Journal of Regenerative Medicine and Molecular Innovation
Vol. 2 No. 1 Maret 2026
E-ISSN: 3090-0824
Open Access: https://journals.ai-mrc.com/jrmmi

Adipose-Derived Mesenchymal Stem Cells as a Drug Delivery System for Breast Cancer Therapy

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Article Info

Article history:
Received 27-01-2026
Revised 01-03-2026
Accepted 17-03-2026

Keyword:
Adipose Derived Mesenchymal Stem Cells; Breast Cancer; Drug Delivery System.

ABSTRACT

Breast cancer is one of the deadliest types of cancer in the world with an incidence rate that is ranked second with a total of 2.2 million patients in the world and a mortality rate fourth in the world with more than 600 thousand cases (30%). The high mortality rate cannot be separated from problems in treatment, such as low targeting, high possibility of systemic side effects which cause a decrease in patient compliance, high treatment prices and the trend of chemotherapy resistance via various mechanism. Therefore, a new breakthrough is needed in the treatment of breast cancer that is more effective and efficient, by using Mesenchymal Stem Cells (MSCs) as a drug delivery system to increase targeting, minimize side effects and potential resistance due to the adaptation mechanism of cancer cells to treatment agents. This study employed a systematic literature review approach by analyzing recent in vitro and in vivo experimental studies investigating MSC-derived drug delivery platforms for breast cancer therapy. Specifically, the review focused on MSC-loaded chemotherapeutic agents (such as doxorubicin and paclitaxel), MSC-derived exosomes as nanocarriers, and genetically engineered MSCs expressing anti-tumor cytokines or pro-apoptotic genes. Data were extracted and synthesized to evaluate targeting efficiency, tumor growth inhibition, apoptotic induction, and reduction of systemic toxicity. Several studies have shown positive results regarding the use of Mesenchymal Stem Cells as a drug delivery system against several types of cancer with increased anti-tumor and anti-cancer activity by inhibiting proliferative cascade pathways and activating the apoptotic pathway. The findings indicate that MSC-mediated drug delivery significantly improves tumor homing capacity, enhances cytotoxic effects on breast cancer cells, reduces tumor volume in animal models, and decreases systemic adverse effects compared to conventional chemotherapy. Furthermore, MSC-derived exosomes demonstrated improved intracellular drug uptake and modulation of resistance-related signaling pathways, suggesting their potential to overcome chemotherapy resistance. These results highlight MSC-based delivery systems as a promising and targeted therapeutic strategy for breast cancer management.

INTRODUCTION

Breast cancer is one of the most common types of cancer, both globally and nationally. Based on data published by the World Health Organization (WHO), breast cancer is ranked second as the most common type of cancer worldwide with a total of 2.2 million patients and a death rate of 600 thousand patients (fourth place in the world). The same data trend is also reflected in national data that breast cancer is the most common type of cancer (66,000 cases with a 30% death rate). WHO also has a projection that breast cancer cases will increase by 52.1% until 2045 [1]. This prevalence causes Indonesia to be on the list of 10 countries with the most breast cancer cases in ASEAN alongside Singapore, the Philippines, Brunei Darussalam and Malaysia. Lifestyle changes in food, drink, sleep patterns, air quality and genetic factors are supporting factors why breast cancer cases are common in society [2,3].

Breast cancer in general is a condition of uncontrolled proliferation of breast epithelial cells due to dysregulation in the cell cycle and changes in the expression of proto-oncogenes to oncogenes. Breast cancer can be divided into 2 (two) types, namely the non-invasive type known as DCIS (Ductal Carcinoma In Situ) and LCIS (Lobular Carcinoma In Situ) and the invasive type known as IDC (Invasive Ductal Carcinoma). Furthermore, molecularly, breast cancer can be further divided into ER+/PR+ (Hormonal Positive), HER2+ and Triple Negative types, each of which has its own characteristics [4,5].

The combination of therapy used still causes quite a lot of problems, including the combination of chemotherapy which does not have high targeting so that the treatment tends not to target the cancer cells properly. This then causes systemic side effects which are detrimental to patients such as hair loss, nausea, vomiting, delirium, Steven Johnson Syndrome (SJS),gastrointestinal disorders, muscular disorders, insomnia and others [6,7]. In addition, there is a trend in chemotherapy resistance by cancer cells by releasing chemotherapy agents through efflux pump channels which causes its own challenges in treatment [8,9,10]. Based on this, a breakthrough and new intervention is needed in breast cancer therapy that is effective and efficient.

A stem cell-based therapy approach can provide a new breakthrough in cancer treatment because of its ability to identify cancer cells and not be considered an enemy, thereby minimizing the escape of the cancer cells themselves [12]. The use of one subtype of stem cell, namely Mesenchymal Stem Cells taken from various sources such as bone marrow (bone marrow - derived MSCs), adipose (adipose derived Stem Cells) and umbilical cord (Umbilical MSCs) has great potential as a chemotherapy drug carrier (drug carrier) so this research is very important to carry out in increasing targeting, reducing systemic side effects, preventing resistance and increasing the effectiveness and cost efficiency of treatment.

Breast Cancer : Epidemiology Approach

In terms of prevalence, breast cancer is ranked second in the world with a total number of sufferers reaching 2,296,840 people with a mortality rate ranked fourth in the world with a death toll of 666,103 people and this also causes breast cancer to become the number one type of cancer that is most commonly suffered in Asia. Furthermore, specifically, the incidence of breast cancer in Indonesia ranks 4th in Asia after China, India and Japan with the number of cases reaching 66,271 people and deaths reaching 22,598 people (34% of total cases). WHO also projects that Indonesia will experience an increase in breast cancer cases of up to 37.8% and an increase in mortality of up to 52.1% in 2045 [1]

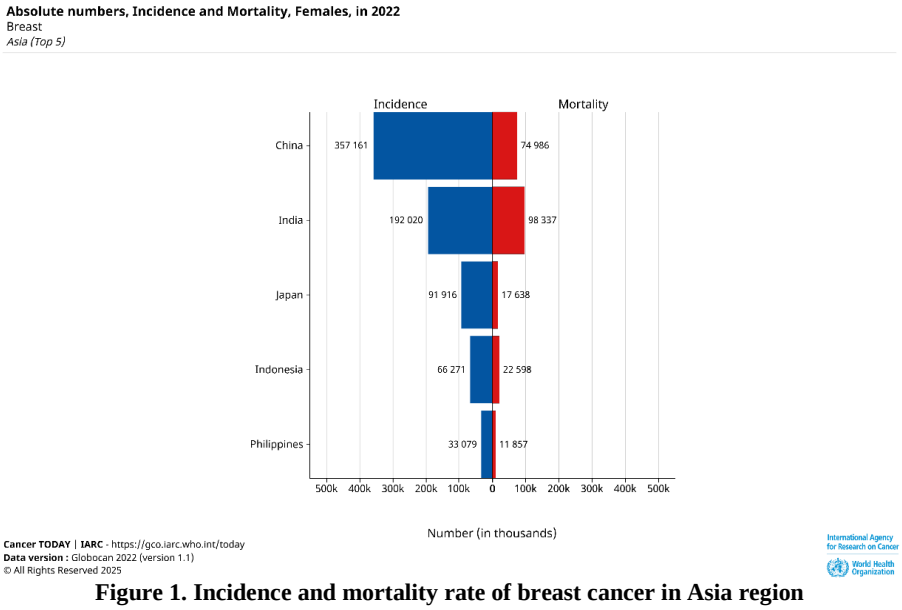

Figure 1. Incidence and mortality rate of breast cancer in Asia region

More specifically, of several types/types of breast cancer (Luminal A, Luminal B, HER2+ and triple negative), the incidence of Luminal type breast cancer (both Luminal A and B) which is caused by hormonal disorders ranks higher than HER2+ and triple negative types both globally and

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nationally. The fairly high prevalence and the projected growth in incidence and mortality rates which are quite worrying for the next 20 years are essential grounds for the need for new breakthroughs in the management of breast cancer therapy that is more efficient and effective so that it can reduce the incidence and increase life expectancy for sufferers.

Breast Cancer : Molecular Approach

In general, breast cancer can be divided into 2 types, namely non-invasive types (DCIS and LCIS) and invasive types (IDC). However, if we examine it more deeply, breast cancer can actually be specified into several subtypes based on genetic expression mapping. In order to determine the type of breast cancer, there are at least 3 (three) tumor markers that are studied, namely ER-estrogen receptor status, PR-progesterone receptor status and HER-2 status so that the classification of breast cancer can be further specified into several types as follows.

1. HR+/HER2- : refers to a type of breast cancer caused by excessive hormonal activity (also known as Luminal A subtype). This type of cancer has a slower cell growth rate with low aggressiveness (characterized by low Ki-67 protein values).
2. HR+/HER2+ : refers to a type of breast cancer caused by hormonal activity and HER2 overexpression (referred to as Luminal B subtype). This type of cancer has rapid cell growth with quite high aggressiveness (characterized by high Ki-67 protein values)
3. HR-/HER2+ : refers to a type of breast cancer that occurs only due to excessive expression of HER2 (HER2 positive type breast cancer). HER2 type has a faster cell growth rate compared to Luminal B and has a low prognosis.
4. HR-/HER2- : in some cancer cases negative values can also be found for both hormonal receptors and HER2 so that this class is included in the TNBC (Triple Negative Breast Cancer) type which is generally caused by genetic mutations in BRCA1/BRCA2.

Intrinsic subtype	Characteristics	Common metastatic site
Luminal A	ER+ and/or PR+, HER2- Low Ki67 Best prognosis, high survival	Bone, skin
Luminal B	ER+ and/or PR+, HER2+ High Ki67 Poorer prognosis than luminal A, high survival	Bone, skin
HER2-enriched	ER/PR-, HER2+ Poor prognosis	Bone, liver, lungs, brain
Basal-like	Generally triple-negative Poor prognosis Express basal cytokeratins High Ki67	Brain, lungs
Claudin-low	Generally triple-negative Low expression of luminal differentiation markers and claudins Low Ki67 compared to basal-like Enrichment of EMT and stem cell genes Poor prognosis	Unknown

Figure 2. Molecular Classification of Breast Cancer

Hormonal type breast cancer (both luminal A and luminal B) is a type of breast cancer with a fairly high prevalence both globally and in Indonesia. This cancer occurs due to excessive activity of the hormones estrogen and progesterone, which causes amplification of gene expression which is responsible for cell proliferation and migration, especially in cells in breast tissue. Chemically, estrogen and progesterone are chemical compounds belonging to the cholesterol category (having the structure of cyclopentanoperhydrophenanthrene) with modifications to the side chain groups but have the same physical properties, namely hydrophobic, so they are able to penetrate cell membranes directly without the need for cell membrane transporters [13]. In the cascade, estrogen and progesterone can be divided into 2 (two) types, namely as follows :

1. Genomic pathway: the genomic cascade pathway is the main mechanism by which estrogen can control gene expression through its receptor activity. The bond between estrogen and its receptor will cause a translocation process to the nucleus to combine with the ERE (Estrogen Response

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Element), which is a specific DNA sequence in the promoter of the target gene. Activation of the ERE will cause the emergence of co-activators such as SRC, CBP/p300 which increase the transcription and translation activity of genetic material, leading to increased proliferation, differentiation and inhibition of apoptosis.

2. Non-genomic pathway: is a cascade pathway that does not involve direct changes in gene expression, it is a fast response pathway that is different from the genomic pathway. The bond between estrogen and its receptor will cause activation of mER (Membrane Associated Estrogen) and GPER (G-Protein Coupled Estrogen Receptor) so that estrogen does not enter the nucleus. In this pathway, estrogen will activate several cascades such as PI3K / AKT / mTOR, MAPK / ERK and in some cases can experience crosstalk with the EGFR2 / HER2 pathway which leads to increased proliferation activity, differentiation and inhibition of apoptosis [13,14].

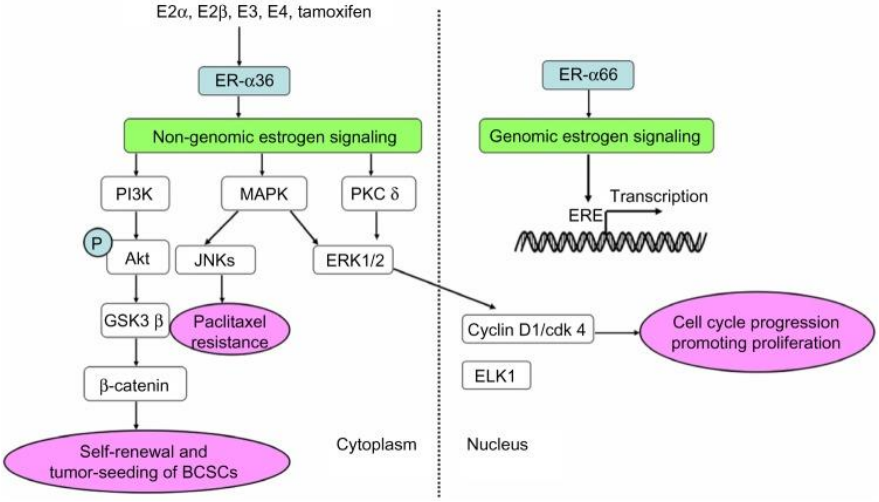

Figure 3. Genomic and Non Genomic pathway of Estrogen

On the other hand, HER-2 positive breast cancer (HER-2 Positive Breast Cancer) occurs due to amplification of the ERBB2 gene or can also occur as a result of transcriptional deregulation which causes overexpression of the HER2 receptor and this excessive expression will cause the formation of dimers against HER-2 which will then form HER2-HER2 dimerization. In the case of HER2 Positive Breast Cancer, overexpression of HER2 is an early stage of neoplastic transformation and generally lasts until tumor formation and metastasis occur. The HER2 protein itself is basically a receptor on breast cells which under normal conditions functions in controlling growth, proliferation and repair of damaged cells. However, it is very unfortunate that in HER-2 positive breast cancer sufferers, the ERBB2 gene does not work according to its pathway, thus making excess copies of the gene and further causing the breast cells to produce too many HER-2 receptors (overexpression of HER-2 receptor) which ends up triggering an uncontrolled proliferation process and a tendency to transform into malignancy. Of course, over-expression of the HER-2 receptor has a strong association with poor histopathological grade, larger tumor size, metastasis to lymph nodes or other surrounding nodes and lower survival rates [15,16].

As for triple negative breast cancer, it is a type of cancer that does not express the estrogen receptor (ER), progesterone receptor (PR) and HER2 receptor, so this type of breast cancer does not respond well to hormonal therapy (SERM or Aromatase Inhibitor group) or HER2-targeted therapy (Pertuzumab or Trastuzumab). Generally, TNBC (Triple Negative Breast Cancer) has heterogeneous characteristics, but the pattern that often appears is the presence of genetic mutations in p53, BRCA1/BRCA2, overexpression of EGFR, Androgen Receptor and PIK3CA. Genetic mutations in these genes will also have an impact on cell proliferation and differentiation pathways, namely PI3K/AKT/mTOR, MAPK/ERK, JAK-STAT and many more.

If viewed molecularly, the HER2 receptor is part of the Receptor Tyrosine Kinase (RTK) which is a type of receptor that catalyzes phosphorylation (the process of transferring phosphate from ATP to the tyrosine hydroxyl group on the target protein). The tyrosine receptor in its initial state is monomeric (only has one sub-unit / one transmembrane segment), when the phosphorylation process occurs it will merge (dimerization) into a homodimer (has 2 sub-units of the transmembrane segment). The process of phosphorylation on the Tyrosine Kinase Receptor is also called autophosphorylation /

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transphosphorylation / autotransphosphorylation. This can also be interpreted that tyrosine kinase can phosphorylate the same unit or different units. In the case of cancer cells, it can be seen that the receptor tyrosine kinase fails to process phosphorylation properly. Physiologically, the phosphorylation process can only occur if there is aggregation between the ligand linked to the receptor, but in cancer cells the phosphorylation process can occur without aggregation with the ligand (ligand-dependent firing) or cancer cells can also produce excessive receptors (overexpression) which causes increased stimulation of cell proliferation and migration. [17]

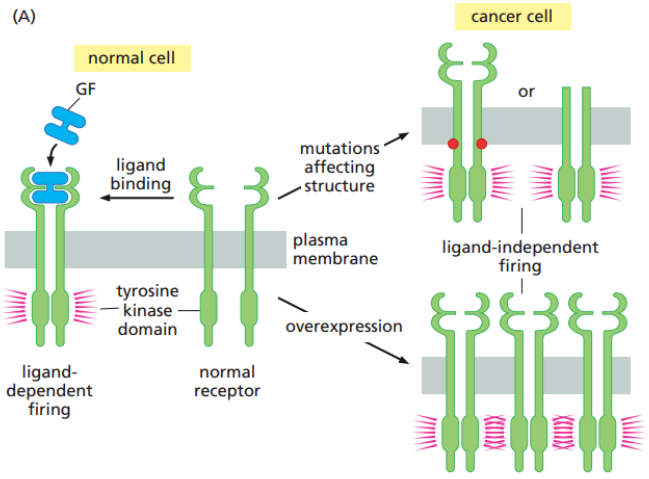

Figure 4/ Fosforilation process on Tyrosine Receptor Kinase

Both activation of the estrogen receptor, which is an intracellular receptor, and activation of the HER2 receptor, which is part of the receptor kinase, both will lead to the same cascade pathway, namely activation of the Ras protein. Hyperactivity in HER2 and ER will cause stimulation of the RAS protein and there are at least 3 (three) alternative cascades that can be carried out by RAS, namely as follows :

1. RAS/RAF/MEK (MAPKKK) pathway : is a cascade that is activated by Ras and will pass through several transmission proteins such as MAPKKK → MAPKK → MAPK which will ultimately lead to proliferative expression such as chromatin remodeling, protein synthesis and increasing the rate of transcription.
2. PI3K/AKT pathway : is a pathway that functions in suppressing the apoptosis process and stimulating cell proliferation and this cascade will start with the Phosphorylation process. Phosphorylation of PI3K will cause the activation of several other proteins such as PI (Phosphatidylinositol) and PIP2 ((Phosphatidyl Inositol 4,5 diphosphate) where further the PIP2 protein can be converted into IP3 and DAG or into PIP3 which is responsible for activating several other proteins that play a role in reconstructing the cell cytoskeleton and cell migration (Rho-GEF). What is of important concern is that the expression and production of PIP3 is regulated by PTEN and in some cases In cancer, there is dysregulation of PTEN so that PI3K and PIP3 activity becomes wild and uncontrolled.
3. Ral-GEFs pathway: RAS activation can induce Ral-A and Ral-B proteins with the help of Ral-GEF. Activation of the Ral pathway will further activate the next targets, namely Cdc42 (reorganizes actin in the cytoskeleton and controls filopodia) and Rac (controls lamellipodia formation). The Ral protein plays a role in cell motility, hyperactivity can result in cell metastasis [18]

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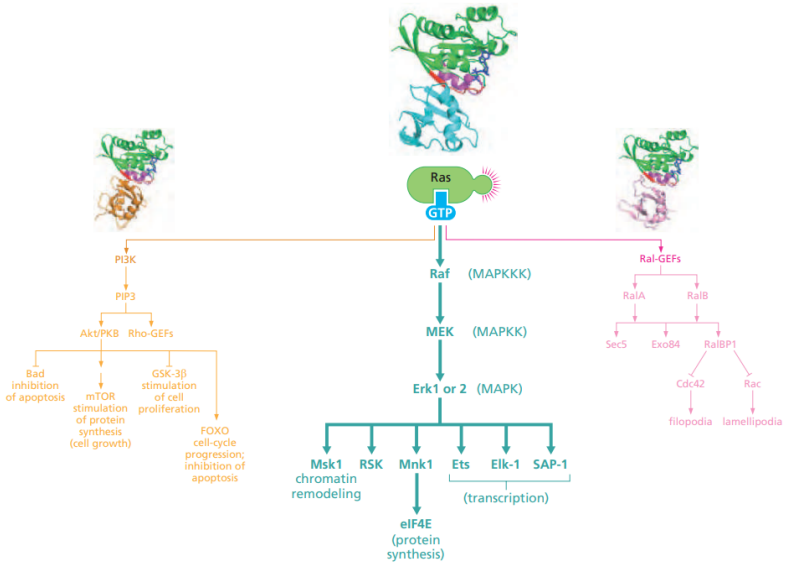

Figure 5. RAS/MAPK pathway as main pathway of cancer

The effects on the RAS/MAPK cascade and other pathways due to overexpression of the HER2 receptor have a greater impact, not only disrupting the cell proliferation cascade but also impacting tumor suppressor genes (pRb and p53) which are responsible as the final gatekeepers in the cell cycle. Physiologically, every cycle and phase carried out by cells is a fundamental and important process so there can be no mistakes. On this basis, cells have various monitoring mechanisms that monitor cell movement in each phase and determine whether the cell can continue the process or exit the cycle. When this process for one reason or another becomes chaotic, the monitoring system will work and inhibit the cell proliferation cycle until the problem that occurs can be resolved and this monitoring mechanism is often referred to as a checkpoint or checkpoint controls [19].

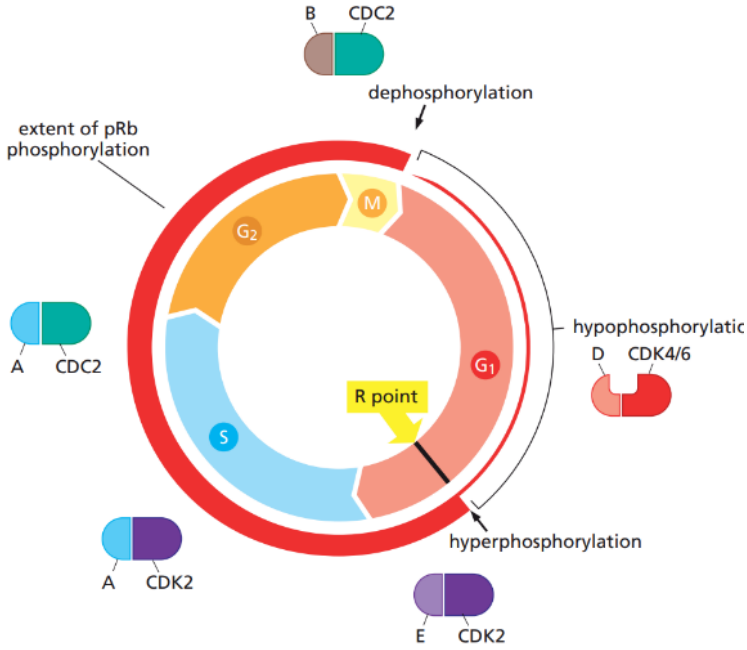

Figure 6. Cyclin and Cyclin Dependent Kinase as gateway of cells

Cyclin and CDK are important components that only appear at certain parts of the cell cycle. Each Cyclin and CDK will specifically regulate a certain part of the cell cycle, for example Cyclin B will only be present in the mitosis process while Cyclin D will be present in the G1 phase. Naturally, because Cyclin-CDK plays a role in promoting cell proliferation, to avoid excessive expression there is an antagonist component called CDK Inhibitor, known as INK-4 ($p16^{INK4A}$, $p15^{INK4B}$, $p18^{INK4C}$) and KIP-1 ($p21^{Waf1/Cip1,}$ $p27^{Kip1}$). It is worth underlining that in the cascade Cyclin is a protein whose

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activity and expression can be induced from the same pathway as proto-oncogenes (RAS protein, Wnt-Frz protein, HER-2/neu and β-catenin) so that when there is an excessive expression process of both tyrosine kinase receptors, Wnt-Frz, GPCR, Integrin and various other growth receptors, it will indirectly impact Cyclin-CDK (especially Cyclin-D1) [20,21]

Furthermore, apart from being able to influence the expression of Cyclin D1, cancer cells can also perform other functions by directly interfering with the activity of pRB and p53. For example, in pRb, cancer cells are able to change the position of E2F (transcription factor) so that E2F can roam freely and induce uncontrolled transcription and proliferation processes. In contrast to pRB, the process of inhibiting p53 by cancer cells is not that simple and in general p53 is called the main guard and executioner because it is closely related to the apoptosis process. Protein 53 (p53) is present to ensure that cells are well maintained, if this protein receives information regarding cell damage, it will immediately stop all proliferation actions and at the same time also facilitate the repairs needed by the cell. If p53 assesses that the damage caused cannot be further repaired then it will facilitate the process of programmed cell death known as apoptosis. In its activity, p53 is controlled by other proteins, namely mdm-2 and mdm-X, which will be phosphorylated (inactive) if p53 activity is needed [21,22].

In terms of the apoptotic process, both those induced by p53 and mitochondrial activity will lead to executioner Caspase activity (Caspase 3,6 and 7) which will execute the destruction of the target cell. Apart from targeting gene suppressor proteins, cancer cells also target executioner caspase inactivation so that the apoptosis process can be prevented and minimized. Apart from the intrinsic apoptotic mechanism carried out by the executioner Caspase, cancer cells can also alter the extrinsic apoptotic pathway carried out by death receptors such as Fas, TNF-α and TRAIL thereby ensuring that the apoptotic pathway is completely inactive [22,23,24].

Mesenchymal Stem Cells and cells-derived as drug delivery system for breast cancer

Mesenchymal Stem Cells (Mesenchymal Stem Cells) are a type of stem cell possessed by humans in addition to embryonic, hematopoietic and various other stem cells. In terms of differentiation capacity, mesenchymal stem cells have limitations, unlike embryonic stem cells which can differentiate into any cells. In general, mesenchymal stem cells can differentiate into bone, fat, cartilage and muscle cells. Mesenchymal Stem Cells are often used in research because their sources are quite numerous, they can be found in various locations in the body, starting from the spinal cord (Bone Marrow MSC), fat tissue (Adipose Derived MSC), and the umbilical cord (Umbilical Cord MSC). In terms of cell characteristics, Mesenchymal Stem Cells have the expression of specific markers, namely CD73, CD990 and CD105, which can be identified using several methods, one of which is flowcytometry [25].

In correlation with cancer, which is a condition of abnormal cell proliferation or a condition of tissue wounds that cannot be healed (non-healing wounds), Mesenchymal Stem Cells have the capability to secrete chemical compounds that facilitate tissue regeneration and repair. Mesenchymal Stem Cells via a homing and migration mechanism can selectively and specifically move to the tumor/cancer location by utilizing paracrine communication and are furthermore not considered a threat to cancer because they release the same cytokines as TGF-β, CCL2, CCL5, CXCL12 and others [26].

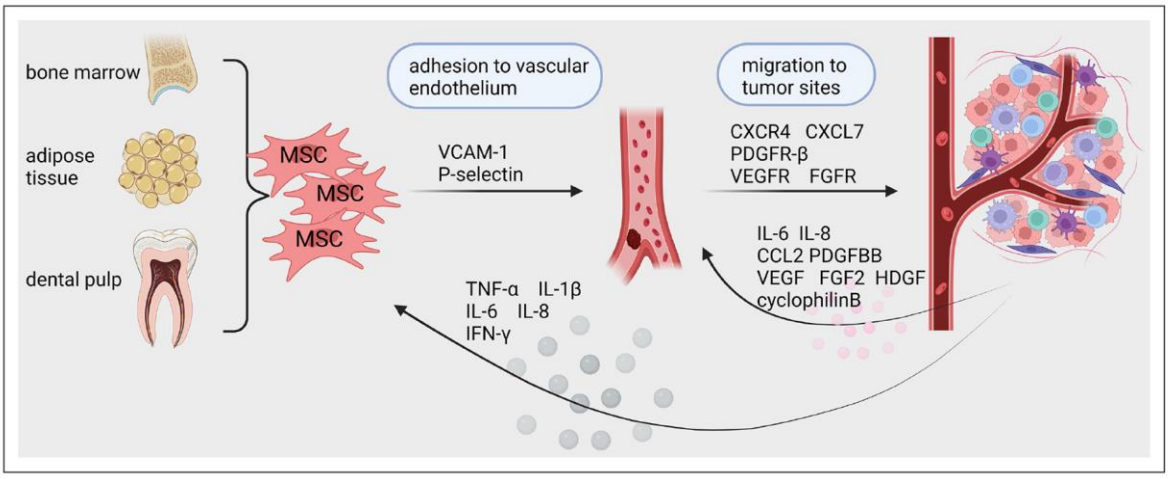

Figure 7 Tumour microenvironment activity by Mesenchymal Stem Cells

A growing tumour can recruit various cells from the surrounding (local) and systemic environment (cells located far away) by emitting chemical signals from the cancer cells and their surroundings. The recruited cells can significantly change the composition of the TME (Tumor Microenvironment) thereby facilitating complex interactions between cells so that cancer cells are further labelled as wounds that cannot heal. Mesenchymal Stem Cells have a strong attraction to tumor cells and tend to migrate to damaged tissue areas both experimentally and clinically. The tumor microenvironment (TME) regulates various inflammatory cytokines and chemokines that induce the migration process of Mesenchymal Stem Cells which involves the adhesion process of Mesenchymal Stem Cells to the vascular endothelium followed by traversal and the endothelial layer. Several cytokines and chemokines play a role, such as TNF-α, Il-1β, IFN-γ and VCAM-1 and also CXCL5, CXCL6, CXCL7 and other molecules [27]. At least, there are several records of similar research that utilize the capabilities of mesenchymal stem cells as cancer therapy both on an in vivo and in vitro scale.

Table 1. Research of Mesenchymal Stem Cells as drug delivery system

Source of MSCs	Type of Cell lines	Research Model	Result	Ref
BMSCs	MDA-MB 231 T47D	In vivo dan in vitro	There is an elaboration mechanism where MSCs-Exos deliver BCC to dedifferentiate and culminate in an inactive/dormant stage	(27)
BMSCs	MCF-7	*In vitro*	Promotes dormancy of BCC by inhibiting cell proliferation and adhesion	(28)
BMSCs	MCF-7, MCF-10A, MDA-MB231	*In vivo* dan *in vitro*	Mesenchymal stem cells are filled with Paclitaxel and are able to inhibit the growth of cancer cells	(29)
ADSCs	MCF-7, MDA-MB231	*In Vitro*	Inhibits cell metastasis and EMT pathways and induces dormancy	(30)
UCMSCs	MCF-7, MDA-MB231	*In Vitro*	Inhibits the process of migration and invasion of tumor cells	(31)

Apart from using whole Mesenchymal Stem Cells, drug delivery systems can use derivative products from Mesenchymal Stem Cells, namely exosomes, which also provide a new alternative as a cancer therapy with the same activity as the parent cells. Exosomes are nano-sized vesicles (30-200 nm) originating from the late endosomal stage with surface markers in the form of CD9, CD63, CD81 and TSG101. Exosomes naturally have the ability to act as transport cargo for proteins, lipids, nucleic acids and various other biological components. These nano-sized vesicles also play a role in cancer in the TME (tumour microenvironment) both as a diagnosis, prognosis and as a drug delivery system for cancer37. The following are several studies on the use of Mesenchymal Stem Cells and their derivatives, as follows [27]

Table 2 Incorporation of different types of chemotherapeutic agents into AD-MSCs [27]

Type of Stem Cells and	Cell lines target	Incorporation	Target of disease

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Cell derived		Component	
AD-MSCs	MCF-7	Doxorubicin	Breast Cancer
AD-MSCs (Exosomes)	MDA-MB-231	Doxorubicin	Breast Cancer
AD-MSCs (Exosomes)	H9 Human embrionic Stem Cells	Paclitaxel	Pancreatic Cancer
AD-MSCs	Pancreatic Cancer cell line	Gemcitabine	Pancreatic Cancer
AD-MSCs	Pancreatic Cancer cell line	Camptohecin	Cervical Cancer

In the process, exosomes can be obtained through various methods, each of which has its advantages and disadvantages as presented in the following table.

Table 3. Types of method of exosomes extraction [27]

Separation Techniques	Principles	Advantages	Disadvantages
Ultracentrifugation	Using the size and density differences between the initial solution components	1. Well-established 2. Simple 3. Suitable for substantial volume	1. Long time consuming 2. Low efficacy 3. Damage structure
Density Gradient Ultracentrifugation	Different components have different densities	High purity	High costs and low exosome recovery
Size Exclusion Chromatography	The flow velocity of molecules with different particle size in fixed phase pores	Retain functionality and structural integrity	Large size distribution

As a drug delivery system, Mesenchymal Stem Cells and their derivatives have advantages as anti-tumor drugs, namely protecting therapeutic agents from rapid biodegradation, reducing systemic side effects that can be caused and increasing direct targeting of cancer cells. Several other studies also show that there is increased activity in several chemotherapy agents such as Paclitaxel, Docletaxel, Gemticitabine and Permetrexed when loaded into mesenchymal stem cells. This strategic innovation not only increases drug loading capacity but also increases efficiency in recognition and binding to specific tumor cells {33,34]. Apart from the effectiveness and efficiency of drug delivery to target tumor cells, the use of MSCs and their derivatives also has several other advantages, namely as follows :

1. Low immunogenicity : Mesenchymal stem cells (MSCs) are not identified as foreign antigens by the host immune system so they do not cause cases of rejection in various individual patients
2. Controlled localization : MSCs have specific chemotactic properties directly towards damaged/inflamed areas such as tumor/cancer cells. This means that if MSCs are used as drug carrier molecules, the delivery system will be directly targeted to tumor cells, thereby minimizing the occurrence of systemic side effects and toxicity.
3. Promote tissue repair and regeneration : apart from being a drug delivery system, MSCs can also play a role in catalyzing tissue repair and regeneration in areas damaged/inflamed by cancer cells

However, the use of MSCs and their derivatives also has its own challenges, namely the potential for pro-tumorigenic and carcinogenic effects when using MSCs. Basically, MSCs cells are a type of cell that is still classified as a stem cell, which has the basic properties of increasing proliferation activity and differentiation into other, more specific cells. This causes the use of MSCs as cancer therapy to be carried out using the principle of caution, measurement and optimization of the research process so that it does not produce effects that are opposite to those expected.

CONCLUSION

The application of Mesenchymal Stem Cells (MSCs) and their derivatives as a drug delivery system for breast cancer is a promising alternative treatment method for overcoming various existing pharmacological intervention problems such as optimizing targeting of cancer cells, reducing systemic side effects and increasing the effectiveness of treatment. However, in its use there needs to be a principle of caution because of the potential for dualism, namely pro-tumorigenic effects that may arise from Mesenchymal Stem Cells. Future research should focus on clarifying the molecular mechanisms underlying the pro-tumorigenic versus anti-tumorigenic behavior of MSCs, particularly in different breast cancer subtypes and tumor microenvironment conditions. Standardization of MSC sources, isolation protocols, dosing strategies, and delivery routes is also necessary to ensure reproducibility and safety. Furthermore, long-term in vivo studies and well-designed preclinical models are required to evaluate biodistribution, immunogenicity, genetic stability, and potential tumor-promoting risks before advancing to large-scale clinical trials. Clinical translation will require rigorous phase I/II trials to determine optimal therapeutic windows, safety profiles, and combinational strategies with existing chemotherapeutic or targeted agents. Addressing these limitations will be

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essential to bridge the gap between experimental findings and the safe, effective clinical application of MSC-based drug delivery systems in breast cancer therapy.

CONFLICT OF INTEREST

There is no confict of interest

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