

Review

Research progress of psychological intervention assisted gold nanoparticles drug delivery in the treatment of triple-negative breast cancer patients

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Abstract: Objective: Breast cancer represents the most prevalent malignant tumor among women worldwide. Among the subtypes of breast cancer, triple-negative breast cancer (TNBC) exhibits the highest rates of recurrence and mortality. Early diagnosis and effective treatment play a crucial role in delaying the progression of TNBC, prolonging patient survival, and enhancing the quality of life. Therapeutic strategies that leverage gold nanoparticles for targeted drug delivery show significant potential in improving outcomes for patients with TNBC, and adjuvant therapy with early psychological intervention for patients has also attracted much attention. This paper reviews the current advancements in the application of psychological intervention combined with gold nanoparticles in targeted drug delivery and treatment strategies for TNBC, providing a theoretical framework for their clinical application in managing this aggressive breast cancer subtype. **Methods:** Literature in this article was obtained primarily by searching the PubMed database. We used keywords to search articles: breast cancer, triple-negative breast cancer, nanoparticles, gold nanoparticles, drug delivery, psychological intervention, drug therapy. **Results:** We found that targeted drug delivery with gold nanoparticles was significantly effective in the treatment of TNBC patients, but psychological intervention assisted targeted drug delivery with gold nanoparticles was significant for improving the survival time and quality of life of patients. **Conclusion:** Therapeutic strategies for targeted drug delivery with gold nanoparticles are increasing and technology is becoming more and more mature. Targeted drug delivery with gold nanoparticles combined with psychological intervention can effectively delay the process of disease development while improving the survival beliefs of patients with TNBC.

Keywords: gold nanoparticles; triple-negative breast cancer; drug delivery; psychological intervention; AuNPs antibody complex

1. Introduction

Breast cancer is the leading cause of cancer-related mortality among women, with its incidence accounting for 23.8% of all female malignancies [1]. Triple-negative breast cancer (TNBC) is defined as a subtype of breast cancer characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), representing approximately 15%–20% of breast cancer cases [2,3]. TNBC is characterized by a high invasiveness and high recurrence rate, and anthracycline or paclitaxel alone or in combination with chemotherapy remains the first-line clinical drug of choice for the treatment of TNBC, but molecular heterogeneity, variable response to chemotherapy, and 5-year survival rate of TNBC patients of less than 5% are still urgent problems to be conquered at this

stage [4–6]. The introduction of a new immunotherapy regimen with terlizumab combined with paclitaxel (albumin-bound) injection in patients with first-diagnosed stage IV or recurrent metastatic TNBC significantly prolonged progression-free survival (PFS) and overall survival (OS) in the PD-L1-positive population, with a 35% reduction in the risk of disease progression or death [7]. In addition to terliplumab, the layout and development of more targeted individualized innovative treatment strategies in the field of TNBC has become a current research hotspot.

In recent years, gold nanoparticles (AuNPs) have garnered significant attention due to their excellent physicochemical properties and potential for applications in biomedicine. It has been shown that AuNPs can effectively intercalate within TNBC cells and induce localized hyperthermia through near-infrared radiation, leading to the destruction of tumor cells via photothermal therapy [8,9]. Furthermore, AuNPs can be used as carriers of chemotherapeutic drugs such as adriamycin and paclitaxel, improving therapeutic efficacy through targeted drug release and enhanced delivery [10]. Additionally, AuNPs can be employed to transport specific tumor antigens or immune activators, such as interleukin-12 (IL-12), thereby augmenting the body's anti-tumor immune response [11]. However, the psychological status of the patient plays an integral role in the response to treatment and the outcome of the disease. Psychological intervention can affect neuroendocrine (such as cortisol) and immune function indicators, especially lymphocyte proliferation and TH1 cytokine production [12], and premature discontinuation and non-compliance caused by negative treatment are also the main factors to reduce the survival rate of breast cancer patients [13]. Psychological intervention in advance improves the psychological status of patients, helps patients better cope with psychological pressure, and improves treatment compliance with far-reaching significance.

2. Methods

This is a narrative review based on a literature search that summarizes the application of AuNPs in TNBC and the relevant research literature on the therapeutic effect of psychological intervention assisted by AuNPs for TNBC. We aimed to determine the therapeutic effect of AuNPs drug delivery on TNBC, and evaluate the feasibility of psychological intervention assisted by AuNPs drug delivery in the treatment of TNBC patients so as to provide personalized diagnosis and treatment strategies for TNBC patients and improve the life cycle and quality of life of patients.

We primarily searched articles by using the PubMed electronic database. We used key search terms: breast cancer, triple negative breast cancer, nanoparticles, gold nanoparticles, drug delivery, psychological intervention, drug therapy.

3. Characteristics of AuNPs

Nanomaterials refer to solid materials composed of very fine particles with characteristic sizes in the order of nanometers (1–100 nm) [14]. AuNPs are classified as metal-based synthetic nanomaterials and represent the most extensively studied category of noble metal nanomaterials. This prominence can be attributed to their various surface functionalities and unique surface plasmon resonances, which confer significant advantages for various biomedical applications. Researches have

demonstrated that gold nanomaterials can adsorb apolipoproteins to complete drug delivery on their surface. The efficiency of drug delivery via these nanomaterials is influenced by their size, shape, and the conjugation of targeting ligands. The ability of AuNPs to accumulate in vascular pores allows them to penetrate cancer cells directly, inducing apoptosis and enabling targeted therapy [15]. AuNPs have easily adjustable and powerful optical properties, which can be coupled with specific recognition sites for the detection of biomolecules. Their strong sensitivity to cancer cells, blood glucose, bacteria, viruses, biotoxins, pollutants, pathogens and biomolecules enhances their utility in medical applications. Moreover, proteomic studies of the biocorona formed around AuNPs have the potential to uncover serum protein biomarkers in TNBC [16], which play a crucial role in the early diagnosis and treatment of this aggressive cancer type.

4. Application of AuNPs in TNBC

TNBC is characterized by a relatively high burden of tumor mutations and a lack of sensitivity to both endocrine therapy and HER2-targeted therapies [5,17]. Theoretically, there are three directions for systemic therapy of breast cancer: cytotoxic chemotherapy, hormonal therapy, and tumor cell-specific targeted therapy [18]. However, due to the absence of actionable targets in TNBC, treatment choices beyond conventional chemotherapy are quite limited, which can lead to suboptimal efficacy particularly for patients exhibiting significant tumor heterogeneity. Given the advancements in nanotechnology for cancer treatment, individualized treatment options for the high heterogeneity of TNBC patients are of great significance to improve the survival and quality of life.

4.1. Mechanism of AuNPs in radiosensitization and photothermal therapy in TNBC

AuNPs exhibit several important biological mechanisms, including mitochondrial destruction, DNA damage, and induction of apoptosis in TNBC cells. Light-based therapies, owing to their simplicity, cost-effectiveness, and good controllability, serve as effective stimuli for promoting the aggregation of nanomaterials. In the tumor microenvironment, effective aggregation of AuNPs can be triggered due to high local concentrations of H_2O_2 , and cell death can be promoted by photothermal effects for optical trapping of tumors or other mechanisms when gold nanoparticles accumulate in the tumor area [19]. AuNPs can overexpress luteinizing hormone-releasing hormone (LHRH) receptors on the surface of MDA-MB-231 cells, resulting in adhesion levels five times greater than that observed with normal breast cells [20]. By converting near-infrared light into thermal energy, AuNPs can deplete intracellular glutathione and induce high levels of H_2O_2 , synergizing with modified iron oxide nanoparticles in a strong Fenton reaction to augment oxidative stress and induce apoptosis in malignant cells [3,21] (e.g., **Figure 1**). Gold nanoskeleton (AuNBs) heterostructures can be used as electrochemiluminescence (ECL) sensors and have good photothermal conversion ability [22], which can capture miRNA-26a, miRNA-585-3p, miRNA-522 and other markers in the serum of TNBC patients and are important for early and sensitive detection of tumor metastasis, and can

significantly improve the photothermal treatment effect of highly invasive TNBC [23–25].

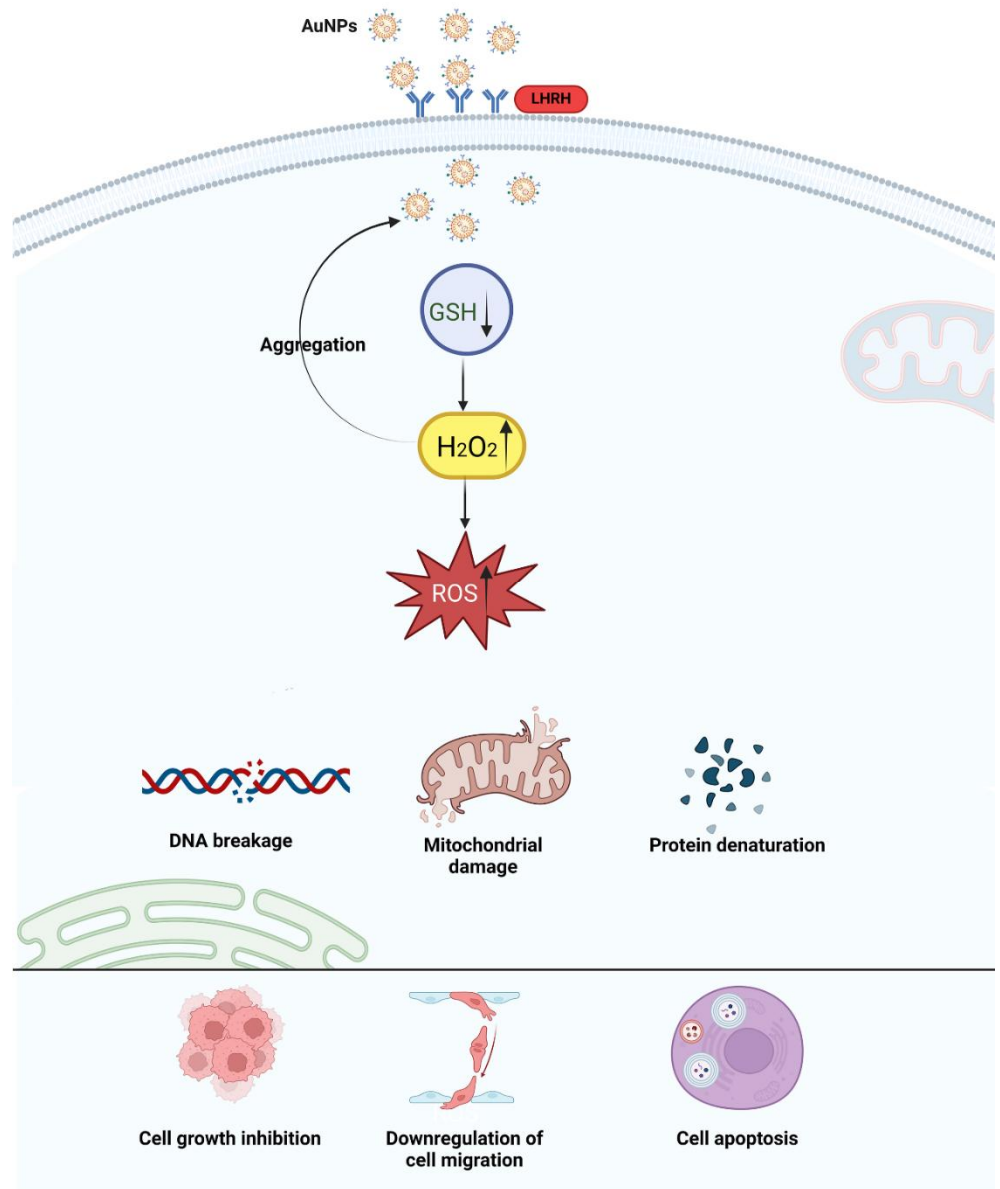


Figure 1. Mechanism of AuNPs in radiosensitization and photothermal therapy in TNBC.

4.2. Effect of AuNPs antibody complex in TNBC

AuNPs antibody complexes are closely related to the formation and development of TNBC. Cancer cells and endothelial cells combined with integrin-targeting peptide-drug conjugates as a strategy for TNBC chemoimmunotherapy [26], provide new ideas for the application of AuNPs antibody complexes in TNBC. Small-sized AuNPs are more suitable for in vivo tumor therapy due to their longer blood circulation time, shorter biological half-life, and enhanced tissue penetration, and the use of AuNPs to construct tumor vascular permeability can regress primary tumors and reduce tumor metastasis [27]. However, AuNPs are easily captured by the reticuloendothelial system

and excluded resulting in poor therapeutic efficacy. Stimulating AuNPs with biomolecules such as thiol-containing compounds, PH, enzymes, DNA, antibodies, and peptides enhances their aggregation and therapeutic effectiveness [19]. AuNPs antibody complexes play an integral role in the treatment of tumors. The Fc segment of the antibody can mediate the cross-linking of proteins through tyrosine phosphorylation, facilitating phagosome formation [28]. In a sophisticated design, a flexible polypeptide is conjugated at both ends to AuNPs, allowing tunable conformational dynamics to enhance specificity and affinity for targeted analytes, mimicking the antigen recognition capabilities of natural antibodies [29,30]. Conjugating multiple nanobodies against survival proteins on ultra-small AuNPs can not only achieve intracellular uptake, but also cross-link survival proteins and interfere with the mitotic progression of living cells [31], which has a direct cytotoxic effect on cancer cells. Antibody drug conjugates (ADC) covalently bind monoclonal antibodies to cytotoxic drugs, which are released intracellularly, thereby improving tumor selectivity and potentially a larger therapeutic window [32]. The multivalent nanobody system of nanobody conjugates and DNA, which can substantially increase the binding ability of nanobodies to specific antigens, has an extremely strong ability to resist spike proteins and inhibit the invasion of pathogenic microorganisms [33]. Assembling therapeutic antibodies on nanoparticles by biomineralization film-coating method allows antibody nanoparticle complexes to have high antibody load and targeting efficiency [34].

AuNPs antibody complexes also play an extremely significant role in the blocking and treatment of breast cancer. It has been shown that AuNPs loaded with large amounts of electroactive toluidine blue (TB) and HER2 secondary antibodies (Ab2) can greatly improve the detection sensitivity for the breast cancer biomarker HER2 [35]. ⁹⁰Y-AuNPs combined with novel nanomaterials of anti-pd-11 antibodies, using anti-pd-11 antibodies coupled with doxorubicin-loaded gold polylactide-glycolate nanocapsules, by photochemical combination therapy, can treat primary tumors and inhibit the growth of secondary tumors, significantly reducing the survival rate of TNBC tumors in Balb/c mice [22,36]. However, the combination of biocompatible multifunctional lipid-coated calcium phosphate nanoparticles (LCP NPs) with a certain number of folic acid or EGFR-specific single-chain fragment antibodies (ABX-EGF scfv) can significantly improve the cellular uptake and transfection efficiency of siRNA in MDA-MB-468 breast cancer cells [37], can be used as an efficient targeted delivery system for gene/photothermal combination therapy, and targets epidermal growth factor receptor (EGFR) expressed on MDAMB-468 cells by non-covalent binding bispecific antibodies (BsAb) to the PEG (mPEG) methoxy group on the particle surface and inhibits the growth of TNBC (MDA-MB-468) in vitro and in vivo [38]. AuNPs antibody complexes are involved in the regulation of different stages of TNBC formation, suggesting that AuNPs antibody complexes play an important role in TNBC development (e.g., **Table 1**).

Table 1. Effect of AuNPs Antibody Complex in TNBC.

AuNPs antibody complex	Drug	Function	Reference
HER2 (Ab2)	TB	Improve the detection sensitivity for the breast cancer biomarker HER2.	[35]
pd-11	Doxorubicin	Treat primary tumors and inhibit the growth of secondary tumors.	[36]
EGFR	Folic acid	Improve the cellular uptake and transfection efficiency of siRNA in MDA-MB-468 breast cancer cell.	[37]
BsAb		Inhibits the growth of TNBC (MDA-MB-468) in vitro and in vivo.	[38]

5. Effect of psychological intervention assisted AuNPs drug delivery in TNBC treatment

5.1. Drug delivery of AuNPs in TNBC

Radiation therapy (RT) is a widely used clinical treatment for cancer that uses high-energy radiation to generate reactive oxygen species (ROS) and damage DNA. However, due to insufficient DNA damage to tumors and harmful effects on normal tissues, its therapeutic effect is greatly limited [35]. Nanomedicine delivery systems address these limitations by selecting AuNPs of appropriate size and shape to enhance accumulation in the liver and spleen [39]. It has been shown that the efficacy comparison between nanovolcanized particle systems and non-targeted free drugs in human cervical adenocarcinoma cell models revealed that nanovolcanized particle systems have stronger advantages in costimulatory response and effective transport control [40]. The cytotoxic efficacy of pH-sensitive doxorubicin-loaded AuNPs and their doxorubicin counterparts was compared in a HeLa cell model in vitro. Compared to free drugs, AuNPs perform significantly better than non-specific drugs and effectively deliver payloads in a controlled manner, thereby improving chemotherapy outcomes [41]. Recently, it has been shown that ultrasound (US) can induce drug release from nanoscale drug delivery systems (NSDDS) and enhance drug penetration and uptake in tumors [42]. Therapeutic ultrasound (TUS) can independently trigger anti-cancer therapy and also trigger on-demand release of chemotherapeutic agents from AuNPs, thereby affecting cellular function and delivery of anti-cancer agents [43,44]. The application of a combined protocol of low-intensity pulsed ultrasound (LIPUS) with AuNPs has achieved that, allowing AuNPs to easily load different types of anticancer drugs and effectively induce the release of anticancer drugs from the surface of AuNPs [45]. At the same time, the combination of AuNPs surface isoforms provides a strong guarantee for personalized precise treatment of patients. AuNPs have unique structural and electrochemical properties, while nano-heterostructures of AuNPs/Zn MOF or AuNPs doped graphene quantum dots (AuS/QD) can improve the catalytic activity of the isomers, achieve a fold increase in ROS, and significantly inhibit tumor growth, which can be used as an effective regimen for bimodular therapy of TNBC in situ [46–48]. The generation of AuNPs binding isoforms plays a crucial role in the development of TNBC.

The surface of AuNPs can be combined with drugs, genes or other biomolecules by chemical modification, thereby achieving targeted drug delivery and controlled release. AuNPs combined with cancer therapeutics play an active role in inhibiting tumor growth. MCF-7 and MDA-MB-231 cells have a high uptake of fructose [49],

and AuNPs can exhibit glucose oxidase-like activity, hinder the biosynthesis of reduced glutathione (GSH), and prevent the recycling of coenzyme Q10 (CoQ10) to CoQ10H2, thereby inhibiting the anti-iron failure pathway in tumor cells [50]. Multifunctional chitosan-bimetallic nanocarrier delivery of 5-fluorouracil with photothermal response increases the cytotoxicity of MDA-MB 231 and PANC-1 cells by eliciting oxidative stress-mediated cell death for intensive treatment of pancreatic cancer and TNBC [51]. EN1-RGD-iPeps functionalized docetaxel nanoparticles significantly reduced TNBC growth both in vitro and in vivo [52]. Camptothecin (CPT), a highly cytotoxic chemotherapeutic compound loaded into porous silicon nanoparticles (pSiNP), can target the epidermal growth factor receptor (EGFR) targeting antibody (Ab) cetuximab as a soluble nanoscale delivery vehicle for primary tumor therapy [53]. Nanoparticles encapsulated with polymer doxorubicin (iNPG-pDox) effectively inhibited TNBC lung metastasis [54]. In a nanosystem (Fe (III)) (Cu-TCPP (Fe)) of cu-(4-carboxyphenyl) porphyrin chlorometallic organic framework (MOF), a drug delivery system (Au SeMSN) of resveratrol loaded with silica mesoporous nanoparticles (MSN) significantly improved the chemotherapeutic effect of resveratrol in TNBC tumor mice [55]. Studies related to AuNPs and TNBC drugs have further provided new strategies for personalized diagnosis and treatment of breast cancer (e.g., **Figure 2**).

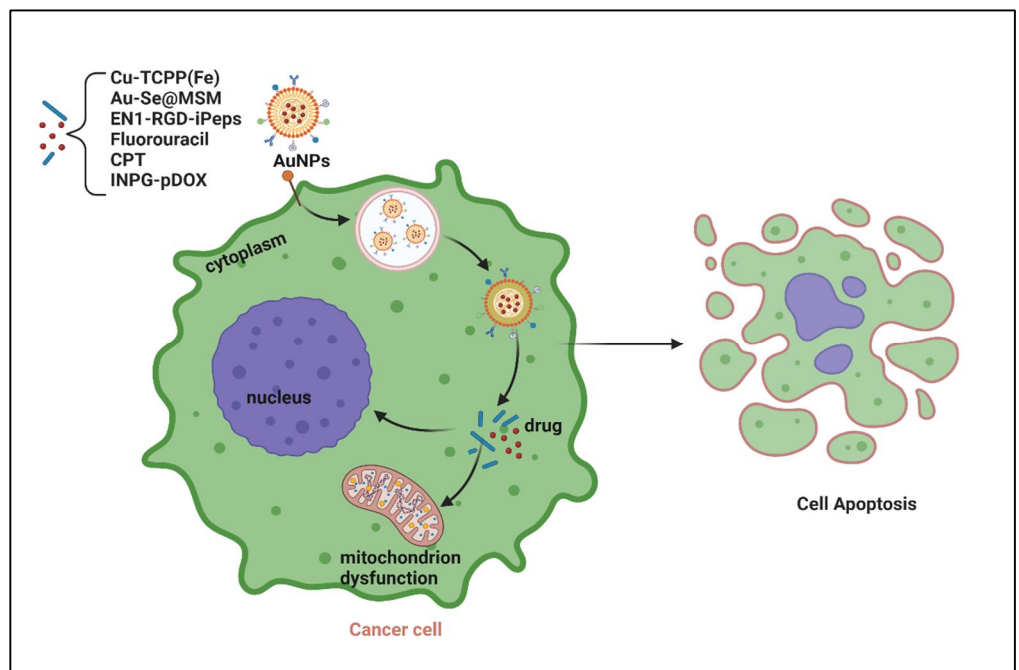


Figure 2. Drug delivery of AuNPs in TNBC.

5.2. Potential synergistic effect of psychological intervention with AuNPs treatment

Psychological distress negatively impacts a variety of cancer-related biological processes. Perioperative stress and inflammatory signaling can activate pro-metastatic molecules in cancer patients, potentially worsening the patient's disease [56]. Long-term psychological stress may inhibit immune function through neuroendocrine pathways and affect anti-tumor efficacy. Studies have shown that psychological

interventions (such as cognitive behavioral therapy and health education) can significantly improve the psychological status of patients, thereby reducing the release of stress hormones (such as cortisol), enhancing the activity of immune cells (such as CD8 + T cells) in patients, indirectly improving the therapeutic effect of patients [12], and enhancing their confidence and compliance with treatment. Shifting patients' attention away from cancer is an effective strategy to relieve physical and psychological stress in cancer patients [57,58].

Reducing anxiety is essential to help patients cope with unfamiliar environments, actively treat them, and control side effects [59]. Relieving patient anxiety can make patients more likely to complete the complex treatment cycle of photothermal therapy with multiple AuNPs combined with chemotherapy. Improvement of psychological status may enhance the body 's immune activation effect mediated by AuNPs (such as promoting T-cell infiltration). Psychological support has been shown to have a positive impact in chemotherapy and immunotherapy, for example in the KEYNOTE-522 study, patient education significantly improved survival with immunization combined with chemotherapy [60]. The potential synergistic effect of early psychological intervention with AuNPs treatment provides an effective basis for the development of tailored interventions to improve disease progression in TNBC patients (e.g., **Table 2**).

Table 2. Future perspective.

Core direction	Specific study route	Key innovation points
Combined treatment strategy	1) Photothermal-immune synergy: AuNPs mediate photothermal therapy combined with IL-12 delivery to activate CD8 + T cells 2) Deepening of Reflex Sensitization Mechanisms: Exploring Immunogenic Death Mechanisms of DNA Damage Pyroptosis Induced by AuNPs @ AgBiS 3) Psychological intervention integration: development of patient anxiety index monitoring APP, dynamic adjustment of AuNPs administration dose and psychological support program	Dual channel synergism via AuNPs mediated "physical killing + immune activation"; Establishing a Personalized Therapy Model of Psycho-Physiological Linkage
Integrated diagnosis and treatment application	AuNPs capture circulating miRNAs (e.g., miR-522) and dynamically monitor treatment response	Achieve closed loop of "diagnosis, treatment and detection" to promote accurate classification and dynamic treatment plan adjustment of TNBC
Clinical translational studies	1) Standardization of psychological intervention: developing an SOP process for cognitive behavioral therapy combined with AuNPs treatment 2) Clinical comparison: Initiating a multicenter interventional study to compare the overall survival rate of traditional chemotherapy and AuNPs-psychological combination regimen	Establishing the first evidence-based guideline for psycho-nanotherapy of TNBC

6. Clinical implications

Patients with TNBC differ in the face of disease and in cooperating with disease treatment. Discussions and research in this area have reduced the potential barriers to disadvantaging TNBC populations in the face of treatment due to knowledge blindness and psychological fear and fully elucidated the necessity of psychological intervention assisted AuNPs targeted therapy for TNBC. The widespread use of AuNPs in the field of cancer as well as diverse diagnosis and treatment strategies provide favorable options for personalized treatment of TNBC patients, but patients face the fear of the disease as well as negative treatment psychology hindering the treatment. The physical

fitness and pathogenesis of different TNBC patients are also difficult problems to cause treatment, and the development of personalized AuNPs combined with modified materials for targeted therapy is the direction of our future research. Active and effective psychological intervention for TNBC patients delivered by AuNPs targeted drugs strives for the best treatment time for patients in order to effectively control the progression of TNBC patients.

7. Study limitations

Systematic studies and literature support for psychological interventions to assist AuNPs related issues in populations with different breast cancer subtypes are lacking. This review carefully incorporates relevant literature on the therapeutic effect of psychological intervention assisted by AuNPs on TNBC patients based on the existing literature, but the relationship between psychological intervention and other tumors as well as the relationship between non-tumor patients needs to be further evaluated. This paper only highlights the necessity of psychological intervention assisted by AuNPs for TNBC treatment in order to determine the feasibility of a psychological intervention assisted TNBC treatment program so as to better solve the complex problems of treatment barriers caused by psychological pressure in patients.

8. Conclusions

While combined chemoradiotherapy and immunotherapy have shown promise in advancing disease outcomes for TNBC patients, conventional therapeutic agents remain non-specific and are associated with significant toxicities, limiting their ability to effectively target tumors. AuNPs have emerged as a powerful tool in cancer therapy because of their excellent biocompatibility, low toxicity, good controllability and multifunctional capabilities, enabling imaging and treatment,- and controlled drug release in response to changes in the tumor microenvironment (e.g., pH, temperature, etc.). These features offer innovative strategies for addressing the safety and personalization disparities encountered in TNBC therapies, enhancing the treatment framework for affected patients, and early psychological intervention may enhance the efficacy of patients by improving their psychological status and immune function. Continued investigation into psychological intervention-assisted targeted drug therapies involving AuNPs holds considerable promise for improving the therapeutic landscape and quality of life for TNBC patients.

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