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MINI-REVIEW ARTICLE

Phytochemicals as PI3K/ Akt/ mTOR Inhibitors and Their Role in Breast Cancer Treatment

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Abstract: ***Background*:** Breast cancer is the predominant form of cancer in women; various cellular pathways are involved in the initiation and progression of breast cancer. Among the various types of breast cancer that differ in their growth factor receptor status, PI3K/Akt signaling is a common pathway where all these converge. Thus, the PI3K signaling is of great interest as a target for breast cancer prevention; however, it is less explored.

***Objective*:** The present review is aimed to provide a concise outline of the role of PI3K/Akt/mTOR pathway in breast carcinogenesis and its progression events, including metastasis, drug resistance and stemness. The review emphasizes the role of natural and synthetic inhibitors of PI3K/Akt/mTOR pathway in breast cancer prevention.

***Methods*:** The data were obtained from PubMed/Medline databases, Scopus and Google patent literature.

***Results*:** PI3K/Akt/mTOR signaling plays an important role in human breast carcinogenesis; it acts on the initiation and progression events associated with it. Numerous molecules have been isolated and identified as promising drug candidates by targeting the signaling pathway. Results from clinical studies confirm their application in the treatment of human breast cancer alone and in combination with classical chemotherapeutics as well as monoclonal antibodies.

***Conclusion*:** PI3K/mTOR signaling blockers have evolved as promising anticancer agents by interfering breast cancer development and progression at various stages. Natural products and bioactive components are emerging as novel inhibitors of PI3K signaling and more research in this area may yield numerous drug candidates.

Keywords: Breast cancer, carcinogenesis, curcumin, drug development, metastasis, natural products, PI3K/Akt/mTOR pathway.

1. INTRODUCTION

The Phosphoinositide 3-kinase or Phosphatidylinositol-3 Kinase (PI3Ks) is a group of intracellular lipid kinases responsible for the phosphorylation of a variety of cellular enzymes involved in metabolism and growth. Cantley [1] described the pathway in the early 1980s, which combines with the downstream effector molecules such as protein kinase B (Akt), mechanistic Target Of Rapamycin (mTOR) as well as the inhibitor Phosphatase and Tensin Homologue Deleted on Chromosome 10 (PTEN) (Fig. **1**) [2]. The pathway plays significant roles in the normal physiological processes like glucose and lipid metabolism, cell proliferation and survival. Besides, the Akt isoforms are important signaling molecules for normal breast development and lactation. However, the pathway has been reported to be overexpressed or mutated in most human cancers, including colon [3], breast [4], liver [5] and pancreas [6].

The signaling is the second most altered pathway in breast cancers after the p53 gene [7]. Mutations and overexpression of the PI3K/Akt/mTOR pathway and its downstream effector molecules have been evident in different subtypes of Breast Cancer (BC) [8]. Clear information on the pathway involved in various processes, including carcinogenesis, proliferation, cell survival, metastasis, drug resistance and cancer stemness in BC, is available [9]. The present article thus summarizes the available information on the role of PI3K/Akt/mTOR pathway BC as well as the functional targeting of this signaling in BC prevention by synthetic inhibitors, monoclonal antibodies and emerging natural bioactive components [9].

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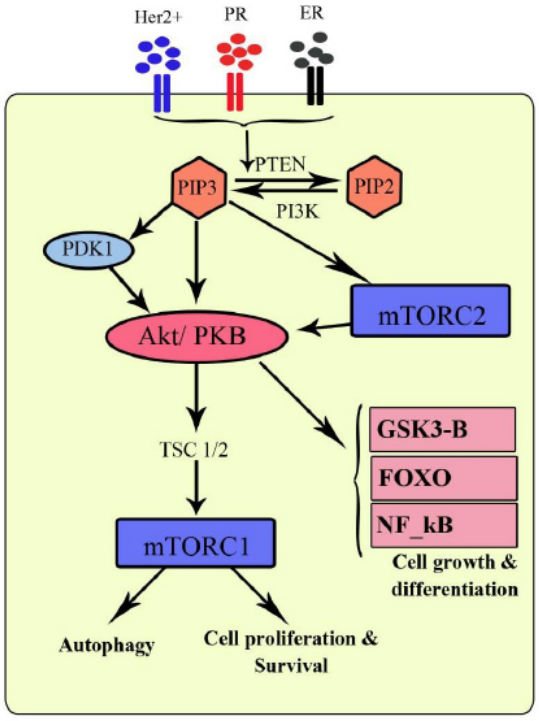

Fig. (1). The hormone and growth factor receptors in breast cancer activates PI3K/Akt pathway and their downstream effectors including NF-kB, FOXO, or GSK3β. They control the physiological functions including cell proliferation, survival, motility and even drug resistance. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

2. PI3K/ AKT/ mTOR SIGNALING IN BREAST CANCER

Cancer is a leading cause of morbidity and mortality among developing and developed countries [10-12]. Breast cancer is the predominant type of cancer in females, which is also the prime cause of death due to cancers [13]. Risk factors associated with breast cancer include hereditary factors, hormonal factors, obesity and lack of physical activities [14]. Hereditary factors include mainly genetic factors such as mutations in genes like BRCA, P53 and overexpression of hormone receptors, etc [15].

Breast Cancer Gene (BRCA) is the most commonly mutated tumour suppressor gene; the protein performs important roles in DNA damage repair and thereby prevents the carcinogenesis in breast tissues [16]. The two isoforms BRCA1 and BRCA2 are commonly expressed in breast tissues and the former codes for DNA repair and the latter is responsible for homologous recombination [17]. However, mutations in these genes lead to the progression of cell cycle and the accumulation of undesired mutations in the DNA, thereby inducing the transformation of normal mammary cells into malignant phenotype [18, 19].

On the contrary, HER2 is a receptor tyrosine-protein kinase erbB-2 (sometimes referred to as CD340), which is actively involved in cell growth and proliferation [20]. Increased expression and mutations of HER2 are associated with breast cancer incidence in Irish women [21]. Likewise, increased expression of HER2 has also been observed in metastatic breast tumours [22], drug resistance [23] as well as cancer recurrence [24].

Breast cancer is further classified into subtypes depending on the distribution pattern of various receptors, especially that of Estrogen Receptor (ER), progesterone receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) [25-27]. Based on this, breast cancers are generally of luminal type A (ER+& PR+, HER2-), luminal type B (ER+& PR+, HER2- and elevated Ki67 expression), HER2+ type and Triple-Negative Breast Cancer (TNBC) [27].

Various signaling pathways are involved in breast cancer initiation and progression; these pathways control the various processes, including cell proliferation, resistance to apoptosis, acquiring the invasive potentials, resistance to various therapies and stem cell-like properties. It has been evident that PI3K/Akt/mTOR is involved in most of the variants of breast cancers, thereby making it an attractive target for drug candidates (Table **1**) [28-36]. Among the various pathways, the predominant ones include EGFR signaling [10], hormone receptor signaling, MAPK pathway, toll-like receptor signaling [37], Heat shock protein signaling [38], NRF2-glutathione system [39] as well as PI3K/Akt/mTOR pathway [40].

The PI3K/Akt pathway comprises mainly three factors, which include the PI3K, serine-threonine kinase Akt and the PI3K inhibitor PTEN [41]. Among these, Akt has three dif-

Table 1. Different Roles of PI3K/Akt/mTOR Signaling in Breast Cancer.

Model	Effect	Reference
Triple-negative breast cancer	Inhibitors of PI3K in TNBC	[28]
MCF-7 and MDA-MB-231 Cells	Inhibition of the PI3K-AKT-mTOR pathway suppresses the adipocyte-mediated proliferation and migration	[29]
MCF-10A and MDA-MB-231 Cells	HER2/EGFR-AKT signaling switches TGFβ from inhibiting cell proliferation to promoting cell migration	[30]
ERα +, PI3K-mutant breast cancer	Strategically timing inhibition of Phosphatidylinositol 3-Kinase to maximize therapeutic index	[31]
MDA-MB-231 cells	Integrin□Linked Kinase (ILK) overexpression promotes cell proliferation by activating the PI3K/Akt pathway.	[32]
Metastatic breast cancer patients	PI3K pathway mutations and PTEN levels in primary and metastatic breast cancer	[33]
Breast cancer patients	PI3K pathway activation increases the basal-like phenotype and cancer-specific mortality	[34]
In vitro & *in vivo* breast cancer	PI3K activates Doxorubicin and Adriamycin resistant tumour growth in animal model studies	[35, 36]

ferent isoforms, Akt1, Akt2 and Akt3 [42]. The signaling cascade begins with the activation of PI3K through any RTKs, especially growth factor receptors; the PI3K promotes the phosphorylation of PIP2 to PIP3 [43]. The PIP3 is a second messenger, which in turn, activates Phosphoinositide-Dependent Kinase 1 (PDK1) and, subsequently, Akt; the activation of Akt additionally requires mTOR-rictor kinase complex. Phosphorylation of Akt results in the activation of downstream signaling molecules mTORC1, FOXO, NF-kB, and GSK3β [44]. The function of the PI3K/Akt signaling includes regulation of glucose metabolism employing GLUT4; in addition, the pathway also activates ATP citrate lyase and subsequently controls fatty acid synthesis [45, 46]. Apart from this, the pathway also influences cell cycle transition and apoptosis; Akt phosphorylates a pro-apoptotic protein BAD and the inhibition of which results in cell survival [47] (Fig. **1**).

The PI3K/Akt/mTOR signaling is important in normal breast development and lactation. It has been reported that deletions of Akt isoforms reduce mammary gland development and lead to the absence of lactation. In mice carrying a mutant allele of ErbB3, a member of the EGFR family of receptor tyrosine kinases, uncoupling of PI3K leads to the impaired development of mammary glands [48, 49]. Among the different isoforms, Akt1 plays a central role in lactation by promoting the phosphorylation of Stat5a (Signal Transducer and Activator of Transcription 5A) and thereby promoting mammary gland differentiation and lactation; however, Akt2 works as an antagonist to the Akt1 [50-52]; on the contrary, PTEN gene functions as an inhibitor of mammary development and lactation [53]. Dietary fatty acids such as oleic [54] and lauric acid [55] promote lactation in animals by influencing PI3K/Akt pathway, whereas stearic acid suppresses the same [56].

Despite the roles of PI3K/Akt/mTOR signaling in the normal development of mammary glands, numerous reports are available on the involvement of this pathway in breast cancer development and progression. The early events of breast carcinogenesis are driven by the mutations in the PI3K signaling [57]. Increased expression of the ErbB3 gene (Erb-B2 Receptor Tyrosine Kinase 3) has been reported to enhance BC cell proliferation [58]. Supporting the study, it has also been proven that conditional loss or ablation of the ErbB3 gene leads to a reduction in mammary carcinogenesis in mice model [59, 60].

Epithelial to mesenchymal transition is the initial step in cancer progression [61]; several signaling pathways mediate the EMT changes in breast cancers, of which TGF β induced EMT is the prominent one [62]. In breast cancer, PI3K/Akt plays a significant role in the development of EMT mediated through the expression of vimentin [63] and Cytosolic Phospholipase A2α (cPLA2α) [64]. Activation of Akt and its downstream effectors has been depicted to have significant roles in hormone and drug resistance in breast cancer cells [65]. Studies have also indicated a positive correlation between PI3K activation and invasive phenotype in mammary cells [66]. Expression of insulin receptor substrate 4 (IRS4) has been shown to induce mammary tumorigenesis and also mediates drug resistance by constitutive activation of PI3K/Akt signaling [67]. Doxorubicin resistance in BC cells is also mediated through PI3K overexpression [68] and partially driven by the PTEN inhibition by miR-202-5p [69]. Further, activation of Ribosomal S6 protein Kinase 4 (RSK4) is a negative regulator of PI3K/Akt, and restores the DOX sensitivity [70]. Resistance to Cisplatin is also mediated through the EGFR dependent PI3K/Akt activation, where pharmacological inhibition of the pathway restores sensitivity in TNBC cells [71]. Apart from the drug resistance, the PI3K/Akt pathway is also involved in the self-renewal of breast cancer stem cells [72]. Cyclooxygenase- 2 drives stem cell-like properties *via* the PI3K/Akt/Notch pathway; besides, the COX2 overexpression increases the motility and spheroid formation in breast cancer cells [73].

3. INHIBITORS OF PI3K/AKT SIGNALING AS ANTICANCER AGENTS

PI3K signaling is a key regulator of cellular events like growth, proliferation, survival and invasiveness. Therefore, the pathway is widely elucidated as a target for cancer prevention and such compounds are emerging as a drug candidate. As indicated by Table **2** [74-87], several natural products are efficient inhibitors of PI3K signaling and able to prevent various chronic diseases.

Likewise, several natural products are also attracting interest as anticancer drug candidates by interfering with the PI3K/Akt signaling (Table **3**) [88-103].

Table 2. Natural Products Prevent Various Diseases by Inhibiting PI3K/Akt Signaling.

Natural Product	Disease	Model	Reference
Curcumin	Insulin resistance and obesity	Mice	[74]
D-chiro-Inositol	Hepatic steatosis and insulin resistance	Mice and Cultured hepato-cytes	[75]
Didymin	Type 2 diabetes	*In vitro*	[76]
Irisin	Inhibit hepatic glucogenesis	*In vitro*	[77]
MDG-1 (Polysaccharide)	Type 2 Diabetes	Mice	[78]
Mulberry Anthocyanin	Insulin resistance	Mice	[79]
New Norditerpenoid Alkaloids	Anti-diabetic property	*In vitro*	[80]
Quercetin	Diet-induced NAFLD	Mice	[81]
Resveratrol	Obesity-related osteoarthritis	Mice	[82]
Resveratrol	Smooth muscle cell proliferation and atherosclerosis	Cultured cells	[83]
Resveratrol	Brain ischemia injury	Rats	[84]
Salidroside	Alzheimer's disease	Drosophila model	[85]
Sheng-Jiang Powder	Non-alcoholic fatty liver disease	Rats	[86]
α-Methyl Artoflavanocoumarin	Type 2 Diabetes	*In vitro*	[87]

Table 3. Natural Products as Inhibitors of PI3K Signalling in Multiple Forms of Cancers.

Natural Product	Cancer	Result	Reference
Piperlongumine	Colon cancer	Inhibits tumor cell growth and proliferation in DMH/DSS induced colon cancer	[88]
Dihydromethysticin		Inhibits proliferation, migration, invasion, apoptosis, cell cycle, and angiogenesis	[89]
Daphnane Diterpenoids		Inhibit cell proliferation and induce cell cycle arrest and apoptosis	[90]
Isoliquiritigenin		Inhibits cell growth and proliferation	[91]
Sinomenine	Gastric cancer	Sensitizes gastric cancer cells to cisplatin	[92]
Chaetocin		Inhibition of gastric cancer proliferation via ROS-mediated inhibition of PI3K	[93]
Shikonin		Inhibits proliferation, migration, invasion of gastric cancer cells	[94]
Salidroside		Inhibits cell proliferation and autophagy, thereby inducing apoptosis	[95]
Sanggenol L	Prostate cancer	Inhibits cell proliferation and induce cell cycle arrest via activation of p53	[96]
DT-13 (saponin monomer)		Inhibits proliferation and metastasis of human prostate cancer cells	[97]
Isorhamnetin		Inhibits the proliferation and metastasis of androgen-independent prostate cancer cells	[98]
Quercetin		Reverses docetaxel resistance in prostate cancer via androgen receptor signaling	[99]
Jatrorrhizine-Platinum(II) Complex	Thyroid cancer	Induces apoptosis in thyroid cancer cells	[100]
Resveratrol		Enhances the anti-tumor effects of rapamycin in papillary thyroid cancer	[101]
Oridonin	Oral cancer	Inhibits oral cancer growth and proliferation	[102]
Lycopene		Inhibits the proliferation and invasion	[103]

4. NATURAL INHIBITORS OF PI3K/ AKT/ mTOR IN BREAST CANCER THERAPY

Various natural products target the PI3K signaling pathway in many forms of cancers; among these, a considerable number of molecules are useful for preventing and treating breast cancers (Table **4**).

Glyceollin, a member of prenylated pterocarpans, has been shown to inhibit the mTOR signaling in ER+ breast cancer [104]. Strictinin, a member of the ellagitannin family, has also been shown to interfere with the kinase activity of Akt, thereby inhibiting the proliferation of TNBC [105]. Further, Tetrandrine, an isoquinoline alkaloid, exerted its anticancer effects by inhibiting the PI3K/Akt pathway in TNBC cells [106].

Diosgenin, a natural steroid in plants, has been shown to inhibit fatty acid synthase activity by blocking Akt/mTOR phosphorylation as well as enhance the apoptotic effect of paclitaxel in HER2+ breast cancer cells [107]. Similar properties have also been shown by tea polyphenol, epigallocatechin-3-gallate [108] and osthole (a natural coumarin) [109].

A dual inhibitor of PI3K/mTOR, 5-ureidobenzofuranone, also induced apoptotic effects in animal and *in vitro* models of TNBC [110]. A natural stilbenoid compound Resveratrol enhances the antitumor activity of mTOR inhibitor, rapamycin, in multiple breast cancer cells [111]. Antrocin, a sesquiterpene lactone, has been shown to inhibit the metastatic changes and cancer stemness in TNBC cells by modulating the Akt and its downstream effectors mTOR,

Table 4. Natural Inhibitors of PI3K/Akt/mTOR in Breast Cancer Therapy.

Inhibitor	Nature of Breast Cancer	Effect	Model	Reference
Glyceollin	ER+	Inhibits mTOR/p70S6 and induces apoptosis	*In vitro*	[104]
Strictinin	ER-, PR- & Her- (TNBC)	Inhibits survival and migration via suppression of PI3K/Akt	*In vitro*	[105]
Tetrandrine	ER-, PR- & Her- (TNBC)	Induces autophagy by inhibiting PI3K/AKT/mTOR signalling	*In vitro*	[106]
Resveratrol	Multiple BC cells	Enhances the anti-tumor activity of rapamycin	*In vitro*	[111]
Wedelolactone	ER-, PR- & Her-	Inhibits breast cancer-induced osteoclastogenesis via blocking the Akt/mTOR signaling	*In vitro*	[125]
Ascofuranone	ER-, PR- & Her- (TNBC)	Suppresses EGF-induced Akt/mTOR/p70S6K pathway	*In vitro*	[114]
Tanshinone IIA	ER+, PR+ and TNBC	Inhibits HIF-1alpha and VEGF expression via mTOR/p70S6K/ RPS6/4E-BP1 pathway	*In vitro*	[126]
Cyclovirobuxine D	ER+, PR+ cells	Induces autophagy-associated cell death via the Akt/mTOR pathway	*In vitro*	[127]
Piperlongumine	ER-, PR- & Her- (TNBC)	Inhibition of PI3 K/Akt/mTOR signaling axis to induce caspase-dependent apoptosis	*In vitro*	[128]
Berberine	ER+, PR+	Reverses Doxorubicin resistance by inhibiting autophagy through the PTEN/Akt/m-TOR signaling	*In vitro*	[129]

Table 5. Synthetic Compounds Patented as PI3K Inhibitors in Cancer Therapy.

Compounds	Reference
Heteroaryl compounds	[132]
Oxazolidin-2-one	[133]
Benzopyran and benzoxepin	[134]
Pyrazolopyrimidine	[135]
2-carboxamide cycloamino ureas	[136]
Combinations of the inhibitors BTK, PI3K, JAK-2, PD-1, and PD-L1 Inhibitor	[137]
Heterocyclic compounds	[138, 139]
Combination of PI3K and JAK inhibitors	[140]

NF-kB, and GSK3β [112, 113]. Ascofuranone inhibits the synthesis of Hypoxia-inducible factor 1 protein by downregulating the Akt/mTOR signaling in TNBC cells [114]. Anthricin, a podophyllotoxin derivative, has been shown to inhibit the growth of multiple breast cancer cells by inhibiting autophagy and by blocking the Akt/mTOR axis [115]. Quercetin is a flavonoid compound widely distributed in plants; it has been shown to induce PI3K/Akt/mTOR inhibition and thereby prevent the proliferation and motility in BC cells [116, 117].

Melittin and Apamin, two bioactive compounds derived from bee venom, have been shown to inhibit the EGF induced motility and invasive potentials in breast cancer cells [118]. Another animal product that was found to have mTOR inhibitory effect is bovine lactoferrin, which has been shown to induce antiproliferative effect and cell cycle arrest in breast cancer cells, however without apoptosis [119]. Similarly, the N-3 polyunsaturated fatty acid, docosahexaenoic acid, has also been shown to induce apoptosis in breast cancer cells by upregulating the oxidative stress-induced growth inhibitor 1 and subsequent ROS generation [120].

Apart from these, several plant extracts are in the preliminary stages of drug development that are known to inhibit PI3K signaling. Among these, Blueberry phytochemicals have been shown to reduce the levels of tumor marker levels and prevent PI3K/Akt mediate metastasis in TNBC [121]. Apart from these, extracts of *Cochinchina momordica* [122], *Spatholobus suberectus* [123], and Huaier plants have been shown to induce antiproliferative effects mediated by autophagy or cell cycle arrest in multiple breast cancer cell types along with the inhibition of PI3K signaling. *Taraxacum officinale* extract has been shown to inhibit the DMBA induced breast cancer model in rats by abrogating PI3K signaling [124].

5. PATENTS ON PI3K INHIBITORY NATURAL PRODUCTS AS ANTICANCER AGENTS

It has been identified that PI3K inhibitors are well known anticancer agents; supporting these observations, several patents have also been registered on the PI3K inhibitors as anticancer agents [130]. PI3K isoforms modulators are efficient as anticancer agents against multiple forms of cancers [131]. Several such synthetic modulators and antagonists are available and are being patented; they are listed in Table **5** [132-140].

Limited patents are available on the PI3K inhibitory natural products; among these, the well-known anticancer compound curcumin is the predominant one [141]. Apart from curcumin, several curcuminoids have also been shown to have anti-breast cancer effects [142, 143]. A combination of ceramide, Epigallocatechin Gallate (EGCG), and curcumin has also been proven to inhibit breast cancer cell proliferation by inhibiting PI3K signaling [144]. Apart from curcumin, chloroquine compound has also been shown to have an anticancer effect [145, 146]. Silibinin is an anticancer com-

pound, which has been proven to be efficient in the prevention of multiple cancers, including breast [147, 148]. Apart from these, the stilbenoid resveratrol has been proven to be an efficient anticancer agent [149]. Other natural products such as hexahydro-isoalpha acid act as strong inhibitors of PI3K signaling and thereby inhibit the cancer cell proliferation *in vitro* [150-152]. Likewise, xanthohumol is another compound that has been patented as a PI3K inhibitor and emerged as an anticancer agent for multiple organs [153, 154].

CONCLUSION

PI3K/Akt signaling plays an important role in various cellular processes, including proliferation, growth and metabolism. It also plays important roles in the normal development of an organism as well as wound healing and various other regeneration events. However, abnormal activation of the pathway has been reported in various types of malignancies, including breast cancer. The pathway influences various steps in the carcinogenesis, including proliferation, survival, invasiveness and migration as well as drug resistance [40, 155-161]. Several synthetic inhibitors of PI3K/Akt signaling have been prepared and are being evaluated in breast cancer [162, 163]. However, most of these molecules are still under various stages of phase trials and some of them have shown no significant efficacy in Phase II studies. At present, there is no available information on the reduced efficacy of these inhibitors in phase trials. It is expected that the reduced bioavailability and biological half-life may be responsible for their limited efficacy. In addition, these molecules have several side effects, which delimit their usefulness in wide application context [164]. However, natural molecules show higher efficacies due to their multi-targeted nature; they are thus becoming more interesting and expected drug candidates by inhibiting PI3K signaling. The multiple inhibitions of PI3K signaling at various levels, such as inhibition of PI3K or Akt or mTOR, help to attain higher inhibition and thereby exert more profound anticancer potentials. Hence, the multi-targeted nature of the natural products is helpful to target the PI3K signaling at various levels. Hence, the review concludes that despite certain missing links, the natural products or bioactive components seem to be promising drug candidates.

CURRENT & FUTURE DEVELOPMENTS

Though the studies on natural products have proved them to be promising in drug development, many more concerns remain, which need to be solved in future studies. The concern regarding the natural products is due to their bioavailability problems; however, these concerns can be overridden utilizing novel drug delivery systems, including nano--formulations or liposomal assemblies, which have been found to be an effective strategy against various signaling pathways [165-169]. Several molecules have been patented as anticancer drugs for targeting various signaling pathways. However, limited patents have been available on PI3K inhibitory natural products as anticancer agents. Considering the crucial roles of PI3K in breast cancer, it is high time that the natural products shall evolve as inhibitors of the pathway and need to be formulated into drug compounds and patented. Besides, these molecules should proceed to the clinical trials, considering their efficacy in animal model studies. The most promising molecules that are already in clinical trials include curcumin, sulforaphane, resveratrol, and tea polyphenol compounds.

Unlike other cancers, the therapy is more complicated in the case of breast cancer. The breast cancers vary in their growth factor receptor profiles; however, most of these signaling pathways culminate in the PI3K/Akt pathway. Hence, it is easier to target breast cancer using PI3K inhibitors, rather than various other drugs. The inhibitory molecules can block the overall receptor signaling and thereby induce apoptotic changes in most of the types of breast cancer. The review thus concludes that PI3K/Akt inhibitors, especially natural products, can exhibit promising efficacy against multiple types of breast cancers.

LIST OF ABBREVIATIONS

Akt	=	Protein Kinase B
BC	=	Breast Cancer
COX2	=	Cyclooxygenase 2
DOX	=	Doxorubicin
EGFR	=	Epidermal Growth Factor Receptor
mTOR	=	Mammalian Target of Rapamycin
PI3K	=	Phosphoinositide 3-Kinase
PTEN	=	Phosphatase and Tensin Homologue
RSK4	=	Ribosomal S6 Protein Kinase 4 (RSK4)
TNBC	=	Triple-Negative Breast Cancer
ER	=	Estrogen Receptor
PR	=	Progesterone Receptor
HER2	=	Human Epidermal Growth Factor Receptor 2

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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