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Polymeric Nanoparticles for Breast Cancer Therapy: A Comprehensive Review

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Abstract: Breast cancer is a leading death cause in women globally. Since therapeutic products do not yet approach the tumor tissue at adequate levels; therefore, nanoparticle-based chemotherapy has been explored nowadays. Implementing nanotechnology to the treatment of breast cancer renders chemotherapy very successful and efficacious but far less toxic. In this review article, literature about polymeric nanoparticles applications in breast cancer was retrieved from PubMed, ScienceDirect, and Google Scholar databases. This review paper briefly addresses molecular targets in breast cancer's pathophysiology, drawbacks of current therapies for breast cancer, and polymeric nanoparticles as an evolving breast cancer chemotherapy that includes benefits, critical characteristics, and passive and active tumor targeting via polymeric nanoparticles. An outline of progression in polymeric nanoparticles for breast cancer treatment reports in current publications; patents available and clinical trials conducted for breast cancer in the last few years have been reviewed briefly.

Keywords: breast cancer; chemotherapy; clinical trials; patents; polymeric nanoparticle; tumour targeting.

1. Introduction

Breast cancer is the most frequent carcinoma in females and a common cause of cancer-related mortality in women worldwide [1,2]. Chemotherapeutic agents, combined with radiation therapy and surgical intervention, constitute the first treatment option for breast cancer [3]. However, pharmacotherapy has been modified since medicinal products do not yet penetrate the tumor site at adequate levels, increasing systemic side effects, and reduced pharmacokinetics. The application of nanotechnology for breast cancer treatment makes chemotherapy more efficient and successful, and less harmful. Several types of cancers acquire multidrug resistance, which seems to be a critical reason for several chemotherapeutics categories' failure.

Consequently, over the past couple of years, different hybrid polymer nanoparticles have been designed to treat breast cancer. In recent years, nanoparticles have been designed for *in-vivo* cancer diagnostics, molecular biology screening of biological markers for tumors, and targeted medications delivery. Such nanotechnology-based strategies could be primarily used to treat various malignant conditions [4].

The literature was retrieved from databases like PubMed, Google Scholar, and ScienceDirect for this article's compilation. Patents regarding nanoparticles in the treatment of breast cancer have been collected from the WIPO. Clinical trials based related to breast cancer

have also been summarized in this review. The key terms utilized were ‘breast cancer’, ‘polymeric nanoparticles’, and ‘formulation for breast cancer’ in different combinations. This review article briefly discusses molecular targets in breast cancer pathophysiology, limitations of current breast cancer treatments, and polymeric nanoparticles as a promising technology designed for breast tumor treatment, which includes advantages, essential characteristics, and active and passive tumor targeting polymeric nanoparticles. An overview of polymeric nanoparticles' advancements for breast cancer therapy reported in recent publications, patents published, and clinical trials conducted related to breast cancer therapy in the last few years has been summarized.

2. Molecular Targets, Types, and Detection of Breast Cancer

The main molecular targets identified to be involved in the pathophysiology of breast cancer include estrogen receptor alpha (ERα) and epidermal growth factor-2 (ERBB-2). ERα is a steroid hormone receptor expressed in about 70% of cases of invasive breast cancers. It is a transcription factor which on activation through estrogen, stimulates oncogenic development pathways within breast cancer cells [5-11]. ERBB-2 is over-expressed in around 20% of breast cancers. Besides these, triple-negative breast cancer (TNBC) accounts for approximately 15% of all breast tumors. It has been characterized by a lack of activation of molecular targets such as estrogen and progesterone receptors or ERBB2 receptors. The different types of breast cancer and TNBC have been depicted in Figure 1 [12-19].

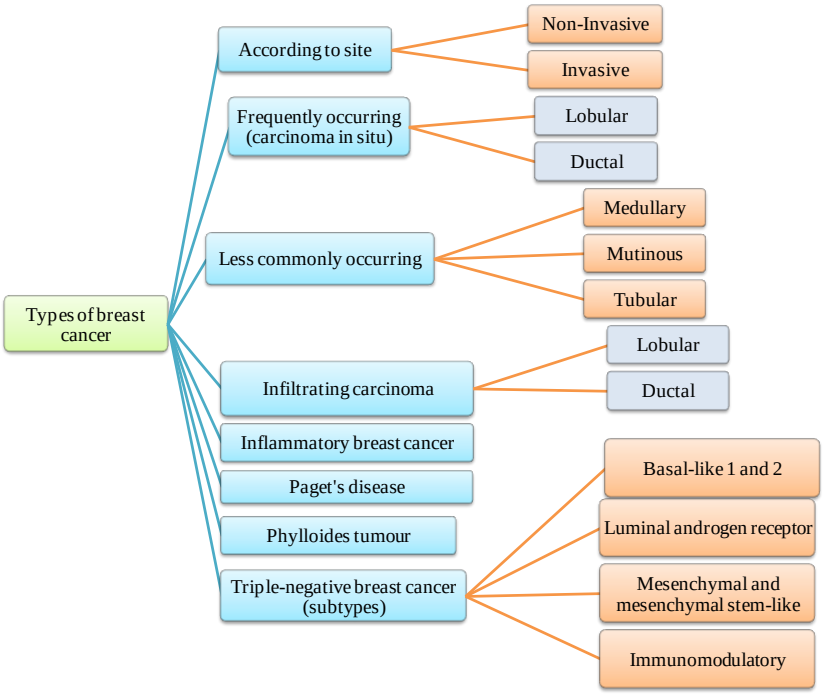

Figure 1. Types of breast cancer.

Basal-like-1 TNBC is characterized by a high response to DNA damage as well as Ki67 levels. The androgen receptor is abundantly expressed in the luminal androgen receptor, with an abundance 10-times stronger than the other subtypes. The mesenchymal stem-like TNBC is distinguished by elements that interact with G-protein receptors, calcium signaling, and EGFR. The immunomodulatory TNBC is attributed to the greater expression of STAT genes that control T and B-cells and natural killer cells. The techniques for breast cancer detection have been depicted in Figure 2 [20-30].

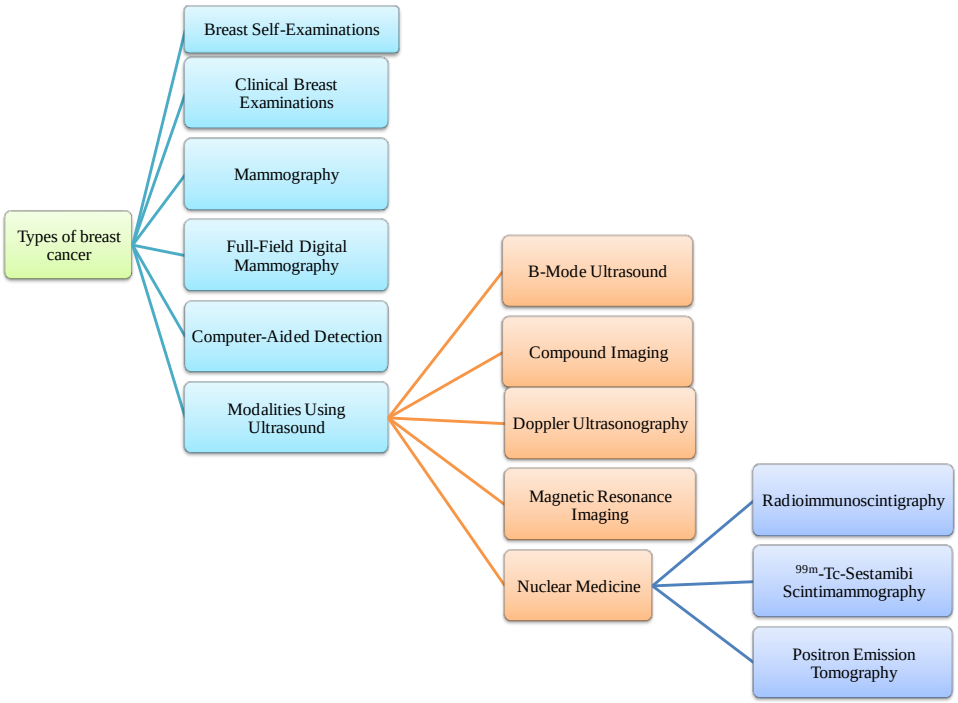

Figure 2. Technique for the detection of breast cancer.

3. Limitations of Current Breast Cancer Treatments

Existing treatment strategies have several shortcomings in the treatment of breast cancer, which includes lack of selective toxicity, which leads to diminished therapeutic efficacy and, as an outcome, the medical diagnosis being impaired; injury to healthy tissues and therefore, decreased doses of anticancer medicines are generally delivered to minimize toxicity to normal tissues; poor bio-distribution and drug penetration in solid tumors; heterogenic vessels in tumor sites increases extravasation of drugs. Current treatments tend greater drug deposition in normal viscera (10- to 20-fold greater) than that in a comparably loaded tumor site, and several chemotherapeutic agents are unable to permeate from the vasculature more than 40-50 mm (equivalent to the combined diameter of three to five cells) which could result in multiple drug resistance (MDR) and ultimately therapeutic failure. Furthermore, the development of MDR in tumor cells on treatment with one anticancer molecule could generate resistance to an entire range of drugs owing to over-expression of drug efflux proteins [31-34].

4. Polymeric Nanoparticle as an Emerging Technology for Breast Cancer Therapy

4.1. Advantages of polymeric nanoparticles.

Nanotechnology offers a more targeted stratagem for resolving conventional chemotherapies' shortcomings and may have great advantages for people living with cancer. Polymeric nanoparticles include several benefits against free drugs, such as drug safety against initial deterioration, increased drug permeability into a targeted tissue, controlled delivery of drug and augmented intracellular permeation, drug avoidance from preterm physiological interference, and diminished toxicity [35, 36].

4.2. Essential characteristics of polymeric biomaterials.

Biocompatible polymers must be employed to manufacture polymeric nanoparticles to acquire quick and effective clinical translation. Furthermore, these nanocarriers should be

surface functionalized to achieve extended biological circulation, least tendency to aggregation, and superior uptake efficiency in targeted tumor cells. The examples of polymers that could be utilized for the manufacturing of polymeric nanoparticles include poly-lactic-co-glycolic acid (PLGA), poly-lactic acid (PLA), polyethylene glycol (PEG), chitosan, alginate, and pectin [35, 36].

4.3. Active tumor targeting.

Targeting agents that could be conjugated over the surface of nanocarriers includes proteins, i.e., antibodies, peptides, aptamers, nucleic acids, small organic molecules, vitamins, and carbohydrates. The particular marker should be over-expressed on cancerous cells in comparison to healthy tissues, and targeting nanocarriers should have great selectivity to molecules that are distinctively expressed over the tumor cell's surface. When specific entities are being used to transmit nanocarriers to solid tumors, it's indeed vitally important that agents links to receptors specifically expressed on the target cells [37-42].

4.4. Passive targeting.

Passive targeting of circulating nanoparticles into tumor cells could be achieved through enhanced permeation and retention effect (EPR), which has been schematically represented in Figure 3 [37-42].

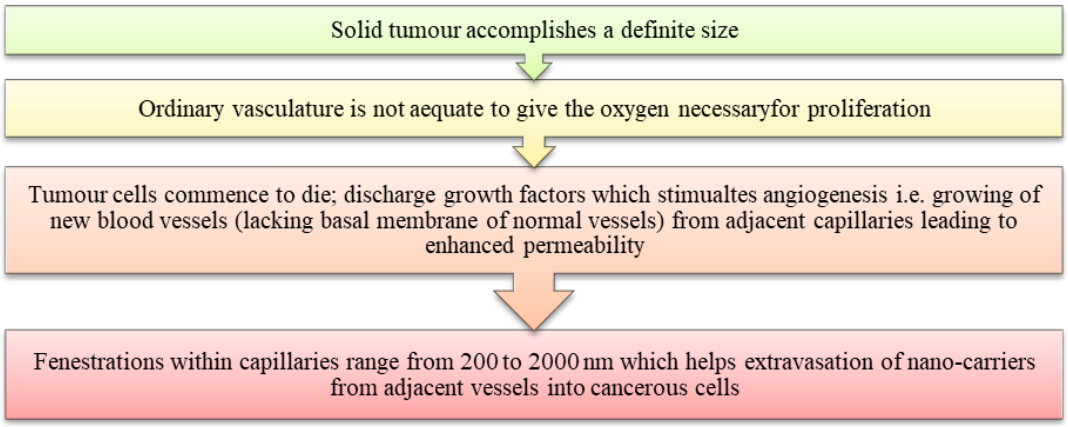

Figure 3. Passive tumor targeting via enhanced permeation and retention effect.

5. Recent Advancements in Nanotechnology-Based Formulation for Breast Cancer Therapeutics

Innovative nanotechnology approaches have become essential for dealing with challenging illness conditions. Consequently, the relevance of promising polymeric nanoparticles strategies like stealth, magnetic, conjugated, and hybrid nanoparticles for breast cancer therapy has become necessary currently. Table 1 summarizes the recent applications of polymeric nanoparticles for breast cancer chemotherapeutics. Table 2 recapitulates the current patents based on the relevance of nanoparticles in breast tumor management.

Table 1. Recent polymeric nanoparticles explored for breast cancer therapeutics.

Drug	Polymer/lipid	Preparation technique	Outcomes	Refs.
Doxorubicin	Poloxamer 407, holo-transferrin	Modified thin-film hydration	Overcome drug-resistant chemotherapy	[43]

Drug	Polymer/lipid	Preparation technique	Outcomes	Refs.
Doxorubicin	HPMA, GFLGKGLFG (peptide)	RAFT polymerization	Potential drug delivery vehicle for breast cancer	[44]
Erlotinib and Doxorubicin	N,N-Diisopropylethylamine, N-hydroxysuccinimide	Nano-precipitation	Enhanced therapeutic effects and sequential drug delivery	[45]
Tamoxifen	Pluronic F-68, Pluronic F-108, Poly-(ethylene oxide)-modified polycaprolactone	Solvent displacement	Preferential tumor-targeting and circulating drug reservoir	[46]
Paclitaxel	Polyethoxylated castor oil (Cremophor)	-	Treatment of patients with advanced breast cancer	[47]
Docetaxel	Triethylamine, PLGA, antibody-conjugated magnetic nanoparticles	Solvent evaporation	Showed sustained release; great affinity and ultra-sensitivity to cancer cell	[48]
Rapamycin, Piperine	PLGA	Nano-precipitation	Superior treatment of breast cancer via co-delivery	[49]
Rapamycin	PLGA	Single emulsion solvent evaporation	Drug targeted to epidermal growth factor receptor; efficient tumor selectivity	[50]
Danamycin	PLGA, N,N-dicyclohexyl-carbodiimide, triethylamine	Nano-precipitation	Folate receptor targeted	[51]
Curcumin	Bovine serum albumin	Desolvation	Treatment of breast cancer	[52]
Doxorubicin hydrochloride	PLGA 50:50	Double emulsion diffusion evaporation	Reduced cardio-toxicity	[53]
Salinomycin, Paclitaxel	PLGA	Emulsion solvent diffusion	Overcome cancer recurrence due to resistant cell population	[54]
AXT050 (collagen-IV derived bio-mimetic peptide)	PLGA-PEG nanoparticle	Emulsion method	Enhanced anticancer activity	[55]
Calcitriol	PLA	Nano-precipitation	Sustained and prolonged anticancer activity; Improved therapeutic efficiency	[56]
Paclitaxel	PLGA 50:50	Emulsion solvent diffusion evaporation	Efficacy enhancement in chemotherapy	[57]
Docetaxel	PLGA, PEG, super-paramagnetic iron oxide	Modified emulsion evaporation	Outstanding drug delivery strategy for breast cancer	[58]
Doxorubicin	Poly-(methacrylic acid), Polysorbate 80-grafted-Starch		Targeting brain metastases of breast cancer	[59]
Tamoxifen citrate	PLGA	Multiple emulsion solvent evaporation	Enhanced permeation into breast cancer cells	[60]
Paclitaxel-thymo-quinone		Single emulsion solvent evaporation	Dual drug therapy displayed superior anticancer activity and could alleviate the toxic effects of paclitaxel through dose reduction	[61]
Curcumin; doxorubicin (pH-sensitive)	PLGA, Polyethylene glycol, L-glutamic acid	Nano-precipitation	Potentially useful for refractory breast cancer	[62]
Taxols, Trastuzumab, Paclitaxel	PLGA, montmorillonite (Multi-functional nanoparticle)	Modified solvent extraction/ evaporation	Provides effective breast cancer therapy	[63]
Methotrexate, Curcumin	PLGA, Resomer		Treatment or control of cancer progression	[64]
Docetaxel	Poly-(L-g-glutamyl glutamine)	Nano-precipitation	Targeted, localized, and effective delivery in the tumor site	[65]
Docetaxel	Poly (ε-caprolactone), Pluronic F68	Modified solvent displacement	Potential therapy of breast cancer	[66]
Paclitaxel	5-methyl-2-(2,4,6-trimethoxyphenyl)-[1,3]-5-dioxanylmethyl methacrylate), (1,4-O-methacryloylhydroquinone)	Miniemulsion polymerization	Treatment of breast cancer	[67]
Rapamycin	Hyaluronic acid, CD44-tropic (ligand), 3-amino-4-methoxy-benzoic acid	Chemical reaction and conjugation	Localized, sustained, and controlled drug delivery to CD44-positive breast cancer cells	[68]
Paclitaxel	PLGA	Modified nano-precipitation	Breast cancer treatment	[69]
Docetaxel	Mannitol, poly-(D,L-lactide-co-glycolide)-D-α-tocopheryl polyethylene glycol 1000 succinate	Modified nano-precipitation	Breast cancer treatment	[70]
Paclitaxel, lapatinib	Pluronic F127	Thin-film hydration	Better therapy in drug resistant metastatic breast cancer	[71]
Paclitaxel	Polyvinylpyrrolidone, polyethyleneimine, poly(methyl vinyl ether-alt-maleic	Solvent evaporation	Improved drug delivery to cancer cells	[72]

Drug	Polymer/lipid	Preparation technique	Outcomes	Refs.
	hydrochloride), poly(allylamine hydrochloride), poloxamer 188			
Doxorubicin (Thiolated chitosan)	(N-acetyl cysteine-chitosan), (N-acetyl penicillamine-chitosan), ASOND	Gelation	Efficient drug delivery system	[73]
Baicalin	PLGA, Labrafil M2125 CS oil, Tween 80, Poloxamer P407	Nano-precipitation	Promising in potentiating anticancer activity	[74]
Tamoxifen	PLGA, poly(vinyl alcohol), polyvinyl-pyrrolidone, HER2-antibody (conjugation)	Double emulsion-solvent evaporation (multi-functional nanoparticle)	Improved efficiency; targeted and sustained delivery	[75]
Doxorubicin	Monophosphoryl lipid A, Thioketal cross-linker	Conjugation (ROS switchable nano-platform)	Good tumor-targeting; reduced systemic toxicity	[76]
Doxorubicin	Polyvinyl alcohol, PEG, polyvinylpyrrolidone	Chemical reduction (silver/polymeric dual nanoparticle)	Enhanced cytotoxic effect by combinatorial therapy	[77]
Vincristine sulfate	PLGA, PEG, folic acid (conjugation)	Emulsion solvent evaporation	Enhanced cellular uptake and higher cytotoxicity	[78]
Curcumin	N-isopropylacrylamide, Methacrylic acid	Polymerization	Breast cancer treatment	[79]
Simvastatin	Cholic acid, PLGA	Modified nano-precipitation	Breast cancer chemotherapy	[80]
Doxorubicin	Chitosan, Copper (II) Chloride, doxorubicin	Single reduction (pH sensitive coated copper oxide nanoparticle)	Showed pH-dependent drug release	[81]
Curcumin	Bovine serum albumin, polyethylene glycol	Desolvation	Improved efficacy for breast cancer	[82]
Cisplatin, paclitaxel	Poly(2-oxazoline)	Thin film	Improved chemotherapy of ovarian and breast cancer; potential for clinical translation	[83]
Chrysin-	PEG, PLGA		Promising in breast cancer therapy	[84]
Paclitaxel	Alginate	Nano-emulsification polymer cross-linking	Enhanced antitumor effects for breast cancer	[85]
Docetaxel Trastuzumab	Chitosan, D-α-tocopherol polyethylene glycol 1000 succinate	Modified solvent evaporation	Improved targeted drug delivery; less toxicity	[86]
Letrozole	Poly (D, L-Lactide)	Emulsion-solvent evaporation	Treatment of hormonally-positive breast cancer in postmenopausal women	[87]
Docetaxel	Human serum albumin	High-pressure homogenization	Promising as immuno-nanoparticle delivery for breast cancer	[88]
Paclitaxel	PLGA, hyaluronic acid (surface engineering)	o/w emulsion	Decreased IC50 of paclitaxel on triple-negative breast cancer cells	[89]
Methotrexate, Beta-carotene		Nano-precipitation (hybrid nanoparticle)	Treatment of Breast cancer	[90]
Doxorubicin [Folic acid and trastuzumab conjugated]	PEG, (Redox responsive random multi-block co-polymeric nanocarrier)	Nano-precipitation	Targeted drug delivery in cancer therapy	[91]
Anastrozole	Polycaprolactone, PEG, stearic acid	Direct emulsification solvent evaporation (hybrid nanoparticle)	Enhanced therapeutic activity	[92]
Docetaxel	H40 (dendritic polyester), poly-(D,L-lactide)	Modified nano-precipitation	Feasible for cancer treatment	[93]
Docetaxel	PLA, Labrafac CC	Emulsion diffusion (oily core polyester nanocapsule)	Controlled drug delivery	[94]
Simvastatin	PLGA	Nano spray drying (polymeric submicron particles)	Treatment of solid tumor	[95]
Thiolated nanoparticle	Gelatin, PEG		Utilized to target drugs/genes to solid tumors passively	[96]
Lapatinib ditosylate	Tocopheryl polyethylene glycol-1000 succinate, PLGA	Polymerization	Optimal therapeutic effect in breast cancer treatment	[97]
Nutlin-3a	PLGA	Single oil-in-water emulsion	Targeted drug delivery for breast cancer therapy	[98]
Doxorubicin 17-AAG	PEG-b-PGA copolymer, polypeptide-based nano-gel	Block ionomer complex	Synergistic combination overcomes drug's solubility issues	[99]
Thymo-quinone	PLGA, PEG, Pluronic F68	Solvent evaporation	Showed selective cytotoxic result toward UACC 732 compared to MCF-7 breast cancer cells	[100]

Drug	Polymer/lipid	Preparation technique	Outcomes	Refs.
Doxorubicin, GG918 (Elacridar)		Ultra-sonication	Simultaneous delivery with the superior treatment of multidrug-resistant breast cancer	[101]
Vinorelbine	PLGA, PEG, aptamer (bio-conjugate)	Emulsion/solvent evaporation	Targeted effect for breast cancer	[102]
Paclitaxel, (stealth nanoparticle)	Poly-(ethylene glycol)-block-poly(ε-caprolactone), soybean phosphatidylcholine, cholesterol	Thin film hydration	Improved drug accumulation at the target tumor site achieved via PEG modification	[103]
Docetaxel	PLGA (polymer hybrid nanoparticle)	Nano-precipitation	Advanced therapeutics to combat breast cancer	[104]
Doxorubicin	PLGA, lecithin, DSPE-PEG-2000 (Lipid-polymer hybrid nanoparticle)	Single-step modified nano-precipitation	Controlled drug (both hydrophilic/ lipophilic form) delivery	[105]
Docetaxel	Mono-methoxy-PEG-PLA	Thin-film hydration	Showed better antitumor efficacy in breast cancer therapy	[106]
Curcumin-	PLGA	Solvent evaporation	Improved bioavailability of curcumin for the treatment of severe malignant breast cancer	[107]
Curcumin	Chitosan, folic acid	-	Potential drug delivery for breast cancer therapy	[108]
Dasatinib	Poly(cyclohexene phthalate)	Nano-precipitation	Controlled drug delivery for breast cancer treatment	[109]

17-AAG: 17-allylaminodemethoxygeldanamycin; ASOND: antisense oligonucleotide; IC50: drug concentration which is required for 50% inhibition in-vitro; DSPE-PEG-2000: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000]; HPMA: N-(2-Hydroxypropyl) methacrylamide); PEG: polyethylene glycol; PLGA: Poly-(D,L-lactide-co-glycolide); PLA: Poly-(D,L-lactic acid), RAFT: reversible addition-fragmentation chain-transfer; ROS: reactive oxygen species.

Table 2. Recent patents based on the relevance of nanoparticles in breast cancer therapy.

Patent name	Patent number	Applicant	Year	Refs.
Liposomal curcumin for the treatment of cancer	WO/2004/080396	The University of Texas Md Anderson	2004	[110]
In vivo imaging and therapy with magnetic nanoparticles conjugates	WO/2007/021621	Board of supervisors of Louisiana state university and agricultural and mechanical college	2007	[111]
In-vivo imaging and therapy with magnetic nanoparticles conjugates	EP1912564	Univ Lousiana state	2008	[112]
Breast cancer therapy based on hormone receptors status with nanoparticles comprising a taxane	WO/2008/076373 CA2672618 EP2117520 US20100048499	Abraxis Bioscience, LLC	2008	[113] [114] [115] [116]
In-vivo imaging and therapy with magnetic nanoparticle conjugates	US20090169478	Board of supervisors of Louisiana state university	2009	[117]
Hydrogel nanoparticles used as injectable subcutaneous implant agent	CN101953775	Zhengzhou University	20111	[118]
Target cellular delivery nanoparticles	US20110077581	Georgia Tech Research Corporation	2011	[119]
Bioconjugation of calcium phosphosilicate nanoparticles for selective targeting of cells *in vivo*	WO/2011/057216	The Pennsylvania state research foundation	2011	[120]
All field simultaneous radiation therapy	US08173983	Sahadevan Velayudhan	2012	[121]
Specific detection method of human breast cancer cells MCF-7 based on surface-enhanced Raman spectroscopy	CN102608102	Nanjing Normal University	2012	[122]
Development and use of polymer nanoparticles comprising poly[epiloncaprolactone and doxorubicin	WO/2012/104461	Servicio Andaluz De Salud, Universidad De Granada	2012	[123]
NTS-polyplex nanoparticles system for gene therapy of cancer	WO/2012/107908	Centro De Investigación Y De Estudios Avanzados Del Instituto Politécnico Nacional	2012	[124]
Nano-gelatin encapsulated composition of glutathione reductase and lycopene	IN3233/CHE/2012	Mary Anne Preethe. K	2012	[125]
Tripterine nanostructure lipid carrier modified by lentiviral vector and appliance for preparing and treating	CN102670510	Jiangsu Provincial Academy of Traditional Chinese Medicine	2012	[126]

Patent name	Patent number	Applicant	Year	Refs.
prostatic cancer, lung cancer, and breast cancer drug				
Popcorn shape gold nanoparticles for targeted diagnosis, photothermal treatment, and in-situ monitoring therapy response for cancer and multiple drug resistance bacteria	US20120302940	Ray Paresh Chandra	2012	[127]
Immune-Stimulating photoactive hybrid nanoparticles	WO/2013/012628	University of Georgia Research Foundation, Inc.	2013	[128]
Breast cancer therapy based on hormone receptor status with nanoparticles comprising taxane	US20130280337	Abraxis BioScience, Lic.	2013	[129]
NTS-polyplex nanoparticles system for gene therapy of cancer	CN103458931	Ct Investig Y Estudios Del Ipn	2013	[130]
Methods of treating breast cancer using nanoparticles comprising taxane-based on hormone receptor status	JP2014080443	Abraxis BioScience, LLC	2014	[131]
Modular polymer hydrogel nanoparticles and methods of their manufacture	US20140220346	Memorial Sloan-Kettering Cancer Center Massachusetts Institute of Technology	2014	[132]
Immune-stimulating photoactive hybrid nanoparticles	US20140220143	University of Georgia Research Foundation, Inc.	2014	[133]
Methods for detecting single mismatches in DNA hybridization reaction using gold nanoparticles	KR1020140097679	Korea university research and business foundation	2014	[134]
Targeting modified gold nanorod targeted drug delivery compound and application of the delivery compound to antitumor photothermal therapy	CN104368000	Second Military Medical University, PLA	2015	[135]
Method used for detecting the content of adenosine triphosadenine in the breast cancer cell with the colorimetric biosensor and constructed based on gold nanoparticles	CN105717103	Nanjing Medical University	2016	[136]
Aptamer-modified gold nanoparticle-graphene composite material and preparation method and application thereof	CN105879027	Suzhou Institute of Nano-Tech and Nano-Bionics, Chinese Academy of Sciences	2016	[137]
Nanoparticle-assisted ultrasound for breast cancer therapy	US20150328485	Academia Sinica	2016	[138]
Fabrication method and application of cellulose membrane of a drug loading breast cancer- targeting magnetic nanoparticles	CN106310256	South china normal university	2017	[139]
A process of preparing efficient herbal nanoparticles of solasodine for breast cancer	IN781/KOL/2015.	Sarthak Bhattacharya		[140]
Methods and compositions for assaying blood levels of legumain	US20170089909	Xiaohong Yu Fang Guo	2017	[141]
Methods and compositions for assaying blood levels of legumain	US20170089910	Xiaohong Yu Ningbo ziyuan medical devices Inc.	2017	[142]
Preparation method and application of photosensitive magnetic nanoparticles system capable of inhibiting the growth of breast cancer cells	CN106668871	South China Normal University		[143]
Combination therapy comprising nanoparticles of a taxane and albumin with abt-263 in methods for treating cancer	US20170202782	Abraxis BioScience, LLC	2017	[144]
Hyaluronic acid-based nanoparticles as biosensors for imaging-guided surgery and drug delivery vehicles and methods associated therewith	US20170202982	Wake Forest University	2017	[145]
An anticancer compound	US201741022701	Sree Balaji Medical College & Hospital, Biher- Bharath University	2017	[146]

Patent name	Patent number	Applicant	Year	Refs.
Application of N-fullerene amino acid derivative nanoparticles to the preparation of medicine for treating tumor under illumination condition and medicine	CN107551272	Beijing Funakang Biotechnology Ltd	2017	[147]
Nanoparticles silica gel capable of being used as an injectable subcutaneous implant.	CN107595768	Chengdu Angduo Biotechnology Co., Ltd	2018	[148]
Test support method for supporting the prediction of complete pathological response (PCR) using fluorescent nanoparticles	EP3321682	Konica Minolta Inc	2018	[149]
Electrochemical detection method for stem cells	CN108088882.	China Stem Cell Group Shanghai Biotechnology Co., Ltd.	2018	[150]
Polypeptide for promoting apoptosis of breast cancer cells by targeted uptake of siRNA	CN108117585	Hefei Novel Gene Technology Service Co., Ltd	2018	[151]
Multifunctional RNA nanoparticles and methods for treating cancer and therapeutic resistant cancer	WO/2018/106992	University of Cincinnati	2018	[152]
Therapeutic cationic peptides and unimolecular nanoparticles for efficient delivery thereof	US20180235897	Wisconsin Alumni Research Foundation	2018	[153]
Hyaluronic acid-decorated thymoquinone-loaded Pluronic® P123-F127 mixed polymer nanoparticles as targeted therapy against triple-negative breast cancer	IN201831021395	Adhikary, Arghya	2018	[154]
Specific targeted breast cancer cell mesoporous silicon nanometer drug loading system and preparation method thereof	CN108671236.	Maanshan People's Hospital	2018	[155]
Keratin based nanobiocomposite for cancer cell targeting and imaging	IN201741017595	C.Vijayalakshmi, R.Srinivasan, Venkatesan	2018	[156]
Preparing of polyethyleneimine modified photosensitizer-carried Prussia blue magnetic nanoparticles	CN108904803	Southwest University	2018	[157]
Silk fibroin-based nanodrug for targeted combined chemotherapy of breast cancer, and preparation method thereof	CN108926567	Southwest University	2018	[158]
Gold nanoparticles and synthetic method thereof.	CN109047791	Henan University	2018	[159]
Methods and compositions for assaying blood levels of Legumain.	20190011451	Ningbo Ziyuan Medical Devices Inc	2019	[160]
HER2-targeted phase-change PLGA nanoparticles, application and preparation method thereof	CN109172829	Chongqing Medical University	2019	[161]
Osteotropic nanoparticles for prevention or treatment of bone metastases	US20190022235	Paul N. Durfee; Charles Jeffrey Brinker; Yu-shen Lin; Hon Leong	2019	[162]
Hyaluronic acid appended PEG-PLGA coated quarternized mesoporous Silica nanoparticles for delivery of Mirnas in TNBC	IN201931006560	Adhikary, Arghya	2019	[163]
Near-infrared responsive nano-composite supramolecular hydrogel and preparation method thereof.	CN109503862	Tianjin University	2019	[164]
Application of nanogold-based composite supermolecular hydrogel as a biomedical material	CN109504648	Tianjin University	2019	[165]
Method and system for synthesizing "green" biocompatible organic-inorganic hybrid electrospun nanofibers for potential biomedical applications	IN201741034940	Kanapathy Gopalakrishnan	2019	[166]
Development of engineered gold nanoparticles for high contrast imaging of tumor in x-ray	IN201741038811	Selvamani Vijayakumar	2019	[167]

Patent name	Patent number	Applicant	Year	Refs.
photography and pharmacokinetic studies in vivo				
Improved pharmaceutical compositions of docetaxel polymeric nanoparticles and preparations thereof	IN201711038532	Department of Pharmaceutical Engineering &Technology	2019	[168]
Macrophages membrane coated breast cancer targeted nanoparticles and preparation method thereof	CN109953972	Fudan University	2019	[169]
ROS-sensitive tumor-targeted gene delivery system and preparation method thereof	CN109985249	Fudan University	2019	[170]
Preparation method of quercetin nanoparticles and application of quercetin nanoparticles in preparing a drug for resisting breast cancer	CN109999002	Fuzhou University	2019	[171]
Pullulan nanoparticles with co-supported lovastatin and doxorubicin and preparation method thereof.	CN110201181	Hunan Normal University	2019	[172]
Preparation and application of nanoparticle doped RNA hydrogel for targeted triple-negative breast cancer	CN110327464.	Linyi University	2019	[173]
Novel RGD-chitosan oligosaccharide silicon oxide/BCSG1-siRNA nanoparticle breast cancer targeted therapy method	CN110339372	Henan Cancer Hospital	2019	[174]
Decreased adhesivity receptor-targeted nanoparticles for Fn14-positive tumors	US20190328677	University of Maryland, Baltimor	2019	[175]
Preparation and application of nano-immunological preparation based on porous calcium carbonate	CN110420335	Shandong Normal University	2019	[176]
Multifunctional RNA nanoparticles and methods for treating cancer and therapeutic resistant cancer	US20190351067	University of Cincinnati	2019	[177]
Fructose and RGD peptide co-modified dual-targeting triple-negative breast cancer lipid material	CN110522923	Sichuan University., assignee. Fructose	2019	[178]
Green synthesis of gold nanoparticles using fruit extracts-bael fruit, eugenia jambolana, and sours	IN201741038806.	Selvamani Vijayakumar	2019	[179]
Lipid Nanoparticles Loaded with Ceranib-2 as Anticancer Agent.	WO/2020/018049.	Invokat Intellectual Property Services	2020	[180]
Gold nanoparticle-ligand conjugates and methods of use	WO/2020/041267.	University of Okalahoma	2020	[181]
Preparation and application of breast cancer targeted liposome modified by biotin and glucose	CN110840844	Sichuan University	2020	[182]
Preparation method of CPZ-coupled MS2 protein nanoparticles and application thereof in breast cancer resistance	CN110841073	Fuzhou University	2020	[183]
Application of copper-palladium alloy nanoparticles and autophagy inhibitors in preparing tumor-killing drugs or kits based on photothermal effects	CN110893237	South China University of Technology	2020	[184]
Preparation and application of multi-branch biotin modified breast cancer targeted liposomes.	CN110917139	Sichuan University	2020	[185]
Calcium phosphate-lipid nano-drug co-delivery system consisting of low molecular weight heparin and prodrug of natural drug	CN110960507	Fudan University	2020	[186]

Patent name	Patent number	Applicant	Year	Refs.
Adriamycin-indocyanine green bionic nanoparticles and application thereof	CN111000822	Shenyang Pharmaceutical University	2020	[187]
Use of mutant P53 gene-targeted lead borate nanoparticles in cancer treatment and production method of these nanoparticles	WO/2020/086014	Yeditepe University	2020	[188]
Ph-Activated nanoparticles	WO/2020/092602	Ohio State Innovation Foundation	2020	[189]
A formulation and evaluation of the peptide Hif9 loaded chitosan nanoparticles	IN202041013943	Manimaran, D.; N Elangovan.; Jagatheeh, K	2020	[190]
Targeted nanoparticles for glioblastoma theranostics	US20200206144	Lauren Lukas VanderSpek	2020	[191]
Therapeutic cationic peptides and unimolecular nanoparticles for efficient delivery thereof	US20200276130	Wisconsin Alumni Research Foundation	2020	[192]

6. Clinical Trials of Nanotechnology-Based Formulation for Breast Cancer Therapeutics

The outlook of the nano-medicine industry for cancer therapy is quite optimistic. It is well known and scientifically illustrated that such formulations tend to augment anticancer medicines drugs' efficacy to facilitate specific selective drug delivery. Table 3 outlines clinical trials involving the study of nano-formulations for the treatment of breast cancer.

Table 3. Recent clinical trials conducted for breast cancer therapeutics.

Study Title	Sponsor	NCT No.	Phase	Refs.
A clinical trial to study the effects of nanoparticles-based paclitaxel drug, which does not contain the solvent cremophor, in advanced breast cancer	Fresenius Kabi Oncology Ltd.	NCT00915369	Phase 1	[193]
Bevacizumab, doxorubicin, and cyclophosphamide followed by paclitaxel albumin-stabilized nanoparticles formulation and bevacizumab in treating patients who have undergone surgery for early-stage breast cancer	Memorial Sloan Kettering Cancer Center	NCT00436709	NA	[194]
Paclitaxel albumin-stabilized nanoparticles formulation in treating patients of different ages with metastatic breast cancer	City of Hope Medical Center	NCT00609791	Phase 2	[195]
Targeted biopsy of carbon nanoparticles labeled axillary node for cn+ breast cancer	The First Affiliated Hospital with Nanjing Medical University	NCT04482803	NA	[196]
Nanoparticles Albumin-Bound (Nab) Paclitaxel/Cyclophosphamide in Early-Stage Breast Cancer	SCRI Development Innovations, LLC	NCT00629499	Phase 2	[197]
Topical Fluorescent Nanoparticles Conjugated Somatostatin Analog for Suppression and Bioimaging Breast Cancer	Al-Azhar University	NCT04138342	Phase 1	[198]
An early-phase study of abraxane combined with phenelzine sulfate in patients with metastatic or advanced breast cancer (epi-primed)	EpiAxis Therapeutics	NCT03505528	Phase 1	[199]
Carboplatin and nab-paclitaxel with or without vorinostat in treating women with newly diagnosed operable breast cancer	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	NCT00616967	Phase 2	[200]
Doxorubicin hydrochloride, cyclophosphamide, and filgrastim followed by paclitaxel albumin-stabilized nanoparticles formulation with or without trastuzumab in treating patients with breast cancer previously treated with surgery	University of Washington	NCT00407888	Phase 2	[201]
Nab-paclitaxel and bevacizumab followed by bevacizumab and erlotinib in metastatic breast cancer	University of Washington	NCT00733408	Phase 2	[202]

Study Title	Sponsor	NCT No.	Phase	Refs.
A study to evaluate safety/tolerability of immunotherapy combinations in participants with triple-negative breast cancer or gynecologic malignancies	Arcus Biosciences, Inc.	NCT03719326	Phase 1	[203]
Carboplatin+Nab-paclitaxel, Plus Trastuzumab (HER2+) or Bevacizumab (HER2-) in the Neoadjuvant Setting	University of California, Irvine	NCT00618657	Phase 2	[204]
Targeted silica nanoparticles for real-time image-guided intraoperative mapping of nodal metastases	Memorial Sloan Kettering Cancer Center	NCT02106598	Phase 1 Phase 2	[205]
Schedules of nab-paclitaxel in metastatic breast cancer (snap)	International Breast Cancer Study Group	NCT01746225	Phase 2	[206]
Phase II lapatinib plus nab-paclitaxel as first and second-line therapy in her2+ mbc	Novartis Pharmaceuticals	NCT00709761	Phase 2	[207]
Neoadjuvant pembrolizumab(pbr)/nab-paclitaxel followed by pbr/epirubicin/cyclophosphamide in tnbc (nib)	Institut fuer Frauengesundheit	NCT03289819	Phase 2	[208]
Nanoparticles albumin-bound rapamycin in treating patients with advanced cancer with mtor mutations	Mayo Clinic	NCT02646319	Early Phase 1	[209]
Nab-paclitaxel and alpelisib for the treatment of anthracycline refractory triple-negative breast cancer with pik3ca or pten alterations	M.D. Anderson Cancer Center	NCT04216472	Phase 2	[210]
Cryoablation, atezolizumab/nab-paclitaxel for locally advanced or metastatic triple-negative breast cancer	Mayo Clinic	NCT04249167	Early Phase 1	[211]
Nab-paclitaxel and durvalumab with or without neoantigen vaccine in treating patients with metastatic triple-negative breast cancer	National Cancer Institute (NCI)	NCT03606967	Phase 2	[212]
Study to evaluate cort125134 in combination with nab-paclitaxel in patients with solid tumors	Corcept Therapeutics	NCT02762981	Phase 1 Phase 2	[213]

7. Conclusions

Conventional chemotherapy approaches have numerous drawbacks like lack of selective toxicity, damage to normal tissues, poor bio-distribution and drug penetration, and the tendency of greater drug deposition in normal viscera. Polymeric nanoparticles have various advantages, including passive or active drug targeting in tumor tissues and improved intracellular penetration. Several publications, patents, and clinical trials based on the application of polymeric nanoparticles for breast cancer treatment give the impression that the integration of polymeric nanoparticle-based techniques in cancer therapy will be an innovative and futuristic approach producing superior efficacious and drug targeting with reduced toxicity.

8. Current & Future Developments

The integration of current nanoparticles based techniques will be part of the future of anticancer therapy. Consequently, it's essential to decide which approaches perform effectively in a coordinated way to acquire the maximum anticancer effect. The optimal pharmacological treatments to kill cancer cells can be developed by comprehending the underlying mechanisms under which medicines destroy tumor cells. Nowadays, the most effective chemotherapeutic approach is nanoparticle-based medicines. Undoubtedly, to maximize traditional chemotherapy's therapeutic effectiveness, the domain of nano-medicine can be explored in prospects.

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Conflicts of Interest

The authors declare no conflict of interest.

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