Review Article

The Impact of miRNAs on the Efficacy of Tamoxifen in Breast Cancer Treatment: A Systematic Review

Nima Nikbin Kavishahi,[1] Aryan Rezaee,[2] Sara Jalalian[3]

Abstract

Seventy percent of breast cancer patients have an active estrogen receptor. Tamoxifen interferes with estrogen's ability to bind to cancer cells. The most challenging aspect of tamoxifen, however, is that breast cancer cells become resistant to its effects. Some studies have shown that alterations in miRNA expression contribute significantly to drug resistance in breast cancer. Therefore, the present systematic review aims to investigate miRNAs that significantly influence the response to tamoxifen treatment. The present study follows the PRISMA instructions. The Web of Science, PubMed, and Scopus databases were searched to retrieve English articles. The searches were conducted up to September 11, 2022. The search strategy included the terms "Tamoxifen", "Breast Neoplasm", and "MicroRNA". The inclusion criteria of this study are English, original, and experimental studies investigating miRNAs that are effective in the treatment efficacy of tamoxifen. A total of 565 articles were retrieved. After screening, 75 studies met our inclusion criteria. This systematic review study examined 105 miRNAs, of which 44 have a positive effect, and 47 miRNAs inhibit tamoxifen function. Fourteen miRNAs have a controversial effect, ie, some studies show positive and negative effects. The study of miRNAs affecting tamoxifen function in breast cancer patients may facilitate the identification of individuals at higher risk of disease recurrence. Conversely, it can potentially utilize appropriate interventions to defeat drug resistance effectively.

Clinical Breast Cancer, Vol. 24, No. 4, 341–350
Keywords: Estrogen receptor, Non coding RNA, Mammary carcinoma, Chemotherapy, Resistance

Introduction

One of the leading causes of death worldwide is breast cancer.[1] The most prevalent cancer in women is breast cancer.[2] A subtype of breast cancer must be identified before drug treatment.[3] After a biopsy of a breast cancer tumor, the cancer cells are examined for the human epidermal growth factor receptor 2 (HER2) protein and the estrogen receptor (ER) and progesterone receptor (PR) proteins.[4] Seventy percent of breast cancer patients have active estrogen receptor signaling.[5] Hormone therapy, or endocrine therapy, is a treatment that prevents this hormone from binding to its receptors.[4] Tamoxifen is an example of such a therapy that interferes with the ability of estrogen to bind to cancer cells.[4] The most challenging aspect of tamoxifen is that breast cancer cells become resistant to its effects.[6] It is said that treatment with tamoxifen fails in 30%-40% of patients, and almost every patient with metastatic disease develops tamoxifen resistance.[7] The main causes of tamoxifen resistance can be categorized into 2 groups: (1) genetic mutations leading to loss or gain of estrogen receptor function and (2) mechanisms controlling estrogen-related carcinogenic pathways.[8] Some studies have shown that alterations in the expression of microRNAs (miRNAs) contribute significantly to drug resistance in breast cancer.[9,10] In addition, miRNAs could potentially play a role in the regulation of ER.[11]

MiRNAs are a class of short, noncoding RNAs that play a crucial role in regulating numerous biological processes.[12,13] These entities act as post-transcriptional regulators, targeting mRNAs and interfering with mRNA translation.[14,15] This regulation controls cellular processes such as self-renewal, differentiation, growth, migration, and apoptosis.[14,15]

In a review article, Barazetti et al.[16] investigated the role of noncoding RNAs, particularly miRNAs and lncRNAs, in tamoxifen-resistant breast cancer patients. In their study, the authors identified the role of 75 miRNAs and 22 lncRNAs. Zhang et al.[17] conducted a review article on the involvement of miRNA in tamoxifen resistance. They found that many miRNAs have regulatory

[1]Department of Medical Genetics, Student Research Committee, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2]Student Research Committee, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[3]Medical Doctor Student, Student Research Committee, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran

Submitted: Sep 8, 2023; Revised: Jan 17, 2024; Accepted: Jan 22, 2024; Epub: 26 January 2024

Address for correspondence: Sara Jalalian, Medical Doctor Student, Student Research Committee, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran.
E-mail contact: Rezaee.aryan@gmail.com, S.jalalian@nkums.ac.ir

Aryan Rezaee, Student Research Committee, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
E-mail contact: Rezaee.aryan@gmail.com, S.jalalian@nkums.ac.ir

1526-8209/$ - see front matter
https://doi.org/10.1016/j.clbc.2024.01.015

Table 1 Search Strategy in Databases

Date	September 11, 2023	
Language	English	
Databases	PubMed, Scopus, Web of Science (WOS)	
Pubmed	((((((((((“Tamoxifen”[Title/Abstract]) OR (ICI-47699[Title/Abstract])) OR (Nolvadex[Title/Abstract])) OR (Novaldex[Title/Abstract])) OR (“Tamoxifen Citrate”[Title/Abstract])) OR (“Tomaxithen”[Title/Abstract])) OR (“Zitazonium”[Title/Abstract])) OR (“ICI-46474”[Title/Abstract])) OR (“ICI-46,474”[Title/Abstract])) OR (“Soltamox”[Title/Abstract])) AND ((((((((((“Breast Neoplasm”[Title/Abstract]) OR (“Breast Tumor”[Title/Abstract])) OR (“Breast Cancer”[Title/Abstract])) OR (“Malignant Tumor of Breast”[Title/Abstract])) OR (“Breast Malignant Tumor”[Title/Abstract])) OR (“Cancer of the Breast”[Title/Abstract])) OR (“Cancer of Breast”[Title/Abstract])) OR (“Malignant Neoplasm of Breast”[Title/Abstract])) OR (“Breast Malignant Neoplasm”[Title/Abstract])) OR (“Mammary Cancer”[Title/Abstract])) OR (“Human Mammary Carcinoma”[Title/Abstract])) OR (“Human Mammary Neoplasm”[Title/Abstract])) OR (“Breast Carcinoma”[Title/Abstract]))) AND (((((((((“MicroRNA”[Title/Abstract]) OR (“miRNA”[Title/Abstract])) OR (“Primary MicroRNA”[Title/Abstract])) OR (“Primary miRNA”[Title/Abstract])) OR (“pri-miRNA”[Title/Abstract])) OR (“stRNA”[Title/Abstract])) OR (“Small Temporal RNA”[Title/Abstract])) OR (“pre-miRNA”[Title/Abstract]))	131
Scopus	TITLE-ABS (“Tamoxifen”) OR TITLE-ABS (ici-47699) OR TITLE-ABS (nolvadex) OR TITLE-ABS (novaldex) OR TITLE-ABS (“Tamoxifen Citrate”) OR TITLE-ABS (“Tomaxithen”) OR TITLE-ABS (“Zitazonium”) OR TITLE-ABS (“ICI-46474”) OR TITLE-ABS (“ICI-46,474”) OR TITLE-ABS (“Soltamox”) AND TITLE-ABS (“Breast Neoplasm”) OR TITLE-ABS (“Breast Tumor”) OR TITLE-ABS (“Breast Cancer”) OR TITLE-ABS (“Malignant Tumor of Breast”) OR TITLE-ABS (“Breast Malignant Tumor”) OR TITLE-ABS (“Cancer of the Breast”) OR TITLE-ABS (“Cancer of Breast”) OR TITLE-ABS (“Malignant Neoplasm of Breast”) OR TITLE-ABS (“Breast Malignant Neoplasm”) OR TITLE-ABS (“Mammary Cancer”) OR TITLE-ABS (“Human Mammary Carcinoma”) OR TITLE-ABS (“Human Mammary Neoplasm”) OR TITLE-ABS (“Breast Carcinoma”) AND TITLE-ABS (“MicroRNA”) OR TITLE-ABS (“miRNA”) OR TITLE-ABS (“Primary MicroRNA”) OR TITLE-ABS (“Primary miRNA”) OR TITLE-ABS (“pri-miRNA”) OR TITLE-ABS (“stRNA”) OR TITLE-ABS (“Small Temporal RNA”) OR TITLE-ABS (“pre-miRNA”)	123
WOS	(((((((((TS=(“Tamoxifen”)) OR TS=(ICI-47699)) OR TS=(Nolvadex)) OR TS=(Novaldex)) OR TS=(“Tamoxifen Citrate”)) OR TS=(“Tomaxithen”)) OR TS=(“Zitazonium”)) OR TS=(“ICI-46474”)) OR TS=(“ICI-46,474”)) OR TS=(“Soltamox”) AND ((((((((((TS=(“Breast Neoplasm”)) OR TS=(“Breast Tumor”)) OR TS=(“Breast Cancer”)) OR TS=(“Malignant Tumor of Breast”)) OR TS=(“Breast Malignant Tumor”)) OR TS=(“Cancer of the Breast”)) OR TS=(“Cancer of Breast”)) OR TS=(“Malignant Neoplasm of Breast”)) OR TS=(“Breast Malignant Neoplasm”)) OR TS=(“Mammary Cancer”)) OR TS=(“Human Mammary Carcinoma”)) OR TS=(“Human Mammary Neoplasm”)) OR TS=(“Breast Carcinoma”) AND (((((((((TS=(“MicroRNA”)) OR TS=(“miRNA”)) OR TS=(“Primary MicroRNA”)) OR TS=(“Primary miRNA”)) OR TS=(“pri-miRNA”)) OR TS=(“stRNA”))) OR TS=(“Small Temporal RNA”)) OR TS=(“pre-miRNA”)	311

functions in breast cancer progression, including metastasis, treatment resistance, and carcinogenesis.[17] In 2015, Muluhngwi et al.[18] investigated microRNAs that interfere with the efficacy of antiestrogen therapy. Finally, they found that the dysregulation of miRNAs plays a role in developing endocrine resistance.[18] Accordingly, the target genes of miRNAs that prevent apoptosis, promote cell proliferation, and activate the epithelial-mesenchymal transition (EMT) are disrupted, leading to resistance to tamoxifen and aromatase.[18]

The study of miRNAs affecting tamoxifen mechanisms in breast cancer patients may facilitate the identification of individuals at higher risk of disease recurrence. Conversely, it can potentially deploy appropriate interventions to combat drug resistance effectively. Despite the importance of this topic, no thorough investigation has yet been conducted on this subject. Therefore, the present systematic review aims to investigate miRNAs that significantly influence the response to tamoxifen treatment.

Material and Methods

This systematic review follows the PRISMA instruction[19] to investigate miRNAs significantly influencing tamoxifen's efficacy in treating breast cancer.

Inclusion Criteria

The inclusion criteria of this study are English-language, original, and experimental studies (in which breast cancer cell lines were examined) investigating miRNAs that significantly affect the response to tamoxifen treatment in breast cancer patients. All short articles, letters to the editor, conference abstracts, observational studies, review articles, descriptive studies, analytical studies, case-control studies, and bioinformatic studies, as well as articles for which the full version was not available and articles in a language other than English were excluded from the study.

Databases and the Search Strategy

The Web of Science (WOS), PubMed, and Scopus databases were searched to retrieve articles in English. The searches were conducted until September 11, 2022. The search strategy included the terms “Tamoxifen,” “Breast Neoplasm”, and “MicroRNA” (Table 1), which 2 authors designed.

Selection of Articles

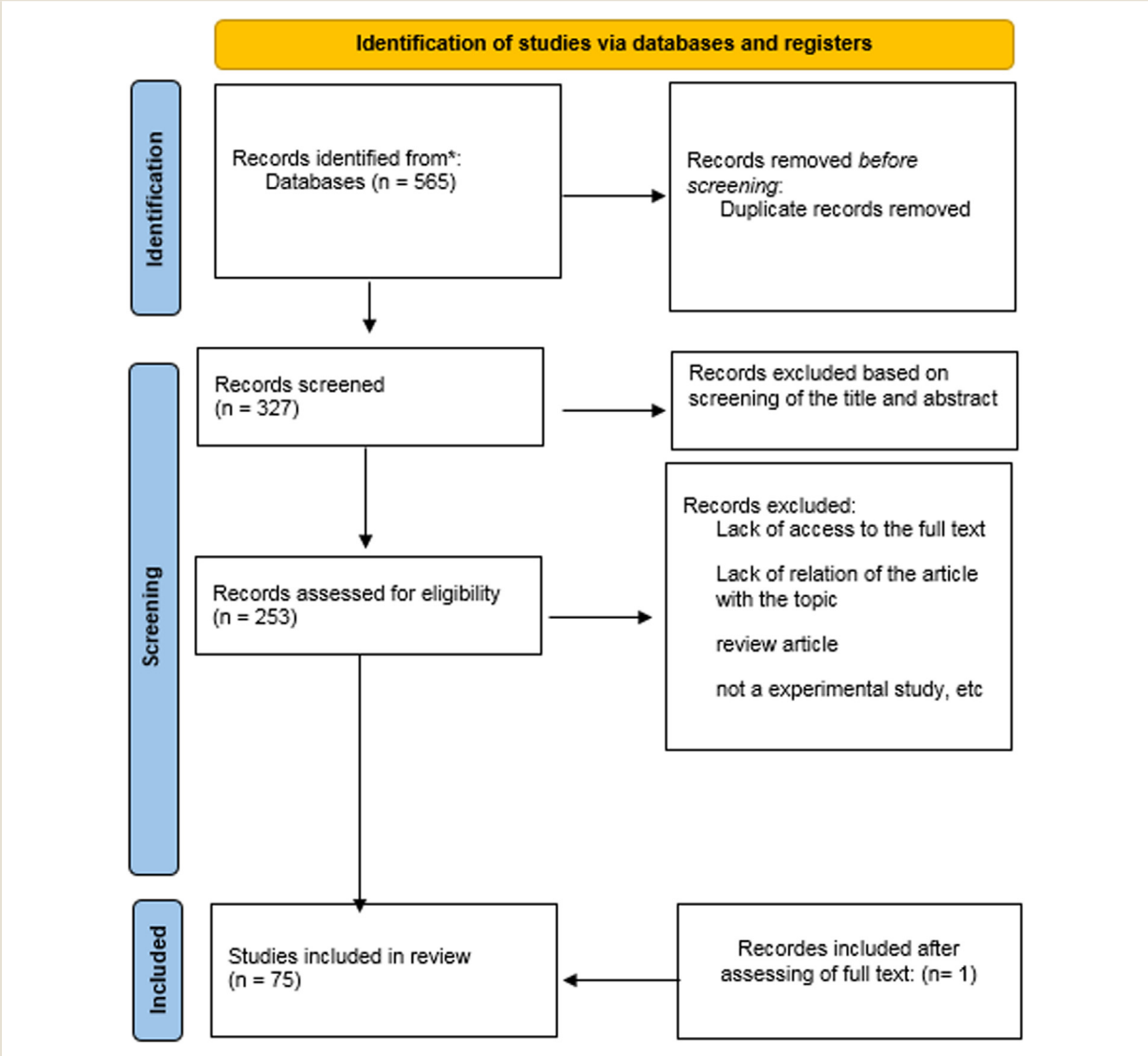
The studies retrieved based on the search strategy were added to the EndNote reference management software. First, duplicate articles were identified and removed using the software. Then, the titles and abstracts of all studies were checked based on the inclusion criteria, and, if necessary, the full text was read.

Two researchers selected the studies independently and referred them to a third researcher if necessary.

Data Extraction

After selecting the studies according to the inclusion and exclusion criteria, the following information was extracted using the data

Figure 1 Process of screening and including the studies.



extraction form based on the study objectives. These data include microRNAs, first author, target genes or molecular processes (Tables 2A–C).

Results

In the first review of 3 databases, 565 articles were retrieved and imported into the Endnote references management software. After removing duplicate and unrelated articles based on the title, abstract, and full text of the articles, 74 articles remained, but in the process of screening the articles, we found 1 article that met all of our inclusion criteria; therefore, 75 articles were included in this study. Figure 1 shows the process of screening and inclusion of the studies.

The descriptive representation of the studies can be found in Table 2. The studies were conducted in China, America, Netherlands, Denmark, Belgium, South Korea, Turkey, Indonesia, Japan, Spain, France, Germany, Russia, Australia, Iran and Egypt. Most of the articles relate to China and America, accounting for 49.3% and 20% of the articles, respectively. In this study, 105 miRNAs were identified, of which 44 have positive effects, 47 have negative effects, and the remaining miRNAs have unclear and contradictory effects. Their efficacy in treating breast cancer with tamoxifen is shown in Figure 2.

The most important miRNAs in this systematic review were those investigated in more than one study, and their role in the efficacy of tamoxifen was also consistent in the studies.

These miRNAs are categorized into 2 groups, that include:

1. miRNAs that enhance the efficacy of tamoxifen in cancer cells, ie, miRNA-342, 135a, 146a, 200a, 200b, 200c, and 27a, respectively.

Table 2A Descriptive Representation of the Studies, miRNAs With a Positive Effect

miRNAs With a Positive Effect	First Author	Target Gene/Molecular Process
miR–342	Yue–Jun He,[1] Tejal Joshi,[2] Diana M Cittelly,[3] Peng Ye,[4] Qian Zhou[5]	FYN,TGFBR1, COL4A6, CDKN1A, and Ephrins EPHA4/7, GEMIN4 and BMP, SEMAD
miR-135a	Tejal Joshi,[2] Weijie Zhang[6]	FYN, ESR1, ESRRA, and NCOA1
Mir-146a	Nguyen Thi Thuy Phuong,[7] Peng Ye[4]	NF-κB, TRAF6 and IRAK1, PI3K/Akt
Mir-200a	Ke Hu,[8] Tissa T. Manavalan[9]	CYP1B1, ZEB1
Mir-200b	Tissa T. Manavalan,[9] Tissa T. Manavalan[10]	CYP1B1, ZEB1
Mir-200c	Tissa T. Manavalan,[10] Tissa T. Manavalan[9]	CYP1B1, ZEB1
Mir-27a	Peng Ye,[4] Bojan Ljepoja[11]	ESR1, adenosine five-triphosphate binding cassette subfamily B member 1
hsa-miR-30a-3p	Germán Rodríguez-González[12]	Ceramide signaling pathway RAC1 cell motility signaling pathway
hsa-miR-30c	Germán Rodríguez-González[12]	ER, signal transduction, and oncology pathway RAC1 cell motility signaling pathway
hsa-miR-182	Germán Rodríguez-González[12]	***
miR-363	Lili Ren,[13] Ying Li[14]	Trefoil factor 1 (TFF1), SERTAD3
miR-193-3p.	Manoj M Pillai[15]	NCOA3
Has-let-7i	Liming Weng[17]	TRAF1
let-7d	Qian Zhou[5]	***
miR-593	Tejal Joshi[2]	SNA12
miR-33b	Tejal Joshi[2]	FYN
miR-135b	Tejal Joshi[2]	***
miR190b	Tejal Joshi[2]	
Mir-146b	Nguyen Thi Thuy Phuong[7]	NF-κB, TRAF6 and IRAK1, PI3K/Akt
miR-29b-3p	Carolyn M. Klinge[18]	PR action and TGFβ signaling pathways
Mir-125a- 3p	Lufeng Zheng[19]	CDK3
miR-770-5p	Senem Noyan[20]	Focal adhesion, MAPK and ErbB signaling
miR-204-5p	Enshuang Xu[21]	SOX4
Mir-93	Tissa T. Manavalan[9]	ERBB3
miR-1254	Gaopeng Li[22]	NCOA1, NCOA3, EGFR, ERBB2, SNAI1
miRNA-503	XIA PAN[23]	eIF4G
miR-26a	JIAN LIU[24]	E2F7
miR-148a	PENG YE[4]	***
miR-138	Qian Zhou[5]	EZHH2
miR-1228	Qian Zhou[5]	***
miR-3178	Qian Zhou[5]	***
miR-1226	Qian Zhou[5]	***
miR-31	Qian Zhou[5]	***
miR-1288	Qian Zhou[5]	***
hsa-miR-136-5p	Charlène Thiebaut[25]	ERalpha36
hsa-miR-1299	Liang Gao[26]	***
miR-22-3p	Li Che[27]	OAS1, SIRT1
miR-378a-3p	Kazuhiro Ikeda[28]	GOLT1A
MiRNA-320a	Mingrong Lu"[29]	ARPP-19, ERRc
miR-500a-3p	Ye Sol Kim[30]	LY6K
miR-125a-3p	Lufeng Zheng[31]	CDK3
miR-1972	Behringer[32]	***
miR-451	Bergamaschi[33]	HER2, EGFR, MAPK
miR-186-3p	Mengjia He[34]	EREG

Table 2B Descriptive Representation of the Studies, miRNANAs With a Negative Effect

miRNAs With Negative Effect	First Author	Target Gene/Molecular Process
miR-221	Yifang Wei[35] Tejal Joshi[2] Gan[36] Tyler E. Miller[37] Rao[38]	P27, Era
miR-9-5p	Jianhui Liu[39] Manoj M Pillai[15]	ADIPOQ, ER protein, NCOA3
miR-10a	Tissa T. Manavalan[9] Liang Gao[26]	***
miR-181a	Andreeva[40] Tissa T. Manavalan[9]	AKT signalling, Erα
miR-181b	Tejal Joshi[2] Behringer[32]	HEY1, CA2, PIK3R1, LYN, ESR1, JUN, STAT1, MYB,BCL2, CYCS, BAMBI, CTGF and SOX9
miR-551b	Qian Zhou5 Tejal Joshi[2]	***
miR-519a	Tejal Joshi[2] Aoife Ward[41]	PTEN, CDKN1A/p21
miR-455-3p	Tejal Joshi[2] Behringer[32]	***
miR-409-3p	Liang Gao[26]	***
miR-182-5p	Yuting Sang[42]	FOXO3a
miR-210	Franc¸oise Rothe[43]	ACVR1B (activin receptor 1B), CBFA2T1, MTG16,DICER1
Mir 1290	Yumi Endo[44]	N-acetyltransferase 1 (NAT1)
miR-10b	Aamir Ahmad[45]	HDAC4
, miR-521	Tejal Joshi[2]	***
miR-1266	Carolyn M. Klinge[18]	***
mir1268a	Carolyn M. Klinge[18]	***
mir671-3p	Carolyn M. Klinge[18]	FOXM1
Mir125b	Tissa T. Manavalan[9]	ERBB3
miR-197-3p	Hongjuan Li[46]	HIPK3
miRNA-7	K. Uhr[47]	EGFR 22
miR-145	Peng Ye[4]	***
miR-4532	Qian Zhou[5]	***
miR-3180-3p	Qian Zhou[5]	***
miR-1825	Qian Zhou[5]	***
miR-1244	Qian Zhou[5]	***
miR-2276	Qian Zhou[5]	***
miR-939	Qian Zhou[5]	***
miR-18a	Ginés Luengo-Gil[48]	Erα
miRNA-130a-5p	Y.-F. SHI[49]	PTEN
hsa-miR-195—5p	Liang Gao[26]	***
miR-485-5p	Liang Gao[26]	***
miR-495-3p	Liang Gao[26]	***
miR-105-5p	Liang Gao[26]	***
miR-370-3p	Liang Gao[26]	***
miR-432-5p	Liang Gao[26]	***
miR-767-5p	Liang Gao[26]	***
miR-134-5p	Liang Gao[26]	***

(*continued on next page*)

Table 2B (*continued*)

miRNAs With Negative Effect	First Author	Target Gene/Molecular Process
miRNA-155	Rong Shen[50]	SOCS6
miR-192-5p	Ye Sol Kim[30]	ESR1
miR-335-5p miR-335-3p	Elizabeth C. Martin[51]	CDH1 stability, RAC1 activity, PDGFR signaling, and Era
miRNA 15b	Yanhong Wang[52]	FOXO1
miR-204	Liu and Li[53]	ERα، Caspase 3
miR-575	Liu[54]	CDKN1B, BRCA1
miR-34a	Shaymaa M. M. Yahya[55]	MET BCL-2, SIRT1, CDK and CCND1
miR98	Shaymaa M. M. Yahya[55]	***
miR-214	Shaymaa M. M. Yahya[55]	***

Table 2C Descriptive Representation of the Studies, miRNAs With Contradictory Effect

Contradictory miRNAs	First Author	Target Gene/Molecular Process
miR-222	Studies report negative effect: X Rao,[38] Tyler E. Miller,[37] R Gan,[36] Tissa T. Manavalan,[9] Tejal Joshi,[2] Yifang Wei [35] Studies report positive effect: Carolyn M. Klinge[18]	p27Kip1, TIMP3. ERBB3,ESR1
miR-375	Studies report negative effect: Tejal Joshi[2] Studies report positive effect: Behringer,[32] Qiong Zhao,[56] A Ward[57]	JAK2, MTDH
miR-205	Studies report negative effect: Tejal Joshi,[2] Yan Zhao[58] Studies report positive effect: Hong–Yan Zhang[59]	E2F1, ZEB1/2
miR-21	Studies report negative effect: Peng Ye,[4] Xinfeng Yu[60] Studies report positive effect: Carolyn M. Klinge,[61] Tissa T. Manavalan[9]	PDCD4 and PTEN, BCL2
miR-486	Studies report negative effect: Peng Ye[4] Studies report positive effect: Qian Zhou,[5] Mansoori B[62]	PIM-1, HMGA1
miR-489	Studies report negative effect: Qian Zhou,[5] Liang Gao[26] Studies report positive effect: Mithil Soni[63]	p38 and PTPN11
miRNA-101	Studies report negative effect: M Sachdeva[64] Studies report positive effect: Liu[65]	LC3,Beclin-1, MAGI-2
Let-7c	Studies report negative effect: Peng Ye[4] Studies report positive effect: Xin Sun[66]	
let-7e	Studies report negative effect: Peng Ye[4] Studies report positive effect: Qian Zhou[5]	
miR-29a	Studies report negative effect: Tissa T. Manavalan[9] Studies report positive effect: Carolyn M. Klinge[18]	PR action and TGFβ signaling pathways
miR-125b-5p	Studies report negative effect: Liang Gao[26] Studies report positive effect: Fujun Li[67]	PAD2
Mir-22	Studies report negative effect: Tissa T. Manavalan[9] Studies report positive effect: Cheng Yang[68]	ERBB3, c-Myc
mir 27b 3p	Studies report negative effect: Jiang Zhu[69] Studies report positive effect: Liang Gao[26]	NR5A2 and CREB1
miR-23b-3p	Studies report negative effect: Panhong Zhang[70] Studies report positive effect: Liang Gao[26]	ZBTB1

2. miRNAs with adverse effects that lead to tamoxifen resistance in cancer cells. These include miRNA 221, 9-5p, 10a, 181a, 181b, 551b, 519a, and 455-3p, respectively.

Discussion

This systematic review study investigates the miRNAs that influence how well tamoxifen works in treating breast cancer patients. In other words, this study seeks to identify the miRNAs that influence the response of breast cancer cells to tamoxifen.

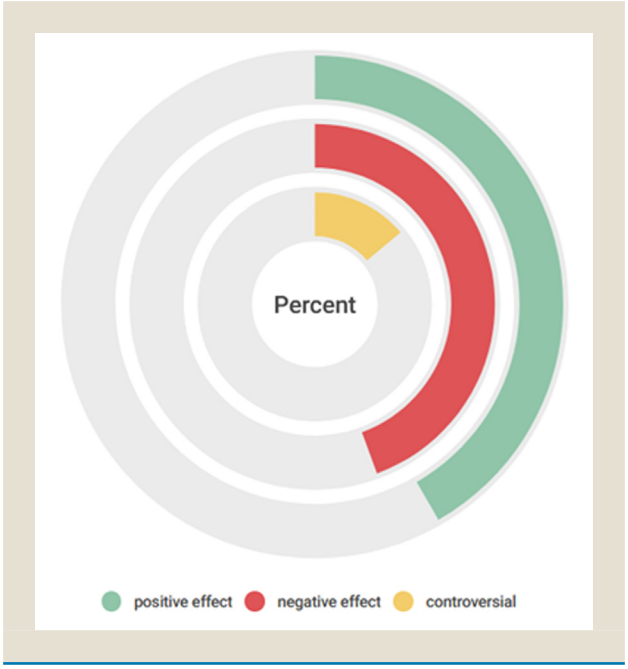
The results of the current study show that two major groups of miRNAs influence the efficacy of tamoxifen. These 2 groups are 1-miRNAs with a positive effect on tamoxifen and 2-miRNAs with a negative effect on tamoxifen efficacy.

Slightly more than 44.7% of the miRNAs detected had adverse effects, while 42% had a positive effect.

In the first group, miRNA-342, 135a, 146a, 200a, 200b, 200c, and 27a are the most intensively researched miRNAs that had been investigated in more than 1 study, and the results of these studies also confirmed that these miRNAs increase the efficacy of tamoxifen in cancer cells.

Similar to the review study by Barazetti et al.[16] showed these miRNAs positively affect tamoxifen therapy. However, in the case of

Figure 2 Impact of miRNAs in the effectiveness of tamoxifen.



miRNA-342, this review concluded from a study by Cittelly et al.[3] that this miRNA is increased in tamoxifen-resistant cells. However, according to Cittelly et al.,[3] increasing the expression of this miRNA is a treatment approach for tamoxifen-resistant cancer cells. As a result of this study, we believe that this miRNA positively influences tamoxifen function, such that a reduction in its expression may lead to tamoxifen resistance, similar to the bioinformatic study by Young et al.[71] The influence of miRNA-342 and miRNA-200b/c was shown in a review study by Zhang et al. in a manner comparable to the current study.

MiRNA-342 is effective in regulating the expression of genes involved in the regulation of the cell cycle of cancer cells, leading to the regulation of apoptosis, which is one of the activities of tamoxifen.[3] The expression of miRNA-342 is associated with the expression of the gene EVL (Ena/Vasodilator-stimulated phosphoprotein-like).[4] It appears that the expression of this gene is reduced in ER+ breast cancer cells resistant to tamoxifen, suggesting that miRNA-342 is inhibited in tamoxifen-resistant cancer cells.[3] Yue-Jun et al.[1] showed a positive correlation between the expression of miRNA-342 and ERα in breast cancer cells. Also, he found that these cells were sensitized to tamoxifen through the induction of apoptosis. One of the predicted targets of miRNA-342 was the FYN gene. Joshi et al.[2] observed an axis between miRNA-342-3p/5p and miRNA-33b/FYN, which is important for resistance. In agreement with this study, Elias et al.[72] found that decreased expression of FYN in tamoxifen-resistant cancer cells increases the susceptibility of these cells to tamoxifen.

miRNA-135a is one of the miRNAs that are consistently downregulated in tamoxifen-resistant cancer cells.[2] Targets of miRNA-135a are ESR1, ESRRA, and NCOA1, which inhibit ERα signaling[6] Zhang et al.[6] demonstrated that a reduction in miRNA-135a expression can lead to tamoxifen resistance through activation of ERK1/2 and Akt signaling pathways, which are the direct targets of miRNA-135a.

miRNA-146a is a negative regulator of NF-κB activity by decreasing the expression of IRAK1 (interleukin–1 receptor–associated kinase 1) and tumor necrosis factor receptor-associated factor 6 (TRAF6). miRNA-146a can enable cancer cells to become resistant to tamoxifen when the function of inactivating TRAF6/IRAK1 genes in the NF-KB pathway is impaired.[7]

Manavalan et al.[9] by applying the miRNA microarray method, demonstrated that the expression of miRNA-200a decreased in tamoxifen-resistant cancer cells compared to tamoxifen-sensitive cancer cells. The study by Hu et al.[8] showed that a circular RNA called UBE2D2 (circ-UBE2D2) can bind to miRNA-200a and enhance tamoxifen resistance in breast cancer cells by decreasing the expression of miRNA-200a.

The CYP1B1 gene, a cytochrome P450 enzyme, is one of the putative targets of the miRNA-200 family, and polymorphisms in this gene are also associated with the development of breast cancer. Manavalan et al.[9] observed increased expression of the CYP1B1 gene in cancer cells treated with 4-hydroxytamoxifen (4-OHT) due to reduced expression of miRNA-200b and miRNA-200c. Increased expression of miRNA-200b/c sensitizes tamoxifen-resistant cancer cells to inhibit progression by ER antagonists such as tamoxifen. Meanwhile, suppression of the ZEB1 gene as a target of these miRNAs serves the same function as increasing miRNA-200b/c expression and sensitizing cancer cells to tamoxifen.[10]

Like miRNA-342, miRNA-27a sensitizes cancer cells to tamoxifen via a positive feedback mechanism with the estrogen receptor gene (ESR1).[11]

The second group contains miRNA-221, 9-5p, 10a, 181a, 181b, 551b, 519a, and 455-3p, the most studied miRNAs, that showed a negative effect in tamoxifen efficacy in all studies.

Similar results were found in the review study by Barazetti et al.[16] for miRNA-221, 9-5p and miRNA-519a. Regarding miRNA-181a/b, similar results were observed by Miller et al.[37] Eskiler et al.[73] showed that injection of tamoxifen in the form of solid lipid nanoparticles reduced the expression level of miRNA-181, making it resistant to tamoxifen. Comparable results were observed for miRNA-181, 221, and 519a in the review study by Zhang et al. However, the results for miRNA-10a were different, and this miRNA was shown to suppress tamoxifen resistance.

Wei et al.[35] discovered that the expression of miRNA-221 reduced the expression of P27 and ERα genes, which may lead to tamoxifen resistance. In contrast, as mentioned above, miRNA-342 and 27a have positive feedback with the ERα gene, leading to better efficacy of tamoxifen. It was shown that by transfecting the antisense RNA of miRNA-221 (AS-miRNA-221) into breast cancer cell lines, these cell lines sensitize to tamoxifen treatment due to decreased expression of miRNA-221 and increased expression of its target, tissue inhibitor of metalloproteinase-3 (TIMP3).[36] Joshi et al.[2] provided evidence that miRNA-221 has a negative impact on the efficacy of tamoxifen by demonstrating the increased expression of this miRNA in tamoxifen-resistant cell lines.

In a study by Pillai et al.,[15] miRNA-9-5p was found to be involved in the regulation of endocrine signaling in breast cancer and

produces tamoxifen resistance. Similar to miRNA-221, miRNA-9-5p also has a negative effect on ER gene expression.[15] It was shown that the transfer of miRNA-9-5p into breast cancer cell lines leads to tamoxifen resistance in these cells due to decreased expression of the ADIPOQ gene, a target of miRNA-9-5p.[39]

In a study by Manavalan et al.,[9] the expression of miRNA-10a was increased in tamoxifen-resistant cancer cell lines compared to tamoxifen-sensitive cancer cell lines. In a transcriptomic analysis by Gao et al.,[26] 2 upregulated miRNAs in tamoxifen-resistant cancer cells, miRNA-10a-5p and miRNA-134-5p, were found in both a network of long noncoding RNAs (lncRNAs)- miRNA-mRNA and a miRNA-mRNA correlation network. Previous studies also suggest that these miRNAs play a role in tamoxifen resistance in ER-positive breast cancer cell lines.

Transfection of miRNA-181a-2 into breast cancer cell lines leads to tamoxifen resistance in these cell lines by suppressing the ER signaling pathway and stimulating the PI3K/Akt signaling pathway.[40] Manavalan et al.[9] also indicate that miRNA-181a is downregulated in tamoxifen-sensitive breast cancer cell lines compared to tamoxifen-resistant breast cancer cell lines.

Like miRNA-221, miRNA-181b regulates its target, the TIMP3 gene, and overexpression of TIMP3 in mouse tamoxifen-resistant xenograft model restored sensitivity to tamoxifen. Other targets of miRNA-181b implicated in drug resistance include HEY1, CA2, PIK3R1, LYN, ESR1, JUN, STAT1, MYB, BCL2, CYCS, BAMBI, CTGF and SOX9.[2]

By comparing the expression profile of miRNAs between fulvestrant-resistant breast cancer cell lines and tamoxifen-resistant breast cancer cell lines, Zhou et al.[5] showed that some miRNAs, such as miRNA-551b were exclusively upregulated in tamoxifen-resistant cell lines. However, the exact molecular mechanism of this miRNA leading to tamoxifen resistance is unclear. miRNA-519a and miRNA-181a can induce tamoxifen resistance in ER-positive breast cancer cells by regulating tumor suppressor genes in the PI3K pathway as its direct target genes.[41]

Apart from these 2 large groups of miRNAs that have either a positive or negative effect on the efficacy of tamoxifen, which was demonstrated in several studies, there is a smaller group of miRNAs with controversial effects, as the results of the studies are inconsistent.

Most studies have demonstrated the negative influence of miRNA-222 on the efficacy of tamoxifen.[2,9,35–38] However, the study by Klinge et al.[18] has shown that tamoxifen resistance is caused by increased expression of a ribonucleoprotein called HNRNPA2/B1 and decreased expression of miRNA-222, which can drive the TGF-beta signaling pathway and likely contributes to resistance to tamoxifen. As a result, the TGF-beta signaling pathway is suppressed by the expression of miRNA-222, increasing tamoxifen's efficacy.[18]

Ye et al.[4] showed that increased expression of miRNA-486 in cancer cells leads to resistance to tamoxifen, in contrast to most studies demonstrating its beneficial effect on tamoxifen.[5,62]

Although Zhou et al.[5] and Gao et al.[26] showed that the expression of miRNA-489 was upregulated in tamoxifen-resistant cancer cells, Soni et al.[63] found that the expression of miRNA-489 was downregulated, leading to resistance to tamoxifen through the inhibition of estrogen receptor (ER) signaling.

Zhang et al.,[59] in contrast to Joshi et al.[2] and Zhao et al.,[58] suggested that increasing miRNA-205 expression by suppressing ZEB1/2 gene expression causes cancer cells to be more sensitive to tamoxifen.

Joshi et al.[2] found that tamoxifen-resistant cancer cells expressed miRNA-375 more frequently. However, other studies have found that this increased miRNA expression makes cancer cells more sensitive to tamoxifen by regulating the expression of the MTDH and JAK2 genes.[32,56,57]

miRNA-21 has been the subject of numerous studies. Yu et al.[60] demonstrated that miRNA-21 can suppress the PI3K-AKT-mTOR pathway by interfering with the PTEN gene; reduced expression of this miRNA, therefore, leads to autophagy and cancer cell death, as well as preventing tamoxifen resistance in cancer cells. Furthermore, in Ye et al.[4] study, miRNA-21 was increased in tamoxifen-resistant cancer cells. In contrast to these results, miRNA-21 expression decreased in tamoxifen-resistant cancer cells in studies by Manavalan et al.[10] and Klinge et al.[61] In addition, Klinge et al.[61] showed that increased expression of miRNA-21 and ER46 makes cancer cells more susceptible to the effects of tamoxifen.

Patients with tamoxifen-resistant cancer will be spared additional costs with advances in research. Tamoxifen is the first-line treatment for breast cancer, but further studies on the miRNA genes could help treat patients by finding ways to decrease the expression of miRNAs with adverse effects or increase the expression of miRNAs with favorable effects. Further studies on miRNAs with conflicting findings are needed, and not enough research has been done to understand the molecular mechanisms of tamoxifen resistance by miRNAs.

This study has several limitations. First, it focuses exclusively on experimental studies, excluding other studies such as descriptive, analytical, case-control, and bioinformatics. Second, the scope of the study is also limited to articles from PubMed, Web Of Science, and Scopus databases. Third, only articles written in English were considered for inclusion in the study.

Conclusion

This systematic review suggests that miRNA-342, 135a, 27a, 200a, 200b and 146a might positively affect tamoxifen's mechanisms in treating breast cancer patients. In contrast, miRNA-9-5p, 221, 10a, 181b, 181a, 551b, 519a, 409-3p, and 455-3p might have an adverse effect. These findings could improve prognostic approaches of breast cancer patients who received tamoxifen as their first line of treatment and improve personalized medicine. Although the mechanism of resistance to tamoxifen remains uncertain and further researches are needed to realize the molecular basis, targeting miRNAs with adverse effects or restoring the expression of miRNAs with positive effects could be promising therapeutic approaches to overcome tamoxifen resistance and sensitizing cancer cells to tamoxifen.

Disclosure

The authors have no conflict of interest to declare.

CRediT authorship contribution statement

Nima Nikbin Kavishahi: Project administration, Writing – original draft, Writing – review & editing. **Aryan Rezaee:** Writing – original draft, Writing – review & editing. **Sara Jalalian:** Writing – original draft, Writing – review & editing.

References

1. He YJ, Wu JZ, Ji MH, et al. miR–342 is associated with estrogen receptor–α expression and response to tamoxifen in breast cancer. *Experiment Therap Med*. 2013;5(3):813–818.
2. Joshi T, Elias D, Stenvang J, et al. Integrative analysis of miRNA and gene expression reveals regulatory networks in tamoxifen-resistant breast cancer. *Oncotarget*. 2016;7(35):57239–57253.
3. Cittelly DM, Das PM, Spoelstra NS, et al. Downregulation of miR-342 is associated with tamoxifen resistant breast tumors. *Mol Cancer*. 2010;9:317.
4. Ye P, Fang C, Zeng H, et al. Differential microRNA expression profiles in tamoxifen-resistant human breast cancer cell lines induced by two methods. *Oncol Lett*. 2018;15(3):3532–3539.
5. Zhou Q, Zeng H, Ye P, Shi Y, Guo J, Long X. Differential microRNA profiles between fulvestrant-resistant and tamoxifen-resistant human breast cancer cells. *Anticancer Drugs*. 2018;29(6):539–548.
6. Zhang WJ, Wu MM, Chong QY, et al. Loss of estrogen-regulated MIR135A1 at 3p21.1 promotes tamoxifen resistance in breast cancer. *Cancer Res*. 2018;78(17):4915–4928.
7. Phuong NTT, Kim SK, Im JH, et al. Induction of methionine adenosyltransferase 2A in tamoxifen-resistant breast cancer cells. *Oncotarget*. 2016;7(12):13902–13916.
8. Hu K, Liu X, Li Y, et al. Exosomes mediated transfer of Circ_UBE2D2 enhances the resistance of breast cancer to tamoxifen by binding to MiR-200a-3p. *Med Sci Monit*. 2020;26:e922253.
9. Manavalan TT, Teng Y, Appana SN, et al. Differential expression of microRNA expression in tamoxifen-sensitive MCF-7 versus tamoxifen-resistant LY2 human breast cancer cells. *Cancer Lett*. 2011;313(1):26–43.
10. Manavalan TT, Teng Y, Litchfield LM, Muluhngwi P, Al-Rayyan N, Klinge CM. Reduced expression of miR-200 family members contributes to antiestrogen resistance in LY2 human breast cancer cells. *PLoS One*. 2013;8(4):26–43.
11. Ljepoja B, Garcia-Roman J, Sommer AK, Wagner E, Roidl A. MiRNA-27a sensitizes breast cancer cells to treatment with selective estrogen receptor modulators. *Breast*. 2019;43:31–38.
12. Rodríguez-González FG, Sieuwerts AM, Smid M, et al. MicroRNA-30c expression level is an independent predictor of clinical benefit of endocrine therapy in advanced estrogen receptor positive breast cancer. *Breast Cancer Res Treat*. 2011;127(1):43–51.
13. Ren L, Zhou H, Lei L, Zhang Y, Cai H, Wang X. Long non-coding RNA FOXD3 antisense RNA 1 augments anti-estrogen resistance in breast cancer cells through the microRNA-363/trefoil factor 1/ phosphatidylinositol 3-kinase/protein kinase B axis. *Bioengineered*. 2021;12(1):5266–5278.
14. Li Y, Liu L, Lv YD, et al. Silencing long non-coding RNA HNF1A-AS1 inhibits growth and resistance to TAM of breast cancer cells via the microRNA-363/SERTAD3 axis. *J Drug Targeting*. 2021;29(7):742–753.
15. Pillai MM, Gillen AE, Yamamoto TM, et al. HITS-CLIP reveals key regulators of nuclear receptor signaling in breast cancer. *Breast Cancer Res Treat*. 2014;146(1):85–97.
16. Barazetti JF, Jucoski TS, Carvalho TM, et al. From micro to long: non-coding RNAs in tamoxifen resistance of breast cancer cells. *Cancers*. 2021;13(15):3688.
17. Weng L, Ziliak D, LaCroix B, Geeleher P, Huang RS. Integrative "omic" analysis for tamoxifen sensitivity through cell based models. *PLoS One*. 2014;9(4).
18. Klinge CM, Piell KM, Tooley CS, Rouchka EC. HNRNPA2/B1 is upregulated in endocrine-resistant LCC9 breast cancer cells and alters the miRNA transcriptome when overexpressed in MCF-7 cells. *Sci Rep*. 2019;9(1):9430.
19. Zheng LF, Li XM, Meng X, et al. Competing endogenous RNA networks of CYP4Z1 and pseudogene CYP4Z2P confer tamoxifen resistance in breast cancer. *Mol Cell Endocrinol*. 2016;427(C):133–142.
20. Noyan S, Gurdal H, Gur Dedeoglu B. Involvement of miR-770-5p in trastuzumab response in HER2 positive breast cancer cells. *PLoS One*. 2019;14(4):e0215894.
21. Xu ES, Hu MX, Ge RD, et al. LncRNA-42060 regulates tamoxifen sensitivity and tumor development via regulating the miR-204-5p/SOX4 axis in canine mammary gland tumor cells. *Front Vet Sci*. 2021;8.
22. Li G, Wu X, Qian W, et al. CCAR1 5′ UTR as a natural miRancer of miR-1254 overrides tamoxifen resistance. *Cell Res*. 2016;26(6):655–673.
23. Pan X, Yang X, Zang J, et al. Downregulation of eIF4G by microRNA-503 enhances drug sensitivity of MCF-7/ADR cells through suppressing the expression of ABC transport proteins. *Oncol Lett*. 2017;13(6):4785–4793.
24. Liu J, Li X, Wang M, et al. A miR-26a/E2F7 feedback loop contributes to tamoxifen resistance in ER-positive breast cancer. *Int J Oncol*. 2018;53(4):1601–1612.
25. Thiebaut C, Chesnel A, Merlin JL, et al. Dual epigenetic regulation of ER36 expression in breast cancer cells. *Int J Mol Sci*. 2019;20(11).
26. Gao L, Shen K, Yin N, Jiang M. Comprehensive transcriptomic analysis reveals dysregulated competing endogenous RNA network in endocrine resistant breast cancer cells. *Front Oncol*. 2020;10.
27. Che L, Yang H, Wang D, Liu S. Corylin sensitizes breast cancer cells to overcome tamoxifen resistance by regulating OAS1/miR-22-3p/SIRT1 axis. *Acta Biochim Pol*. 2021;68(4):757–764.
28. Ikeda K, Horie-Inoue K, Ueno T, et al. miR-378a-3p modulates tamoxifen sensitivity in breast cancer MCF-7 cells through targeting GOLT1A. *Sci Rep*. 2015;5:13170.
29. Lu MR, Ding KH, Zhang GF, et al. MicroRNA-320a sensitizes tamoxifen-resistant breast cancer cells to tamoxifen by targeting ARPP-19 and ERR gamma. *Sci Rep*. 2015;5.
30. Kim YS, Park SJ, Lee YS, Kong HK, Park JH. miRNAs involved in LY6K and estrogen receptor α contribute to tamoxifen-susceptibility in breast cancer. *Oncotarget*. 2016;7(27):42261–42273.
31. Zheng LF, Meng X, Li XM, et al. miR-125a-3p inhibits ER alpha transactivation and overrides tamoxifen resistance by targeting CDK3 in estrogen receptor-positive breast cancer. *FASEB J*. 2018;32(2):588–600.
32. Behringer A, Stoimenovski D, Porsch M, et al. Relationship of micro-RNA, mRNA and eIF expression in tamoxifen-adapted MCF-7 breast cancer cells: impact of miR-1972 on gene expression, proliferation and migration. *Biomolecules*. 2022;12(7).
33. Bergamaschi A, Katzenellenbogen BS. Tamoxifen downregulation of miR-451 increases 14-3-3ζ and promotes breast cancer cell survival and endocrine resistance. *Oncogene*. 2012;31(1):39–47.
34. He MJ, Jin QN, Chen C, et al. The miR-186-3p/EREG axis orchestrates tamoxifen resistance and aerobic glycolysis in breast cancer cells. *Oncogene*. 2019;38(28):5551–5565.
35. Wei Y, Lai X, Yu S, et al. Exosomal miR-221/222 enhances tamoxifen resistance in recipient ER-positive breast cancer cells. *Breast Cancer Res Treat*. 2014;147(2):423–431.
36. Gan R, Yang Y, Yang X, Zhao L, Lu J, Meng QH. Downregulation of miR-221/222 enhances sensitivity of breast cancer cells to tamoxifen through upregulation of TIMP3. *Cancer Gene Ther*. 2014;21(7):290–296.
37. Miller TE, Ghoshal K, Ramaswamy B, et al. MicroRNA-221/222 confers tamoxifen resistance in breast cancer by targeting p27Kip1. *J Biol Chem*. 2008;283(44):29897–29903.
38. Rao X, Di Leva G, Li M, et al. MicroRNA-221/222 confers breast cancer fulvestrant resistance by regulating multiple signaling pathways. *Oncogene*. 2011;30(9):1082–1097.
39. Liu J, Zhu S, Tang W, Huang Q, Mei Y, Yang H. Exosomes from tamoxifen-resistant breast cancer cells transmit drug resistance partly by delivering miR-9-5p. *Cancer Cell Int*. 2021;21(1):55.
40. Andreeva OE, Sorokin DV, Mikhaevich EI, et al. Towards unravelling the role of ERα-targeting miRNAs in the exosome-mediated transferring of the hormone resistance. *Molecules*. 2021;26(21).
41. Ward A, Shukla K, Balwierz A, et al. MicroRNA-519a is a novel oncomir conferring tamoxifen resistance by targeting a network of tumour-suppressor genes in ER+ breast cancer. *J Pathol*. 2014;233(4):368–379.
42. Sang YT, Chen B, Song XJ, et al. circRNA_0025202 regulates tamoxifen sensitivity and tumor progression via regulating the miR-182-5p/FOXO3a axis in breast cancer. *Mol Ther*. 2019;27(9):1638–1652.
43. Rothe F, Ignatiadis M, Chaboteaux C, et al. Global MicroRNA expression profiling identifies MiR-210 associated with tumor proliferation, invasion and poor clinical outcome in breast cancer. *PLoS One*. 2011;6(6).
44. Endo Y, Yamashita H, Takahashi S, et al. Immunohistochemical determination of the miR-1290 target arylamine N-acetyltransferase 1 (NAT1) as a prognostic biomarker in breast cancer. *BMC Cancer*. 2014;14:990.
45. Ahmad A, Ginnebaugh KR, Yin SP, Bollig-Fischer A, Reddy KB, Sarkar FH. Functional role of miR-10b in tamoxifen resistance of ER-positive breast cancer cells through down-regulation of HDAC4. *BMC Cancer*. 2015;15.
46. Li H, Li Q, He S. Hsa_circ_0025202 suppresses cell tumorigenesis and tamoxifen resistance via miR-197-3p/HIPK3 axis in breast cancer. *World J Surg Oncol*. 2021;19(1):39.
47. Uhr K, Sieuwerts AM, de Weerd V, et al. Association of microRNA-7 and its binding partner CDR1-AS with the prognosis and prediction of 1(st)-line tamoxifen therapy in breast cancer. *Sci Rep*. 2018;8(1):9657.
48. Luengo-Gil G, Garcia-Martinez E, Chaves-Benito A, et al. Clinical and biological impact of miR-18a expression in breast cancer after neoadjuvant chemotherapy. *Cell Oncol*. 2019;42(5):627–644.
49. Shi YF, Lu H, Wang HB. Downregulated lncRNA ADANITS9-AS2 in breast cancer enhances tamoxifen resistance by activating microRNA-130a-5p. *Eur Rev Med Pharmacol Sci*. 2019;23(4):1563–1573.
50. Shen R, Wang Y, Wang CX, et al. MiRNA-155 mediates TAM resistance by modulating SOCS6-STAT3 signalling pathway in breast cancer. *Am J Transl Res*. 2015;7(10):2115–2126.
51. Martin EC, Conger AK, Yan TJ, et al. MicroRNA-335-5p and-3p synergize to inhibit estrogen receptor alpha expression and promote tamoxifen resistance. *FEBS Lett*. 2017;591(2):382–392.
52. Wang Y, Wang Q, Li X, et al. Paeoniflorin sensitizes breast cancer cells to tamoxifen by downregulating microRNA-15b via the FOXO1/CCND1/β-catenin axis. *Drug Des Devel Ther*. 2021;15:245–257.

53. Liu JB, Li Y. Trichostatin A and tamoxifen inhibit breast cancer cell growth by miR-204 and ER alpha reducing AKT/mTOR pathway. *Biochem Biophys Res Commun*. 2015;467(2):242–247.
54. Liu SS, Li Y, Zhang H, et al. The ERα-miR-575-p27 feedback loop regulates tamoxifen sensitivity in ER-positive Breast Cancer. *Theranostics*. 2020;10(23):10729–10742.
55. Yahya SMM, Elmegeed GA, Mohamed MS, Mohareb RM, Abd-Elhalim MM, Elsayed GH. The effect of newly synthesized heterosteroids on miRNA34a, 98, and 214 expression levels in MCF-7 breast cancer cells. *Indian J Clin Biochem*. 2018;33(3):328–333.
56. Zhao Q, Liu YC, Wang T, et al. MiR-375 inhibits the sternness of breast cancer cells by blocking the JAK2/STAT3 signaling. *Eur J Pharmacol*. 2020;884.
57. Ward A, Balwierz A, Zhang JD, et al. Re-expression of microRNA-375 reverses both tamoxifen resistance and accompanying EMT-like properties in breast cancer. *Oncogene*. 2013;32(9):1173–1182.
58. Zhao Y, Jin LJ, Zhang XY. Exosomal miRNA-205 promotes breast cancer chemoresistance and tumorigenesis through E2F1. *Aging (Albany NY)*. 2021;13(14):18498–18514.
59. Zhang HY, Liang F, Zhang JW, Wang F, Wang L, Kang XG. Effects of long noncoding RNA-ROR on tamoxifen resistance of breast cancer cells by regulating microRNA-205. *Cancer Chemother Pharmacol*. 2017;79(2):327–337.
60. Yu X, Li R, Shi W, et al. Silencing of MicroRNA-21 confers the sensitivity to tamoxifen and fulvestrant by enhancing autophagic cell death through inhibition of the PI3K-AKT-mTOR pathway in breast cancer cells. *Biomed Pharmacother*. 2016;77:37–44.
61. Klinge CM, Riggs KA, Wickramasinghe NS, et al. Estrogen receptor alpha 46 is reduced in tamoxifen resistant breast cancer cells and re-expression inhibits cell proliferation and estrogen receptor alpha 66-regulated target gene transcription. *Mol Cell Endocrinol*. 2010;323(2):268–276.
62. Mansoori B, Najafi S, Mohammadi A, et al. The synergy between miR-486-5p and tamoxifen causes profound cell death of tamoxifen-resistant breast cancer cells. *Biomed Pharmacother*. 2021;141.
63. Soni M, Saatci O, Gupta G, et al. miR-489 confines uncontrolled estrogen signaling through a negative feedback mechanism and regulates tamoxifen resistance in breast cancer. *Int J Mol Sci*. 2022;23(15).
64. Sachdeva M, Wu H, Ru P, Hwang L, Trieu V, Mo YY. MicroRNA-101-mediated Akt activation and estrogen-independent growth. *Oncogene*. 2011;30(7):822–831.
65. Liu J, Yue W, Chen H. The correlation between autophagy and tamoxifen resistance in breast cancer. *Int J Clin Exp Pathol*. 2019;12(6):2066–2074.
66. Sun X, Xu C, Xiao G, et al. Breast cancer stem-like cells are sensitized to tamoxifen induction of self-renewal inhibition with enforced Let-7c dependent on Wnt blocking. *Int J Mol Med*. 2018;41(4):1967–1975.
67. Li F, Miao L, Xue T, et al. Inhibiting PAD2 enhances the anti-tumor effect of docetaxel in tamoxifen-resistant breast cancer cells. *J Exp Clin Cancer Res*. 2019;38(1):414.
68. Yang C, Zhang X, Han B, Tian XS. Sensitization to tamoxifen by tanshinone IIA in tamoxifen-resistant breast cancer cells in vitro. *Int J Clin Exp Med*. 2017;10(2):2660–2671.
69. Zhu J, Zou ZZ, Nie PP, et al. Downregulation of microRNA-27b-3p enhances tamoxifen resistance in breast cancer by increasing NR5A2 and CREB1 expression. *Cell Death Dis*. 2016;7.
70. Zhang P, Yang Y, Qian K, et al. A novel tumor suppressor ZBTB1 regulates tamoxifen resistance and aerobic glycolysis through suppressing HER2 expression in breast cancer. *J Biol Chem*. 2020;295(41):14140–14152.
71. Young J, Kawaguchi T, Yan L, Qi Q, Liu S, Takabe K. Tamoxifen sensitivity-related microRNA-342 is a useful biomarker for breast cancer survival. *Oncotarget*. 2017;8(59):99978–99989.
72. Elias D, Vever H, Lænkholm AV, et al. Gene expression profiling identifies FYN as an important molecule in tamoxifen resistance and a predictor of early recurrence in patients treated with endocrine therapy. *Oncogene*. 2015;34(15):1919–1927.
73. Eskiler GG, Cecener G, Dikmen G, Egeli U, Tunca B. Solid lipid nanoparticles: reversal of tamoxifen resistance in breast cancer. *Eur J Pharm Sci.*. 2018;120:73–88.