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NARRATIVE REVIEW

Molecular mechanisms of drug resistance in breast cancer and potential strategies for overcoming resistance: A literature review

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Abstract

Breast cancer is the most common cause of death from cancer in the world, and drug resistance is one of the most significant barriers to successful therapy for the disease. It is critical to have a solid understanding of the molecular processes driving treatment resistance in breast cancer to design targeted therapies with the potential to overcome this resistance. These complex and multifaceted mechanisms include the activation of signaling pathways that promote cell survival and proliferation, the upregulation of drug efflux pumps, the emergence of cancer stem cells, and genetic and epigenetic changes. This literature review provides an overview of these mechanisms. It discusses potential strategies for overcoming drug resistance in breast cancer, including targeted therapies targeting the pathways and agencies involved in drug resistance. The review also highlights the need for further research to identify effective strategies for overcoming drug resistance and improving treatment outcomes in breast cancer patients.

Keywords:
MESH: Breast Neoplasms; Molecular Mechanisms of Pharmacological Action; Signal Transduction; Neoplastic Stem Cells; Genetic Diseases, Inborn.

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Introduction

Drug resistance is a significant obstacle to effective breast cancer treatment and is the most prevalent cause of cancer death worldwide [1]. Developing targeted therapeutics to overcome drug resistance in breast cancer requires an in-depth understanding of the molecular processes behind this phenomenon. Activation of signaling pathways that increase cell survival and proliferation is a mechanism of treatment resistance in breast cancer [1]. It has been

shown, for instance, that resistance to chemotherapy and targeted treatments in breast cancer is often connected with the activation of the epidermal growth factor receptor (EGFR) pathway [2]. The PI3K/Akt/mTOR pathway, the MAPK pathway, and the Wnt/beta-catenin system are other signaling pathways implicated in treatment resistance in breast cancer [3]. Upregulation of drug efflux pumps is the second mechanism of drug resistance that reduces the intracellular concentration of chemotherapeutic medicines and hence their efficacy [1]. Two well-known drug efflux pumps commonly overexpressed in breast cancer cells and contributing to drug resistance are P-gp and breast cancer resistance protein (BCRP) [1, 4]. The emergence of cancer stem cells (CSCs) has also been linked to drug resistance in breast cancer [5]. CSCs are a small population of cancer cells with stem cell-like properties, including the ability to self-renew and differentiate into various cell types [5]. CSCs are thought to be resistant to chemotherapy and targeted therapies and may contribute to breast cancer recurrence after treatment [5]. In addition, genetic alterations and epigenetic changes have been implicated in breast cancer drug resistance. For instance, mutations in TP53 and BRCA1/2 have been linked to chemotherapy and targeted treatment resistance in breast cancer [6]. By controlling the expression of genes involved in drug metabolism and resistance, epigenetic alterations, including DNA methylation and histone modification, can contribute to drug resistance [6, 7].

Overall, the molecular mechanisms of drug resistance in breast cancer are complex and multifaceted, and further research is needed to identify effective strategies for overcoming this resistance [1]. Targeted therapies targeting the pathways and mechanisms involved in drug resistance may hold promise for improving treatment outcomes in breast cancer patients [8]. This literature review aims to provide an overview of the molecular mechanisms of drug resistance in breast cancer and discuss the potential strategies for overcoming this resistance. This review highlights the various pathways and mechanisms that contribute to drug resistance in breast cancer, including the activation of signaling pathways, the upregulation of drug efflux pumps, the emergence of cancer stem cells, and genetic and epigenetic changes. The review also discusses the need for further research to identify effective strategies for overcoming drug resistance in breast cancer and the potential of targeted therapies for improving treatment outcomes in breast cancer patients.

Breast cancer subtypes

Breast cancer is a heterogeneous disease, meaning a wide range of molecular and clinical features characterize it. To better understand the underlying biology of breast cancer and develop targeted therapies, researchers have classified breast cancer into several molecular subtypes based on the expression of specific proteins and genetic features. Here is a brief overview of the main molecular subtypes of breast cancer:

1. Luminal A subtype: The luminal A subtype is characterized by the expression of estrogen and progesterone receptors (ER+/PR+) and the absence of human epidermal growth factor receptor 2 (HER2) (Table 1). This subtype is typically slow growing and is often treated with hormone therapy [9, 10].
2. Luminal B subtype: The luminal B subtype is also characterized by the expression of ER+/PR+ but is distinguished from the luminal A subtype by the presence of HER2 overexpression or gene amplification [11] (Table 1). This subtype is typically more aggressive than

the luminal A subtype and may be treated with hormone therapy, chemotherapy, and targeted therapies [9, 10].

3. HER2-positive subtype: The HER2-positive subtype is characterized by the overexpression or amplification of the HER2 gene [12] (Table 1). This subtype is typically more aggressive than the luminal subtypes and may be treated with targeted therapies that inhibit HER2, such as trastuzumab and pertuzumab, as well as chemotherapy [13].

4. Triple-negative subtype: The triple-negative subtype is characterized by the absence of ER, PR, and HER2 expression [14] (Table 1). This subtype is typically more aggressive than the other subtypes and is more challenging to treat because it does not respond to hormone therapy or targeted therapies [15]. Chemotherapy is typically the primary treatment option for triple-negative breast cancer [15].

5. Basal-like subtype: The basal-like subtype is characterized by the expression of certain cytokeratins and the absence of ER, PR, and HER2 expression [10] (Table 1). This subtype is typically more aggressive than the other subtypes and is often treated with chemotherapy [11].

It is important to note that breast cancer subtypes are not mutually exclusive, and many breast cancers exhibit features of multiple subtypes [16]. Understanding the molecular subtype of breast cancer can help inform treatment decisions and predict patient outcomes.

Table 1. Breast cancer molecular subtypes and their protein expression.

BC subtypes	ER	PR	HER-2	Others
Luminal A	+	+	-	Low level of protein Ki-67
Luminal B	+	+	+/-	High level of Ki-67
Triple negative/basal-like	-	-	-	overexpress P-cadherin, EGFR
Her-2 enriched	-	-	+	

Treatment for breast cancer

Breast cancer treatment may involve a combination of chemotherapy, targeted therapy, and immunotherapy [8, 17]. Chemotherapy is a type of cancer treatment that uses drugs to kill cancer cells [17]. It may be used alone or with other treatments, such as surgery or radiation therapy [8, 17]. Targeted therapies are a type of cancer treatment explicitly targeting the molecular abnormalities that drive cancer growth and progression [17]. They have been developed to target specific signaling pathways, receptors, enzymes, and other molecular targets often overexpressed or mutated in cancer cells [13]. Targeted treatment may be employed independently or in combination with chemotherapy [13]. Immunotherapy is a method of treating cancer that stimulates the immune system to attack the disease, and it may be used alone or in combination with chemotherapy or targeted therapy [17].

Breast cancer treatment plans vary from case to case based on factors including the patient's overall health and personal preferences, as well as the kind and stage of the disease [18]. Patients must discuss their treatment options with their healthcare team and consider their needs and preferences when making treatment decisions [18].

Chemotherapy drugs used to treat breast cancer include anthracyclines such as doxorubicin and epirubicin, taxanes such as paclitaxel and docetaxel, cyclophosphamide, capecitabine, and methotrexate [17]. Targeted therapies used to treat breast cancer include trastuzumab, which targets HER2; lapatinib, which targets HER2 and EGFR; pertuzumab, which targets HER2; and palbociclib, which targets CDK4 and CDK6 [13, 20]. Immunotherapies used to treat breast cancer include pembrolizumab, which targets PD-L1, and nivolumab, which targets PD-1 [8, 21]. Not all breast cancer patients will respond to these therapies, and the specific treatment approach will depend on the type and stage of cancer and the patient's overall health and treatment preferences [22]. Treatment decisions are typically made by a team of healthcare professionals, including a medical oncologist, a surgical oncologist, and a radiation oncologist, who will consider the specific characteristics of the patient's cancer and the potential benefits and risks of each treatment option [16, 23]. Patients need to discuss their treatment options with their healthcare team and consider their individual needs and preferences when making treatment decisions [16].

Molecular Mechanisms of drug resistance in breast cancer

Epidermal growth factor receptor (EGFR) pathway

The EGFR pathway is activated by ligands such as epidermal growth factor (EGF) and is involved in cell growth, proliferation, and survival [2]. Overexpression or activation of the EGFR pathway has been linked to drug resistance in breast cancer. Several targeted therapies that inhibit the EGFR pathway, such as monoclonal antibodies (e.g., trastuzumab) and tyrosine kinase inhibitors (e.g., lapatinib), have been developed to treat breast cancer. Still, resistance to these therapies is a common problem [19].

PI3K/Akt/mTOR pathway

Growth factors and hormones activate the PI3K/Akt/mTOR pathway, which plays a crucial role in cell growth, proliferation, and survival [24]. Activation of this pathway has been associated with resistance to chemotherapy and targeted therapies in breast cancer [24]. Inhibitors of the PI3K/Akt/mTOR pathway, such as PI3K and mTOR inhibitors, are being developed as potential therapies for breast cancer. Still, resistance to these agents is a significant challenge [25].

MAPK pathway

The MAPK pathway is activated by growth factors, hormones, and stress signals, and it plays a role in cell growth, proliferation, and survival [26]. Activation of this pathway has been linked to drug resistance in breast cancer. Several targeted therapies that inhibit the MAPK pathway (e.g., MEK inhibitors) are in development to treat breast cancer [26].

Wnt/beta-catenin pathway

The Wnt family of proteins activates the Wnt/beta-catenin pathway and plays a role in cell growth, proliferation, and differentiation [27, 28]. Dysregulation of this pathway has been linked to drug resistance in breast cancer. Targeting the Wnt/beta-catenin pathway with small molecule inhibitors or monoclonal antibodies is a potential strategy for overcoming this resistance [29]. Tamoxifen is a common endocrine therapy drug for estrogen receptor-positive breast cancer. However, tamoxifen resistance can reduce its effectiveness. In a study on breast cancer cells, researchers found that CXXC4 protein expression was lower in tamoxifen-resistant cells than in nonresistant cells [30]. They also found that silencing the CXXC4 gene in cancer cells increased their sensitivity to tamoxifen and inhibited the Wnt/β-catenin signaling pathway, while overexpression of CXXC4 had the opposite effect [30]. The small molecule inhibitor XAV939 was also shown to suppress Wnt signaling and increase tamoxifen sensitivity in resistant cells [30]. These results suggest that targeting the Wnt pathway may be a potential strategy for overcoming tamoxifen resistance in breast cancer treatment [30]. In addition, triple-negative breast cancer (TNBC) is a type of breast cancer that does not have estrogen or progesterone receptors and does not overproduce the HER2 protein [29]. TNBC tends to have more aggressive characteristics than other types of breast cancer and is associated with high recurrence rates [29]. Researchers are working to identify biomarkers and understand the signaling pathways that may be targeted in TNBC treatment [29, 31, 32]. The Wnt/beta-catenin signaling pathway is involved in developing TNBC and resistance to cancer therapies. Inhibiting this pathway alone or combined with chemotherapy or targeted therapy may be a promising strategy for treating TNBC [29]. However, more research is needed to fully understand the role of Wnt signaling in TNBC and to develop safe, effective combination therapies.

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)

P-gp and BCRP are drug efflux pumps that are overexpressed in many breast cancer cells and contribute to drug resistance [33]. Inhibitors of P-gp and BCRP, such as verapamil and elacridar, are being explored as potential therapies for breast cancer, but resistance to these agents is a significant challenge [1].

Cancer stem cells (CSCs)

CSCs are a small population of cancer cells with stem cell-like properties and are thought to be resistant to chemotherapy and targeted therapies [34]. CSCs may contribute to breast cancer recurrence after treatment, and targeting CSCs with specific therapies is a promising strategy for overcoming drug resistance [35, 36].

Genetic alterations and epigenetic changes

Genetic mutations, such as TP53 and BRCA1/2, and epigenetic changes, such as DNA methylation and histone modification, have been linked to drug resistance in breast cancer [6, 37]. Identifying and targeting the genetic and epigenetic changes contributing to drug resistance is a promising approach for improving treatment outcomes in breast cancer patients [38]. Breast cancer drug resistance is a significant obstacle to effective treatment, and understanding the mechanisms underlying drug resistance is crucial for developing targeted therapies that can overcome this resistance [37].

Resistance to targeted therapies in breast cancer

Targeted therapies are a type of cancer treatment designed to specifically target the molecular abnormalities that drive cancer growth and progression [19]. These therapies effectively treat several types of cancer, including breast cancer, but resistance to these therapies is a common problem [22]. Several resistance mechanisms to targeted therapies in breast cancer include the activation of alternative signaling pathways, the upregulation of drug efflux pumps, the emergence of cancer stem cells, and genetic and epigenetic changes [39]. Strategies being investigated to overcome resistance to targeted therapies in breast cancer include combination therapies, the development of targeted therapies that inhibit alternative signaling pathways, and the identification of biomarkers that can predict patient response to targeted therapies [8].

Several targeted therapies have been reported to be associated with resistance to breast cancer.

1. Trastuzumab: Trastuzumab is a monoclonal antibody that targets human epidermal growth factor receptor 2 (HER2), which is overexpressed in approximately 20% of breast cancers [40]. Trastuzumab is effective in treating HER2-positive breast cancer, but resistance to this therapy is a common problem [19]. Mechanisms of resistance to trastuzumab include the activation of alternative signaling pathways, such as the PI3K/Akt/mTOR pathway, and the upregulation of drug efflux pumps, such as P-gp [41].
2. Lapatinib: Lapatinib is a tyrosine kinase inhibitor targeting the HER2 and epidermal growth factor receptor (EGFR) pathways [41]. It has been approved for treating HER2-positive breast cancer, which has progressed after treatment with trastuzumab, but resistance to lapatinib is also a common problem [40]. Mechanisms of resistance to lapatinib include the activation of alternative signaling pathways, such as the MAPK pathway, and the emergence of cancer stem cells [41].
3. Palbociclib: Palbociclib is a CDK inhibitor that targets the CDK4 and CDK6 pathways, which regulate the cell cycle [20]. It has been approved for treating hormone receptor (HR)-positive, HER2-negative advanced breast cancer, but resistance to palbociclib is a common problem [42]. Mechanisms of resistance to palbociclib include activating alternative signaling pathways, such as the PI3K/Akt/mTOR pathway, and upregulating drug efflux pumps, such as BCRP [3, 20].

Overall, the mechanisms of resistance to targeted therapies in breast cancer are complex and multifaceted, and further research is needed to identify effective strategies for overcoming this resistance. Systems under investigation include using combination therapies that target multiple pathways and mechanisms, developing targeted therapies that inhibit alternative signaling ways, and identifying biomarkers that can predict patient response to targeted therapies.

microRNAa (miRNAs) in breast cancer

One area of research that has gained significant attention in recent years is the interplay between microRNAs (miRNAs) and the tumor microenvironment in developing breast cancer drug resistance [43]. miRNAs are small noncoding RNA molecules that regulate gene expression by binding to the 3' untranslated region (UTR) of mRNA and inhibiting its translation [31]. Some miRNAs are involved in various cellular processes, including cell proliferation, differentiation, apoptosis, and angiogenesis, and they have been implicated in developing drug resistance in breast cancer [36].

Studies have shown that the expression levels of specific miRNAs are altered in breast cancer tissues compared to normal breast tissues. These miRNAs may have oncogenic (tumor-promoting) and tumor-suppressive effects [43]. For example, some miRNAs have been found to downregulate the estrogen receptor (ER) expression, which is involved in the development and progression of breast cancer [43]. On the other hand, other miRNAs, such as miRNA-27a, have been shown to act as oncogenic factors and increase ER expression, potentially exacerbating cancer progression [43]. miRNAs may also help predict the risk of tumor relapse and the survival rate of breast cancer patients and understand the molecular basis of different breast cancer subtypes [43]. Recent studies have demonstrated that miRNAs can modulate the tumor microenvironment and influence drug resistance in breast cancer [43]. A study reported that miR-210 promoted angiogenesis and stimulated the proliferation of CSCs, leading to drug resistance in breast cancer [31]. Other miRNAs, such as miR-9, miR-124, and miR-214, have been shown to inhibit angiogenesis and suppress the proliferation of CSCs, leading to enhanced sensitivity to chemotherapy and targeted therapies [43]. Further research is needed to fully understand the roles of miRNAs in breast cancer and how they can be harnessed for diagnostic and therapeutic purposes.

New insights into CRISPR/Cas9-based therapy for breast cancer

CRISPR/Cas9 is a genome editing tool that allows researchers to make precise changes to the DNA of living cells [44]. It works by using a small RNA molecule called gRNA to guide an enzyme called Cas9 to a specific location in the genome, where it can cut the DNA at that location [45]. This allows researchers to delete or modify particular genes to study their function or to correct genetic mutations that cause diseases [44]. The CRISPR/Cas9 system has been widely used in various applications in the past 20 years and has become a powerful tool in cancer research [44]. The development of breast cancer is influenced by a complex interplay of genetic mutations, transcriptional regulatory networks, and signaling pathways that regulate the growth and survival of breast cells [46]. Mutations in specific genes, such as BRCA1/2, PTEN, TP53, mTOR, TERT, AKT, and PI3K, have been linked to an increased risk of breast cancer [46]. These genes play essential roles in regulating cell growth and survival, and their dysregulation can contribute to the development and progression of the disease [46].

To better understand the underlying mechanisms of breast cancer and identify potential therapeutic targets, researchers are using advanced genetic tools and techniques, such as the CRISPR/Cas9 system, to build transcriptional regulatory networks that govern the development and progression of the disease [38]. The CRISPR/Cas9 system allows

researchers to delete or modify specific genes to study their function and understand their role in the development of breast cancer [38]. The CRISPR/Cas9 system has been used to generate breast cancer-specific transgenic cell lines and animal models, which can be used to decipher the role and interactions of different genes in the development of breast cancer and to identify potential therapeutic targets. In addition, the CRISPR/Cas9 system has the potential to be used in the development of early diagnostic tools and treatments for breast cancer [47].

Drug resistance, including breast cancer [44]. One way to address this issue is to combine different drugs with different targets to minimize acquired drug resistance [44]. Drug interactions involving many modes of action are notoriously complex [44]. Increasing the specificity of anticancer medicines is another option for dealing with the problem of drug resistance, particularly in the event of multidrug resistance (MDR) [44]. In addition, current cancer therapies may be repurposed if resistance factors are blocked or reversed. Traditional methods for studying oncogenes and drug resistance genes, such as loss-of-function approaches (e.g., RNA interference) and gain-of-function approaches (cDNA-based overexpression), have played a significant role in cancer research but have limitations [38, 47]. For example, cDNA-based expression systems can produce supraphysiological levels of gene expression, leading to artifact effects, and the knockdown of a gene by RNA interference is often incomplete. Genome engineering in animal models has been technically challenging and time-consuming [47].

The CRISPR/Cas9 system is an effective and rapid tool for editing specific genes within an organism. Successful gene editing in recognized cell lines and patient-derived xenografts has been performed to create indel mutations, alterations, and chromosomal rearrangements in a broad spectrum of cancer cells [47]. Genome editing using tools such as CRISPR/Cas9 has made creating mutations in either somatic or germ cells simpler [47]. When cells stop dividing and enter a resting phase, this is called cell cycle arrest [47]. Specifically, the cells stopped dividing in the G2/M phase of the cell cycle [44]. The evidence also shows that MCF-7 cells, a specific type of breast cancer cell, may grow tumors in the mammary gland and start the process of angiogenesis, in which new blood vessels are produced, even when they have not been transfected [45].

Conversely, tumors were kept relatively contained when transfected cells were used, and tumor invasion and infiltration were significantly reduced. These data show that CDK4 knockdown and CDH1 activation may have a suppressive effect on the proliferation and spread of breast cancer cells [45]. One study used CRISPR/Cas9 to downregulate the MYC gene, which is often overexpressed in high-grade breast cancers and is a potential target for cancer therapy [38]. Another study used CRISPR/Cas9 to create knockouts of CXCR7 and CXCR4 in breast cancer cells. The higher expression of these genes has been linked to increased susceptibility to metastasis and poor prognosis in triple-negative breast cancer [48]. CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa) are other approaches that use CRISPR/Cas9 to repress or activate genes, respectively, and have been used in breast cancer treatment [44]. CRISPR/Cas9 has also been used to target the cell cycle kinase MASTL and the tumor suppressor gene TP53 in breast cancer cells [44, 49]. In addition, CRISPR/Cas9 has been used to modify microRNA and noncoding RNA regions, as well as to demethylate promoters and inhibit DNA methyl transferases in breast cancer cells [45].

Overall, using the CRISPR/Cas9 system in breast cancer research can provide important insights into the underlying mechanisms of the disease and identify new therapeutic approaches for the treatment of breast cancer. Further research is needed to fully understand the potential of the CRISPR/Cas9 system in treating breast cancer and to determine the most effective ways to use this technology to benefit patients.

Conclusion and future direction for breast cancer research

Several research areas may be relevant to the future therapeutic management of breast cancer. These include identifying biomarkers that can predict patient response to targeted therapies, developing combination therapies that target multiple pathways and mechanisms, investigating the role of the tumor microenvironment in drug resistance and cancer progression, developing personalized medicine approaches that take into account the individual characteristics of a patient's cancer, and investigating the potential of immunotherapy in the treatment of breast cancer. Developing biomarkers that can accurately predict which patients are likely to respond to specific targeted therapies could optimize treatment decisions and improve patient outcomes. Combination therapies may be more effective at overcoming resistance to targeted therapies and improving treatment outcomes in breast cancer. Research on the tumor microenvironment, which consists of the cells, extracellular matrix, and soluble factors present in the tumor, may provide insight into new therapeutic targets and strategies for overcoming drug resistance in breast cancer. Personalized medicine approaches that consider the specific molecular abnormalities of a patient's cancer may be more effective at targeting the pathways and mechanisms that drive cancer growth and progression. Immunotherapy, which activates the body's immune system to target cancer cells, has shown promising results in treating several types of cancer and may hold potential for treating breast cancer.

Several biomarkers have been singled out as promising avenues for additional research into the prevention and treatment of breast carcinoma. Among these is PIK3CA, which codes for the p110 alpha subunit of the PI3K enzyme and has been associated with resistance to targeted therapy in breast cancer because of its involvement in the PI3K/Akt/mTOR signaling pathway. Overexpression of the HER2 protein, encoded by the ERBB2 gene (also known as HER2), is seen in approximately 20% of breast tumors. Resistance to trastuzumab, a monoclonal antibody that targets HER2, is a prevalent issue despite its status as a mainstay therapy for HER2-positive breast cancer. DNA repair proteins are encoded by the genes BRCA1 and BRCA2, and mutations in these genes are linked to a greater risk of breast and ovarian cancer and resistance to chemotherapy and targeted treatments in breast cancer. Overexpression of the drug efflux pump P-gp is linked to resistance to chemotherapy and targeted therapies in various cancers, including breast cancer. Cancer stem cell features and resistance to chemotherapy and targeted treatments in breast cancer have been related to the cell surface protein CD44. In addition, ongoing research on CRISPR/Cas9 gene-editing tools has shown promise in treating breast cancer, particularly triple-negative breast cancer (TNBC). It can downregulate oncogenes such as MYC and activate tumor suppressor genes

such as PTEN. CRISPR/Cas9 can also be used to knock out or knock out CXCR7 and CXCR4, two receptors linked to the development of TNBC. Other potential targets for CRISPR/Cas9 in breast cancer treatment include MASTL, which regulates protein phosphatase 2A (PP2A) and has been linked to cancer progression, and miRNAs such as miR-23b and miR-27b, which have oncogenic potential. CRISPR/Cas9 has also been used to target the CDK11 and CDH1 genes, resulting in cell cycle arrest and an increase in late apoptosis. While CRISPR/Cas9 has shown promise in treating breast cancer, more research is needed to understand its potential and address potential limitations or challenges fully.

Further research is needed to determine the potential of these and other biomarkers as predictive markers for response to breast cancer therapies. Overall, continued research on the molecular mechanisms of breast cancer and the development of targeted therapies and combination therapies may improve future treatment outcomes in breast cancer patients.

Abbreviations

miRNA: micro RNA.

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Additional files

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Author contributions

Nalinee Pradubyat: conceptualization, validation, visualization, methodology, project management, writing: review, and editing.

Jutatip Laoharuangchaiyot: conceptualization, data curation, formal analysis, fundraising, research, resources, software.

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Competing interests

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