and low cost. Considerably over the past decade, the demand for triterpenes for breast cancer management has increased significantly due to the declining properties of cancer. However, lupeol (LUP) is a dietary triterpene and the active ingredient found in most medicinal plants has indeed been witnessed to manifest numerous pharmaceutical attributes especially anti-cancer activities, and is strongly related to the declining prevalence of breast cancer in Asian countries. Several reports offer valuable input into the lupeol mechanism of action and thereby propose that this was a multi-target substance with massive potential towards breast cancer (BC) by hitting pivotal molecular pathways associated with breast cancer. There seems to be extensive evidence of such a wonderful compound's anti-breast cancer activity. In this review, we strenuously reaffirm lupeol's preventive and therapeutic effects in the breast cancer model, with a focus on multi-targeted biological and molecular effects.

Keywords: Lupeol, Breast cancer, Chemoprevention, Dietary triterpene, Phytochemicals.

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INTRODUCTION

Cancer is the product of a multi-stage, multi-mechanism carcinogenic process involving mutation, epigenetic, and cell death processes in three separates but intimately related phases of inception, promotion, and advancement.[1] This will still be a drastic public health crisis because it's one of the leading causes of morbidity and mortality globally. Among various types of cancer, breast cancer is the general form of cancer in females and it is the foremost reason for cancer-relevant deaths. As recorded in 2020, breast cancer has a prevalence of 11.7% with all other types and is responsible for 6.9% of deaths annually.[2] Chemoprevention is an approved and efficient therapeutic choice to BC, but restricted treatment measures and variable adverse effects of presently available medications like neutropenia, vasomotor syndrome, postmastectomy edema, nausea and vomiting, arthralgia, cachexia, pain, weakness, loss of hair, hot flushes, and psychological stress pose significant obstacles in expanding its reliability.[3] Arising solutions might include finding potential drug targets that are extremely effective in suppressing BC cell growth, with minimal side effects. Overcome by natural agents modern drug discovery programs focus on screening plants and other natural products.

Foods, food handling strategies or nutritional supplements may apply to delaying or inhibiting the progression of cancer in healthy people with genomic or epidemiological proof of a future change of risk. Because it is impossible to reduce the inception stage to nil the highest capable interference would be to remove premalignant cells at the promotion phase until they are cancerous.[4] It gets many years for normal cells to become cancerous. Hence, the idea of reducing or avoiding this change is a feasible and achievable aim and it is only possible by the use of natural dietary supplements. Natural therapeutics is a valuable source of highly effective and less toxic compounds with unique chemical structures. Natural triterpenoids are ubiquitous compounds that are of prior in advance because of their broad range of pharmacological activities. Mounting evidence supports the beneficial impact of natural triterpenoids on various types of human diseases including various cancers. [5] Triterpenoids are promising fighters against BC, which perform a multitude of biochemical events including reducing inflammation, reducing oxidative stress, regulating the cell cycle, suppressing cell proliferation, activating apoptosis, and modulate multiple signaling pathways involved in the proliferation of breast cancer cells.[6]

The noticeable dietary triterpene is lupeol, found mainly in white cabbage, green peppers, strawberries, olives, mangoes, and grapes, which has already been investigated due to its multiple beneficial properties as a treatment and inhibitory agent against breast cancer. LUP has strong anti-

inflammatory, anti-mutagenic, anti-malarial, anti-oxidant, and anti-arrhythmic activity. It has a dual-prong technique of targeting various molecular pathways that respond to angiogenesis induction and tumor production inhibition. Lupeol's underlying anti-cancer mechanism and its function in the regulation of anti-apoptotic and pro-apoptotic genes may open up new possibilities for anti-breast cancer therapy.[7] LUP has therefore been identified as a vital herbal source for defense against breast cancer. In this review, we focused mechanism of action of lupeol against breast cancer activity.

Natural Agents

Natural remedies are quickly discovered and developed around the world. Some drugs are discovered for medical examination of this nature. Among them, LUP is the selected compound. This LUP is one of the natural agents with high triterpenoid potential. Combining natural triterpenes into multiple target drugs is one way to increase their effectiveness. Various natural formulations of triterpene and their triterpene juices can be used and plants such as edible fruits and vegetables can be used as starting materials for pharmaceutical production.[8] In the above conversation, it's now clear that the browsing of naturally occurring bioactive agents in vegetables and fruits may inhibit different pathways of signaling in cells. Therefore, the biological properties of natural triterpenoids may inhibit the growth as well as the function of apoptosis of tumor cells and their use in the treatment of human breast cancer. Consequently, most clinicians highly encourage the use of natural foods because they may interact with cancer-fighting methods by creating natural agents.

Triterpenoid

Triterpenes are the natural constituents of the human diet. Triterpenes are produced in large part from vegetable oils, cereals, and berries. In the Western world, the human intake of triterpenes is estimated at 250 mg per day, with significant weight gain per person in the Mediterranean reaching 400 mg / kg / day. The dishes are based on olive oil.[9] Over the last century, there has been an unparalleled explosion of importance to triterpenes Figure 1.

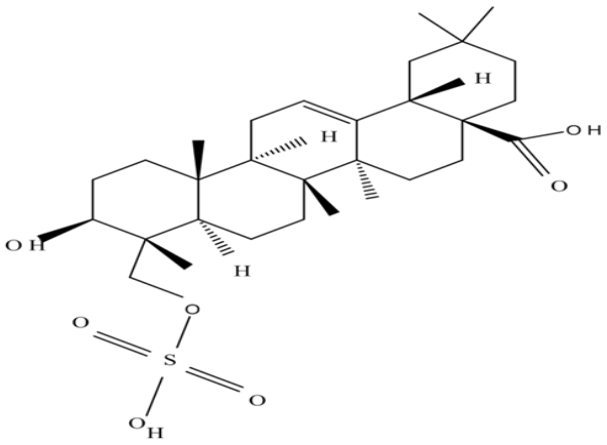

Figure 1: Structure of Triterpenoid

This is isopentenyl pyrophosphate glucan metabolites and it has the biggest number of phytochemicals. More than 20,000 triterpenoids have been predicted to exist in nature. They are found mainly in plant species, like marine weeds also resin adhesives of many fruits and herbal medicines; included cranberries, apples, olives, mistletoe, figs, floral, rosemary, oregano, and tarragon. Triterpenoids are metabolized in plants through the nitration of squalene, a hydrocarbon triterpene, and a prelude of all steroids.[10] LUP is a triterpene with a wide variety of pharmacological behaviors that has drawn the interest of medical practitioners, academics, and pharmaceutical advertisers.

Sources of Lupeol

LUP has also been described to be active in various species of the plant world Table 1. It is present in edible vegetables, white fruits, pepper, mulberry, tomato, carrot, peas, bitter root, black tea, soybean, cucumber, strawberries, mango, guava, red grapes, date palm, and cabbage [11] Table 2. It is also present in some medicinal plants like *American ginseng, Tamarindus indica, Cocoa butter, Himatanthu ssuccuba, Celastruspa niculatus, Allanblac kiamonti cola, Leptadenia hastata, Crataevanur vala, Bombax ceiba,* and *Zanthoxyl umriedelianum*. Native Americans use *Sebastianiaade nophora*, the most significant source of lupeol in Africa, North America, Asia, China, Latin America, and the Caribbean islands. [12]

Table 1: List of selected plant producing lupeol

S. no	Scientific name	General name
1.	Aloe vera	Aloe
2.	Cucumis sativus	Cucumber
3.	Daucus carota	Carrot
4.	Glycine max	Soya bean
5.	Lycopersicon esculentum	Tomato
6.	Olea Europe	Olive
7.	Psidium guajava	Common guava
8.	Capsicum annuum	African Pepper
9.	Morus alba	White mulberry
10.	Gentiana lutea	Bitter root

Table 2: Lupeol content in fruits and plants

S. no	Name of plant & fruits	Lupeol (µg/g)
1.	Mango fruit	1.80 µg/g mango pulp
2.	Olive fruit	3 µg/g fruit
3.	Elm plant	880 µg/g bark
4.	Aloe leaves	280 µg/g dry leaf
5.	Ginseng oil	15.2 mg/100 g of oil
6.	Japanese pear	175 µg/g twig bark

Molecular Structure of Lupeol

The molecular structure of the lupeol element formula is $C_{30}H_{50}O$, Figure 2, and its melting point is 215–216°C. The designed equity from LUP are composition demonstrate that it has a molecular weight of 426.7174 (g/mol), H-B acceptor1, H-B donor1.[13] Infrared spectroscopy of LUP shows the presence of a hydroxyl role and an olefinic moiety, that is present in the spectrum at 3235 and 1640 cm-1 respectively. [14] The 1H-NMR spectrum reveals seven methyl singles and a telephonic activity. A study by Watermark et al., using a high-performance liquid chromatographic (HPLC) method with UV and mass spectrometry (MS), shows that LUP shows a parent ionic peak at m / z 409. [15]

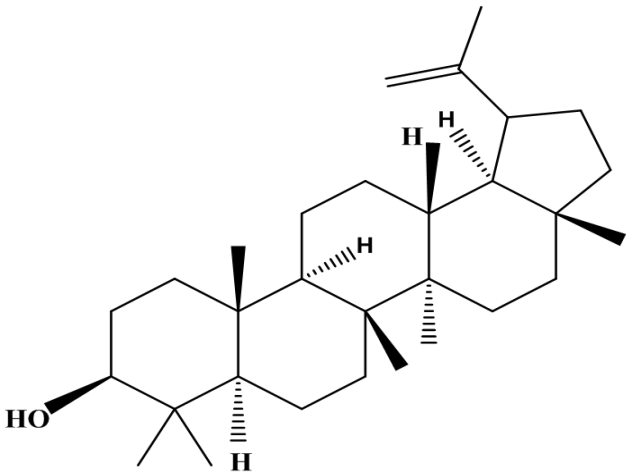

Figure 2: Structure of Lupeol

Biological Properties of Lupeol

LUP is a natural triterpenoid, also identified likes phytosterols are in advance interest due to their wide range of natural activities. It has various strong biological actions against inflammatory, mutagenic, malarial, oxidant, diabetic, cancer, and arrhythmic activity. Potential clinical uses of lupeol in oxidative, atherosclerosis, viral, neurodegenerative, autoimmune, and malignant disorders have been tested accordingly. LUP also has excellent antioxidant properties and prohibits the function in DNA topoisomerase II, and identified targets for anticancer chemoprevention.[16] Thereby LUP biosynthesis occurs in the cytosol and it has derived from acetyl cocaine with increased production of mevalonate, dimethyl pyrophosphate, iodobenzene pyrophosphate, and formula pyrophosphate. Next, the synthase of squalene transforms FPP into squalene. To form a lumenal cation, squalene epoxidase transforms squalene of 2, 3-Oxidasqualene, which can be cycled by LUP isoforms. Finally, through hydrolysis of a 29-methyl group, the lumenal cation is transformed into LUP. The literature available indicates that LUP is an anti-drug which, at doses ranging from 30 to 2000 mg/kg, there is no cause of any chronic toxicity in animals.

Breast Cancer

BC is currently the second-largest malignant tumor in the world, the major cause of cancer mortality in women, and the second most common cause of cancer. The pathology had about 2, 76,480 new cases (about 30% of all cancers reported) and caused about 42,690 deaths in 2020. BC is more common in Western Europe and the United States, while it is less common in Asia and Africa.[17] The principal associated risk factors include being female, genetic predisposition (BRCA1 and BRCA2 mutations), ageing, nulliparity, radiation exposure, breast density, long-term hormonal therapy, and lifestyle-associated factors obesity, etc. In recent years, the survival rate for this disease has improved dramatically, primarily through awareness efforts, self-examination, and the development of more effective therapies. The survival rate has climbed from 75% in the 70s to 81% in the 2020s. Five-year life expectancy is 91 percent. [18]

BC treatment is based on the type of expressed molecular markers such as HER2 / neu, progesterone receptor (PR), and estrogen receptor (ER). The primary treatment for this disease includes surgery, radiation therapy, hormone therapy, and chemotherapy. However, traditional clinical techniques fail to fulfill the main requirements for successful BC treatment. The benefit of naturally derived anti-cancer drugs has emerged as a different safe, reduced, and easy one. Hence the current, natural agent's interventions are encouraging and appear like feasible access for reducing cancer risk worldwide. Thereby LUP has shown well results against BC in many studies conducted. Methanolic extract from the natural agent (lupeol-rich plant) was tested against ER-positive cell line MCF-7 and ER-negative cell line MDA-MB-231, which was highly effective against MDA-MB-231.[19] Another research found that LUP extracted from *natural products* confers its apoptotic action by down-regulation of Bcl-xL and Bcl-2, leading to the release of cytochrome C and the activation of intrinsic pathway apoptosis. This influence was seen only on MCF-7 (breast cancer), but not on MCF-10A (normal line of cells). However, as recently shown, the effect of lupeol on breast cancer may be minimal. LUP can treat invasive cells in apoptosis by invading breast cancer cells, so they can do this by regulating the levels of Bax, cleaved PARP, cleaved caspase-3, B21, and rising p53 in normal breast cells.

Mechanism of Action of Lupeol on Breast Cancer

LUP has received significant interest in clinical oncology. Clinical trial evidence shows that LUP is successful in combating the initiation and progression of BC Table 3. In breast cancer cells, LUP inhibits angiogenesis that causes nutritional deprivation which hypoxia, and eventually results in cell death. [20] LUP inhibited medroxyprogesterone acetate (MPA)-induced secretion of VEGF from breast T47-D cells in a dose-dependent manner. These findings offer a clinically effective method for the inhibiting of MPA-induced VEGF by tumor cells. However, some *In vitro* experiments show that LUP prevents BC metastasis. Setzer

et al. reported LUP has also established potent antiproliferative action towards both MDA-MB-231 and MCF-7 cells[21] Table 3. LUP actions on MDA-MB-231 BC tumors caused by the newly established transcription function stinger technique to transmit estrogen receptor α (ERα) [22] Table 3. LUP induces G2/M arrest and inhibits the proliferation of MDA-MB-231 cell growth in a dose-dependent manner. It also causes apoptosis and reduces migratory activity in MDA-MB-231 cells via inhibiting NF-kB protein production. The exact mechanism by which LUP is selected for cancer cells is not fully revealed; however, it has been suggested that the anticancer potential of LUP depends on its ability to suppress the proliferation of cancer stem/progenitor cells and their offspring by some molecular mechanisms. Prasad *et al*. reported anti-proliferative activities of LUP investigated against various breast tumor cell lines like hormone-dependent, hormone-independent, and multidrug-resistant (MDR) lines. [23] These findings suggest that lupeol's development inhibition effects are time and dose-dependent and that it selectively stops cells in the G2/S phase of the cell cycle.

Separate biologically important correlation among decreased production of Bax and Bcl-2 proteins (Bcl-2 p1⁄20.01, Bax p1⁄20.03) and fibroid carcinomas while examining the relationship among the production of Bcl-2, Bcl-xL and Bax, Figure 3 and other clinic pathological factors Table 3. LUP also induces apoptosis and inhibits the migratory activity of MDA-MB-231 cells by downregulating the protein expression of NF-kappaB p65.[24] LUP has been shown to cause the release of estrogen receptor α (ERα), which should justify its development inhibitory activity in MDA - MB - 231 BC cells. However, LUP induces apoptosis by p53-dependent Bax stimulation in human BC cells. It also inhibits the estradiol of the cell division of immortalized human endothelial nerve cells by up-regulating the cell cycle kinase receptors, p21 WAF1/CIP1, p53, and p27 KIP1 [25] Figure 4. These reports suggest that the consequences of LUP development are time and dose-dependent and that LUP tends to interrupt cells in the cell cycle's G2/S step. A recent study demonstrated that LUP efficacy on MCF-7 cells would overcome the resistance to Adriamycin.[26] It also inhibits the expression of latent infection membrane protein1 (LMP1) induced NF-kB and the survival of lymphoblastoid cell lines (LCL) without detrimental effects on the growth of cells whose viability is irrespective of NF-kB activation.[27]

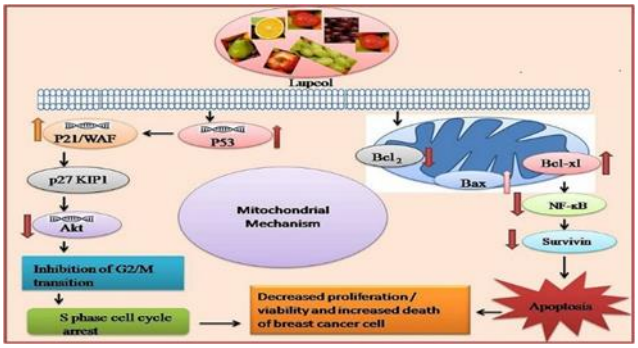

Figure 3: Anticancer mechanism of lupeol

LUP declines the overall HER-2 protein and solubilized HER-2 rates followed by inhibition of cell growth. Also, proteolysis was caused within 24 hours and when treated with high levels (25 and 50 mM) of LUP, over 80 percent of cells were generated in the S and G2/M stages of the cell. Ironically, LUP (20mM) prevents the synthesis of DNA and the proliferation of MCF-7 BC cells. Several cells are stopped in the M phase after 24 h of therapy. The cells have monopolar mitotic spindles. The various cells eventually see more micronuclei in place of independent daughter nuclei after 48 h. Such findings suggest that LUP is presently found as a chemical preventive agent; the potential of LUP to interrupt epithelial helical institutions in MCF-7 cells is highly the likelihood which it can also lead to genomic destabilization. Cancer cells have the strength to overcome immune system monitoring by using excreted exosomes (multifunctional bodies that include a special collection of proteins that may combine with spreading immune system cells). Tumor cytotoxicity of natural killer (NK) an induced IL-2 cell involves Jak3-mediated Stat5 activation, whose activation is highly inhibited by tumor exosomes. LUP in BC has been shown to alter this process and reduce the epithelial-proteasome structure, thereby partially modifying the tumor exosome-mediated inhibition of natural killer cell function. This has been shown in isolated exosomes from lupeol-pretreated tumor cells, which showed low potency to inhibit IL-2 induced NK cell cytotoxicity.

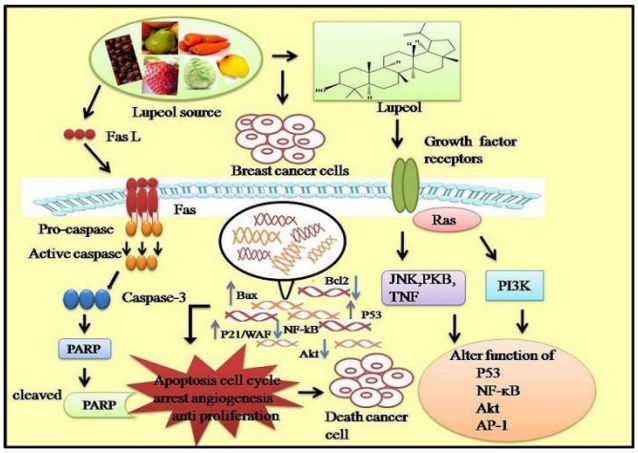

Figure 4: Therapeutic effects of lupeol and breast cancer

The same test has reported that in MDA-MB-435 human breast cancer cells that produce constitutively active STAT3 compared to MDA-MB-231 cells which do not, LUP Q induces apoptosis most potently. The sensitivity of cells in assessment ER, HER2/neu, and P-53 mutations. Another important research suggests the rapid anatomical modifications caused by lupeol B- within 20min of exposure along with chromatin disruption and F-actin had detected by confocal microscopy. Ambasta et al. reported the Activation of the VEGF receptor and its underlying molecules PI3K / p70S6 and PI3K / Akt kinase pathways are effectively blocked that can contribute directly to the antiangiogenesis caused by lupeol plays a major role in tumorigenesis allegedly. By modifying the ratios of Bax and

Bcl-2 protein stages *in vitro* and *in vivo*, LUP prevents the development of highly metastatic tumors of human cancer origin. Also, LUP inhibits substantially the development of metastatic cancer cells which harbor the constitutive triggered of Wnt/β-catenin signaling.[28] The data suggest the potential therapeutic role of lupeol in preventing the inhibition of invasion of breast cancer cells. BC over-expression of matrix metalloprotease (MMPs) is generally associated with the growth of breast tumors. MMP-3 requires extra destruction of the cellular structure, which is the critical step in the intrusion of cancer. MMP-3 also activates Pro MMP-9, leading to active MMP-9 that inhibits the proliferation of tumor cells. Microarray hybridization had performed to classify and describe the LUP-regulated genes in cancer cells (breast cancer and mammalian epithelial cell lines). LUP therapy has altered the function of 104 genomes out of the 214 apoptosis-associated genomes in the series. Nonetheless, genetic information has been modified in MCF-7 breast cancer cell lines up to 14-fold levels with hyper-regulation of 22 genomes and down-regulation of 17 genomes at lupeol doses of both 25µg1^{-1} and 50µg 1^{-1}.

The genomes updated including MCL-1, UBC, HIAP-1, GSTP-1, RBP-2, BCL-2L2, TRAF6, PIG-3, HPRT, CASP-3, CASP-2, GADD-45, CRAF-1, CDC-10, PCNA, and JNK-1. Down-regulated genomes are TRICK-2A, TRAIL-R-2, TNFSF-6, CAS, CASP-9, PKB, IGFBP, TRAIL, IGFBP-3, TNF, and TNFRSF-5.[29] This study demonstrates the dose-dependent effects of LUP on gene expression profile. The ability of LUP to modulate genes involved in the apoptosis pathway indicated that lupeol is an ideal candidate to induce in breast cancer cells as well as an appropriate therapeutic agent for the prevention and treatment of breast cancer. Currently, a new kind of non-apoptotic cell death, termed apoptosis, through autophagic cell death or mitotic catastrophe has been discovered in various types of cancer cells, especially BC. This process was induced by insulin-like growth factor 1 receptor (IGF-1R), epidermal growth factor (EGF), a member of the tumor necrosis factor (TNF) receptor superfamily.

Table 3: Lupeol anti-breast cancer activity

S. no	Cell model	Targets	Effects	Ref.
1.	MDA-MB-231 and MCF-7	T47-D	Inhibit angiogenesis	20, 21
2.	MCF-7, MDA-MB-231	SKBR-3	Inhibit G2/M cell cycle arrest	23
3.	MDA-MB-435S, MDA-MB-231	Bcl-2, Bcl-xL and Bax	Induce apoptosis	22,24
4.	MCF-7 and MDA- MB-231	BRCA-1, BRCA-2, P-53, PTEN, and ATM genes.	Inhibit invasion	24,28
5.	MCF-10A	p-21 WAF-1/CIP1, p-27 KIP1, and p53	Inhibit estradiol	25
6.	MDA- MB-435	PI3K / Akt and PI3K / p70S6	Inhibits metastatic action	28,29

BC is linked to aberrant stimulation of the Wnt/β-catenin signaling pathway and consequent up-regulation of β-catenin driven downstream targets, c-Myc, and cyclin D1. LUP modifying the β-catenin pathway in human breast cancer cells by suppresses cell growth and induces apoptosis. The inhibition effect of LUP on cellular proliferation has been analyzed in human mammary epithelial (MCF-10A) and breast cancer (MCF-7) cells. Cellular proliferation in MCF-7 cells is 6.9-fold higher than in human mammary epithelial cells. It is therefore characterized by the physical expansion of the mitochondria and the development of a large vacuum that begins with the endoplasmic reticulum (ER). LUP treatment is induced in MDA-MB-435, MDA-MB-231, and MCF-7 breast cancer cells and demonstrates that protein synthesis is essential for this process.[30] Furthermore, these authors also found success in lupeol treatment in normal breast cells, including MCF-10A and mammalian epithelial cells. These findings indicate that inducing apoptosis might provide new insight into the processes that are necessary for the LUP selective anticancer activities among BC cells. LUP has been found to have potent anti-mutagenic properties when evaluated *in vitro* and *in vivo*. Our group just released a review article that covers the chemotherapeutic and chemopreventive potential of LUP against a wide range of cancers. It has been shown to decrease tumor development by altering critical molecular pathways involved in proliferation, survival, and apoptosis. The most startling finding is that LUP has no toxicity in normal human cells at the same amount as it kills cancerous cells.

CONCLUSION

In recent years, there has been a growing interest in natural products in the treatment of breast cancer. LUP, a triterpenoid compound derived from herbal plants, is a highly promising, non-toxic, natural antioxidant compound with a broad range of anti-breast cancer activity. The potency of LUP to alter multiple pathways linked to BC was highlighted in this review. It may often function in more than one mechanism. As a natural result, they can exhibit a higher degree of effectiveness against BC. Shortly, LUP increasing identifies the application as a novel drug to control a lot of illnesses, including BC. To elucidate their complete mechanisms of action and their full therapeutic potential, more *in vitro* and *in vivo* studies and human clinical trials are needed.

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