IJBPAS, February, 2021, 10(2): 809-841

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

CHALLENGES AND OPPORTUNITIES IN BREAST CANCER THERAPY: A CRITICAL REVIEW

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Received 10th May 2020; Revised 5th June 2020; Accepted 11th July 2020; Available online 1st March 2021

https://doi.org/10.31032/IJBPAS/2021/10.3.5393

ABSTRACT

One of the most common cancers prevailing among women is Breast cancer which also is the leading cause of cancer deaths. Enormous strategies have been developed so far to combat and treat breast cancer by improving the methodologies followed for treatment. Still we face various challenges like lack in early detection, side effects of chemotherapy, development of secondary cancer, and drug resistance offered by the cancerous cells. These drawbacks could be overcome better by targeted therapy against the various sub-classes of breast cancer, especially triple-negative breast cancer than the conventional ones. Most recent investigation paid paramount attention on the dysregulation of major signaling pathways that leads to cancer. Wnt signaling pathway has been considered as one of the most crucial passages that ends up in breast cancer. In this review we throw more light on the role played by the Wnt signaling pathway in promoting breast cancer and the various treatments which involve the deliberate targeting of the various molecules associated in the pathway.

Key words: Antimicrobial peptides, Wnt signaling pathway, Breast cancer, β-catenin, chemotherapy

INTRODUCTION

Breast cancer has become one of the greatest confrontations in the field of medicine. In the past few decades significant efforts have been put forth for early detection and targeted therapy against breast cancer. Neverthless these new treatment modalities are free from disadvantages. Hence there exists a great desire for supplemental outstretch for the discovery of new approaches and drugs for the superior treatment for breast cancer. A better apprehension on various theories of cancer biology, molecular level targeting and signaling pathways that promote breast cancer, could be a promising course of action and may lead a way in breast cancer therapy.

The breast cancer has been divided into various sub-types depending on the expression or presence of the receptors on the cell membrane, like progesterone receptor (PR), estrogen receptor (ER) and triple‑negative breast cancer (ER−, PR−, and Her2−)(TNBC). The current framework of the breast cancer treatment is carried out according to the presence or absence of these receptors. The hormonal therapy is mostly preferred for the patients who suffer from luminal types of breast cancer **[1]**. Among all the types of breast cancer, the TNBC is regarded as the most deadliest one since its treatment is speculative and too narrow. Currently only chemotherapy is being recommended for those patients which encounters multifarious side-effects **[1, 2]**. Hence comprehensive investigation is called for targeted therapy for TNBC through dissecting the signaling pathways involved in it.

In recent years scientists have rigorously analyzed the miscellaneous signal transduction pathways that lead to the development and prognosis of cancer. Tissues and organs usually depend upon differing signaling pathways that support in their normal development **[3-6]**. However dysregulation of these signaling pathways leads to numerous diseases including cancer. It has been observed that few signaling pathways prove to be distinctive markers for different types of cancers.

Collectively these signaling pathways could prove as an avenue in the development of drugs which would be highly specific in their action and also overcome the problems encountered by the momentarily used drugs. In view of this, Wnt signaling pathway has been ascertained as the most prominent signaling pathway that lead to the development and prognosis of breast cancer

thereby making it a prominent pathway for targeted therapy.

Wnt signaling pathway

The Wnt signaling pathway plays a very important role in determining the fate of a cell. The development and differentiation of the cell is highly regulated by this signaling pathway **[7, 8]**. Malfunctioning of any of the components in the signaling pathway, causes many diseases, comprehending cancer **[8]**. Therefore a clear understanding of the various components and their functioning is a pre-requisite for devising enhancement in the treatment stratergies.

The Wnt signaling pathway comprises of the Wnt receptors and the Wnt ligands **[9]**. The Wnt family gene encompasses 19 genes that codes for 19 Wnt ligands which in turn bring about their action by binding to unique Wnt receptors present on the cell membrane **[10]**. Few of the Wnt ligands make the cells to undergo transformation which leads to the development of malignancies. One of the Wnt ligands, Wnt1 is responsible for the expression of various glycoproteins which is observed in advanced metastatic state of a cancer in patients **[11]**. It has been disclosed that another Wnt ligand namely Wnt3a accelerates cell division in MCF-7 cells through stabilizing cytosolic β-catenin protein **[12]**.

Wnt signaling may follow any one of the two pathways namely canonical or non-canonical **[13]**. The main regulator of the canonical Wnt signaling pathway is the β-catenin protein which helps in either "switching on" or "switching off" the pathway. In the absence of Wnt ligands the Wnt signaling pathway is in "off" state. The adenomatous polyposis coli (APC), Axin (the scaffolding protein), glycogen synthase kinase3β (GSK3β) and casein kinase 1 (CK1) forms a protein complex which in turn captures the cytosolic β-catenin protein **[13, 14]** and phosphorylates it. This phosphorylated form of β-catenin becomes easily susceptible to proteasomal degradation **[14]**. This mechanism helps in retaining low concentration of cytosolic β-catenin. This prevents the entry of β-catenin into the nucleus and thereby activate the target genes **[13-15]**.

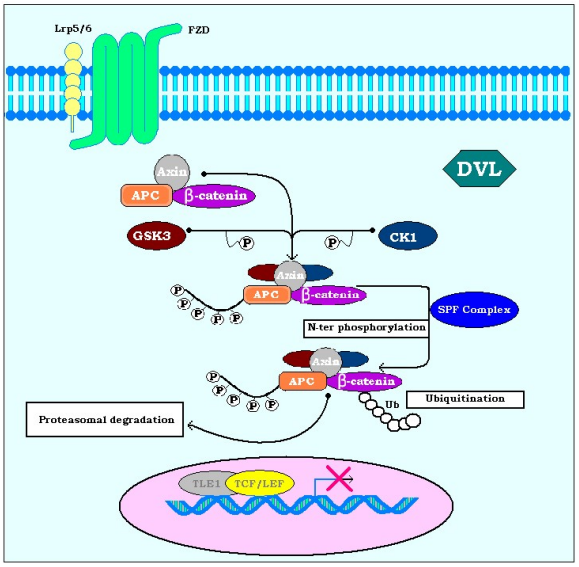

Figure 1: Schematic representation of Wnt signaling pathway in the absence of Wnt ligand: "Off state"

On the other hand the presence of Wnt ligands, flips the complete scenario. The Wnt signaling turns "on" when the Wnt ligand binds to the transmembrane proteins namely Frizzled receptor and the low-density lipoprotein receptor-related proteins (LRP5/6) and attracts CK1 and GSK3β towards itself. This inhibits the β-catenin phosphorylation process .The unphosphorylated form of β-catenin is resistant to proteosomal degradation. More and more β-catenin starts getting accumulated within the cytoplasm which enables it to translocate into the nucleus and activate its downstream target genes **[13-16]**.

Canonical Wnt Signaling Pathway In Breast Cancer

Though extensive research works on breast cancer due to Wnt/β-catenin pathway are being carried out for the past few decades, still it has to be further explored for faultless therapy. Enormous studies have proved that the Wnt pathway is activated and plays a very important role in the development and prognosis of breast cancer **[17, 18]**. The components of the Wnt target genes are dramatically up-regulated in the breast cancer stem cells **[19, 20]**.

Several results have shown that in about 50% of breast cancers, there is accumulation of stabilized cytosolic β-catenin **[21, 22]**. At the same time few reports have proved that Dishevelled (Dvl) protein, which is a positive regulator of Wnt signaling pathway is amplified in 50% of breast cancer cases **[23]**.

On the contrary when the Wnt signaling is in its "on" state the Wnt inhibitors like Frizzled-related protein 1 (FRP1) gets down-regulated significantly in roughly 78% of cruel breast cancers **[24, 25]**. In the metastatic breast cancers a different Wnt inhibitor Dickkopf-1 (DKK1) gets decreased **[26]**. In 36-50% of the breast cancers, one of the most important component in the formation of destruction complex namely APC is lost **[27, 28]**. The basal-like breast cancer shows extensive activation of Wnt signaling pathway which leads to nuclear accumulation of β-catenin correlating with poor prognosis **[29, 30]**. β-catenin has been identified as a multitasking protein which is responsible not only for the development of triple-negative breast cancers but also promotes HER2-driven mammary tumors in-vivo **[31]**.

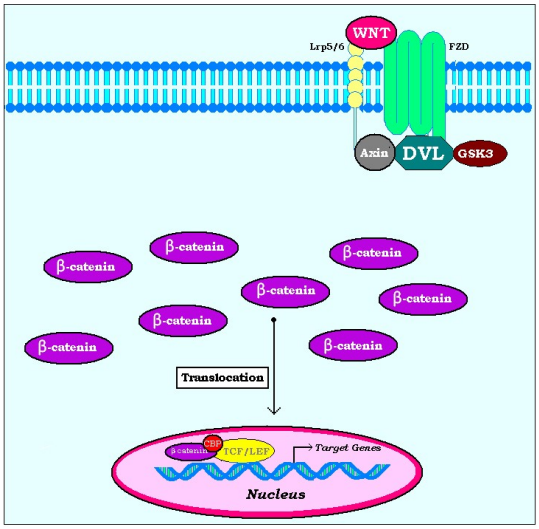

Figure 2: Schematic representation of Wnt signaling pathway in the presence of Wnt ligand: "On state"

The breast cancers which were treated with the Wnt ligands showed appreciable cell motility **[19, 33]**, on the other hand inhibition of Dvl or β-catenin, showed significant decrease in the activity of the breast cancer cells **[19, 32, 33]**.

Similarly the presence of molecules such as sFRP and DKK, arrested the growth of cancer by blocking the Wnt signaling pathway **[33-37]**. One of the major drawbacks of targeting the Wnt pathway in the breast cancer cells is their nature of developing resistance against current anticancer drugs including radiation therapy **[34, 35]**.

Current strategies in use against Wnt signaling pathway:

Handful of knowledge on the importance of Wnt signaling pathway in malignancies has helped in developing profound effect on the therapeutic system. Various drugs have been designed and developed in the past few decades against the Wnt signaling pathway. Among these, only few have successfully entered the early clinical trial phase **[36, 41]**. The foremost requirement of the drug is its ability to selectively target the Wnt signaling pathway of the cancerous cells, leaving the healthy cells unaffected **[37-39]**. Consequently new strategies crack down on specific Wnt molecules that are prominent in cancerous cells.

- **FZD antagonist/monoclonal antibody**
  - **Vantictumab** (OMP-18R5) is a humanized antibody which was able to target the frizzled protein receptors. It has successfully entered the phase I clinical trial (NCT01345201, NCT01973309, NCT02005315 and NCT01957007). It binds to five of the frizzled family proteins namely FZD1, FZD2, FZD 5, FZD 7 and FZD 8 **[40]**. It was able to arrest the growth of tumor in the xenograft profitably **[40]**. Along with these promising results, Vantictumab showed few undesirable effects like bone resorption resulting in bone fracture, fatigue, abdominal pain, vomiting, constipation, nausea and diarrhea **[41]**. The skeletal system was

found to be affected to a greater extent **[42]**. The reason behind this could be the activated Wnt signaling pathway which prevails in normal skeletal system for the development of bone **[43]**. At present in the Phase-I trial, OMP18R5 is given along with taxanes for the patients suffering from breast cancer, pancreatic cancer and non-small lung cancer **[44]**.

- Another antibody from OncoMed, ipafricept (OMP-54F28) also showed results that were more or less analogous to Vantictumab. It was designed to target FZD8. Results from 2 clinical trials were reported out of the four clinical trials (NCT01608867, NCT02092363, NCT02069145 and NCT02050178). Decreased appetite, muscle spasms, alopecia fatigue, anaemia, hypophosphataemia, and vomiting, neutropenia and weight loss were observed in the patients treated with ipafricept **[45, 46]**.
- A radioactive antibody targeting the FZD10 has been developed namely dOTSA101. Presently this is in phase I trial for the treatment of advanced synovial sarcoma **[47]**.

- **Antibody against R-spondin-3**

- Rosmantuzumab (OMP-131R10) is another antibody developed by Oncomed which acts against the R-spondin. Wnt signaling pathway especially the canonical pathway is triggered by various components among which R-spondins the soluble ligands is a prime component **[48, 49]**. Thus R-spondins could prove as a prominent target for breast cancer therapy. Nevertheless the drugs discovered so far are free from adverse effects. Treatment of breast cancer with Rosmantuzumab in the phase-I trial (NCT02482441) resulted in decreased appetite, nausea, vomiting diarrhoea, and unspecified weight loss. Although R-spondin 3 does not show any functional activity in bone formation and maintenance, studies confirm decreased turnover of bone due to therapy **[50, 51]**. This demonstrates the nonspecific activity of rosmantuzumab, which needs to be further explored.

- **Inhibitors of PORCN**

- The PORCN inhibitors like WNT974, CGX1321, RXC004 and ETC-1922159 prevented the secretion of Wnt ligand from the endoplasmic reticulum by inhibiting the post translational acylation process thereby blocked the Wnt signaling pathway. During the clinical trials these drugs were administered orally **[52-55]**. These inhibitors proved

highly satisfied apart from the awful effect on the skeletal system **[56]**.

- IWPs182 is another small molecule inhibitor which acts similarly and proved to reduce the size of the tumor size in the xenotransplants of head and neck cancer **[57]**.
- Presently ETC-159184 another novel drug developed against Porcupine is under clinical trial since July, 2015 **[58]**. Among various stratergies that is under continuous investigation to target the Wnt signaling pathway, inhibition of Wnt secretion is one which has proved to be very effective. Hitherto no drug has shown to be free from side effects. Hence there is unremitting search for an array of molecules that could target specifically the extracellular Wnt ligands apart from the intracellular ones.

- **Wnt5a-mimicking peptide**

- Peptides namely Foxy-5 and Box-5 showed to prevent metastasis in tumors by targeting the Wnt 5a ligand dependent signaling. Promising results have been obtained in the Phase I clinical trial with Foxy-5 **[59]**.

- **Inhibitors targeting the interaction between β-catenin and transcription co-activators**

- Wnt signaling brings about the transformation of a normal cell into a malignant one by up-regulating the expression of many genes especially those that are oncogenic in nature, through β-catenin. Therefore prevention of the β-catenin interaction with the transcriptional factors could help in the prevention of proto-oncogenes getting expressed. Two such drugs which were developed are PRI-724 and CWP232291. PRI-724 interferes with the binding of β-catenin with transcriptional co-activator cAMP response element binding (CREB) protein (CBP) whereas CWP232291 indirectly affects the alternative splicing of the TCF-1 in a complex with CBP by binding to Sam68 (an RNA binding protein). PRI-724[60-62] and CWP232291 **[63]** accomplished favourable results which made them to enter successfully the Phase I cinical trial from preclinical studies. During these trials PRI-724 showed few adverse effects which included thrombocytopenia, fatigue, bilirubin elevation, alkaline phosphatase elevation, hypophosphataemia, nausea, anorexia, and diarrhoea. When CWP232291 was given to the patients, few of them were seen to suffer from nausea, vomiting, infusion-related reaction, anorexia and diarrhoea.

- Carnosic acid, SAH-BLC9 and compound 22 inhibited BCL9 and PYGO **[64, 65]**, which are the co-activators of transcriptional complexes of β-catenin **[66, 67]** thereby switching off the Wnt signaling pathway.
- Another molecule Pyrvinium is able to destroy Pygopus (PYGO) and inhibits the transcription process **[68]**.

World-wide boundless efforts are being undertaken to design a novel drug with utmost effect to treat breast cancer by targeting Wnt signaling pathway, concomitantly studies are also being carried out on the natural products from various sources. Few such natural products revealed promising results to inhibit the binding of β-catenin with TCF4 **[69]**. Ironically these molecules failed to show explicitness towards binding to β-catenin/TCF complex alone.

- PNU 74654 is a synthetic compound which was identified by Trosset *et al* **[70]**. It was expected to target β-catenin/TCF. However its biological activity still remains unreported .
- 2,4-diamino-quinazoline is a recently identified large compound which hampers the β-catenin/ TCF4 interaction. This drug has been reported to be in the developmental stage **[71]**.
- Few small molecules namely "inhibitor of β-catenin responsive transcription" (iCRT) have been identified which hindered the β-catenin/ TCF4 interaction in that way it forbids the transcriptional activity of β-catenin **[72]**.
- Analogously Windorphen is one more small molecule recognized, which specifically stops the β-catenin from binding to one of the transcriptional co-activators namely p300 **[73]**.
- The transcriptional co-activators like CBP, p300, B-cell lymphoma 9 (BCL9), and pygopus are attractive targets in the area of designing target specific drugs **[74-76]**. ICG-100 is one such molecule which specifically targets CBP and does not allow it to bind with the β-catenin protein. Therefore the transcription of the β-catenin down-stream target genes gets inhibited. Unlike other drugs, ICG-100 was found to be highly specific in its action **[77, 78]**.

- **Inhibitors of Tankyrase**

- Tankyrase inhibits the PARsylation of Axin resulting in its stabilization which in turn switches "on" the Wnt signaling pathway. Henceforth arresting the activity of Tankyrase would turn off the Wnt signaling pathway. Few such inhibitors are XAV939 **[79-81]** AZ1366

[82], G007-LK **[83]**, NVP-TNKS656 **[84, 90]**, JW-55, and RK-287107 **[85, 86, 91]**. Eventually several drugs were developed which were designed to target Tankyrase **[94]**. Despite myriad trials, not even a single molecule is under clinical trial presently due to their severe virulent effects observed during their preclinical trials **[80-87]**.

- **Antibodies against Sclerostin (SOST) and DKK1**

➢ An additional approach was devised by focusing on SOST and DKK1. Romosozumab, blosozumab and BPS804, are the antibodies produced against SOST **[88, 89, 96]**. BHQ880, DKN-01and PF-04840082 are the antibodies that target DKK1 specifically **[90-92]**. Another antibody namely Hetero-DS is a bispecific one which targets both SOST and DKK1 **[93]**. Out of the above mentioned antibodies, Romosozumab, blosozumab, BPS804 BHQ880 and DKN-01 have become successful in entering the clinical trials.

- **Inhibitors of β-catenin**

➢ An alternative perspective of switching "off"' the Wnt signaling pathway is by taking the help of β-catenin inhibitors which would render anti-cancerous activity via the down-regulation of the TCF/LEF-target genes. BC2059 **[94]**, CGP049090 **[95]**, CWP232228 **[96]**, ICG-001 **[97]**, LF3 **[98]**, MSAB **[99]**, PKF115-584 **[100]**, PRI-724 **[101]** and SAH-BCL9 **[102]** are few of the β-catenin inhibitors, among which PRI-724 is in clinical trial. These drugs have not only shown anti-tumor activity but also therapeutic activity against pulmonary fibrosis and chronic kidney disease **[103, 104]**.

➢ MSAB (methyl 3-[(4-methylphenyl)sulfonyl]amino-benzoate) is another anti-β-catenin molecule. Unfortunately the drug caused many side-effects like nausea, diarrhea, anorexia, reversible elevated bilirubin, fatigue, thrombocytopenia and hypophosphatemia, **[105, 106]**.

- **Drugs enhancing LRP degradation and FZD endocytosis**

➢ LRP6 undergoes degradation if phosphorylated. Drugs like Salinomycin, monensin and rottlerin phosphorylated the transmembrane protein LRP6 and made them susceptible to degradation **[107-109]**.

➢ The stabilization of the cytosolic β-catenin protein depends on numerous cascade of reactions. One

among them is the pathway involving Wnt3A ligand the activity of which in turn is regulated by FZD1 receptor. Niclosamide is a molecule which was observed to facilitate FZD1 endocytosis, thereby preventing the stabilization of cytoplasmic β-catenin. Regrettably due to unspecific activity, it showed unpleasant effects which included itching, unpleasant taste, dizziness, vomiting, skin rash, and abdominal pain **[110, 120]**.

- **Activators of CK1**

➢ Drugs that promote the activity of CK1 would result in enhancing the phosphorylation of cytosolic β-catenin protein thereby making it more prone to proteosomal degradation. One such drug identified is Pyrvinium, which specifically bound to CK1 family proteins and enhanced their activity **[111]**.

- **Wnt target genes inhibitors**

➢ Serine and arginine-rich splicing factor (SRSF) phosphorylation was found to be successfully inhibited by a small molecule SM08502 (NIH clinical trial number NCT03355066) as a result of which spliceosome activity was interrupted. SM08502 was given orally to the patients and it was observed that SM08502 was able to suppress the expression of Wnt signaling-controlled genes **[112]**.

- **Inhibitors of ATP-binding cassette sub-family B member 1/P-Glycoprotein (ABCB1/P-GP)**

➢ Convincing results were given by the drugs namely Eacridar and Zosuquidar. These drugs were found to be anti-ABCB1 (ATP-binding cassette sub-family B member 1) and also did not show much ill effects in phase I clinical trials. More specifically, Zosuquidar was administered orally for the patients of acute myeloid leukemia. Also they helped in the uptake of daunorubicin, mitoxantrone and idarubicin **[113]**.

➢ Another inhibitor of ABCB1, Tariquidar, repressed the ATPase activity of the extrusion pump. Unfortunately because of awful effects of tariquidar in the Phase III trials no further work was continued **[114]**.

➢ An alkaloid, Tetrandrine which was isolated from Stephania tetrandra, was found to inhibit the function of ABCB1. This alkaloid was tested in the patients suffering from multidrug resistant cancers in phase I trial along with doxorubicin.

(www.clinicaltrials.gov) **[114]**.

- Drugs like Trabectedin, Halaven and cytarabine proved to be effective as reverting the ABC drug transport activity **[115]**.
- Curcumin and quercetin are the phytochemicals that inhibit ABCB1 function thereby nullifying the multi-drug resistance (MDR) in human cancer cell lines **[116, 118]**.

ABCB1, and other pumps are like double edged swords, because they play a very important role in maintaining the integrity of the blood brain barrier along with their activity in normal stem cells. Therefore the drugs that act against these pumps should be highly specific towards the cancerous cells leaving the non-cancerous cells unaffected. So novel compounds are under trial that satisfies these requirements primarily so that the side-effects could be avoided considerably **[114, 118, 119]**.

- **Inhibitors of COX**
  - It was perceived from the previous studies that augmented activity of cyclo-oxygenase dramatically diminished the atropy of β-catenin protein in Wnt signaling pathway. In consequence few Non-steroidal anti-inflammatory drugs like aspirin and sulindac were tested and found to inhibit cyclooxygenase activity to an excellent level **[120-126, 136]**, so that the Wnt signaling pathway got hindered **[126, 127]**.
- **Inhibitors of Wnt signaling pathway**
  - In numerous studies the anti-tumor activity of the active form of Vit D, 1α, 25-dihydroxyvitamin D3, and its synthetic derivatives against various cancers including colon and breast cancer has been reported. Although the exact mechanism of action by which the vitamin arrested the Wnt signaling pathway is yet to be understood completely, theories propose that these vitamins may react with the receptors on the nuclear membrane, compete with TCF and thereby prevent the entry of the β-catenin into the nucleus **[128, 129]**.
- **Activators of GSK-3β**
  - GSK-3β activation down-regulates the Wnt signaling pathway. Two major components namely DIF-1 and DIF-3 were quite effective in activating the GSK-3β. **[130-134]**.
- **Targeting the PDZ domain of Dvl.**
  - The effect of NSC668036, 3289-8625 and FJ9, against Wnt signaling pathway was studied using computational methods and NMR. These molecules proved to stop the Wnt signaling pathway in in-vivo **[135-137]**.

- **Molecules mimicking Wnt ligand-binding domain in FZD**

➢ Plenty of antagonists against the components that promote Wnt signaling are under the discovery stage. It has been observed that SFRPs (Secreted Frizzled-Related Proteins) mimic the Wnt ligand-binding domain in the FZD receptors. So SFRPs compete with the Wnt ligand and inhibit their binding with the FZD receptors, ultimately switching "off" the pathway **[138-140]**. In the preclinical models SFRPs or SFRP-derived peptides proved to possess anti-tumor activity **[141, 142]**.

- **General Wnt inhibitors**

➢ Apart from the synthetic drugs many polyphenols epigallocatechin- 3-gallate (EGCG), and resveratrol showed inhibitory activity against Wnt/β-catenin signaling pathway. The exact mechanism by which these polyphenols act is yet to be unrevealed **[143-149]**.

Table 1: List of chemotherapeutic drugs under trail

Target	Mechanism of Action	Drug	Stage of Drug Development
β-catenin	Blockage of β-catenin Protein-protein interaction	BC2059	Preclinical
		CGP049090	Preclinical
		CWP232228	Preclinical
		ICG-001	Preclinical
		LF3	Preclinical
		MSAB	Preclinical
		PKF115-584	Preclinical
		PRI-724	Preclinical
		SAH-BLC9	Preclinical
		1α,25-dihydroxyvitamin D3	Clinical
Sam-68		CWP232291	Phase-I
β-catenin		PNU 74654	Discovery
		2,4-diamino-quinazoline	Preclinical
		ICG- 001	Phase-I
		Windorphen	Discovery
CK1	β-catenin degradation	Pyrvinium	Preclinical
Wnt target genes		SM08502	Clinical
ABCB1	Unknown	Elacridar	Phase-I
	Unknown	Zosuquidar	Phase-I
	Unknown	Tetrandrine	Phase-I
	Unknown	Tariquidar	Phase-III
	Unknown	Curcumin	Preclinical
	Unknown	Quercetin	Preclinical
β-catenin	Cyclooxygenase inhibitor	Aspirin	Clinical
β-catenin		Sulindac	Clinical
TCF		Celecoxib	Clinical
Inhibitors of Wnt/β pathway	Unknown	Curcumin	Preclinical
		Epigallocatechin-3-gallate (EGCG)	Preclinical
		Quercetin	Preclinical
		Resveratrol	Phase-II
GSK	Activation of GSK	DIF-1	Preclinical

		DIF-3	**Preclinical**
DVL	**Unknown**	**NSC668036**	**Discovery**
	Unknown	**FJ9**	**Discovery**
	Unknown	**3289-8625**	**Discovery**
FZDs	**Anti-FZD1/2/5/7/8mAb**	**Vantictumab**	**Phase-I**
WNT	**FZD-8 binding WNT trap**	**Ipafricept**	**Phase-I**
FZD	**Anti-FZD mAb**	**OMP18R5**	**Phase-I**
FZD-10	**Anti-FZD10 mAb**	**OTSA101**	**Phase-I(Terminated)**
R-spondin	**Unknown**	**Rosmantuzumab**	**Clinical**
ROR1	**ROR1 inhibitor**	**KAN 0439834**	**Preclinical**
	Anti-ROR1 mAb	**Cirmtuzumab**	**Phase-I**
	Anti-ROR1 x Anti-CD3	**ROR1-CD3-DART**	**Preclinical**
	bispecific mAb	**APVO425**	**Preclinical**
WNT	**PORCN inhibitors**	**ETC-1922159**	**Phase-I**
		IWPs182	**Preclinical**
		WNT974	**Phase-I**
		ETC-159184	**Phase-I**
		RXC004	**Phase-I**
		CGX1321	**Phase-I**
AXIN	**Tankyrase inhibitor**	**XAV939**	**Preclinical**
		AZ1366	**Preclinical**
		G007-LK	**Preclinical**
		NVP-TNKS656	**Preclinical**
		JW	**Preclinical**
		G007-LK	**Preclinical**
		RK-287107	**Preclinical**
SOST	**Anti-SOST**	**Romosozumab**	**Clinical**
		Blosozumab	**Clinical**
SOST	**Anti-SOST**	**BPS804**	**Clinical**
DKK1	**Anti-DKK1**	**BHQ880**	**Clinical**
		DKN-01	**Clinical**
		PF-04840082	**Clinical**
Wnt5a-mimicking peptide	**Competes with Wnt 5a ligand**	**Foxy-5**	**Phase-I**
	Competes with Wnt 5a ligand	**Box-5**	**Phase-I**

A great deal of work is under progress for the past few decades in which scientists are striving hard to develop drugs targeting the Wnt signaling pathway in breast cancer. One of the major drawbacks in the erstwhile identified drugs is their non-specific action towards the targeted molecule. Also for few drugs their precise molecular mechanism is yet to be understood. Hence there is an urgent necessity for both novel targets and unique-specific novel drugs. Another crucial hinderance which is prevailing presently is targeting the drug-resistant cancer stem cells. As a result much attention was then paid towards the structural studies involving the interaction of β-catenin with the TCF **[150-152]**. This high affinity protein-protein interaction has been successfully targeted via a small molecule high-throughput screen, to provide a series of inhibitors of TCF/β-catenin-mediated transcription **[153]**.

However, concerns arise about the development of specific inhibitors of this interaction due to the diverse partners besides TCF (e.g., APC and E-cadherin), which also bind to the central Arm repeats of β-catenin **[154]**.

- **Antimicrobial Peptides (AMP) as therapeutic agent for breast cancer**

  The chemotherapeutic drugs presently in use face the greatest challenge of not able to distinguish the malignant cells from the normal cells. As most of these drugs fail to exhibit this specificity property, the normal cells gets damaged along with the cancerous cells which ultimately lead to numerous side-effects. On the contrary the Antimicrobial peptides which have come to the lime light recently are able to differentiate the cancerous cells from the normal cells, ultimately killing the cancerous cells alone and leaving the normal cells unharmed **[155-157]**.

Figure 3: Functions of Antimicrobial Peptides

Table 2: List of Antimicrobial peptides showing anticancer property against breast cancer

S. No.	Peptide	Anticancer activity
1.	Pleurocidin(NRC-3 and NRC-7)	Cell membrane lysis with possible pore formation in mitochondria and ROS production
2.	H1-S6A, F8A	Inhibits C-Myc DNA binding
3.	Pen-ELP-H1	Inhibits C-Myc transcription
4.	BAC-ELP-H1.	Inhibits C-Myc DNA
5.	*Ciso*DGRC (CDAK)	Decreased mitochondrial membrane potential, promotes caspase-3 and inhibitsBcl-2
6.	Temporin-1CEa	Membrane disruption, calcium release,ROS production
7.	Drosocin	Unknown
8.	Cycloviolacin O2	Membrane permeabilization
9.	Cyclosaplin	Unknown
10.	Arachnids. MAP-04-03,	Antiproliferative and antimetastasis
11.	Ranatuerin-2PLx (R2PLx)	Unknown
12.	Quercetin	Inhibits Wnt dependent transcription
13.	NP PKF118-310	Inhibits Wnt dependent transcription
14.	Stapled Axin-derived (StAx) peptides	β-catenin antagonist
15.	Gomesin	Unclear; possible pore formation

16.	**SVS-1**	**Cell membrane disruption via pore formation**
17.	**Dermaseptin**	**Necrosis**
18.	**PTP7**	**Apoptosis induction**
19.	**TfR-lytic peptide**	**Apoptosis induction**
20.	**HNP-1**	**Mediation of antitumor immunity**
21.	**Myristoyl-Cys-Ala-Val-Ala-Tyr-(1,3 dimethyl)His-OMe**	**DNA synthesis/replication inhibition**
22.	**Pentastatin**	**Tumor growth and angiogenesis inhibition**
23.	**Chemokinostatin-1**	**Tumor growth and angiogenesis inhibition**
24.	**Properdistatin**	**Tumor growth and angiogenesis inhibition**
25.	**ERα17p**	**Apoptosis induction and massive necrosis**
26.	**CR1166**	**Apoptosis induction**
27.	**Dox-TAT**	**Helps in drug delivery**
28.	**CT20p-NP**	**Induces cell death**
29.	**PNC-27**	**Inhibits cell transformation target tumour suppressor protein**
30.	**PNC-21**	**Unknown**
31.	**PNC-28**	**Unknown**
32.	**Int-H1-S6A,**	**Targets transcription factors**
33.	**F8A**	**Unknown**
34.	**Magainin II-bombesin conjugate (MG2B)**	**Unknown**

Antimicrobial peptides are present in a wide range of living organisms, in which it renders innate immunity to the organism. Despite their activity against fighting infectious diseases, recently their anticancer property has also been explored. Trials have been undertaken where the effects of the AMPs alone or along with the already existing conventional drugs are investigated. A very interesting finding about the AMPs is that they are mostly either completely free from or have least harmful effects. These peptides recognize the altered cell membrane composition of the malignant cell easily. Hence they are sensitive towards them specifically **[155, 156, 158]**. These AMPs which possess anticancer property are henceforth called as anticancer peptides (ACPs).

Mostly these ACPs are short peptides composed of 5–30 cationic amino acids residues. Few of the ACPs have α-helical structure (e.g., BMAP-27, BMAP-28, Cecropin A and B, LL-37, Magainins etc.) whereas some others folds into a β-sheet (e.g., Defensins, Lactoferricin and Tachylepsin I) and the remaining possess a linear structure (e.g., Tritrpticin and Indolicidin) **[159, 160]**.

Presently ACPs are being tested against few tumors of lung, uterine, cervix, liver, prostate and breast. The mode of action by which the ACPs bring about effect is through enhancing apoptosis or necrosis. Few of the ACPs are seen to damage the intracellular components of the malignant cells. Also a few peptides are multifaceted and thus kill the cancerous cells by more than

one mechanism. Few such ACPs presently under trial are listed below:

- NRC-3 and NRC-7 the cationic peptides of Pleurocidin family **[161]** showed anti-tumor activity against human breast cancers and mouse mammary carcinoma, but failed to show any effect against the human dermal fibroblasts **[162]**. These peptides damaged the cell membrane integrity **[162]**. They were cytotoxic towards a wide range of breast cancers including MCF7-TX400 cells **[174]**. It was observed that when the human breast cancer cells (MDA-MB-231) were treated with NRC-3 or NRC-7, simultaneous administration of cisplatin promoted the cytotoxic effect by 5.5-fold and 1.7-fold, respectively **[162]**.
- A 14 amino acid peptide H1-S6A, F8A, identified by Draeger and Mullen **[163]** was fused with a penetration peptide from Antennapedia by Giorello *et al*. **[164]** leading to the formation of Pen-ELP-H1 **[177, 207]**. Pen-ELP-H1 was observed to induce apoptosis in breast cancer cell line MCF-7 by downregulating the expression of c-Myc gene **[164]**.
- In another study, BAC-ELP-H1 was synthesized by fusing the ELP with a Cancer penetrating peptide which in turn was derived from c-Myc inhibitory peptide (H1-S6A, F8A) and bactenecin**.** This peptide reduced the cell division invitro and decreased the size of the tumour by 80% in rat glioma **[178, 191]**.
- Moreover the AMPs possessing the *Ciso*DGRC (CDAK) subunit exhibited anti-cancer activity towards breast cancer cells MDA-MD-231 and MCF7 *in vitro*. The peptide was able to suppress the tumorous growth by decreasing the mitochondrial membrane potential, enhancing the expression of caspase-3 and arresting the expression of Bcl-2 gene in the breast cancer cell lines. In invivo studies also this peptide was found to be effective in hindering the growth of the xenograft tumour as well as prevented angiogenesis **[166]**.
- A recently identified α-helical AMP composed of 17 amino acid residues is Temporin-1CEa. It was isolated from the secretion of the skin of Chinese brown frog *Rana chensinensis*. A good number of studies have unveiled its efficient anti-tumor activity against MDA-MB-231 and MCF-7 **[166]**. This peptide works by reducing the mitochondrial membrane potential through the leakage of calcium ions into the cytoplasm and

increasing the reactive oxygen species **[166]**. The cytotoxic effect of temporin-1CEa was also observed on ERα negative human breast cancer cell line Bcap-37 **[167]**.

- The ability to recognize the glycosylated membrane exclusively on the breast cancer cells by Drosocin made it one of the most potential anticancer peptide **[168]**.
- Another anticancer peptide Cycloviolacin O2 (CyO_2) has been identified as an effective chemosensitizing agent in drug resistant breast cancers. Also it helps in disrupting the cell membrane integrity of the breast cancer cells **[169]**.
- One more AMP Cyclosaplin isolated from somatic seedlings of sandalwood brings about cell death by triggering apoptosis in human breast cancer cells. At the same time it does not affect the normal fibroblast cells **[170]**.
- An AMP found in the salivary glands of the hard tick MAP-04-03, inhibited the breast cancer proliferation and metastasis **[171]**.
- CDAK is another AMP which was found to display activity against the CD13-/αvβ3 breast cancer cells in vitro alone leaving the normal cells unaffected **[172]**.
- Ranatuerin-2PLx (R2PLx) is a peptide identified in the secretions of the skin of the pickerelfrog (*Rana palustris*) indicated cytotoxic effect against various cancer cell - MCF-7, PC-3, MDA-MB-435S, U251MG and H157 **[186]**.
- One natural peptide PKF118-310 was successful in down-regulating the Wnt signaling pathway by inhibiting the transcription of the respective down-stream target genes **[173]**.
- Peptides like Stapled Axin-derived (StAx) peptides targeted specifically β-catenin in an invitro study. These peptides prohibit the transcription of the Wnt target gene. Concurrently these peptides did not exhibit any effect on the unaffected genes that are involved in other signaling pathways **[188]**.
- Few other AMPs that presented cytotoxic effects against the breast cancers are Gomesin **[174]**, SVS-1 **[175]**, Dermaseptin B2 **[176]**, PTP7 **[177]**, TfR-lytic peptide **[178]**, Myristoyl-Cys-Ala-Val-Ala-Tyr-(1,3 dimethyl)His-OMe **[179]**, Pentastatin-1, chemokinostatin-1, properdistatin **[180]**, ERα17p **[181]**, CR1166 **[182]**, Dox-TAT **[183]**, CT20p-NP **[184]**, PNC-27 **[185-**

187], PNC-21 **[185]** and PNC-28 **[185, 188, 189]**.

- A magainin II-bombesin conjugate (MG2B) presented cytotoxic effect against breast cancer cells in murine models **[190]**.
- Buforin IIb demonstrated anti-cancerous activity towards MX-1 and MCF-7 breast cancer cell lines besides suppressing vascularization and angiogenesis **[191]**.

CONCLUSION

The prevailing therapeutic stratergies are facing various shortcomings which have to be rectified by aquiring a comprehensive knowledge in the unseen side of the present approaches. Hence targeted therapy is the need of the hour. This is feasible if the signaling pathways promoting the development and prognosis of breast cancer are understood at the molecular level. In this review we have thrown much light on the drugs that are designed against the Wnt signaling pathway which plays a very critical role in the development of Breast cancer. Nevertheless none of the drugs is free from the toxicity towards the normal cells along with few drawbacks like multi-drug resistance development and ineffective against the slow growing cancerous cells. It is worth noting that the Wnt signaling pathway is present in the "on" state in few of the normal cells also. Hence the prime requisite of the drugs targeting the components of the Wnt signaling pathway is to differentiate the cancerous cells from the normal cells. In this regard AMP has been recognized as a new frontier in the treatment of varied types of cancers which could fillup the voids observed in the chemotherapy to a greater extent. We have discussed about the anticancer property of few of the AMPs experimented against breast cancer cell lines for the past few decades. The naturally occurring AMPs provide few obstacles to be used as such as an anticancer drug. Therefore in future focused efforts have to be put-forth to overcome the impediments and limitations and which result in the development of promising therapeutic strategies for breast cancer.

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