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Artigo de Revisão

Efficacy of triple-negative breast cancer treatments: a systematic review

Eficácia dos tratamentos do câncer de mama triplo negativo: uma revisão sistemática

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Abstract

Triple-negative breast cancer (TNBC) is a subtype caused by a mutation in the BRCA 1 gene, which is responsible for the components of DNA. In this histological type of cancer, estrogen, progesterone, and HER2 protein receptors are absent, making it very aggressive, with great metastatic potential and a lack of therapies, requiring surgical intervention and a neoadjuvant approach. In this way, the study aims to list and discuss the effectiveness of different treatments for triple-negative breast cancer. This is a systematic review of the effectiveness of treatments for triple-negative breast cancer. A search was carried out in the U.S National Library of Medicine (PubMed) database, with articles searched between 2018 and November 8, 2023, with the descriptors: ("triple-negative breast cancer" OR "triple-negative breast neoplasm") And treatment AND efficiency AND effectiveness. 203 studies were gathered, 200 of which were excluded based on the exclusion criteria. Studies were analyzed resulting from the predictions of the use of SWE images and their effect on TNBC, in addition to the efficacy and prognosis of neoadjuvant chemotherapy (NAC) in conjunction with breast-conserving surgery, as well as the creation of an evaluative measurement index of the efficacy of neoadjuvant systemic therapy. Considering the analysis of these studies, the transition to breast-conserving surgery combined with NAC represents the best strategy, with superior operational results. However, there is a need for more in-depth evaluations regarding research in TNBC treatment.

Keywords: Triple-negative breast cancer; Treatment. Efficacy.

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Resumo

O câncer de mama triplo negativo (TNBC) é um subtipo caracterizado pela mutação no gene BRCA 1, o qual é responsável pela reparação do DNA. Nesse tipo histológico de câncer, está ausente os receptores de estrogênio, progesterona e da proteína HER2, o tornando bastante agressivo, com grande potencial metastático e com uma escassez de terapias, sendo necessária intervenção cirúrgica e a abordagem neoadjuvante. Dessa forma, o estudo visa elencar e discutir a eficácia dos diferentes tratamentos para o câncer de mama triplo negativo. Trata-se de uma revisão sistemática acerca da eficácia dos tratamentos do câncer de mama triplo negativo. Realizou-se uma busca na base de dados do U.S National Library of Medicine (PubMed), sendo pesquisados artigos entre 2018 e 08 de novembro de 2023, com os descritores: ("triple-negative breast cancer" OR "triple-negative breast neoplasm") AND treatment AND efficiency AND Efficacy. Foram reunidos 203 estudos, sendo excluídos 200 a partir dos critérios de exclusão. Analisou-se estudos envolvendo a viabilidade do uso de imagens de SWE e seu efeito no TNBC, além da eficácia e do prognóstico da quimioterapia neoadjuvante (NAC) em conjunto com a cirurgia conservadora de mama, como também a criação de um índice avaliativo de medição da eficácia da terapia sistêmica neoadjuvante. Considerando a análise desses estudos, a transição para a cirurgia conservadora de mama combinada à NAC representa a melhor estratégia, com resultados operatórios superiores, embora exista a necessidade de avaliações mais aprofundadas com relação às pesquisas no campo de tratamento do TNBC.

Palavras-chave: Câncer de mama triplo negativo; Tratamento. Eficácia.

INTRODUCTION

Breast cancer is a malignant neoplasm characterized by uncontrolled and atypical growth of breast cells, recognized as the most prevalent type of cancer in females globally (INCA, 2023). Among its risk factors are advanced age, often manifesting after 50 years, belonging to the non-Hispanic white racial group, early menarche (before 12 years), late menopause (after 55 years), first pregnancy after 30 years, adoption of postmenopausal hormone replacement therapy, sedentary lifestyle, alcohol consumption, and family history (INCA, 2023). Additionally, breast cancer can be categorized based on the site of origin or the type of receptor mutation, such as triple-negative.

Triple-negative breast cancer (TNBC) is a subtype believed to be characterized by a mutation in the BRCA1 gene, responsible for DNA repair. Inactivation of this gene leads to uncontrolled proliferation of cancer cells, resulting in the absence of receptors for estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) (Abbas *et al*., 2021). This neoplasm is considered the most aggressive form of breast cancer, presenting a complicated prognosis due to its higher propensity for metastasis and invasion, complicating the treatment process (Abbas *et al*., 2021).

In this context, investigations into treatments for triple-negative breast cancer differ from therapeutic approaches for other subtypes of breast cancer, such as antiestrogenic and anti-HER2 therapy developed to inhibit receptors already absent in TNBC. As a result, non-hormonal treatments, including nonspecific chemotherapies, breast-conserving surgery, radical mastectomy, and immunotherapy, currently form the primary foundations of TNBC treatment, although the efficacy of these treatments is not fully established (Pinto, 2019).

In this scenario, it is observed that due to TNBC being a histological type of breast cancer lacking receptors for the most common forms of treatment, it impacts the search for the most effective therapeutic intervention, hindering the best prognosis for patients. Therefore, there is a

need for further studies on treatments for triple-negative breast cancer to discuss their efficiency and applicability, promoting a personalized approach based on the patient's cancer stage and their organism. The purpose of this review is to list and discuss the effectiveness of different treatments for triple-negative breast cancer.

METHOD

Search strategy

The U.S. National Library of Medicine (PubMed) was the database used, with articles searched up to November 8, 2023. The following keywords were employed in the search: ("triple-negative breast cancer" OR "triple-negative breast neoplasm") AND treatment AND efficiency AND efficacy, published between 2018 and 2023. The research question this study aimed to address was: “Which treatments are most effective for triple-negative breast cancer?”.

Selection criteria

The selection criteria included texts addressing the effectiveness and efficiency of treatments for triple-negative breast cancer. The inclusion criteria were:

a) Treatment of triple-negative breast cancer at all stages;

b) In vivo tests on diagnosed female individuals.

The inclusion criteria were:

b) In vitro and in vivo tests on animals;

c) All studies that do not qualify as cross-sectional, cohort, or case-control studies.

Identification and selection of studies

The titles, abstracts, and summarization were initially read using the PICO strategy for the pre-selected studies, aiming to identify literature that met the inclusion criteria. In the second stage, full-text articles were read, employing the same selection process as in the initial screening.

Data extraction

In the data collection process, the extracted characteristics included: journal title, year of publication, author names, study objective, study type, methodological aspects, key results, and conclusions. Finally, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were followed for the execution of this systematic review.

RESULTS AND DISCUSSION

Of the 203 studies gathered through the search strategy, 106 were selected for complete in-depth reading. After the reading, 103 articles were excluded for not aligning with the research question and/or differing from the methodological design adopted in this manuscript. Table 1 provides the classification of the initial 203 texts according to the inclusion and exclusion criteria. Subsequently, Table 2 describes the 3 selected texts for the article, explaining the focus, objective, and sample characteristics.

EXHIBITS

Table 1- Classification of texts identified in the first search in the database, according to inclusion and exclusion criteria (continue)

	TITLE	INCLUSION	EXCLUSION
1	Triple Negative Breast Cancer: A Review of Present and Future Diagnostic ModalitiesTriple Negative Breast Cancer: A Review of Present and Future Diagnostic Modalities		d
2	Multienzyme-like Reactivity Cooperatively Impairs Glutathione Peroxidase 4 and Ferroptosis Suppressor Protein 1 Pathways in Triple-Negative Breast Cancer for Sensitized Ferroptosis Therapy		**c**
3	The pathways related to glutamine metabolism, glutamine inhibitors and their implication for improving the efficiency of chemotherapy in triple-negative breast cancer		**c**
4	Optimizing cisplatin delivery to triple-negative breast cancer through novel EGFR aptamer-conjugated polymeric nanovectors		**c**
5	Subtyping-based platform guides precision medicine for heavily pretreated metastatic triple-negative breast cancer: The FUTURE phase II umbrella clinical trial		**c**
6	Pathogenesis and Potential Therapeutic Targets for Triple-Negative Breast Cancer		**c**
7	Targeting Glucose Metabolism to Overcome Resistance to Anticancer Chemotherapy in Breast Cancer		**c**
8	Metal-Polyphenol-Network Coated Prussian Blue Nanoparticles for Synergistic Ferroptosis and Apoptosis via Triggered GPX4 Inhibition and Concurrent In Situ Bleomycin Toxification		**c**
9	Effective Triple-Negative Breast Cancer Targeted Treatment Using iRGD-Modified RBC Membrane-Camouflaged Nanoparticles		**c**
10	An Injectable Epigenetic Autophagic Modulatory Hydrogel for Boosting Umbilical Cord Blood NK Cell Therapy Prevents Postsurgical Relapse of Triple-Negative Breast Cancer		**c**
11	Triple-negative breast cancer treatment in xenograft models by bifunctional nanoprobes combined to photodynamic therapy		**c**
12	Single-cell RNA-sequencing uncovers compound kushen injection synergistically improves the efficacy of chemotherapy by modulating the tumor environment of breast cancer Cancer		**c**
13	Vaccines for Triple-Negative Breast Cancer: A Systematic Review		**d**
14	Biomimetic nanoparticles drive the mechanism understanding of shear-wave elasticity stiffness in triple negative breast cancers to predict clinical treatment	**a**	
15	Targeted treatment of triple-negative-breast cancer through pH-triggered tumour associated macrophages using smart theranostic nanoformulations		**c**

EXHIBITS

Table 1- Classification of texts identified in the first search in the database, according to inclusion and exclusion criteria (continuation)

	TITLE	INCLUSION	EXCLUSION
16	Enhanced Killing of Triple-Negative Breast Cancer Cells by Reassortant Reovirus and Topoisomerase Inhibitors		**c**
17	Epigenetic Regulation of Immunotherapy Response in Triple-Negative Breast Cancer		**c**
18	Doxorubicin Conjugation to Reovirus Improves Oncolytic Efficacy in Triple-Negative Breast Cancer		**c**
19	Fabrication of Ginsenoside-Based Nanodrugs for Enhanced Antitumor Efficacy on Triple-Negative Breast Cancer		**c**
20	Nanomaterial-assisted CRISPR gene-engineering - A hallmark for triple-negative breast cancer therapeutics advancement		**c**
21	Comparative efficacy and safety of first-line neoadjuvant treatments in triple-negative breast cancer: systematic review and network meta-analysis		**d**
22	Cascade Release Nanocarriers for the Triple-Negative Breast Cancer Near-Infrared Imaging and Photothermal-Chemo Synergistic Therapy		**c**
23	Peptide-functionalized therapeutic nanoplatform for treatment orthotopic triple negative breast cancer and bone metastasis		**c**
24	Antitumor efficacy of the Runx2-dendritic cell vaccine in triple-negative breast cancer in vitro		**c**
25	Validation of Dual-Action Chemo-Radio-Labeled Nanocarriers with High Efficacy against Triple-Negative Breast Cancer		**c**
26	Targeting triple-negative breast cancer with an aptamer-functionalized nanoformulation: a synergistic treatment that combines photodynamic and bioreductive therapies		**c**
27	Mechanism-Based Sonodynamic-Chemo Combinations against Triple-Negative Breast Cancer		**c**
28	Breast-Conserving Surgery in Triple-Negative Breast Cancer: A Retrospective Cohort Study	**b**	
29	Ginsenoside Rg3 nanoparticles with permeation enhancing based chitosan derivatives were encapsulated with doxorubicin by thermosensitive hydrogel and anti-cancer evaluation of peritumoral hydrogel injection combined with PD-L1 antibody		**c**
30	Therapeutic efficacy and mechanism of CD73-TGFβ dual-blockade in a mouse model of triple-negative breast cancer		**c**
31	Detachable Liposomes Combined Immunochemotherapy for Enhanced Triple-Negative Breast Cancer Treatment through Reprogramming of Tumor-Associated Macrophages		**c**
32	Histone deacetylase inhibitor panobinostat in combination with rapamycin confers enhanced efficacy against triple-negative breast cancer		**c**
33	Optical imaging of the whole-body to cellular biodistribution of clinical-stage PEG-b-pHPMA-based core-crosslinked polymeric micelles		**c**
34	Therapeutic efficacy and cardioprotection of nucleolin-targeted doxorubicin-loaded ultrasound nanobubbles in treating triple-negative breast cancer		**c**
35	Improved Anti-Triple Negative Breast Cancer Effects of Docetaxel by RGD-Modified Lipid-Core Micelles		**c**
36	Molecularly Engineering Triptolide with Aptamers for High Specificity and Cytotoxicity for Triple-Negative Breast Cancer		**c**
37	HC-1119, a deuterated Enzalutamide, inhibits Migration, Invasion and Metastasis of the AR-positive triple-negative breast Cancer cells		**c**

EXHIBITS

Table 1- Classification of texts identified in the first search in the database, according to inclusion and exclusion criteria (continuation)

	TITLE	INCLUSION	EXCLUSION
38	Encapsulating Halofuginone Hydrobromide in TPGS Polymeric Micelles Enhances Efficacy Against Triple-Negative Breast Cancer Cells		**c**
39	LHRH-Targeted Redox-Responsive Crosslinked Micelles Impart Selective Drug Delivery and Effective Chemotherapy in Triple-Negative Breast Cancer	**a**	
40	Efficacy of fluvastatin and aspirin for prevention of hormonally insensitive breast cancer		**c**
41	HDAC Inhibitors Enhance Efficacy of the Oncolytic Adenoviruses AdΔΔ and Ad-3Δ-A20T in Pancreatic and Triple-Negative Breast Cancer Models		**c**
42	Discovery of novel PARP/PI3K dual inhibitors with high efficiency against BRCA-proficient triple negative breast cancer		**c**
43	Ratiometric co-delivery of doxorubicin and paclitaxel prodrug by remote-loading liposomes for the treatment of triple-negative breast cancer		**c**
44	Self-Assembled Fluorosome-Polydopamine Complex for Efficient Tumor Targeting and Commingled Photodynamic/Photothermal Therapy of Triple-Negative Breast Cancer		**c**
45	Trojan-Like Peptide Drug Conjugate Design and Construction for Application in Treatment of Triple-Negative Breast Cancer		**c**
46	Tumor-targeted molybdenum disulfide@barium titanate core-shell nanomedicine for dual photothermal and chemotherapy of triple-negative breast cancer cells		**c**
47	NIR diagnostic imaging of triple-negative breast cancer and its lymph node metastasis for high-efficiency hypoxia-activated multimodal therapy		**c**
48	An Orally Available Tubulin Inhibitor, VERU-111, Suppresses Triple-Negative Breast Cancer Tumor Growth and Metastasis and Bypasses Taxane Resistance		**c**
49	Repurposing maduramicin as a novel anticancer and anti-metastasis agent for triple-negative breast cancer as enhanced by nanoemulsion		**c**
50	A DNA damage nanoamplifier for the chemotherapy of triple-negative breast cancer via DNA damage induction and repair blocking		**c**
51	Novel Dual-Mode NIR-II/MRI Nanoprobe Targeting PD-L1 Accurately Evaluates the Efficacy of Immunotherapy for Triple-Negative Breast Cancer		**c**
52	Cannabidiol loaded extracellular vesicles sensitize triple-negative breast cancer to doxorubicin in both in-vitro and in vivo models		**c**
53	Tumor targeted combination therapeutic system for the effective treatment of drug resistant triple negative breast cancer		**c**
54	Amphiphilic phosphorous dendron micelles co-deliver microRNA inhibitor and doxorubicin for augmented triple negative breast cancer therapy		**c**
55	A MCL-1-targeted photosensitizer to combat triple-negative breast cancer with enhanced photodynamic efficacy, sensitization to ROS-induced damage, and immune response		**c**
56	Novel Combination Therapy for Triple-Negative Breast Cancer based on an Intelligent Hollow Carbon Sphere		**c**
57	A Strategy to Fight against Triple-Negative Breast Cancer: pH-Responsive Hexahistidine-Metal Assemblies with High-Payload Drugs		**c**
58	Pegylated liposomal encapsulation improves the antitumor efficacy of combretastatin A4 in murine 4T1 triple-negative breast cancer model		**c**
59	Effect of Bicalutamide on the proliferation and invasion of human triple negative breast cancer MDA-MB-231 cells		**c**
60	Cerasomal Lovastatin Nanohybrids for Efficient Inhibition of Triple-Negative Breast Cancer Stem Cells To Improve Therapeutic Efficacy		**c**

EXHIBITS

Table 1- Classification of texts identified in the first search in the database, according to inclusion and exclusion criteria (continuation)

	TITLE	INCLUSION	EXCLUSION
61	Capecitabine Efficacy Is Correlated with TYMP and RB1 Expression in PDX Established from Triple-Negative Breast Cancers		**c**
62	A triple combination gemcitabine+romidepsin+cisplatin to effectively control triple-negative breast cancer tumor development, recurrence, and metastasis		**c**
63	Anticancer effect and safety of doxorubicin and nutraceutical sulforaphane liposomal formulation in triple-negative breast cancer (TNBC) animal model		**c**
64	Synergistic enhancement of apoptosis by coralyne and paclitaxel in combination on MDA-MB-231 a triple-negative breast cancer cell line		**c**
65	Selective Photo-Assisted Eradication of Triple-Negative Breast Cancer Cells through Aptamer Decoration of Doped Conjugated Polymer Nanoparticles		**c**
66	A review of immune checkpoint blockade in breast cancer		**d**
67	Engineering macrophage-derived exosomes for targeted chemotherapy of triple-negative breast cancer		**c**
68	Endogenous Akt Activity Promotes Virus Entry and Predicts Efficacy of Novel Chimeric Orthopoxvirus in Triple-Negative Breast Cancer		**c**
69	Polymeric graphene oxide nanoparticles loaded with doxorubicin for combined photothermal and chemotherapy in triple negative breast cancer		**c**
70	Innovative Betulin Nanosuspension exhibits enhanced anticancer activity in a Triple Negative Breast Cancer Cell line and Zebrafish angiogenesis model		**c**
71	NIR-laser-triggered gadolinium-doped carbon dots for magnetic resonance imaging, drug delivery and combined photothermal chemotherapy for triple negative breast cancer		**c**
72	Current State of Platinum Complexes for the Treatment of Advanced and Drug-Resistant Breast Cancers		**d**
73	Nanoparticles Loaded with the BET Inhibitor JQ1 Block the Growth of Triple Negative Breast Cancer Cells In Vitro and In Vivo		**c**
74	A Light-Triggered Mesenchymal Stem Cell Delivery System for Photoacoustic Imaging and Chemo-Photothermal Therapy of Triple Negative Breast Cancer		**c**
75	Transdermal delivery of brucine-encapsulated liposomes significantly enhances anti-tumor outcomes in treating triple-negative breast cancer		**c**
76	Engineering Diselenide-IR780 Homodimeric Nanoassemblies with Enhanced Photodynamic and Immunotherapeutic Effects for Triple-Negative Breast Cancer Treatment		**c**
77	Colchicine-Binding Site Agent CH-2-77 as a Potent Tubulin Inhibitor Suppressing Triple-Negative Breast Cancer		**c**
78	Mitochondria-Targeted Nanosystem Enhances Radio–Radiodynamic–Chemodynamic Therapy on Triple Negative Breast Cancer		**c**
79	ZD2-Engineered Gold Nanostar@Metal-Organic Framework Nanoprobes for T1-Weighted Magnetic Resonance Imaging and Photothermal Therapy Specifically Toward Triple-Negative Breast Cancer		**c**
80	Coaxial electrostatic spray-based preparation of localization missile liposomes on a microfluidic chip for targeted treatment of triple-negative breast cancer		**c**
81	Evaluation of methotrexate encapsulated polymeric nanocarrier for breast cancer treatment		**c**
82	Laser activatable nanographene colloids for chemo-photothermal combined gene therapy of triple-negative breast cancer		**c**
83	Design and Investigation of Core/Shell GQDs/hMSN Nanoparticles as an Enhanced Drug Delivery Platform in Triple-Negative Breast Cancer		**c**

EXHIBITS

Table 1- Classification of texts identified in the first search in the database, according to inclusion and exclusion criteria (continuation)

	TITLE	INCLUSION	EXCLUSION
84	Camptothesome Potentiates PD-L1 Immune Checkpoint Blockade for Improved Metastatic Triple-Negative Breast Cancer Immunochemotherapy		**c**
85	Novel delivery of sorafenib by natural killer cell-derived exosomes-enhanced apoptosis in triple-negative breast cancer		**c**
86	Formulation of a triple combination gemcitabine plus romidepsin + cisplatin regimen to efficaciously and safely control triple-negative breast cancer tumor development		**c**
87	Folate-Functionalized DNA Origami for Targeted Delivery of Doxorubicin to Triple-Negative Breast Cancer		**c**
88	Quercetin-loaded solid lipid nanoparticles exhibit antitumor activity and suppress the proliferation of triple-negative MDA-MB 231 breast cancer cells: implications for invasive breast cancer treatment		**c**
89	Effect of Cellular and Microenvironmental Multidrug Resistance on Tumor-Targeted Drug Delivery in Triple-Negative Breast cancer		**c**
90	Folic Acid Functionalized Diallyl Trisulfide-Solid Lipid Nanoparticles for Targeting Triple Negative Breast Cancer		**c**
91	Deep exploration of PARP inhibitors in breast cancer: monotherapy and combination therapy		**d**
92	Half-Chain Cetuximab Nanoconjugates Allow Multitarget Therapy of Triple Negative Breast Cancer		**c**
93	Formulation and in vitro evaluation of a siRNA delivery nanosystem decorated with gH625 peptide for triple negative breast cancer theranosis		**c**
94	Phenyl boronic acid-modified lipid nanocarriers of niclosamide for targeting triple-negative breast cancer		**c**
95	Ultrasound-targeted photodynamic and gene dual therapy for effectively inhibiting triple negative breast cancer by cationic porphyrin lipid microbubbles loaded with HIF1α-siRNA		**c**
96	Bio-nanocomplexes with autonomous O2 generation efficiently inhibit triple negative breast cancer through enhanced chemo-PDT		**c**
97	Rumex vesicarius L. boosts the effectiveness of sorafenib in triple-negative breast cancer by downregulating BCl2, mTOR, and JNK, and upregulating p21 expression		**c**
98	A Novel Nanoemulsion Formula for an Improved Delivery of a Thalidomide Analogue to Triple-Negative Breast Cancer; Synthesis, Formulation, Characterization and Molecular Studies		**c**
99	A MOF-Based Potent Ferroptosis Inducer for Enhanced Radiotherapy of Triple Negative Breast Cancer		**c**
100	Mimetic sHDL nanoparticles: A novel drug-delivery strategy to target triple-negative breast cancer		**c**
101	Synchronous targeted delivery of TGF-β siRNA to stromal and tumor cells elicits robust antitumor immunity against triple-negative breast cancer by comprehensively remodeling the tumor microenvironment		**c**
102	The programmed site-specific delivery of LY3200882 and PD-L1 siRNA boosts immunotherapy for triple-negative breast cancer by remodeling tumor microenvironment		**c**
103	Light-controllable charge-reversal nanoparticles with polyinosinic-polycytidylic acid for enhancing immunotherapy of triple negative breast cancer		**c**

EXHIBITS

Table 1- Classification of texts identified in the first search in the database, according to inclusion and exclusion criteria (continuation)

	TITLE	INCLUSION	EXCLUSION
104	Surfaceome analyses uncover CD98hc as an antibody drug-conjugate target in triple negative breast cancer		**c**
105	Targeting CXCL12-CXCR4 Signaling Enhances Immune Checkpoint Blockade Therapy Against Triple Negative Breast Cancer		**c**
106	Platinum-based adjuvant therapy was efficient for triple-negative breast cancer: a meta-analysis from randomized controlled trials		**d**
107	Enhanced bioreduction-responsive diselenide-based dimeric prodrug nanoparticles for triple negative breast cancer therapy		**c**
108	Downregulation of MCL-1 and upregulation of PUMA using mTOR inhibitors enhance antitumor efficacy of BH3 mimetics in triple-negative breast cancer		**c**
109	Mifepristone Derivative FZU-00,003 Suppresses Triple-negative Breast Cancer Cell Growth partially via miR-153-KLF5 axis		**c**
110	RAD6 inhibition enhances paclitaxel sensitivity of triple negative breast cancer cells by aggravating mitotic spindle damage		**c**
111	Calycosin inhibits triple-negative breast cancer progression through down-regulation of the novel estrogen receptor-α splice variant ER-α30-mediated PI3K/AKT signaling pathway		**c**
112	Improved delivery of miR-1296 loaded cationic nanoliposomes for effective suppression of triple negative breast cancer		**c**
113	Core-Shell-Satellite Nanomaces as Remotely Controlled Self-Fueling Fenton Reagents for Imaging-Guided Triple-Negative Breast Cancer-Specific Therapy		**c**
114	The anti-cancer effect of chitosan/resveratrol polymeric nanocomplex against triple-negative breast cancer; an in vitro assessment		**c**
115	Core-Shell Nanosystems for Self-Activated Drug-Gene Combinations against Triple-Negative Breast Cancer		**c**
116	Nanodroplet-enhanced sonodynamic therapy potentiates immune checkpoint blockade for systemic suppression of triple-negative breast cancer		**c**
117	Macrophage-Derived Extracellular Vesicles as Drug Delivery Systems for Triple Negative Breast Cancer (TNBC) Therapy		**c**
118	IR792-MCN@ZIF-8-PD-L1 siRNA drug delivery system enhances photothermal immunotherapy for triple-negative breast cancer under near-infrared laser irradiation		**c**
119	Chemotherapy drugs derived nanoparticles encapsulating mRNA encoding tumor suppressor proteins to treat triple-negative breast cancer		**c**
120	Inhibition of 6-Phosphogluconate Dehydrogenase Reverses Epirubicin Resistance Through Metabolic Reprograming in Triple-Negative Breast Cancer Cells		**c**
121	Chlorin e6-EGF conjugated gold nanoparticles as a nanomedicine based therapeutic agent for triple negative breast cancer		**c**
122	Hinokitiol-iron complex is a ferroptosis inducer to inhibit triple-negative breast tumor growth		**c**
123	Nanosensitizer-mediated augmentation of sonodynamic therapy efficacy and antitumor immunity		**c**
124	Dual drug loaded PLGA nanospheres for synergistic efficacy in breast cancer therapy		**c**
125	A rationally designed ICAM1 antibody drug conjugate eradicates late-stage and refractory triple-negative breast tumors in vivo		**c**

EXHIBITS

Table 1- Classification of texts identified in the first search in the database, according to inclusion and exclusion criteria (continuation)

	TITLE	INCLUSION	EXCLUSION
126	Anti-migratory Properties of Cryoprotective Isoliquiritigenin-zein Phosphatidylcholine Nanoparticles Prevent Triple-negative Breast Cancer through PI3K-mTOR and MMP2/9 Pathways		**c**
127	Smart drug delivery of p-Coumaric acid loaded aptamer conjugated starch nanoparticles for effective triple-negative breast cancer therapy		**c**
128	Erythrocyte membrane-camouflaged Prussian blue nanocomplexes for combinational therapy of triple-negative breast cancer		**c**
129	Combined NK Cell Therapy and Radiation Therapy Exhibit Long-Term Therapeutic and Antimetastatic Effects in a Human Triple Negative Breast Cancer Model		**c**
130	Photothermic therapy with cuttlefish ink-based nanoparticles in combination with anti-OX40 mAb achieve remission of triple-negative breast cancer		**c**
131	[Multi-center real world study of the efficacy and safety of albumin-bound paclitaxel in the treatment of advanced breast cancer]		**c**
132	Relaxin-encapsulated polymeric metformin nanoparticles remodel tumor immune microenvironment by reducing CAFs for efficient triple-negative breast cancer immunotherapy		**c**
133	Prolonged Local In Vivo Delivery of Stimuli-Responsive Nanogels That Rapidly Release Doxorubicin in Triple-Negative Breast Cancer Cells		**c**
134	Systemic Delivery of Tumor-Targeting siRNA Nanoparticles against an Oncogenic LncRNA Facilitates Effective Triple-Negative Breast Cancer Therapy		**c**
135	Neoadjuvant Therapy with Concurrent Docetaxel, Epirubicin, and Cyclophosphamide (TEC) in High-Risk HER2-Negative Breast Cancers		**c**
136	Auger Emitter Conjugated PARP Inhibitor for Therapy in Triple Negative Breast Cancers: A Comparative In-Vitro Study		**c**
137	A Synergistic Combination of Niclosamide and Doxorubicin as an Efficacious Therapy for All Clinical Subtypes of Breast Cancer		**c**
138	Effective in vitro delivery of paclitaxel by nanocargo of mesoporous polycaprolactone against triple negative breast cancer cells by minimalizing drug		**c**
139	Tellurium-driven maple leaf-shaped manganese nanotherapeutics reshape tumor microenvironment via chemical transition in situ to achieve highly efficient radioimmunotherapy of triple negative breast cancer		**c**
140	Discovery of Potent and Selective CDK9 Degraders for Targeting Transcription Regulation in Triple-Negative Breast Cancer	**c**	
141	Lysosome-targeting phenalenones as efficient type I/II photosensitizers for anticancer photodynamic therapy	**c**	
142	Self-activated arsenic manganite nanohybrids for visible and synergistic thermo/immuno-arsenotherapy	**c**	
143	Preclinical antitumor efficacy of senescence-inducing chemotherapy combined with a nanoSenolytic	**c**	
144	Improved chemotherapeutic efficacy against resistant human breast cancer cells with co-delivery of Docetaxel and Thymoquinone by Chitosan grafted lipid nanocapsules: Formulation optimization, in vitro and in vivo studies	**c**	
145	Rad51 Silencing with siRNA Delivered by Porous Silicon-Based Microparticle Enhances the Anti-Cancer Effect of Doxorubicin in Triple-Negative Breast Cancer	**c**	
146	Photochemical Internalization Using Natural Anticancer Drugs, Antimetabolites, and Nanoformulations: A Systematic Study against Breast and Pancreatic Cancer Cell Lines	**c**	

EXHIBITS

Table 1- Classification of texts identified in the first search in the database, according to inclusion and exclusion criteria (continuation)

	TITLE	INCLUSION	EXCLUSION
147	Multifunctional Theranostic Nanoparticles for Enhanced Tumor Targeted Imaging and Synergistic FUS/Chemotherapy on Murine 4T1 Breast Cancer Cell		**c**
148	Gold nanoplatform for near-infrared light-activated radio-photothermal gas therapy in breast cancer		**c**
149	Synergetic effects of thymoquinone-loaded porous PVPylated Fe3O4 nanostructures for efficient pH-dependent drug release and anticancer potential against triple-negative cancer cells		**c**
150	Synthetic Indolactam V Analogues as Inhibitors of PAR2-Induced Calcium Mobilization in Triple-Negative Breast Cancer Cells		**c**
151	Volume change rate before and after neoadjuvant systemic therapy of breast cancer is an efficacious evaluation index to predict pathological complete response	**a**	
152	Folic Acid-Functionalized Carbon Dot-Enabled Starvation Therapy in Synergism with Paclitaxel against Breast Cancer		**c**
153	Site-selective superassembly of biomimetic nanorobots enabling deep penetration into tumor with stiff stroma		**c**
154	A multifunctional nanodiamond-based nanoplatform for the enhanced mild-temperature photothermal/chemo combination therapy of triple negative breast cancer via an autophagy regulation strategy		**c**
155	Immunomodulator-Mediated Suppressive Tumor Immune Microenvironment Remodeling Nanoplatform for Enhanced Immuno/Chemo/Photothermal Combination Therapy of Triple Negative Breast Cancer		**c**
156	Noncanonical Cell Death Induction by Reassortant Reovirus		**c**
157	Design of PLGA nanoparticles for sustained release of hydroxyl-FK866 by microfluidics		**c**
158	Construction of an immune-related genes nomogram for the preoperative prediction of axillary lymph node metastasis in triple-negative breast cancer		**d**
159	Computational reactive-diffusive modeling for stratification and prognosis determination of patients with breast cancer receiving Olaparib		**d**
160	Smart Lipid-Polysaccharide Nanoparticles for Targeted Delivery of Doxorubicin to Breast Cancer Cells		**c**
161	Mito-Bomb': a novel mitochondria-targeting nanosystem for ferroptosis-boosted sonodynamic antitumor therapy		**C**
162	Restoration of p53 activity via intracellular protein delivery sensitizes triple negative breast cancer to anti-PD-1 immunotherapy		**C**
163	Mitochondria-anchoring self-assembled nanoparticles for multi-path energy depletion: A "nano bomb" in chemo-co-starvation therapy		**c**
164	Leveraging intracellular ALDH1A1 activity for selective cancer stem-like cell labeling and targeted treatment via in vivo click reaction		**c**
165	Effectiveness of a novel gene nanotherapy based on putrescine for cancer treatment		**c**
166	Enhancing Therapeutic Efficacy of Oncolytic Herpes Simplex Virus-1 with Integrin β1 Blocking Antibody OS2966		**c**
167	Enhancing TNBC Chemo-immunotherapy via combination reprogramming tumor immune microenvironment with Immunogenic Cell Death		**c**
168	Targeting bromodomain protein ANCCA/ATAD2 enhances the efficacy of DNA-damaging chemotherapy agents and radiation		**c**

EXHIBITS

Table 1- Classification of texts identified in the first search in the database, according to inclusion and exclusion criteria (continuation)

	TITLE	INCLUSION	EXCLUSION
169	Targeting of the Eukaryotic Translation Initiation Factor 4A Against Breast Cancer Stemness		**c**
170	Cell membrane-camouflaged liposomes for tumor cell-selective glycans engineering and imaging in vivo		**c**
171	Cyclic Peptide-Gadolinium Nanocomplexes as siRNA Delivery Tools		**c**
172	Passerini chemistries for synthesis of polymer pro-drug and polymersome drug delivery nanoparticles		**c**
173	Combined in vitro/in vivo genome-wide CRISPR screens in triple negative breast cancer identify cancer stemness regulators in paclitaxel resistance		**c**
174	All-natural-molecule, bioluminescent photodynamic therapy results in complete tumor regression and prevents metastasis		**c**
175	Melflufen, a peptide-conjugated alkylator, is an efficient anti-neo-plastic drug in breast cancer cell lines		**c**
176	Sensitizing Tumors to Immune Checkpoint Blockage via STING Agonists Delivered by Tumor-Penetrating Neutrophil Cytopharmaceuticals		**c**
177	Efficiently restoring the tumoricidal immunity against resistant malignancies via an immune nanomodulator		**c**
178	TRAIL-modified, doxorubicin-embedded periodic mesoporous organosilica nanoparticles for targeted drug delivery and efficient antitumor immunotherapy		**c**
179	The Streptococcus virulence protein PepO triggers anti-tumor immune responses by reprograming tumor-associated macrophages in a mouse triple negative breast cancer model		**c**
180	Sequential targeting biomimetic nano platform for enhanced mild photothermal therapy and chemotherapy of tumor		**c**
181	Dimeric Prodrug Self-Delivery Nanoparticles with Enhanced Drug Loading and Bioreduction Responsiveness for Targeted Cancer Therapy		**c**
182	Dual Roles of Metal-Organic Frameworks as Nanocarriers for miRNA Delivery and Adjuvants for Chemodynamic Therapy		
183	Engineered vitamin E-tethered non-immunogenic facial lipopeptide for developing improved siRNA based combination therapy against metastatic breast cancer		**c**
184	Investigating the Impact of Optimized Trans-Cinnamic Acid-Loaded PLGA Nanoparticles on Epithelial to Mesenchymal Transition in Breast Cancer		**c**
185	Development and Characterization of a Fucoidan-Based Drug Delivery System by Using Hydrophilic Anticancer Polysaccharides to Simultaneously Deliver Hydrophobic Anticancer Drugs		**c**
186	Purification and In Vitro Evaluation of an Anti-HER2 Affibody-Monomethyl Auristatin E Conjugate in HER2-Positive Cancer Cells		**c**
187	Lipid-polymer hybrid nanoparticle with cell-distinct drug release for treatment of stemness-derived resistant tumor		**c**
188	Candidate drugs associated with sensitivity of cancer cell lines with DLST amplification or high mRNA levels		**c**
189	Antifouling Dendrimer-Entrapped Copper Sulfide Nanoparticles Enable Photoacoustic Imaging-Guided Targeted Combination Therapy of Tumors and Tumor Metastasis		**c**
190	Gold Nanostar@Polyaniline Theranostic Agent with High Photothermal Conversion Efficiency for Photoacoustic Imaging-Guided Anticancer Phototherapy at a Low Dosage		**c**

EXHIBITS

Table 1- Classification of texts identified in the first search in the database, according to inclusion and exclusion criteria (conclusion)

	TITLE	INCLUSION	EXCLUSION
191	Heavy-Atom-Modulated Supramolecular Assembly Increases Antitumor Potency against Malignant Breast Tumors via Tunable Cooperativity		**c**
192	Development of BET inhibitors as potential treatments for cancer: A new carboline chemotype		**c**
193	Codelivery of Que and BCL-2 siRNA with Lipid-Copolymer Hybrid Nanocomplexes for Efficient Tumor Regression		**c**
194	Discovery and Optimization of Novel Hydrogen Peroxide Activated Aromatic Nitrogen Mustard Derivatives as Highly Potent Anticancer Agents		**c**
195	Transforming growth factor-β blockade modulates tumor mechanical microenvironments for enhanced antitumor efficacy of photodynamic therapy		**c**
196	Co-Delivery Nanomicelles for Potentiating TNBC Immunotherapy by Synergetically Reshaping CAFs-Mediated Tumor Stroma and Reprogramming Immunosuppressive Microenvironment		**c**
197	Hyaluronan nanogel co-loaded with chloroquine to enhance intracellular cisplatin delivery through lysosomal permeabilization and lysophagy inhibition		**c**
198	Self-propelled nanomotor reconstructs tumor microenvironment through synergistic hypoxia alleviation and glycolysis inhibition for promoted anti-metastasis		**c**
199	Platelet extracellular vesicles are efficient delivery vehicles of doxorubicin, an anti-cancer drug: preparation and in vitro characterization		**c**
200	Stromal depletion by TALEN-edited universal hypoimmunogenic FAP-CAR T cells enables infiltration and anti-tumor cytotoxicity of tumor antigen-targeted CAR-T immunotherapy		**c**
201	Highly Efficient Photothermal Therapy with Cell-Penetrating Peptide-Modified Bumpy Au Triangular Nanoprisms using Low Laser Power and Low Probe Dose		**c**
202	Presentation and Delivery of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand via Elongated Plant Viral Nanoparticle Enhances Antitumor Efficacy		**c**

In Study 1, a sample of 3 patient groups with breast cancer was used, divided between those who only underwent surgery and those who had undergone neoadjuvant therapy until surgical resection, before treatment or after resection, aiming to investigate the feasibility of using SWE images to predict their effect on TNBC. In Study 2, the efficacy and prognosis of neoadjuvant chemotherapy combined with breast-conserving surgery were analyzed in patients diagnosed with clinical stage I or II triple-negative cancer. Study 3 aimed to create an evaluative index to measure the effectiveness of neoadjuvant systemic therapy in patients with biopsy-confirmed invasive breast cancer.

Neoadjuvant therapy (NAC) involves therapeutic intervention for cancers with challenging prognoses, administered before definitive treatment to reduce tumor size, control, or possibly eliminate it, enabling less invasive surgical methods. Furthermore, NAC can be administered in the form of chemotherapy, hormone therapy, or targeted therapy, making cancer more susceptible to

conservative approaches. Among therapeutic modalities, the promising use of albumin-bound paclitaxel nanoparticle (NAB-P) stands out, recognized for its ability to eliminate and/or reduce cancer cells (Liu *et al*., 2023).

Table 2 - Articles included in the systematic review after a complete reading of the studies selected in the first stage of analysis

	TITLE	STUDY DESIGN	LOCAL	OBJECTIVE	SAMPLE CHARACTERISTICS
1	Biomimetic nanoparticles drive the mechanism understanding of shear-wave elasticity stiffness in triple negative breast cancers to predict clinical treatment	Retrospective cohort study	China	Investigation of the feasibility of using SWE imaging to predict the effect of neoadjuvant therapy for triple negative breast cancer.	Three groups of breast cancer patients: 1- Patients before treatment or after surgical resection. 2- Patients who only managed surgery. 3- Patients who had undergone neoadjuvant therapy until surgical resection.
2	Breast-Conserving Surgery in Triple-Negative Breast Cancer: A Retrospective Cohort Study	Retrospective cohort study	China	To evaluate the efficacy and prognosis of neoadjuvant chemotherapy (NAC) in conjunction with breast-conserving surgery (BCS) in the treatment of triple-negative breast cancer (TNBC).	Patients diagnosed with triple negative breast cancer who received treatment with neoadjuvant chemotherapy combined with breast-conserving surgery or modified radical mastectomy. Clinical stage was I or II.
3	Volume change rate before and after neoadjuvant systemic therapy of breast cancer is an efficacious evaluation index to predict pathological complete response	Retrospective cohort study	China	Create an assessment index to measure the effectiveness of neoadjuvant systemic therapy in breast cancer.	Patients with invasive breast cancer confirmed by biopsy.

Moreover, the use of neoadjuvant intervention in TNBC patients is supported by the distinctive characteristic of increased stiffness found in this type of tumor, as demonstrated by shear-wave elastography (SWE) (Chang *et al.*, 2022). Additionally, the presence of a more significant amount of fibrosis and expanded fibroblast activity in TNBC patients contribute to this stiffer characteristic, making SWE suitable for validating the efficacy of neoadjuvant therapy in this specific context (Chang *et al.*, 2022).

Modified radical mastectomy has traditionally been considered the standard approach in breast cancer treatment; however, breast-conserving surgery (BCS) combined with neoadjuvant therapy has become the preferred strategy due to its superior operative outcomes and reduced surgical complications (Liu *et al.*, 2023). However, there was no difference in distant metastasis, local recurrence, and overall survival, highlighting the need for further assessment of this outcome (Liu *et al.*, 2023).

According to the study, the expression of the nuclear Ki-67 protein tends to be a potential predictor of NAC efficacy, prognosis, and overall survival (OS) (Chen *et al.*, 2023). Moreover, high Ki-67 expression influences the choice and intensity of treatment, becoming a long-term predictor

of neoadjuvant chemotherapy in TNBC patients, especially when considering the higher tumor stiffness and the expression of this protein compared to non-TNBC patients (Chen *et al.*, 2023).

CONCLUSION

The study encompasses the effectiveness of different therapeutic methods used in the treatment of triple-negative breast cancer (TNBC). Neoadjuvant chemotherapy (NAC) is administered before definitive treatment, showing a significant reduction in tumor size, especially when shear-wave elastography is utilized. The transition to breast-conserving surgery combined with NAC represents the best strategy, with superior operative outcomes, although the need for more in-depth assessments is evidenced by the lack of significant differences in distant metastases. The expression of the Ki-67 protein emerges as a crucial predictor of NAC effectiveness, influencing the choice and intensity of treatment, especially in TNBC patients. Despite the findings of this review demonstrating significant therapeutic advancements, further exploration is required regarding research in the field of TNBC treatment.

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