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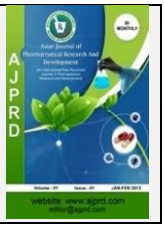

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Review Article

Recent Insights into Breast Cancer Metastasis: Molecular Pathways, Prognostic Markers and Novel Therapies

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A B S T R A C T

Breast cancer metastasis remains a major challenge, contributing significantly to its high mortality rate despite progress in early diagnosis and localized treatments. This review consolidates recent advancements in three crucial areas: molecular mechanisms underlying metastatic progression, prognostic biomarkers for disease prediction, and emerging therapeutic strategiestargetingmetastasis. Keysignaling pathways, including MAPK,PI3K/AKT/mTOR, and Wnt/β-catenin, as well as tumor microenvironment interactions and epithelial-mesenchymal transition, are explored for their role in tumor dissemination and colonization of distant organs. The discovery of prognostic markers such as circulating tumor cells (CTCs), exosomal micro RNAs, cell-free DNA, and genetic alterations like BRCA1/2 mutations and HER2 amplification has revolutionized precision oncology by enabling real-time disease monitoring and patient stratification. Additionally, advancements in transcriptomic and proteomic profiling have introduced novel biomarkers that enhance metastaticrisk assessment and therapeutic decision-making. In parallel, innovative treatment approaches offer new prospects for managing metastatic breast cancer. Immunotherapy strategies, including cancer vaccines, immune checkpoint inhibitors, and adoptive cell therapies, are reshaping treatment paradigms, while targeted small-molecule inhibitors, such as PARP and CDK4/6 inhibitors, alongwith nanotechnology-based drug delivery systems, are improving therapeutic efficacy while minimizing adverse effects. However, challenges such as tumor heterogeneity, resistance to therapy, and variable patient responses highlight the need for further research and clinical trials. By bridging molecular insights with clinical applications, this review aims to provide a comprehen sivere source on the evolving land scape of metastatic breast cancer, focusing on molecular mechanisms, prognostic advancements, and novel therapeutic developments.

KEY WORDS: Breast Cancer Metastasis, Molecular Pathways, Prognostic Biomarkers, Innovative Treatments

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INTRODUCTION

Breast cancer is the most commonly diagnosed malignancy in women and continues to be a leading cause of cancer-related mortality worldwide. The high morbidity and mortality rates of breast cancer are primarily due to its metastatic nature, in which tumor cellsmigrate fromthe primary site to distant organs such as the brain, liver, lungs, and bones [1]. Metastasis is a multistep process that includes ellular mechanisms[2]. local invasion, extravasation, circulation, intravasation, and colonization, all of which are regulated by intricate molecular and Understanding these mechanismsis critical for improving therapeutic outcomes and survival rates in patients with metastatic disease. Molecular research has highlighted several critical pathways in metastasis progression-MAPK, PI3K/AKT/m TOR, and Wnt–β-catenin signaling cascades [3–5]. These pathways regulate crucial processes such as invasion, survival, cell proliferation and migration. Additionally, epithelial-mesenchymal transition, a process in which epithelial cells lose their structural integrity, adhesion properties, and acquire mobile traits to adopt mesenchymal characteristics, has been recognized as a key factor in driving metastasis[6]. EMT isregulated by transcription factors such as Slug, Twist, and Snail, along with signaling moleculesand tumor microenvironmental factors[7]. Despite advance sin our understanding of these pathways, their precise roles inmetastatic initiation and progression remain in completely understood, under scoring the need for continued research.

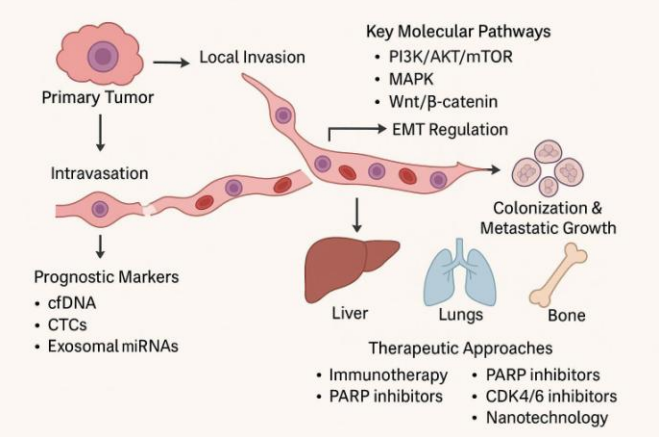

Figure 1: Schematicre presentation of breast cancer metastasis

The identification of reliable prognostic markers has transformed breast cancer management by enabling risk stratification and real-time disease monitoring. Cell-free DNA (cfDNA), protein-based biomarkers ,circulating tumor cells (CTCs),and exosomalmicro RNAs

(miRNAs) have shown significant potential in predicting metastasisand therapeutic response [8–10]. For example, HER2 amplification, BRCA1/2 mutations, and ESR1 mutations have been linked to metastatic risk and treatment resistance, aiding in the development of personalized therapeutic strategies [11–12]. However, variability in the specificity and sensitivity of these markers highlights the ongoing challenges in biomarker validation and clinical implementation. In parallel, the development of novel therapeutic strategies targeting metastatic breast cancer has shown significant promise. Immunotherapy, especially through immune check point inhibitors suchasanti-PD-1/PD-L1 antibodies, has revolutionized cancer treatment by harnessing the body's immune system to combat tumor growth [13]. Similarly, treatments such as PARP inhibitors, targeted therapies, PI3K inhibitors, and CDK4/6 inhibitors have shown efficacy in specific molecular subtypes of metastatic breast cancer [14–16]. The advent of nanotechnology has further enabled the design of sophisticated drug delivery systems for targeting anticancer drugs and improving bioavailability [17]. Nevertheless, challenges such as therapy-induced resistance and tumor heterogeneity continue to limit therapeutic efficacy, emphasizing the need for innovative approaches and combination therapies [18–19].

This review aims to offer an in-depth examination of the molecular pathways, prognostic markers and therapeutic strategies associated with breast cancer metastasis. By integrating insights from recent research studies, this paper aims to connect the gap between clinical application and molecular research, highlighting emerging trendsand future directions in the field. Specifically, it will focus on:

Molecular Pathways: Exploring key signaling cascades and processes such as EMT, angiogenesis and tumor microenvironment dynamics that drive metastatic progression. **Prognostic Markers:** Review in gadvances in the identification and validation of biomarkers for predicting metastatic risk and monitoring disease progression.

Novel Therapies: Discussing the current landscape of therapies targeting metastatic breast cancer, including immunotherapy, targeted therapies and novel drug delivery systems.

By addressing these themes, this review intends to add to the expanding understanding of breast cancer metastasis, offering valuable insights for stakeholders,clinicians and researchers in the fight against this devastating disease.

Molecular Pathways in Breast Cancer Metastasis:-

Themetastatic progression of breast cancer involvesa series of highly coordinated molecular events that enable tumor cells to invade, survive in circulation, and colonize distant organs. Several signaling pathways and processes-suchasthe MAPK,PI3K/AKT/mTOR, and Wnt/β-catenin signaling cascades, epithelial-mesenchymal transition (EMT), and tumor microenvironment dynamics-play pivotal roles in this process. These pathways regulate key cellular behaviors such as invasion, proliferation, migration and resistance to apoptosis, making them critical targets for understanding and combating metastasis[1,3,5].

1. *PI3K/AKT/m TOR Pathway:*

The PI3K/AKT/m TOR pathway is frequently alteredin breast cancer and playsa crucialrole inblood vessel formation, promoting tumor growth and facilitating the spread of cancer cells throughout the body [4]. Activation of this pathway begins with receptor tyrosine kinases (RTKs), such as EGFR and HER2, which phosphorylate phosphatidylinositol-3-kinase (PI3K). This activation leads to the phosphorylation of AKT, a serine/threonine kinase that regulates down stream targets such a sm TOR,which plays a vital role in protein synthesis, cell survival, and metabolic reprogramming [2]. Dysregulation of the PI3K/AKT/mTOR pathway is strongly linked to the acquisition of metastatictraits, including enhanced cell motility and resistance to therapy [16]. PIK3CA mutations, which encodes the catalytic subunit of PI3K, are frequently observed in breast cancer and are of ten associated with poor prognosis[12]. Additionally, the interaction between PI3K/AKT/mTOR and other signaling pathways, such as MAPK, has been shown to drive tumor heterogeneity and metastasis [14]. Therapeutic strategies targeting this pathway, such as PI3K inhibitors (e.g.,alpelisib) andm TOR inhibitors (e.g.,everolimus),

have shown promisein clinical trials; however, resistance mechanism sremaina challenge [15].

2. *MAPKPathway:*

The mitogen-activated protein kinase(MAPK) pathway isanother crucial regulator of breast cancer metastasis. This signaling cascade is activated by cytokines and growth factors, resulting in the sequential phosphorylation of RAF, MEK, and ERK kinases [17]. Once activated, ERK translocate to the nucleus, where it regulates the expression of genes involved in cell proliferation, invasion, and migration [10]. In metastatic breast cancer, abnormal activation of the MAPK pathway has been associated with enhanced epithelial-mesenchymal transition (EMT), extracellular matrix (ECM) remodeling, and angiogenesis [13]. HER2- over expressing breast cancers frequently exhibithy peractivation of this pathway, further driving tumor aggressiveness and resistance to anti-HER2 therapies such as trastuzumab [8]. Combining the inhibition of both MAPK and PI3K pathways has been explored asa strategy to prevent resistance and metastatic spread [7].

3. *Wnt/β-Catenin Pathway:*

The Wnt/β-catenin pathway is crucial for maintaining tissue homeostasis but is frequently hijacked during breast cancer progression to drive metastasis [9]. Canonical Wnt signaling stabilizes β-catenin and facilitates its nuclear translocation, where it acts as a transcriptional coactivator for genes associated with epithelial-mesenchymal transition (EMT), stem cell properties, and invasion [19]. Aberrant activation of Wnt signaling is frequently observed in basal-like and triple-negative breast cancers (TNBCs), which exhibit high metastatic potential and are associated with poor prognosis[6].

Additionally, interactions between Wnt signaling and the tumor microenvironment, particularly via cancer-associated fibroblasts (CAFs), further enhance metastatic dissemination [18]. Targeting Wnt signaling for therapeutic intervention remains challenging; however, inhibitors aimed at β-catenin stabilization and Wnt receptor-ligand interactions are currently under investigation [17].

4. *Epithelial-MesenchymalTransition(EMT):*

EMT is a cellular process that allows epithelial cells to acquire mesenchymal-like characteristics, enhancing their invasive and migratory capabilities. This transformation is regulated by transcription factors such as Slug, Twist, and Snail, which suppress epithelial markers like E-cadherin while promoting the expression of mesenchymal markers like vimentin [20]. In breast cancer, the process of EMT is strongly linked to stemness, drug resistance, and immune evasion [21]. EMT is often induced by signals from the tumor microenvironment, including TGF-β, hypoxia, and inflammatory cytokines [22]. Notably, EMT is a dynamic and reversible process, enabling metastatic cells to transition back to an epithelial state (MET) while colonizing distant sites [23]. Targeting EMT-associated transcription factors or their upstream regulators has demonstrated promise in preclinical models, yet clinical application remains challenging [24].

5. *TumorMicroenvironment(TME):*

The tumor microenvironment (TME) plays a key role in shaping the metastatic potential of breast cancer cells. It comprises various elements, including immune cells, cancer-associated fibroblasts (CAFs), the extracellular matrix (ECM), and soluble factors such as growth factors and cytokines [25]. CAFs secrete ECM components and remodeling enzymes, such as matrix metalloproteinases, which facilitate invasion and intravasation [26]. Immune cells present in the tumor microenvironment, especially tumor-associated macrophages (TAMs), promote immunosuppression and angiogenesis through the secretion of VEGF and IL-10 [27]. Additionally, exosomes released by cancer and stromal cells playakeyrolein establishing the pre-metastatic niche by delivering oncogenic moleculesto distant sites [28]. Recent research has emphasized the dynamic cross talk between the tumor microenvironment and key signaling pathways like Wnt and PI3K/AKT, highlighting the need for a comprehensive strategy to combat metastasis [29]. Approaches focused on modifying the tumor microenvironment, including immune checkpoint inhibitors and ECM-targeting agents, are actively being investigated in clinical trials [30].

Table 1: MajorMolecularPathways Implicated in Breast CancerMetastasis: Key Components, Functions, and Therapeutic Targets.

Pathway	Key Components	Metastatic Functions	Clinical Targetability	Refs
PI3K/AKT/mTOR	PI3K, AKT, mTOR, PTEN	Promotes survival, invasion, angiogenesis	Alpelisib,Everolimus	[4,12,15]
MAPK	RAF,MEK, ERK	EnhancesEMT, ECM remodeling, proliferation	Trametinib, MEK/ERK inhibitors	[7,8,17]
Wnt/β-catenin	β-catenin,APC, Wnt ligands	Induces EMT, stemness,drug resistance	Porcupine inhibitors (LGK974)	[6,10,19]
Notch	Notch1,Jagged, TGF-β cooperativity	PromotesEMT, cell plasticity	Gamma-secretase inhibitors(intrials)	[46]
Hedgehog(Hh)	Smo,Gli1	Drives metabolic flexibility, resistance	Vismodegib(early-phase trials)	[47]

An increasingly recognized contributor to breast cancer metastasis is the crosstalk between thePI3K/AKT/mTOR pathway and the tumor microenvironment (TME). Studies indicate that PI3K

activation not only drives intrinsic tumor cell survival but also modulates stromal fibroblasts and immune cells in the TME, enhancing metastatic potential. Forinstance, PI3Kα signaling in breast cancer cells promotes secretion of pro-tumorigenic cytokines like IL-6 and CXCL8, which facilitate the formation of a pre-metastatic niche [35].

The Notch signaling pathway, beyond its canonicalrolesin stemnessand EMT, has also been shown to synergize with TGF-β and Wnt/β-cateninin metastaticre programming. Specifically, Notch1 can upregulate TGF-β receptor expression, enhancing SMAD-mediated transcription of pro-metastatic genes. This cooperation amplifies cell plasticity and enables efficient transition to a mesenchymal phenotype during invasion [36].

Moreover, the Hedgehog (Hh) signaling pathway has emerged as a regulator of metabolic plasticity in metastatic breast cancer. Activation of Hh promotes glycolytic reprogramming and fatty acid oxidation, crucial for the energy-demanding process of metastatic dissemination. This pathway, particularly in triple-negative breast cancer, contributes to therapeutic resistance and metastasis through Smo-dependent activation of downstream effectors like Gli1 [37].

Prognostic Markersin Breast Cancer Metastasis:-

Prognostic markers are crucial in forecasting disease progression and patient outcomes in breast cancer. They provide critical insights into tumor aggressiveness, likelihood of recurrence, and therapeutic response. The integration of molecular pathways with clinically relevant biomarkers has advanced the understanding of breast cancer metastasis, facilitating more personalized treatment approaches [1,3,5]. This section explores key prognostic markers associated with the MAPK, PI3K/AKT/mTOR, Wnt/β-catenin pathways, the tumor microenvironment (TME) and epithelial-mesenchymal transition (EMT).

1. *PI3K/AKT/m TOR Pathway-Associated Markers:*

The PI3K/AKT/mTOR pathway frequently becomes activated in breast cancer as a result of PIK3CA mutations, PTEN loss, or AKT amplification. Among these, PIK3CA mutations have emerged as key prognostic markers, correlating with poor survival and increased metastatic potential [2,16]. PTEN loss is also associated with aggressive tumor pheno types and resistance to therapies such as trastuzumab [15]. In addition, phosphorylated AKT (p-AKT) levels in tumor tissues serve as a prognostic marker, with higher levels linked to reduced disease-free survival and increased recurrence risk [7]. Serum levels of down stream effectors, such as phosphorylated S6 kinase, have been proposed as non-invasive markers of pathway activation [8].

2. *MAPK Pathway-Associated Markers:*

Markerslinked to the MAPK pathway, including RAF and ERK activation, have been studied extensively for their prognostic relevance. Elevated phosphorylated ERK (p-ERK) levelsare linked to poor prognosis, especially in triple-negative breast cancer (TNBC) and HER2-positive cases [25]. Mutations in genes encoding upstream regulators of the MAPK pathway, such as KRAS and BRAF, have also been identified as prognostic markers. These mutations contribute to aggressive phenotypes and poor responses to conventional therapies [28]. Moreover, the up regulation of down stream transcription factors, including c-FOS and ELK1, is associated with increased metastatic potential [23].

3. *Wnt/β-Catenin Pathway-Associated Markers:*

The Wnt/β-catenin pathway has been identified as a significant contribut or to metastasis, with β-catenin nuclear localization servingasa hallmark of pathway activation. Nuclear β-catenin levels are strongly correlated with poor prognosis, stem-like tumor characteristics, and chemoresistance [18,29]. Additionally, alterations in APC, a key suppress or of the Wnt pathway, have been identified in metastatic breast cancer and are associated with unfavorable survival outcomes [24]. Serum concentrations of Wnt pathway regulators, including Wnt inhibitory factor-1 (WIF1) and Dickkopf-1 (DKK1), have been explored as potential prognostic biomarkers [10].

4. *EMT-Associated Markers:*

Epithelial-mesenchymal transition (EMT) is a key driver of metastasis and its associated markers have significant prognostic value. The reduction of epithelial markers like E-cadherin, along with the elevated expression of mesenchy malmarkers such as N-cadherin and vimentin, is closely linked to poor prognosis and heightened metastatic potential [27]. Transcription factors that induce EMT, suchas Slug,Twist, and Snail, function as prognostic markers, with their elevated expression associated with tumor progression, immune evasion, and therapy resistance [13]. Elevated circulating tumor cells (CTCs) expressing EMT markers have been correlated with reduced overall survival in breast cancer patients[17].

5. *Tumor Microenvironment-Associated Markers:*

The tumor microenvironment (TME) significantly influences metastasis and its components have emerged as valuable prognostic markers. Tumor-associated macrophages (TAMs), characterized by high CD68 and CD163 expression, are associated with poor prognosis due to their role in promoting angiogenesis, immunosuppression and ECM remodeling [19,22]. Similarly, heightened expression of matrixmetallo proteinases (MMPs), including MMP-9 and MMP-2, is associated with greater invasiveness and metastatic potential [30]. Immune checkpoint regulators, including PD-L1, have been recognized as prognostic markers, where elevated expression isassociated with immune evasion and poorer outcomes[26]. Exosome-derived markers, including miRNAs and proteins involved in metastasis, are also under investigation. For instance, miR-21 and

miR-200, which regulate EMT and TME dynamics, are associated with poor prognosis and metastatic progression [6,9].

6. *Integrative Biomarkers and Multi-Pathway Prognostics:*

Given the complexity of metastatic breast cancer, single markers are often insufficient for predicting outcomes. Instead, integrative biomarkers that combine data from multiple pathways are being developed. For example, gene expression signatures such as the Oncotype DX and Mamma Print assays, incorporate multiple prognostic markers to stratify patients by recurrence risk and guide treatment decisions [12,21]. Serum-based panels integrating markers from the MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin pathways, along with TME and EMT components, are under investigation for their potential to offera comprehensive prognosis[28].

Table 2: Prognostic Markers in Breast Cancer Metastasis: Types, Clinical Roles, and Detection Methods.

Marker Type	Examples	Clinical Significance	Detection Method	Refs
Genetic Alterations	PIK3CA,BRCA1/2, ESR1mutations	Predictmetastasis, drugresistance	PCR,NGS	[2,12,16]
Protein Markers	HER2,p-AKT, MMP-9	Prognostic for survival, linkedto invasiveness	IHC, ELISA	[7,8,30]
Circulating Biomarkers	Ct DNA,CTCs, exosomal miRNAs/lncRNAs	Real-time monitoring of progression and recurrence	Liquidbiopsy, qRT-PCR	[9,10,49,51]
Immune-Related	PD-L1,CTLA-4, CD8+ TILs	Predict response to immunotherapyand prognosis	IHC,flow cytometry	[26,48,50]

The **immune checkpoint molecules PD-L1 and CTLA-4** have emerged as significant prognostic biomarkers in breast cancer, particularly in triple-negative subtypes. Elevated PD-L1 expression is associated with immune evasion and poor prognosis but also predicts response to immune check point inhibitors.Co-expression with CTLA-4 further stratifies high-risk patients, suggesting that their combined assessment may guide immunotherapy selection [38].

Exosomal long non-coding RNAs (lnc RNAs) have recently gained attention as stable and non-invasive prognostic markers. Amongthem, exosomallnc RNAHOTAIR has been shown to correlate with lymphnode metastasis, larger tumor size, anddecreasedoverall survival. Its ability to modulate EMT and chromatin remodelling underscores its value as both a prognostic marker and therapeutic target [39].

High levels of **tumor-infiltrating lymphocytes (TILs)** in HER2+ and triple-negative breast cancers have been positivelyassociated with improved disease-free and overall survival. Thepresence of CD8+ T cells in particular is predictive of better responses to chemotherapy and immune-based treatments, making TILs a dynamic biomarker for evaluating prognosis and therapeutic sensitivity [40].

Circulating tumor DNA (ctDNA) has emerged as a real-time, minimal lyinvasive marker for monitoring metastatic progression and relapse risk. Quantitative assessment of ctDNA mutations, such as those in *PIK3CA* or *TP53*, provides prognostic information beyond standard imaging, enabling earlier detection of recurrence and resistance mutations [41].

Novel Therapiesin Breast Cancer Metastasis:-

The complexity of breast cancer metastasis has driven the development of innovative therapeutic strategies aimedat targeting key molecular pathways, prognostic markers, and the tumor microenvironment. Recent advancesin genomics, proteomics, and immunotherapy have enabledthe identification of novel therapeutictargetsand treatment modalities. This section explores targeted therapies, immunotherapies, and emerging approaches based on insights from molecular pathways and prognostic markers.

Targeted Therapies:

PI3K/AKT/mTORPathwayInhibitors:-

Given the frequent dysregulation ofthe PI3K/AKT/mTOR pathway in breast cancer, inhibitors targeting this pathway have shown promise. Alpelisib, aselective PI3Kα inhibitor, has shown effectiveness in patients with PIK3CA-mutated tumors, enhancing progression-free survival when combined with endocrine therapy [16]. Similarly, mTOR inhibitors, including everolimus, have shown effectiveness in hormone receptor-positive breast cancers by helping to overcom eresistance to aromatase inhibitors[15]. Dual inhibitors targeting both PI3K and mTOR areunder clinical investigation, with earlytrials suggesting enhanced therapeutic efficacy [3]. Additionally, the use of pathway biomarkers such as phosphorylated AKT, has enabled patient stratification for these therapies [2].

MAPK Pathway Modulators:-

Therapies targeting the MAPK pathway, including MEK and ERK inhibitors, are gaining attention. Trametinib, a MEK inhibitor, has demonstrated preclinical success in reducing tumor growth inHER2-positive andtriple-negative breast cancer (TNBC) models [28]. Combining MAPK inhibitors with other agents, such as CDK4/6 inhibitors or immune

checkpoint inhibitors, is being explored to overcome resistance mechanisms [12]. These combination strategies rely on prognostic markers, such as p-ERK levels, to identify suitable patients[24].

Wnt/β-Catenin Pathway Inhibitors:-

Therapies targeting the Wnt/β-catenin pathway are in early stages of development but show significant promise. Porcupine inhibitors, such as LGK974, block Wnt ligand secretion and have demonstrated efficacy in preclinical models of TNBC [10]. Monoclonal antibodies targeting Wnt pathway components, such as Frizzled receptors, are also under investigation [6]. Further more, serum biomarkers ,including nuclear β-catenin levels, may guide patient selection for these therapies[9].

Immunotherapies:

Immune Check point Inhibitors:-

Immune checkpoint inhibitors targeting CTLA-4 and PD-1/PD-L1 have reshaped cancer therapy. Atezolizumab, a PD-L1 inhibitor, has demonstrated clinical benefit when combined withnab-paclitaxel for treating metastatic TNBC [21]. Elevated PD-L1 express ion in tumors, along with the presence of tumor-infiltrating lymphocytes (TILs), functions as a predictive biomarker for these therapies [26]. Efforts are underway to combine checkpoint inhibitors with other therapies, such as targeted agentsand radiotherapy, to enhance efficacy [19].

Vaccinesand Cellular Therapies:

Therapeutic cancer vaccin estargeting specific tumor antigens, such as HER2 and MUC1, are under investigation. HER2-targeted vaccines, such as NeuVax, are designed to activate an immune response against HER2-positive tumors [22]. Chimeric antigen receptor (CAR) T-cell therapy, which has shown success in hematologic malignancies, is now being modified for application in breast cancer. Efforts to target antigens such as mesothelin and ROR1 are ongoing, with preclinical studies showing promise [13].

Emerging Therapeutic Approaches:

EMT and CTC-Targeted Therapies:-

Given the role of epithelial-mesenchymal transition in metastasis, therapies targeting EMT markersarebeing developed. Small molecules and monoclonal antibodies designed to inhibit EMT-inducing transcription factors like Twist and Snail are currently being assessed in preclinical studies [17]. Circulating tumor cell (CTC)-targeted therapies, including antibody-drug conjugates, are also being explored. CTCs expressing EMT markers have been identified as key targets for preventing metastatic spread [27].

Tumor Microenvironment Modulation:-

Therapies targeting the tumor microenvironment (TME) aim to disrupt key interactions that promote metastasis. Agents targeting tumor-associated macrophages (TAMs), such as CSF-1R inhibitors, are under clinical investigation [24]. Matrix metalloproteinase (MMP) inhibitors, designed to reduce extracellular matrix degradation, are also being revisited with improved specificity [1]. Exosome-based therapies, including inhibitors of exosome secretion, hold promise for limiting metastatic signaling [31].

Nanotechnology and Drug Delivery Systems:-

Nanoparticle-based drug delivery systems enhance tumor targeting while minimizing systemic toxicity, improving therapeutic efficacy. Liposomal formulations of chemotherapeutics, such as doxorubicin, have shown enhanced efficacy in metastatic breast cancer [30]. Targeted delivery of therapeutic agents using nanoparticles conjugated with antibodies or ligands specifictotumor biomarkers, suchas HER 2, is an emerging area of research [32].

Personalized Medicineand Multi-Omics Integration:

The integration of multi-omics data, including genomics, proteomics and transcriptomics, is driving the development of personalized therapies. Comprehensive molecular profiling enables the identification of action abletargets and prognostic markers, guiding therapy selection [33]. Precision oncology platforms, such asthe use ofliquid biopsiesto monitor circulating tumor DNA (ctDNA) and RNA, are facilitating real-time treatment adjustments [3].The development of combinational biomarker panels encompassing multiple pathways and prognostic markers is expected to enhance therapeutic outcomes [34].

Table 3: Emerging and Approved Therapies Targeting Breast Cancer Metastasis

Drug/Approach	Target	Subtype/Use Case	Trial Phase/Approval	Refs
Alpelisib	PI3Kα (PIK3CA- mutated tumors)	HR+/HER2-MBC	FDAApproved	[16,52]
Atezolizuma b+ nab-paclitaxel	PD-L1	Triple-negative MBC	Approved (TNBC)	[21,48]
Bemcentinib (BGB324)	AXL/EMT	Mesenchymal-like breastcancer	PhaseI/II	[54]
CAR-Tcell therapy	ROR1, Mesothelin	Under study in solid tumors	Preclinical– PhaseI	[13,22]
Exosome inhibitors	Metastatic signal transmission	Experimental	Preclinical	[31]

Recent advances in PI3K inhibition strategies have led to the development of isoform-selective inhibitors such as alpelisib, which targets PI3Kα mutations frequently found in hormone receptor-positive breast cancers. In combination with endocrine therapy, alpelisib has demonstrated significant improvements in progression-free survival and is now an FDA-approved option for PIK3CA-mutant metastatic breast cancer [42].

Targeting the tumor microenvironment (TME) has emerged as a therapeutic strategy to halt metastasis. Agents like losartan and angiotensin inhibitors, originally used in hypertension, are now being repurposed to modulatestromal remodelling, reduce fibrosis, and improve drug delivery in dense breast tumors, particularly in triple-negative subtypes [43].

Inhibitors of epithelial–mesenchymal transition (EMT) have shown promise in preclinical models. For instance, the compound BGB324 (bemcentinib), an AXL tyrosine kinase inhibitor, disrupts EMT signaling and impairs metastatic potential in mesenchymal-like breast cancer cells. It is currently undergoing evaluation in early-phase clinical trials as part of combination therapies [44].

Progress in liquid biopsy-guided therapies has enabled dynamic treatment adaptations based on circulating tumor DNA (ctDNA). For example, early detection of resistance mutations through ctDNA sequencing has facilitated real-time switching of targeted agents in clinical settings, enhancing treatment precision and improving survival in metastatic breast cancer patients [45].

Discussion:

The review highlights critical advancements in understanding breast cancer metastasis, emphasizing molecular pathways, prognostic markers, and novel therapies. The MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin pathways serve as key regulators of tumor progression and metastatic spread, presenting viable therapeutic targets.Targeted inhibitors, such as PI3K and MEK modulators, have demonstrated efficacy in preclinical and clinical settings, yet resistance mechanisms remaina challenge. Combination strategies involving multiple pathway inhibitors or integration with immunotherapies provide promising avenues for overcoming therapeutic resistance. Prognostic markers, including circulating tumor cells (CTCs), tumor- infiltrating lymphocytes (TILs) and EMT-related factors, enable early detection of metastasis and guidetreatment decisions. These biomarkers not only facilitaterisk stratification butalso aid in monitoring therapeutic responses, under scoring their dual diagnostic and prognostic value. The emergence ofliquid biopsies and multi omics technologies further strengthensthe ability to personalize treatment and predict outcomes. The exploration of novel therapies, particularly immune checkpoint inhibitors and nanoparticle-based drug delivery systems, signifies aparadigm shift in metastatic breast cancer management. Immune based approaches, including CAR-T cell therapies and PD-1/PD-L1 inhibitors, have shown encouraging results, particularly in immune-responsive subtypes like TNBC. Nanotechnology enhances drug targeting and reduces systemic toxicity, representing a key innovation in therapeutic delivery. Despite significant advancements, key challenges persist in treating metastatic breast cancer. Tumor heterogeneity complicates therapy prediction and response [18]. Moreover, dynamic EMT plasticity enables reversible transitions that escape targeted interventions [23,54]. Current therapies often fail to eradicate micrometastases due to limited understanding of the pre-metastatic niche [28]. Future directions should prioritize:

- Development of integrative biomarker panels combining genomic, proteomic, and immune profiling [33,34].
- Exploitation fliquid biopsy-guided therapy monitoring to enable early therapeutic switching [51,55].
- Enhancement of combination strategies to overcome resistance mechanisms in immunologically “cold” tumors [13,19].

CONCLUSION:-

This review underscores the intricate molecular mechanisms and clinical advancements in addressing breast cancer metastasis. The MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin pathway sarekey drivers of metastasis, providing critical targets for therapeutic intervention. Prognostic markers such as circulating tumor cells, EMT-related factors and tumor-infiltrating lymphocytes, provide valuable tools for early detection, risk stratification, and treatment monitoring. These insights emphasize the significance of combining molecular and clinical data to improve prognostic precision and optimize therapeutic outcomes. The emergence of noveltherapies, including immune checkpoint inhibitors, targeted drug delivery systems, and exosome-based interventions, highlights the transition toward precision medicine. Combination therapies, leveraging immunotherapies, targeted inhibitors, and biomarker-driven approaches, show potential inovercoming resistance and improving patient survival.Despite these advancements, challenges such as tumor heterogeneity and therapy resistance necessitate continued research to refine biomarker panels and develop personalized treatments. A multidisciplinary, patient-centered approach, combining molecular insights with clinical innovation, remains essential for effectively combating metastatic breast cancer and improving long-term outcomes. Ultimately, aparadigm shifts to war dprecision oncology that leverages real-time molecular monitoring and adaptive therapy is essential. Integrating biomarker-driven strategies with evolving therapeutic platforms will be key to reducing the burden of metastatic breast cancer and enhancing patient survival.

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