People have continued to be petrified by the devastating effects of cancer for decades and thus a pursuit for developing anticancer agents have seen an ever-increasing trend in the past few decades. Globally, breast cancer is the most common malignancy in women and the second most common cause of cancer-related deaths. In Saudi Arabia, breast cancer is the most common type of cancer among women, constituting almost 14.2% of the total cancer burden. Triple-negative breast cancer (TNBC) is a subtype of breast cancer, which is a pathologically diverse disease of higher grade characterized by the absence of the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) expressions. Despite the considerable advancements achieved in the therapeutic management of cancer, TNBC remains an unbeatable challenge, which requires immediate attention as it lacks conventional targets for treatment, leading to a poor clinical prognosis. The present research goals are directed toward the development and implementation of treatment regimens with enhanced bioavailability, targetability, minimized systemic toxicity, and improved outcomes of treatment options. The present treatment and management scenario of TNBC continues to provoke oncologists as well as nanomedical scientists to develop novel and efficient nanotherapies. Lately, scientific endeavors have addressed the importance of enhanced availability and targeted cellular uptake with minimal toxicity, which are achieved by the application of nano drug-carriers. This review intends to summarize the incidence rates of TNBC patients, the importance of nanotherapeutic options for patients suffering from TNBC, the identification of promising molecular targets, and challenges associated with the development of targeted nanotherapeutics with special reference to the Saudi Arabian context.

Keywords: triple negative breast cancer, nanoparticles, targetability, nano carrier and bioavailability, TNBC, nanomedications, breast cancer
1 INTRODUCTION

In 2020, an estimated 19.3 million new cancer cases and about 10.0 million cancer deaths were reported worldwide, leading to an ever-increasing bias in the development of anticancer drugs in the recent decades. Rising population density, industrialization, and other environmental factors lead to a rise in the incidence of cancer cases universally, making scientists work overtime to discover and produce effective anticancer medications with low toxicity, high selectivity, and increased efficacy (1). According to demographics, the Saudi Arabian cancer scene reveals that in 2018 alone, there were 10,518 cancer-related deaths with 24,485 new cancer cases recorded in the kingdom. The most common types of cancer that are trending in Saudi Arabia include breast cancer, colon-rectum (CRC), and prostate cancer.

Breast cancer (BC) has the highest incidence and mortality rates of all cancer types in Saudi Arabia, with rates of 14.8% (cumulative risk of 2.87%) and 8.5% (cumulative risk of 0.81%) for both sexes, respectively. Triple-negative breast cancers (TNBCs) are a subtype of breast cancer, which is an aggressive type of breast cancer that lacks the expression of progesterone, estrogen, and human growth factor receptor 2. Therefore, it lacks particular therapeutic targets, which undermines the prognosis and its treatment becomes a huge challenge. TNBC accounts for 15–20% of all breast cancers (2).

TNBCs are finding their place in the top orders as the search for a new targetable biological traits leading to a sustainable treatment regimen is a top focus at present for researchers. Paclitaxel, classified as a “plant alkaloid,” is one of the most common chemotherapeutic drugs, used as the first-line treatment for TNBC patients. One of the most common side effects of chemotherapeutic treatments includes killing of bulk cancer cells, whereas it has been documented that chemotherapeutic treatment boosts a subpopulation of cells called cancer stem cells (CSCs), which are capable of causing new tumors. CSCs are again a substantial hurdle in the path of effective cancer treatment as it has been observed that CSCs are therapy-resistant and are instrumental in cancer progression, recurrence, and metastasis. Numerous studies have shown that the concentration of CSCs in TNBC cell lines directly contribute to the aggressive nature of TNBC (3).

The different treatment options that are used to treat TNBC patients are: conventional chemotherapy, neoadjuvant chemotherapy, adjuvant chemotherapy, PARP inhibitors, immunotherapy, etc. However, because of heterogeneity and diverse clinical characteristics, special guidelines for the conventional treatment of TNBC are lacking. However, in high-risk TNBC patients, various chemotherapy regimens, including anthracycline-taxane combos, are used. Besides, in moderate to high-risk situations, alternative treatment regimens like epirubicin, 5-fluorouracil, and cyclophosphamide in association with docetaxel (DTX) or paclitaxel (PTX) are used as adjuvant chemotherapy (2, 3). Furthermore, simultaneous neoadjuvant therapies are administered, which include platinum-based drugs such as cisplatin, carboplatin, and anthracycline, which proved more effective in the case of TNBC than adjuvant therapy. All these nanoparticles (NPs), receptor targeting compounds, and antibodies have all been employed in the therapy of hormone-negative breast cancer. Several nanoscale carrier systems have been developed as drug delivery platforms for treating TNBC in recent decades. The leaky vasculature can be penetrated by nanoformulations such as liposomes, polymeric NPs, lipid-based formulations, dendrimers, metallic nanoparticles, micelles, carbon nanoparticles, nanotubes, inorganic nanoparticles, natural agent based nanocarriers, etc. Nanomedicine that has been functionalized will be more able to be used in certain areas, such as ischemic tissue, tumors, and inflammatory areas. The drug is released because of specific enzymes, redox potential, pH and temperature activation.

This review focuses on providing a perspective on TNBCs in the Saudi Arabian context. The review aims to summarize TNBC patient incidence rates, the importance of nanotherapeutic options for TNBC patients, and the challenges associated with the development of targeted nanotherapeutics, with a focus on the Saudi Arabian context.

2 CLASSIFICATION OF BREAST CANCER

Breast cancers are a heterogeneous group of tumors with various classifications, and these classifications determine the type of BC that is most prevalent among the population. Various classifications that are helpful are:

1. Histopathological classification: It helps in the identification of different histologic variants of breast carcinomas, like modular, mucinous, and tubular.

2. Molecular classification: It is based on gene-expression profiling with the use of DNA microarray. Such molecular classification helps in identification into different groups like luminal A, triple negative tumors, luminal B, basal, and normal like tumors, etc. (4).

3. Immunohistochemistry: This can further help with molecular subtyping and is considered the most important test for detecting tumor sensitivity to various therapies (5).

Breast cancer is ordered into 4 major subtypes based on the presence or absence of molecular markers for estrogen receptors (ER) or progesterone receptors (PR) and human epidermal growth factor 2 (ERBB2; formerly HER2).

- HR+/HER2− (“Luminal A”), HR−/HER2− (“Triple Negative”), HR+/HER2+ (“Luminal B”), HR−/HER2+ (“HER2-enriched”).

There are two ER-positive (luminal A and B) and two ER-negative intrinsic breast cancers (HER2+ and TNBC) (6) (Graph 7; Table 1).

Developed countries have a higher prevalence of BC than developing countries, and the death rate due to BC is high in developing countries. Factors responsible for the higher incidence of BC in developing countries may include dismensusia in women, obesity, hormonal therapy, extended exposure to drugs, the lack of use of vitamin supplements,
indiscriminate usage of contraceptives, and having a family history of BC are crucial contributing factors (7, 8). Also, this risk continues to increase if it is the first degree relative who had BC. To identify the cause of genetic and complex diseases, genetic analysis is one of the major milestones that correlates genotype and phenotype of complex diseases like BC, as the causative variants may be identified with this plan. Saudi Arabia has successfully kicked off its first 100,000 genome project (9). This genomic revolution may help in the identification of specific genetic variants that lead to the genetic diseases among their population. This long-term project may help and contribute to disease management and better prognosis of BC, which will in fact help in establishing better genetic testing.

### 3 BREAST CANCER INCIDENCE IN SAUDI ARABIA

Breast cancer is the leading cause of death among the Saudi population, as it is globally. In 2012, according to the Saudi Cancer Registry (SCR), 14.33% of cases of cancer were identified, with 47.5% (men) and 52.6% (women). The year 2014 marked the rise of breast cancer to the top spot among the Saudi population. A reported 15.9% of cases of BC were compared with all other cancers among Saudi nationals, and it accounts for 28.7% of all cancers among females of all ages (10). But it is noteworthy that the incidence of BC is lower but stands at second position based on the death rate due to breast cancer is 62.78% in Saudi Arabia. The mortality was 13,069 (5-year prevalent cases) cases across all ages and genders (Globocan 2020) (Graphs 3, 4).

As per the age-standardized rates (ASR) in different types of cancers, the incidence of all cancers (5-year prevalent cases) was estimated to be 82,640 cases (39,241 men and 43,399 women) in Saudi Arabia. The mortality was 13,069 (5-year prevalent cases) cases across all ages and genders (Globocan 2020) (Graphs 3, 4).

Although detection of breast cancer in early stages has reduced morbidity and mortality rates, there is still a high rate of BC incidence among the Arab population. In 2020, there were 13,069 cancer deaths with 27,885 new cancer cases in Saudi Arabia (total population = 34,813,867) and the number of prevalent cases (5-year) was 82,640. GLOBOCAN reported that BC is the most common type of malignancy with 3,954 new cases (14.2%) during 2020 and the second type of death cause in 2020 (Graphs 5, 6). In 2020, the incidence of breast cancer among females was 29% in Saudi Arabia. It is the most common cancer death in women, followed by thyroid cancer and colon cancer (Graph 6).

### 4 INCIDENCE OF TRIPLE NEGATIVE BREAST CANCER AROUND THE GLOBE AND IN SAUDI ARABIA

Triple-negative breast cancer (TNBC), defined by the absence of estrogen receptor, progesterone receptor, and overexpression of human epidermal growth factor receptor 2 gene (HR−/HER2−), is a particularly aggressive subtype of breast cancer. Triple-negative (TN) tumors are positive for cytokeratin (CK) 5/6. They are usually high grade, with a high risk of relapse within the first few years after early diagnosis. TNBC has a prognostic value in terms of tumor size and p35 status (16, 17). For the identification of TNBC, the absence of estrogen receptor, progesterone receptor, HER2 and positivity for CK 5/6 and p53 are used as specific markers.

TNBC accounts for 15% of breast cancers diagnosed around the globe, which amounts to almost 300,000 cases each year (18). Compared with Luminal A, TNBC is more commonly diagnosed in women younger than the age of 40 (19).

**TABLE 1 |** A standard immunohistochemistry (IHC) panel for the three main clinical biomarkers ER, PR, and HER2 can approximate the four intrinsic breast cancer molecular subtypes.

| Breast cancer subtype | ER   | PR   | HER2 | Triple designation | Percentage |
|-----------------------|------|------|------|--------------------|------------|
| Luminal A             | +    | ±    | –    | ER+/PR−HER2−       | 70%        |
| Luminal B             | +    | ±    | +    | ER+/PR−HER2+       | 15%        |
| HER2+                 | –    | –    | +    | ER−PR−HER2+        | 2%         |
| TNBC                  | –    | –    | –    | ER−PR−HER2−        | 15%        |

All these results in Middle Eastern countries were in contrast to the observations in the United States of America. According to the most recent statistical data from NCI’s Surveillance, Epidemiology and End Results (SEER) Program, women who are >55 years of age have more incidences of breast cancer (65.1%) with a median age of 62 at the time of diagnosis (15). This difference may be a consequence of a lack of high-quality healthcare systems in the Middle East compared to the US (12).

Frontiers in Oncology | www.frontiersin.org 3 July 2022 | Volume 12 | Article 953865
According to the Surveillance, Epidemiology, and End Results (SEER) registries for 5-year breast cancer-specific survival, TNBC is in the fourth position with 76.9% vs 94%, 90%, and 84% for Luminal A, Luminal B, and HER2+, respectively (Graph 8).

Among the Saudi population, Luminal A is the most common subtypes, followed by triple-negative tumors. The frequency of TNBC is high among African, Omani, and Tunisian communities. According to one more study by Tammimi et al. (20) TNBC is the most common subtype of BC in SA, which is a bit different compared to other studies, as most of the studies done in SA clearly indicate that Luminal-A stands in the first position.

Luminal-A was found to be the most common subtype of BC with 59% of cases in Saudi Arabia, according to a study in the western region of the kingdom. In contrast, TNBC and the Her2 subtype were the least common types of BC in the Saudi population, with 16 and 11.4%, respectively (12). According to some studies conducted in the Riyadh region in Saudi Arabia between 2010 and 2014, the triple-negative breast cancer incidence rate was found to be 14.8%. These results are in accordance with previous retrospective analysis conducted in King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia, which states that only 12% were diagnosed with TNBC (62 patients from 514 BC cases) (17).

According to SEER statistics, based on 2014–2018 cases, HR+/HER2− subtype is six times higher than the triple-negative breast cancer rate (13.1) and the HR+/HER2+ breast cancer rate (13.4), and more than 16 times higher than the HR−/HER2+ breast cancer rate (5.5) around the world (Graph 9).

The features of TNBC have been extensively studied in Western populations, but there are fewer studies of TNBC among non-western ethnics, especially among the Saudi population. According to a study conducted in King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia, while comparing TNBC and non-TNBC patients, a high percentage (87.3%) of patients with TNBC expressed grade 3 tumors compared to the control. This percentage is like the others that have been reported in other places (17, 21), and these findings state that TNBC tumors are high-grade tumors. Also, TNBC is diagnosed at a later stage because of its aggressiveness and highly proliferating nature (22).

5 NANOCARRIER MEDIATED TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

5.1 Nanomedicines and Its Applications in TNBC Treatment

Currently, triple-negative breast cancer (TNBC) does not respond to many targeted drugs due to the lack of progesterone receptor, estrogen receptor, and human epidermal growth factor receptor-2, which makes the detection...
and treatment of TNBC difficult and challenging. Metastatic relapse and drug resistance to chemotherapy are the major obstacles to treating triple-negative breast cancer effectively. During the last decade, investigators developed various nanomaterials that are considered a new field of science dealing with dimensions on the nanoscale. Using nanotechnology, scientists have developed various nanoparticles (NPs) for breast cancer diagnosis and therapy (Mahsa Keihan23). Nanomedicines could help overcome the limitations of conventional therapy such as chemotherapy, radiation therapy, etc. (24). The size of the particles ranges between 10 and 100 nm and can be composed of different materials, including metals (gold, silver, and iron), lipids, polymers, silica, protein/peptides, and oligonucleotides (Jaison 25). NPs have gained popularity due to emerging biomedical applications. It can be employed in drug delivery approaches, chemical and biological sensing, gas sensing, and CO2 capture (26–33).

Various nanoparticle-formulated medications are currently being used in clinical trials to treat breast cancer (Table 2).

As cancer is one of the most dreaded diseases, causing most deaths worldwide, more than 12,000 researchers around the world in the last decade have focused on new therapies to target cancer tissues using nanomaterials as drug delivery agents (51).

The major type of nanoparticle used to target cancer cells is coupled to chemotherapeutic drugs, while few studies have focused on the use of nanotechnology in the immunotherapy context to not only induce the cytotoxic effect on cancer cells but also treat and control breast cancer (52).

Recently, several nanomedicine studies have been conducted to specifically target specific pathways involved in cell proliferation and migration in breast cancer (Table 3).

Targeting breast cancer cells by specific nanoparticles depends on the recognition of specific molecules (ligands) on their surface and their interaction with a specific marker expressed on the surface of targeted breast cancer cells (53). These specific receptors facilitate the internalization of nanoparticles through endocytosis, and then by lysosome degradation the biomolecules are released (53) (Figure 1).

Various nanocarriers used for treatment of TNBC are as follows.

5.1.1 Liposomes
Alec D. Bangham first described liposomes in 1961 as spherically shaped microscopic vesicles. The word liposome derives from two Greek words: lipo meaning “fat” and soma meaning “body.” The size of liposomes can vary from 100 to 400 nm vesicles. It is so named because it consists of a central aqueous core surrounded by lipid bilayers of phospholipid, which closely
resemble the structure of cell membranes (Figure 2) and an aqueous phase. The phospholipid bilayer of the liposomes can carry lipophilic drugs, while the aqueous phase can carry hydrophilic drugs.

Liposomes are considered the most versatile nanocarriers, which makes them an attractive alternative for researchers because of their good drug distribution. There are many types of liposomes that are designed by different methods (extrusion, solvent injection, and reverse-phase evaporation), and their nomenclature depends on their method of preparation, special functions, or their structural parameters. The difference between each type of liposome is mainly related to their structure, size, surface charge, lipid composition, and vesicle dimensions. Based on the number of bilayers, liposomes can be classified into two categories: Multilamellar vesicles (MLV) with several lamellar phase lipid bilayers and unilamellar vesicles (ULV) with a single phospholipid bilayer sphere enclosing the aqueous solution. They can be further classified into two subtypes: large unilamellar vesicles (LUV) and small unilamellar vesicles (SUV) (Figure 2).

Based on size, liposomes are classified as

* multilamellar vesicles (MLV; >0.5 um),
* large unilamellar vesicles (LUV >100 nm)
* small unilamellar vesicles (SUV, 20–100 nm),
* Oligolamellar vesicles (OLV >0.1–1 um)
* Unilamellar vesicles (UV all range size)
* Giant unilamellar vesicles (GUV >100 um)
* Multivesicular vesicles (MV >1 um)

Based on composition, liposomes are classified as conventional liposomes (CL), pH-sensitive liposomes, cationic liposomes, long-circulating liposomes (LCL), and immuno-liposomes.

Based on the method of preparation, they are further classified as reverse phase evaporation vesicles (REV), French press vesicles (FPV), and ether injection vesicles (EIV).

5.1.2 Drug delivery by Liposomes
5.1.2.1 Steps of Drug Delivery by Liposome

A. **Adsorption**: the specific structure of liposomes as a phospholipid bilayer can mimic the lipid bilayer membrane of cells and bind to tumor cells.

B. **Endocytosis**: internalization of liposomes by the cell.

C. **Fusion**: liposomes can fuse with the cell membrane by lateral diffusion, causing the delivery of liposomal contents into the cytoplasm.

D. **Drug delivery**: The delivery of drugs into living mammalian cells can be by direct delivery of liposomal content after its fusion with the cell membrane (fusogenic liposome) or via endocytosis, where the liposome is degraded before reaching its destination (endosomal degradation) (54) (Figure 3).

5.1.3 Currently Used Liposome in Triple-Negative Breast Cancer Treatment

Due to the lack of specific cellular receptors on TNBC tumor cells (ER, PR, and HER2), the aggressive nature of developing multidrug resistance (MDR) to conventional chemotherapeutics,
and the metastatic potential, makes drug delivery to the tumor cells challenging (55).

The liposome is one of the most common types of nanocarrier used currently to treat TNBC because of its ability to load drugs into the aqueous core or the lipid bilayer, making it an attractive alternative in clinical trials.

5.1.3.1 Clinical Trials

Liposomes approved by the FDA have been employed to deliver several chemotherapeutic drugs to treat TNBC patients, such as doxorubicin, an anthracycline type of chemotherapy that is used to treat several different types of cancer (Doxil®, Lipodox®, and Myocet®) (56), paclitaxel Lipusu®, approved in China, and daunorubicin (DaunoXome®), which is currently in advanced clinical trials for metastatic breast cancer (57).

Another liposomal paclitaxel (PTX) developed by MedGene known as EndoTAG-1® is positively charged, which increases the permeability of cancer cells and enhances the uptake of anticancer drugs by tumor cells (58).

Awada and coworkers evaluated the antitumor efficacy of EndoTAG with Taxol® in 140 patients in phase II clinical trial (NCT00448305) (59). They stated that EndoTAG-Taxol significantly decreases the tumor proliferation and cell toxicity in healthy cells.

PTEN (phosphatase and tension homolog) is a tumor suppressor frequently decreased in TNBC cells. The loss of PTEN activates mTOR (mammalian target of rapamycin (mTOR), which is a key target for anticancer therapy in TNBC (60).

The inhibition of mTOR by a specific molecule such as Rapamycin (RAPA) has been clinically proven. RAPA shows anti-tumor activity against TNBC, but it can induce drug resistance when used alone (61). Recently, using liposomal DOX in a phase I trial in TNBC patients, Weinbeg et al. stated that liposome DOX-RAPA inhibited the upregulation of hypoxia-inducible factor 1-alpha (HIF-1α), which is a
transcription factor highly expressed in tumor proliferation, migration, and drug resistance.

5.1.4. Liposomes Used in Saudi Arabia to Treat TNBC

In addition, Lamyaa et al. published a recent study evaluating the efficacy of the new miR-1296 liposome in TNBC [Lamyaa (62)].

miR-1296 is a novel cancer-related miRNA found to be dysregulated in various cancers, gastric cancer, prostate cancers, cervical cancer, and TNBC (63, 64). The downregulation of miR-1296 can enhance tumor cell proliferation, but its re-expression blocks cell invasion and metastasis. The efficacy of naked miRNAs evaluated in several studies is still limited due to their short half-life in vivo, biological instability, poor penetration, and rapid clearance by cells (65, 66). The aim of Lamyaa and colleagues was to develop a cationic nanoliposome delivery system for miR-1296 and miR-1269 and to evaluate its cellular uptake and its effect on TNBC cell culture. It was shown that upregulation of miR-1269 inhibits TNBC cell proliferation and promotes cell apoptosis. They demonstrated that the miR-1269 liposome is one of many other miRNAs that can be used in clinical applications of TNBC therapy.

Several deregulated tumor-suppressive miRNAs were involved in cells in TNBC. For instance, MiR-203 is one of the well-described microRNAs that is downregulated in TNBC cells. In addition, mir-200c, miR-205, and mi-206 were found to be downregulated in TNBC and their upregulation was correlated with the inhibition of cell migration and tumor growth (38, 67, 68).

### TABLE 2 | Different types of nanodrugs.

| Type of Nanocarriers                  | References                              |
|---------------------------------------|-----------------------------------------|
| Liposomes                             | Alavi et al. (34) Wu et al. (59) Christensen et al. (36) |
| Carbon-60 fullerenes                  | Lin et al. (37) Wang et al. (38)         |
| Polymer-based platforms               | Wang et al. (39); Bai, X. Zhang et al. (40) |
| Metallic Nanoparticles: ex Goid nanoshells | Xu et al. (41) Park et al. (42)         |
| Dendrimers                            | Sharma et al. (43) Lu et al. (44)       |
| Superparamagnetic nanoparticles       | Mosafar et al. (45)                     |
| Nanocrystal                           | A Fuhrmann et al. (46)                  |
| Silicon and silica-based nanoparticle | Meka et al. (47) Rosenbrand et al. (48) |
| Lipid based drug delivery             | Yingchoncharoen et al. (49)             |
| Nucleic Acid based therapeutics       | Sakib Haque and Sahay (50)              |

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### TABLE 3 | Clinical trials in the area of nanotechnology and triple-negative breast cancer.

| Name of the study                                                                 | Interventions                                                                 | Phase | Trial            |
|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------|------------------|
| Carboplatin and paclitaxel albumin-stabilized nanoparticle formulation before surgery in treating patients with locally advanced or inflammatory triple negative breast cancer | Drug: carboplatin Drug: paclitaxel albumin-stabilized nanoparticle formulation Other: laboratory biomarker analysis | II    | NCT01525966     |
| Study to evaluate CORT125134 with nab-paclitaxel in patients with solid tumors    | Drug: CORT125134 with nab-paclitaxel                                         | III   | NCT02762981     |
| Weekly and Every 3-Week Administration of Paclitaxel Liposome Injection in Metastatic Breast Cancer | Drug: paclitaxel liposome injection                                           | IV    | NCT02142790     |
| Veliparib in treating patients with malignant solid tumors that do not respond to previous therapy | Drug: veliparib                                                             | I     | NCT00892736     |
| Neoadjuvant pembrolizumab/Pbr/Nab-paclitaxel followed by pbr/epirubicin/ cyclophosphamide in TNBC | Pembrolizumab, Nab-paclitaxel, Epirubicin, Cyclophosphamide                  | III   | NCT03289819     |
| AZD2281 plus carboplatin to treat breast and ovarian cancer                       | Drug: AZD2281+carboplatin                                                    | I     | NCT01445418     |
| Evaluate the Efficacy and Safety of Genexol®-PM Compared to Genexol® in Recurrent or Metastatic Breast Cancer | Drug: Genexol-PM Drug: Genexol                                               | III   | NCT00876486     |

FIGURE 1 | Various Nanoparticles to treat Breast Cancer.
The interesting fundamental role of miRNA as a tumor-suppressor made it a good approach to be used along with nanotechnology making a new technology for treating TNBC.

The use of nanocarriers in clinical trials for TNBC is still limited in Saudi Arabia, but many clinicians are still working to evaluate the efficacy of liposomes as a target approach to treat several types of cancers, such as Masood Khan et al., who stated that glycosphingosomes significantly reduce the tumor profile and induce apoptosis.

### 5.2 Metallic Nanoparticles

Metallic nanoparticles (MNPs) are extremely useful in cancer treatment. Nanoparticles can be classified into 2 categories: organic and inorganic NPs. Metallic NPs are listed as inorganic NPs; however, liposomes, micelles, dendrimers, and polymeric NPs are considered organic NPs (69) (Table 4).

Metallic nanoparticles can be classified into 4 major subtypes, including metal-ion NPs, metal oxide NPs, metal sulfide, and bimetallic NPs. The first category of nanomaterial called metal nanoparticles includes different types of metals such as gold (Au), copper (Cu), silver (Ag), titanium (Ti), platinum (Pt), magnesium (Mg), and zinc (Zn) nanoparticles. The metal oxide nanoparticles are a specific group including titanium dioxide, silver oxide, and zinc oxide, which are widely used in therapeutic trials (70). Moreover, metal sulfide nanomaterials (e.g., AgS, CuS, and FeS) are used in various medical applications because of their excellent antimicrobial activities. Bimetallic NPs, as the name suggests, are composed of two different metal elements, such as CuS, Ag2S, FeS, etc.

The most extensively explored metallic nanoparticles in biological applications such as cancer therapy, diagnosis, and drug delivery are gold (Au NPs) (71) and silver NPs (72).

#### 5.2.1 Gold Nanoparticle and TNBC

Gold nanoparticles (AuNPs) have low toxicity and have the ability to attach to anti-cancer drugs such as paclitaxel. Recently used in vivo, the combination of paclitaxel and AuNPs enhanced the efficiency of drug delivery to target cells and reduced BC cell proliferation.

This main idea was supported by Kumar et al. They used paclitaxel and curcumin (Cur) along with gold NP to evaluate the anti-metastatic activity of this chemotherapeutic drug in various...
in vitro and in vivo models of TNBC. They suggested that Au NPs downregulate the expression of VEGF, CYCLIN-D1, and STAT-3 genes and upregulate the apoptotic caspase-9 gene.

The first group of mice that received paclitaxel and curcumin with gold nanoparticles showed a significant reduction in the size of TNBC tumors compared with the second group treated with Cur–paclitaxel alone. Also, Kong et al. stated that gold nanoparticles have little or no toxicity to healthy cells, but they can significantly enhance cancer killing and reduce cell migration and invasion by reducing the rate of energy (73).

Additionally, Andey et al. (74) suggested that using the combination AuNPs–cisplatin, a chemotherapeutic drug, significantly reduces the TNBC proliferation and metastasis.

5.2.2 Silver Nanoparticles and TNBC
Silver nanoparticles (AgNPs) have been extensively used because of their antimicrobial properties and their cytotoxic effects against cancer cells, including breast cancer, ovary cancer, brain cancer, liver cancer, colon cancer, and blood cancer (75–78).

A recent research published by Swanner and colleagues stated that TNBC and nonmalignant breast cells both uptake AgNPs and AgNPs are extremely lethal for TNBC cells because of their rapid degradation in cancer cells. However, they were not cytotoxic to healthy cells (79). After the internalization of AgNPs, the intercellular rate of stress increased due to the high synthesis of cellular antioxidants, which stresses the endoplasmic reticulum in TNBC cells but does not harm normal cells in the same way.

In vivo, the same team showed for the first time that systemically administered AgNPs but can significantly reduce the growth of solid TNBC tumors in mice. However, clinical trials in TNBC patients using AgNPs are still limited.

5.3 Nucleic Acid-Based Therapeutics
Nucleic acids (NA) are the most important information-carrying molecules in all cells and viruses. The main function of NA is to control the expression of genetic information and protein synthesis. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are two natural types of nucleic acids. Therapeutic nucleic acids (TNAs) are nucleic acids themselves or modified RNA or DNA, which have recently proven to be a valuable tool to modulate gene expression (80).

Although various types of TNAs exist, they have successfully proved their ability to target diseases at the genetic level by down or upregulating numerous proteins, which are related to cell proliferation or apoptosis, respectively. The development of nucleic acid (NA)-based therapy, widely explored in the last decade to treat diseases, has produced two independent new strategies, such as DNA and RNA nanotechnology (81).

Targeting the intrinsic cancer pathways altered during tumorigenesis makes RNA-based therapeutics a good tool in the clinic (81). Currently, two major types of RNA-based therapy are used in clinical trials; interference (RNAi), used usually in gene silencing to control cell growth and death; and RNA nanotherapy, widely used in drug delivery to target cells.

RNA interference can be used as a therapeutic tool in two ways: either small interfering RNA (siRNA) or microRNA (miRNA) (82). MicroRNAs can play crucial roles in gene regulation and expression in TNBC. Recently, (82) showed that RNA nanotechnology has clinical applications to deliver miRNA-based therapeutics for TNBC. They used miR-21, an oncogene involved in tumor progression and metastasis in several cancers, including TNBC. They used RNA nanotechnology to deliver mi-ARN and anti-miRNA to cancel cells without causing any damage to healthy cells.

### TABLE 4 | Showing different types of metallic nanoparticles (MNPs) and their composition.

| Type of Metallic NP | composition | Elements |
|--------------------|-------------|----------|
| Metal-ion NPs      | originated from the metal ion itself | Ag, Au, Pt, Ni, Cu |
| Metal oxide NPs    | consist of metal ions in the oxide forms | CuO, ZnO, TiO2, CeO2, SiO2 |
| Metal sulfide NPs  | NP in sulfide form | CuS, Ag2S, FeS |
| Bimetallic NPs     | NP developed from two metals forms a bimetallic NP | FePt, FeCo, FeNi, CuNi |

### GRAPH 9 | Age-Adjusted Rate of New Breast Cases per 100,000 Women, SEER 21 2014–2018.

In the graph, the Age-Adjusted Rate of New Breast Cases per 100,000 Women is shown for the SEER 21 data from 2014 to 2018. The graph is color-coded to differentiate between various HER2 statuses (HR+ HER2−, HR+ HER2+, HR+ HER2+, Unknown) in triple-negative breast cancer (TNBC) patients.
5.4 Dendrimers
Dendrimers are highly branched and symmetrical nanosized agents with 2 to 10 nm in diameter. They possess the unique property of being monodisperse and homogeneous, which makes them ideal nanocarrier-based systems for cancer chemotherapy. They work in cancer therapy via ligand and receptor-mediated endocytosis. In MCF-7 cells, PAMAM dendrimers loaded with functional siRNA are used to target the MDR1 gene, which is responsible for drug resistance development. According to one study, a nanocomplex known as dendriplexes was generated using a phospholipid (PL) modified PAMAM–siMDR1 complex. This complex showed considerable gene silencing, increased siMDR1 uptake and decreased P-gp expression, resulting in increased DOX cellular accumulation (83). In another study, the CXCR4 gene was targeted and inhibited on the surface of BT-549 triple-negative breast cancer cells by developing PAMAM dendrimers encapsulating DOX modified with LFC131 peptide (84). Various scientists have used PPI dendrimers in drug delivery for and against MCF-7 cells for treating breast cancer. Kaur et al. created folate-conjugated polypropylene imine dendrimers to effectively deliver methotrexate (MTX) to MCF-7 cells.

5.5 CRISPR Nanoparticles
Clustered regularly interspaced short palindromic repeats (CRISPR)/associated (Cas9) technology is being widely used along with genome engineering to overcome drug resistance in breast cancer chemotherapy. The CRISPR technology reverses genetic alteration, the major contributing factor in drug-resistance in cancer chemotherapy, by recognizing the possible target areas causing this resistance to drugs. To repair the genetic information in TNBCs, various nanoparticulate systems encapsulated in nanogels have been investigated using CRISPR technology (85). CRISPR/Cas9 is a gene-editing technology that can correct genomic faults. It is a rapid method for activating or deactivating certain genes in cells. CRISPR/Cas9 technology has proven to be an effective technique for treating various genetic diseases, including human breast cancer. Liposome-based hydrogel nanoparticles (LHNPs) have been drafted to convey Cas9 protein and nucleic acids, and they might be programmed to stop genes from being expressed in cancers (63). Thus, CRISPR cab be employed for both experimental and clinical gene therapy in cancer.

5.6 Lipid-Based Nanomedicines
Lipid-based colloids are biodegradable and biocompatible with biomolecules such as phospholipids, cholesterol, and triglycerides, and thus can be used to target different cancerous cells at the same time when constructed as nanostructured lipid carriers. These lipid-based carriers can be made from a variety of materials and have a wide range of therapeutic and diagnostic applications in cancer research. According to Sun et al., nanostructured lipid carriers (NLCs) loaded with Quercetin reduce the solubility problems of Quercetin and the efficacy of entrapment was found to be 95%, while its extended-release resulted in cell killing in MCF-7 and MDA-MB-231 cells (86). Also, DOX and PTX when encapsulated with NLCs target MCF-7, SK-OV3 cell lines, and their other variants. Tamoxifen citrate and camptothecin with solid lipid nanoparticles (SLNs) showed an advantage against MCF-7 and MCF-10A cells (87). Solid lipid nanoparticles (SLNs) have various advantages like protection of drug from degradation, long-term stability, reduce systemic toxicity, are feasible to load lipophilic and hydrophilic drugs, and are easy to scale up, with some disadvantages as well, which include causing unpredictable agglomeration, having a high incidence of polymorphic transition, and drug expulsion (88). They also carry desirable particle sizes. Lipid polymer hybrid nanoparticles are also considered to be reliable lipid-based nanocarriers. They have provision for surface modification and drug entrapment of hydrophilic and lipophilic drugs with high serum stability (89). According to a study by (90) in 2012, the drug mitoxantrone, which is water-soluble, was encapsulated into lipid polymer nanoparticles (LPNs). Mitoxantrone LPN increased cytotoxic action than the drug alone in the MCF-7 and MCF-7-MX. Many other nanoparticles like carbon nanoparticles, exosomes, natural agent based nano-carriers, inorganic nanoparticles, and polymeric micelles are also being used as promising treatments for breast cancer and its subtypes like TNBC.

6 CONCLUSION
TNBC is less studied among non-western ethnic groups, especially among the Saudi population. Also, TNBC is diagnosed at a later stage because of its aggressiveness and highly proliferating nature, and while comparing TNBC and non-TNBC patients, a high percentage of patients with TNBC expressed grade 3 tumors in Saudi Arabia. Nanomedicine aids in the diagnosis and treatment of both hormone-negative and hormone-positive breast cancer and is said to be one of the most promising options among the various treatment methods available for treating TNBC. A wide variety of nanoparticle-centric drug formulations have been developed and are already playing a vital role in treating the disease. Various nanocarriers like liposomes, metallic nanoparticles, dendrimers, nucleic acid-based nanomaterials, CRISPR nanoparticles, lipid-based nanomedications, and others are being extensively used in the treatment of breast cancers like TNBC. In the future, a greater understanding of nanotechnological improvements will undoubtedly aid in the development of more suitable nanomedicines for treating breast cancers.

AUTHOR CONTRIBUTIONS
IN wrote introduction and incidence of TNBC. SBE compiled the data of trials in treatment of TNBC and nanomedicines used in its treatment while SBI and SC helped in manuscript preparation and analysis of all the data. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING
The authors extend their acknowledgment to the Deanship of Scientific Research at King Faisal University, Al Hofuf, Saudi Arabia, under project number AN000480 for the financial support.
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