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Harnessing Plant-Based Nanoparticles for Therapeutic Intervention in Triple-Negative Breast Cancer: Current Insights and Future Directions

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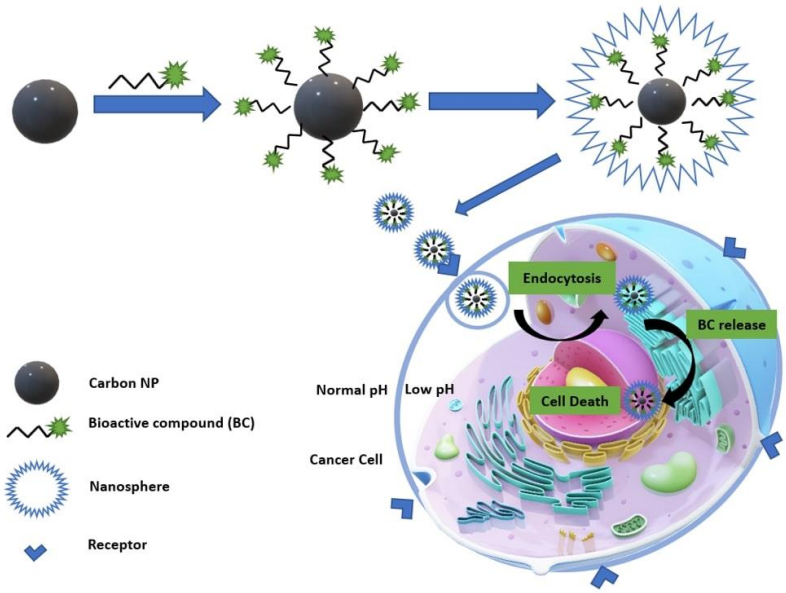
Abstract

Triple-negative breast cancer medication is extremely difficult because of the disease's aggressiveness, poor prognosis, and ineffectiveness against traditional treatments. Modes of Drug delivery based on nanotechnology are a viable option for enhancing treatment results in TNBC. An extensive summary of the possible uses of plant-based nanoparticles in TNBC treatment is given in this review. Plant-derived nanoparticles have special benefits including reduced cytotoxicity, biocompatibility, and environmentally friendly synthesis methods. Recent advancements in the development and synthesis of plant-based nanoparticles, as well as their characterization techniques and functionalization strategies, are discussed. The mechanisms behind plant-based nanoparticle-based targeted drug delivery, encompassing both actively and passively targeted mechanisms, are described. Furthermore, the review explores recent advancements in in vitro and in vivo studies analysing the cytotoxicity, anticancer activity, pharmacokinetics, and biodistribution of plant-based nanoparticles in TNBC models. Future directions and opportunities for novel drug delivery strategies, including combination therapies with immunotherapy or radiotherapy, and personalized medicine approaches utilizing plant-based nano-drug delivery systems are also highlighted. Overall, plant-based nanoparticles present a promising approach for overcoming the challenges in TNBC treatment and improving therapeutic outcomes.

Keywords: Triple-Negative Breast Cancer, Plant-Based Nanoparticles, Drug Delivery Systems, Nanotechnology, Targeted Therapy

Introduction

Graphical Abstract:



Overview of Triple-Negative Breast Cancer

Triple-Negative Breast Cancer (TNBC) lacks the hormone receptor expression like other breast cancer cells and is a subkind of breast cancer that is caused due to the amplification of HER2. TNBC is known to have a high risk of metastasis, high invasiveness, recurrence tendency, and poor prognosis [1]. It is a breast cancer with

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various pathological features and molecular subtypes. Angiogenesis, apoptosis-regulating proteins, immunological checkpoints, DNA damage response regulators, cell proliferation and migratory regulators, and epigenetic changes are among the biomarker features of TNBC [2]. TNBC cells have a highly fermentative condition as their hallmark metabolic phenotype, however they also demonstrate metabolic adaptability. On the other hand, the metabolic landscape becomes extremely unstable following treatment, resulting in different metabolic states for the populations that survive [1],[3]. A promising method to guide treatment plans and track patient outcomes to comprehend and reduce recurrence is longitudinal imaging of tumor metabolism [4]. For TNBC patients, a range of imaging modalities are available to track chemotherapy responses. Figure 1 represents the types of TNBC and their associated pathway.

1.2 Challenges in TNBC Treatment

Drug transport to the intended site presents difficulties in the medication of metastatic TNBC, which results in inferior therapeutic efficacy [5]. Furthermore, clinical difficulties exist in the prediction of therapy resistance and tumor recurrence in individuals with TNBC [6]. Healthcare professionals find it difficult to keep up with the most recent clinical data, and guidelines due to the rapid rate of innovation in TNBC treatment [7]. TNBC is also more challenging to treat due to its aggressive aggressiveness, poor prognosis, and non-reaction to hormone therapy [8]. These difficulties underscore the necessity of enhanced drug delivery mechanisms, prognostic indicators, and all-encompassing approaches for tailored treatment in TNBC. Table 1 shows a few biomarkers associated with TNBC pathology.

Table 1: Few biomarkers and their role in TNBC

Biomarker	Description	Relevance in TNBC Pathophysiology	Ref.
Angiogenesis	The process by which new blood vessels are formed.	Necessary for the development and metastasis of the tumor. TNBC shows elevated levels of angiogenic factors like VEGF, making it a target for therapy.	[9]
Apoptosis-Regulating Proteins	Proteins, such as caspases, p53, and Bcl-2, that control programmed cell death.	Abnormalities in these proteins can lead to uncontrolled cell growth. Mutations in p53 are common in TNBC.	[10]
Immunological Checkpoints	Proteins like PD-L1 on tumor cells and PD-1 on T cells that regulate immune responses.	TNBC often expresses high levels of PD-L1, leading to immune evasion. Checkpoint inhibitors are being explored as treatment options.	[11]
BRCA1/2 Mutations	Mutations in these genes are associated with DNA repair defects.	Up to 20% of TNBC patients carry BRCA mutations, making PARP inhibitors a potential therapeutic strategy.	[12]
Androgen Receptor (AR)	Though TNBC lacks ER and PR, some express the androgen receptor.	AR positivity in TNBC has been associated with a distinct subset that may respond to anti-androgen therapies.	[13]
Epithelial-Mesenchymal Transition (EMT) Markers	Markers indicate a change in status from epithelial to mesenchymal, which aids in metastasis.	EMT markers like N-cadherin and vimentin are upregulated in TNBC, indicating higher metastatic potential and poor prognosis.	[14]
Cytokeratins	Intermediate filament proteins in epithelial cells, including CK5/6, CK14, and CK17.	These are often expressed in TNBC and are used to identify basal-like TNBC, which is associated with a poorer prognosis.	[15]
Growth Factor Signaling	Involves pathways like EGFR, FGFR, and IGFR, important for cell division and survival.	TNBC frequently overexpresses EGFR, making it a target for therapeutic intervention. FGFR and IGFR are also being studied as targets.	[16]
Tumor Infiltrating Lymphocytes (TILs)	Immune cells are seen in the milieu surrounding the tumor.	An improved prognosis and response to neoadjuvant chemotherapy and immunotherapy are linked to high TIL levels in TNBC.	[17]

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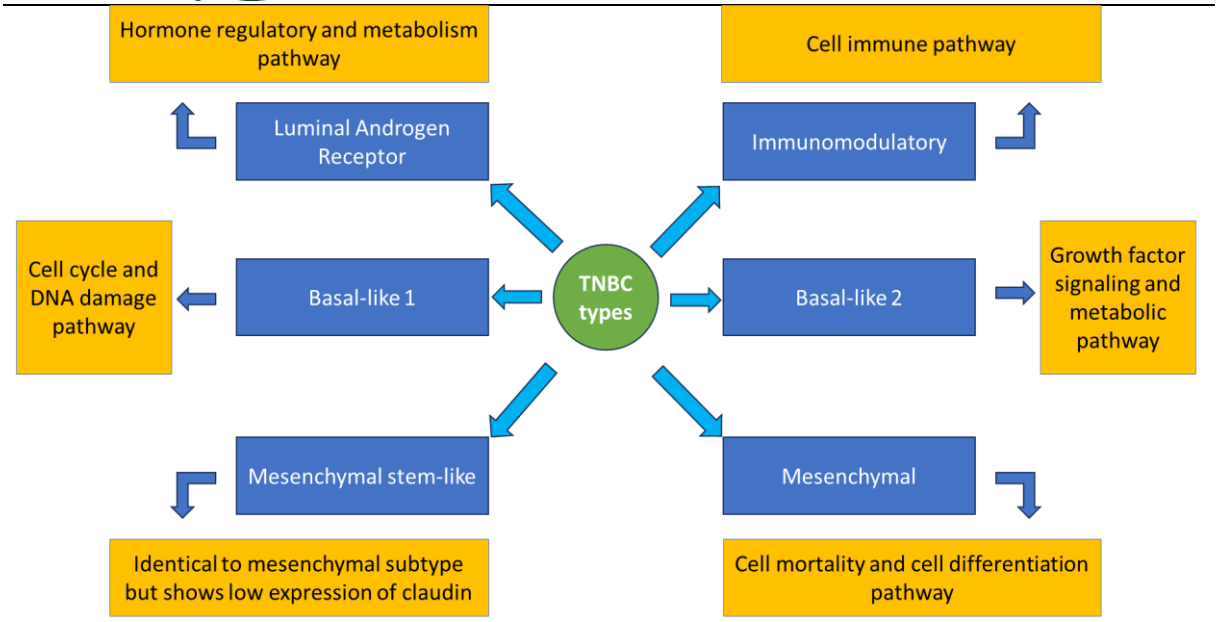

Figure 1: Types of TNBC and their associated pathway

1.3 Introduction to Nanoparticles as Drug Delivery Systems

Plant-based nanoparticles as drug-delivery vehicles for the treatment of TNBC have been demonstrated in various studies [18]. Targeted delivery of treatment regimens to TNBC can be improved by delivery systems dealing with immune cell-based nano-systems, cell membrane-coated nanoparticles, and smart nanoparticles [19]. Furthermore, naturally occurring polysaccharides sourced from plants have been included in drug delivery nanoparticle designs, providing benefits such as reduced cytotoxicity, biodegradability, and biocompatibility [20]. These polysaccharide-based nanoparticles can successfully localize medications to the intended location, minimizing unfavorable side effects. [21]. Furthermore, plant-derived nanoparticles (PDNPs) have gained attention as innovative delivery systems due to their non-toxicity, low immunogenicity, and lipid bilayer protection [22]. PDNPs have been studied for their interactions with mammalian systems and their potential for encapsulating therapeutic molecules. Plant-based nano-drug delivery systems are promising for TNBC medication because they can enhance the bioavailability and effectiveness of plant extracts when combined with herbal therapy.

1.4 Rationale for Using Plant-Based Nanoparticles

TNBC treatment may benefit from the use of plant-derived nanoparticles [23]. TNBC is a variant of breast cancer in which progesterone, estrogen, and human epidermal growth factor receptors are not expressed [24]. Current treatment options for TNBC, such as chemotherapy, have limitations including drug resistance and off-target toxicity [25]. Nanoparticle-based therapy has been proposed as a solution to improve TNBC treatment [26]. Nanoparticles can act as drug carriers and have the potential to reduce toxicity and deliver multiple treatment methods simultaneously [27]. Various types of nanoparticles, including mesoporous silica nanoparticles and plant-derived nanoparticles, have been investigated for their effectiveness in TNBC treatment. Chemotherapeutic medications and immunotherapy medicines can be coated on these nanoparticles to produce a dual-targeted delivery system for the two treatments. The use of plant-derived nanoparticles in TNBC treatment holds promise for improving therapeutic outcomes and overcoming the challenges associated with current treatment options.

Background

2.1 Brief History of Nanoparticles in Cancer Therapy

Plant-based nanoparticles have shown promise in cancer therapy. These nanoparticles can increase phytochemicals' bioavailability., which are compounds derived from plants with anticancer properties [28]. Nanoparticles based on phytochemicals can lessen the adverse effects of traditional chemotherapy, increase the therapeutic effects of anticancer treatments, and improve medication transport to cancer cells. [29]. Additionally, phytochemicals can act as targeting agents, concentrating on cancer stem cells and reducing the risk of tumor relapse and metastasis [30]. Combining phytochemicals with traditional anticancer medications can be administered using nanotechnology-based carriers, such as nanoemulsion, nanosuspension, and polymeric nanoparticles, which will increase their solubility, lessen their side effects, and increase their efficacy

[31]. These plant-based nanoparticles offer a potential solution to the challenges faced by conventional chemotherapy, providing a more effective and targeted approach to cancer treatment.

2.2 Nanoparticle Types for Drug Delivery

Drug delivery techniques frequently employ nanoparticles. Various kinds of nanoparticles, such as liposomes, dendrimers, and micelles, are utilized for this purpose [32]. Magnetic nanoparticles (MNPs) are also frequently employed for drug administration and have many uses within the area of tissue engineering, cancer treatment, and targeted drug delivery [33]. Nanoparticles can assist regulate medication release, increase bioavailability to specific locations or organs, and improve intracellular penetration. [34]. Additionally, nanomaterials can be engineered to react to particular stimuli, such as enzymes, pH, or light, further enhancing their effectiveness in drug delivery [35]. The use of nanoparticles in drug delivery aims to overcome challenges such as reduced biodistribution, non-selectivity, and low bioavailability associated with traditional drug therapies. Table 2 lists various types of nanoparticles and their primary uses in TNBC drug delivery

Table 2: Various types of nanoparticles in TNBC drug delivery

Nanoparticle Type	Description	Primary Use Cases in TNBC Drug Delivery	Ref.
Liposomes	Hydrophilic and hydrophobic medicines can be encapsulated in spherical vesicles with a phospholipid bilayer.	Employed for targeted drug administration to TNBC cells, enhancing the solubility and bioavailability of chemotherapeutic agents.	[36]
Dendrimers	Highly branched, tree-like structures, allow for the attachment of multiple drug molecules.	Employed in targeted therapy, serving as carriers for drugs and genetic material to TNBC cells due to their customizable surface.	[37]
Micelles	Hydrophobic-cored, hydrophilic-shell self-assembling colloidal nanoparticles.	Utilized for solubilizing hydrophobic drugs and targeting them to the tumor site, improving drug accumulation in TNBC cells.	[38]
Magnetic Nanoparticles	Iron-based nanoparticles that can be guided by an external magnetic field.	Applied for hyperthermia treatment and magnetic targeting of drugs to TNBC tumors, enhancing the uptake and efficacy of chemotherapeutics.	[39]
Polymeric Nanoparticles	Made from biodegradable polymers, capable of encapsulating drugs and protecting them from degradation.	Used for targeted delivery and controlled release of drugs, improving the therapeutic outcome in TNBC treatment.	[40]
Solid Lipid Nanoparticles	Composed of solid lipid core matrices that can stably incorporate drug compounds.	Facilitate the targeted and sustained release of drugs, reducing systemic toxicity and improving treatment efficacy in TNBC.	[41]
Gold Nanoparticles	Tiny gold particles with unique optical properties, allow for easy functionalization and targeting.	Leveraged for photothermal therapy and targeted drug delivery, aiming to enhance the specificity and efficacy of TNBC treatment.	[42]

2.3 Characteristics of Plant-Based Nanoparticles

Plant-based nanoparticles have several characteristics that make them advantageous in cancer medication. Firstly, they can improve the bioavailability of phytochemicals, which are compounds derived from plants with anticancer properties [28]. Secondly, plant-based nanoparticles can enhance the targeting effects of anticancer drugs by acting as targeting agents for tumor sites [29]. Additionally, these nanoparticles can control the release of therapeutic substances, increasing their effectiveness and reducing side effects [43]. Additionally, using plant-based compounds in nanoparticle compositions can lessen toxicity and increase biocompatibility [30]. Lastly, phytochemical-based nanoparticles have the potential to reduce the risk by targeting cancer stem cells specifically tumor relapse and metastasis [31]. Overall, plant-based nanoparticles offer a promising strategy for enhancing the safety and effectiveness of cancer drugs.

2.4 Current Treatment Modalities for TNBC

Present healthcare treatment modalities for TNBC include standard cytotoxic chemotherapy with anthracyclines and taxanes [44]. However, TNBC is known for its limited treatment responses and high rates of recurrence and metastasis [45]. To overcome these challenges, various targeted strategies have been investigated, such as immune checkpoint inhibitors, capecitabine, and olaparib [46]. Furthermore, promising outcomes have been observed with targeted therapies based on particular biomarkers, such as entrectinib and larotrectinib for NTRK gene fusion carriers, anti-Trop2 antibody-drug conjugate therapy for heavily pretreated metastatic TNBC, and PARP1 and PARP2 inhibitors for BRCA1/2 germline mutation carriers [47]. Other potential therapeutic options under investigation include inhibitors of the PI3K/Akt/mTOR and EGFR pathways, along with antiandrogens [48]. The goal is to develop more efficient and tailored treatment approaches to improve survival outcomes for TNBC patients.

Recent Advancements in Plant-Based Nanoparticles

3.1 Development and Synthesis Methods

Recent advancements in the development and synthesis methods of plant-based nanoparticles have gained significant interest in various fields. In addition to their affordability, sustainability, and environmental friendliness, plant-derived metal nanoparticles (PDMNPs) have demonstrated enormous potential as medicinal agents and in the production of biomedical equipment. [49]. The use of plant biomass as a substrate for nanomaterial synthesis has appeared as an affordable and environmentally safe substitute for traditional methods [50]. Considering green chemistry-based synthesis using plant-based leaf extracts is inexpensive and poses no risk to humans or the environment, it has been widely used in medicine, healthcare, and drug discovery [51]. Plants have also been explored for their ability to synthesize metal nanoparticles, which have diverse applications in biomedicine, agriculture, optics, and the environment [52]. Plant-mediated sustainable synthesis provides an easy, affordable, long-term, and environmentally beneficial method for producing metal nanoparticles., with potential applications in the treatment of multidrug-resistant bacteria [53]. Table 3 lists some sources of plant materials used in nanoparticle synthesis that are used in TNBC medication.

Table 3: Plant-based nanoparticles and their advanced application in TNBC treatment

Plant-based Nanoparticle	Source	Characteristics	Applications in TNBC Treatment	Ref.
Polymeric Nanoparticles	PLGA from corn and sugarcane	Highly biodegradable and biocompatible; Controlled release capabilities	Targeted drug delivery to TNBC cells, minimizing side effects	[54]
Lipid-based Nanoparticles	Liposomes from soy phospholipids	Biodegradable and biocompatible; Excellent drug carrier	Encapsulation of hydrophobic drugs for TNBC; Enhanced permeability and retention effect	[55]
Metallic Nanoparticles	Gold nanoparticles synthesized using plant extracts	Variable biodegradability; Biocompatibility can be enhanced with coating	Photothermal therapy; Drug delivery; Diagnostic imaging	[56]
Silica Nanoparticles	Mesoporous silica nanoparticles using rice husk	Biodegradable (rate varies); High biocompatibility with proper modification	Drug delivery vehicles for chemotherapy drugs; Controlled release systems	[57]
Carbon-based Nanoparticles	Carbon dots synthesized from fruits	Biodegradability varies; High biocompatibility	Imaging for TNBC; Drug delivery systems; Photothermal therapy	[58]

3.1.1 Green Synthesis Approaches

Various green synthesis approaches for plant-based nanoparticles have been explored. Plant extracts are used in these methods, such as those from diverse plant species, to produce nanoparticles in a single step of synthesis by reducing metal ions [59]. Plant materials are considered advantageous for nanoparticle synthesis as they are easily accessible, inexpensive, safe, and environmentally friendly [60]. Furthermore, microbes such as fungi, bacteria, and algae can be used to create nanoparticles in a more environmentally friendly way [61]. Green nanoparticle production with plant-based materials offers potential applications in catalysis, sensing, electronics, photonics, and medicine [62]. However, there are limitations to the green synthesis method, such as the control of nanoparticle dimensions, crystallinity, and morphology, as well as the polydispersity and longer reaction times associated with this approach [63].

3.1.2 Isolation and Modification Techniques

Various isolation and modification techniques for plant-based nanoparticles have been explored. Plant proteins have been utilized to make nanoparticles via extraction, hydrolyzing, conjugation, microfluidization, and electrospraying. Examples of these proteins include zein, gliadin, soy proteins, wheat glutenin, and proteins from legumes [64]. Green synthesis methods, which are environmentally friendly and economically beneficial, have also been employed for nanoparticle synthesis using plant materials. Various parts of plants have been utilized for green synthesis, with phytochemicals like terpenoids, polyols, and polyphenols playing a role in reducing and capping nanoparticles [65]. Additionally, specific techniques like ultracentrifugation, polyethylene glycol (PEG) extraction, and size exclusion chromatography (SEC) have been used to isolate and purify nanoparticles from plant sources, such as Raphani Semen and ginger rhizome [66,67]. These methods have shown the plant-based nanoparticles' potential for use in medicine delivery, illness treatment, and the creation of functional foods [68].

3.2 Characterization Techniques

3.2.1 Morphological, Structural, and Chemical Characterization

Morphological characterization techniques in plant-based nanoparticle drug delivery involve assessing properties like size, porosity, and surface charge using microscopy and particle size analysis [69]. Structural characterization techniques include X-ray diffraction for crystalline structure determination and transmission electron microscopy for high-resolution imaging of nanoparticles [70,71]. Chemical characterization techniques focus on properties like molecular weight determination, solubility, and purity assessment using spectroscopic techniques like UV, MS, and NMR [72]. Additionally, Fourier transform infrared spectroscopy is utilized for analyzing chemical composition in nano-phytopharmaceuticals [73]. These techniques collectively provide a comprehensive understanding of the physio-chemical, and structural, characteristics of plant-based nanoparticles, essential for optimizing their drug delivery potential.

3.2.2 In vitro and In vivo Evaluation Methods

Various in vitro and in vivo evaluation methods have been used for plant-based nanoparticles. In vitro assessment is a valuable tool for quickly assessing the behavior and activity of nanomaterials, providing early signals of their potential toxicity and activity [62]. Using various cell culture models and evaluative markers to identify cellular changes and their effects, in vitro investigations enable The assessment of nanomaterial activity and hazardous potential [74]. Regarding in vivo assessment, silver nanoparticles produced from plant extracts have been shown to have cytotoxicity and wound-healing ability through a dose-dependent in vivo investigation employing a Drosophila model [75]. This study found that the size, shape, and colloidal stability of the nanoparticles influenced their cytotoxicity and wound-healing capacity [76]. Additionally, in vitro studies using HEK-293 cells have been used to assess the bioactivity and efficacy of rosemary essential oil encapsulated in zein nanoparticles [77]. These studies demonstrate the importance of both in vitro and in vivo evaluation techniques for examining the characteristics and possible uses of nanoparticles derived from plants.

3.3 Functionalization Strategies

3.3.1 Targeting Ligands

Plant-based nanoparticles have shown potential benefits in targeting ligands for TNBC [23]. These nanoparticles can overcome the hydrophobicity, short half-life, lack of target selectivity, and limited bioavailability of traditional TNBC therapies. [78]. By functionalizing the nanoparticles with folic acid, they can specifically target TNBC cells that overexpress the folate receptor, enhancing their effectiveness as a treatment [78]. The use of plant phytochemicals in these nanoparticles has also been explored, as studies have shown that antioxidants derived from plants have potential anticancer effects [79]. These nanoparticles can be optimized to deliver particular bioactive compounds that show promise in preventing human cancer, offering TNBC patients a focused and efficient therapeutic option. [80].

3.3.2 Surface Modifications for Enhanced Drug Loading and Release

In pharmaceutical applications, surface modification techniques are commonly employed to improve drug loading and release. Lipid-based nanocarriers can have their surfaces changed with fatty acids, polymers, ligands, and surfactants to provide targeted drug delivery, improved penetration efficiency, and controlled release [81]. By using highly expressed transporters on cancer cells, carbon dots (CDs) can be altered to enhance their cellular uptake process and accomplish selective cancer cell targeting [82]. To improve transport, absorption, and efficacy at infection sites, antibacterial medicines loaded into nanocarriers can have their surfaces modified with saccharides, polymers, peptides, antibiotics, enzymes, and cell membranes [83]. Improved powder dispersion, lung delivery, and stability without agglomeration can be achieved by modifying

the morphological properties of high-intake dry powder inhalers (DPIs) through the use of particle engineering and formulation techniques like micronization and co-processing with limited excipients [84]. Carbon nanotubes (CNTs) can be surface-modified with stabilizers and targeting ligands to enhance their capacity to transport medications to particular body locations and maintain stability in biological systems [85].

Mechanisms of Targeted Drug Delivery with Plant-Based Nanoparticles

4.1 Active Targeting Mechanisms

Plant-based nanoparticles with active targeting mechanisms have been studied for targeted drug delivery. These nanoparticles have benefits like minimal cytotoxicity, biodegradability, and biocompatibility [86]. For selective targeting, they can have their surfaces altered with targeting ligands [19]. Promising results have been observed when using plant-derived nanoparticles for cancer therapy [18]. Research has been done on the use of nanotechnology-based delivery methods, such as cell membrane-coated and smart nanoparticles, for the treatment of a variety of cancers, including TNBC. [87]. By enhancing selectivity in cytotoxicity and cellular uptake, active targeting nanoparticles in conjunction with targeting ligands, such as proteins and peptides, aptamer, folic acid, hyaluronic acid, and antibodies and antibody fragments have demonstrated improved treatment efficiency and safety [88].

4.1.1 Ligand-Receptor Interactions

Plant-based nanoparticles have drawn interest for targeted drug delivery due to their biodegradability, biocompatibility, and low cytotoxicity [89]. Through ligand-receptor interactions, these nanoparticles can have their surfaces changed with ligands to achieve targeted delivery [19]. Many ligands have been investigated for this function, including hyaluronic acid, folic acid, and transferrin [90]. The efficacy of nanoparticles as medication carriers is also significantly influenced by their size [91]. Furthermore, the retention period of drug delivery at the absorption site can be extended by the mucoadhesive qualities of plant polysaccharides [92]. The nanocarriers' response to outside stimuli is crucial for triggered-release drug delivery. The concentration of membrane receptors on nanocarriers determines their responsiveness to trigger stimuli. However, the scale size of nanocarriers restricts the number of receptors they can be loaded with. Overall, plant-based nanoparticles with ligand-receptor interactions offer a promising approach for targeted drug delivery with reduced side effects.

4.1.2 Cellular Uptake Pathways

Plant-based nanoparticles with cellular absorption pathways have demonstrated promise in targeted medication delivery. These nanoparticles, such as phytochemical-based NPs and plant-derived exosome-like nanoparticles (PELNs), potentially enhance therapeutic effects, improve drug uptake, and mitigate side effects [18,30]. Nanotherapeutic agents, including smart nanoparticles and cell membrane-coated nanoparticles, can facilitate efficient drug delivery by utilizing active or passive targeting mechanisms [19]. Plant polysaccharide-based nanoparticles have benefits such as reduced cytotoxicity, biodegradability, and biocompatibility that make them appropriate for drug delivery systems [87]. Active targeting nanoparticles' surface contains targeting ligands that have been demonstrated to enhance medication selectivity in cancer cells, boosting therapy efficacy and safety [86]. These findings suggest that plant-based nanoparticles can be utilized as effective carriers for targeted drug delivery, offering potential solutions for improving cancer treatment outcomes.

4.2 Passive Targeting Mechanisms

Passive targeting mechanisms in plant-based nanoparticles contribute to the efficiency of drug delivery through several factors. Firstly, plant polysaccharides used in nanoparticle design offer benefits such as reduced cytotoxicity, biodegradability, and biocompatibility, which make them appropriate for medication administration [19]. Further, drug/gene delivery and transmembrane transport depend critically on the size of the nanoparticles, and plant polysaccharides offer a wealth of reactive groups for surface modification and targeted specificity [18]. Plant-derived exosome-like nanoparticles (PELNs) have also been investigated as naturally occurring nano-carriers for medication delivery because of their stability, minimal immunogenicity, and capacity to homing toward tumors. [86]. The use of plant metabolites in green synthesis methods also enables the production of metal nanoparticles for drug delivery, which are cost-effective and eco-friendly [35]. Overall, passive targeting mechanisms in plant-based nanoparticles offer the potential for improved drug delivery efficiency, reduced side effects, and targeted delivery to target sites [35]. Table 4 lists some major phytocompounds and their mechanism of action against TNBC and their outcomes.

Table 4: Plant compounds, mechanism of action, and their effects in TNBC treatment.

Plant/Compound	Mechanism of Action	Clinical Trial Phase	Observed Benefits/Outcomes	Ref.
Paclitaxel (Taxol)	Microtubule stabilization,	Approved	Improved survival rates in	[93]

	inhibiting cell division		combination with chemotherapy	
Curcumin	Inhibition of NF-kB, reduction in cytokine expression, and cell proliferation	Preclinical	Decreased metastasis and tumor development in animal models	[94]
Epigallocatechin Gallate (EGCG) from Green Tea	Antioxidant, apoptotic induction, and suppression of cell proliferation	Preclinical	Inhibited growth and induced apoptosis in TNBC cell lines	[95]
Quercetin	Antioxidant, anti-inflammatory, and antiproliferative effects	Preclinical	Decreased cell viability and caused TNBC cells to undergo apoptosis	[96]
Genistein (Soy)	Tyrosine kinase inhibitor; affects cell cycle and apoptosis	Preclinical	Inhibitory effects on cell proliferation and metastasis	[97]
Resveratrol (Grapes, Berries)	SIRT1 activation, NF-kB inhibition	Preclinical	Suppressed TNBC cell growth and induced apoptosis	[98]
Withaferin A (Ashwagandha)	Inhibitors of NF-kB, Hsp90, and angiogenesis	Preclinical	Reduced tumor size and weight in mouse models of TNBC	[99]
Camptothecin	Topoisomerase I inhibitor, preventing DNA replication	Clinical trials	Shown to have potent antitumor activity, with synthetic derivatives in use	[100]

Employing Plant-Based Nanoparticles for TNBC Therapy

Plant-based nanoparticles have shown potential in the curing of TNBC [18]. These nanoparticles can be used in combination with photodynamic therapy to improve treatment outcomes [101]. By using phytocompounds derived from plants as photosensitizers, the nanoparticles can enhance the photosensitizing properties in the tumor and achieve target-specific accumulation [102]. Additionally, nanoparticles can be modelled for drug carriers, to attain specific targeted delivery of therapeutics to TNBC cells [103]. Furthermore, the use of aptamers as targeting agents for the nanoparticles has been explored [104]. Aptamers are single-stranded, short oligonucleotides that have a strong affinity for certain targets. These aptamer-decorated nano vectors have been shown to efficiently deliver therapeutic payloads, such as small interfering RNA (siRNA), to TNBC cells. Overall, plant-based nanoparticles provide a potentially effective method for treating TNBC. by improving the efficacy and precision of therapy. The numerous kinds of nanoparticles utilized in the drug delivery of breast cancer medications are shown in Figure 2 below.

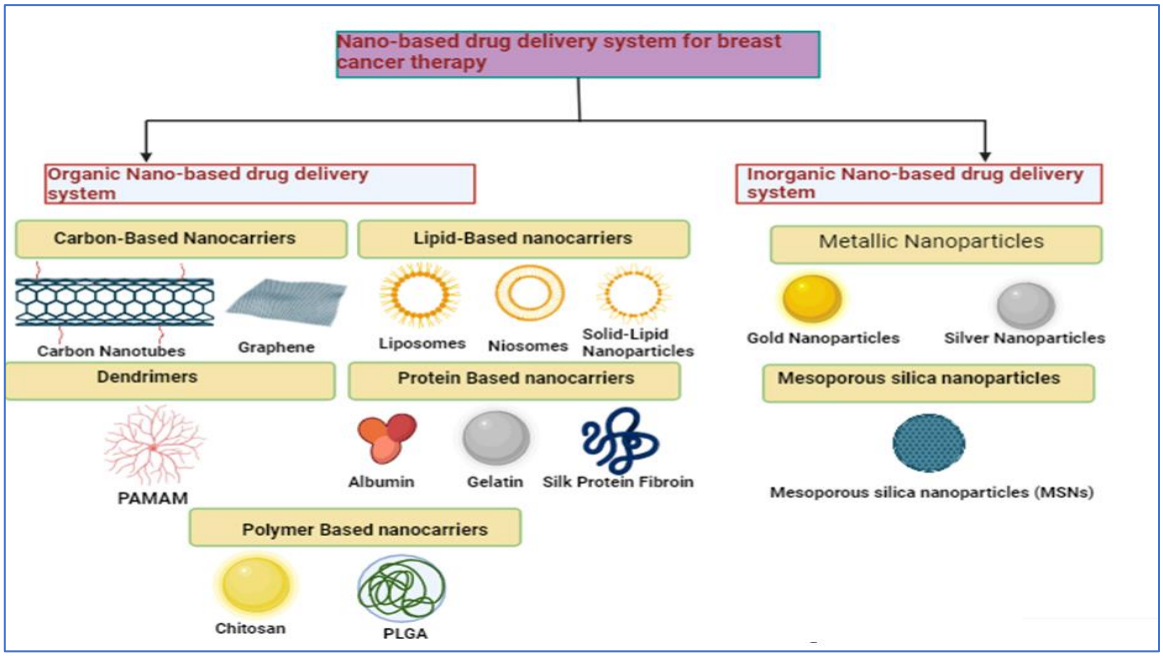

Figure 2: Different nanotechnology-based drug delivery methods for the treatment of TNBC

5.1 In vitro Studies

Plant-based nanoparticles have shown potential in in vitro studies in TNBC [105]. These nanoparticles can improve the bioavailability of phytochemicals, which have chemopreventive properties against prostate cancer [29]. Phytochemicals can be added to nanoparticles to overcome their inadequate circulation time, chemical instability, and poor water solubility [104]. Furthermore, phytocompounds possess the capacity to target tumor locations and improve the nanoparticles' biocompatibility. It has been demonstrated that using these nanoparticles increases the treatment efficacy against TNBC, including the inhibition of the expression of programmed cell death-ligand 1 (PD-L1), an essential element of cancer cells' immunological evasion [101]. These nanoparticles can efficiently deliver siRNA and other therapeutic payloads to TNBC cells, leading to stronger PD-L1 silencing and potential eradication of TNBC cells. Therefore, plant-based nanoparticles provide a viable strategy for enhancing the efficiency of targeted therapies for TNBC.

5.1.1 Evaluation of Cytotoxicity and Anti-Tumor Activity

TNBC has demonstrated significant cytotoxicity and anti-tumor efficacy in plant-based nanoparticles [18,106]. To improve the pharmacokinetic profile and targeted medication delivery to TNBC, nanotechnology-based delivery technologies have been developed, including cell membrane-coated nanoparticles and smart nanoparticles [105]. Protein-based nanosystems, such as casein nanoparticles, have demonstrated excellent biocompatibility and cytotoxicity against TNBC cells [107]. Additionally, green-synthesized potassium-doped zinc oxide nanoparticles have shown higher cytotoxicity against cancer cell lines compared to pure zinc oxide nanoparticles [108]. Furthermore, a silica nanosystem with a complex of MnO2 and doxorubicin has exhibited favorable biosafety and antitumor effects against TNBC. These findings suggest that plant-based nanoparticles, along with nanotechnology-based delivery systems and protein-based nanosystems, show promising activity for the formulation of safe and effective therapies for TNBC.

5.2 In vivo Studies

Advances in in vivo studies have focused on pharmacokinetics and biodistribution, as well as therapeutic efficacy in animal models of plant-based nanoparticles. Animal models are frequently opted to assess the toxicity and effectiveness of nanomedicines, particularly medication formulations based on nanoparticles. These models help assess the therapeutic indices of nanomedicines in specific diseases such as diabetes [109]. In the field of cancer management, experimental animal models have been used to assess the efficacy of potential chemo-preventive agents, including nano-delivery vehicles. These models comprise zebrafish, cell line-induced models, genetically modified models, chemically induced animal models, small and large animals, xenografts, and Drosophila models [110]. Drug delivery relies heavily on nanoparticles, and knowledge of their pharmacokinetic profile is critical to comprehending both their benefits and drawbacks. The biological destiny of nanoparticles is influenced by size, shape, surface chemistry, and administration routes, among other factors [111]. Novel drug delivery systems have been created to enhance the therapeutic efficacy, safety, and bioavailability of plant-active metabolites. Among these systems are phytosomes, liposomes, nanoparticles, and polymeric micelles. [112].

Future Directions and Opportunities

6.1Novel Drug Delivery Strategies

6.1.1 Combination Therapies with Immunotherapy or Radiotherapy

Plant-based novel drug delivery systems have shown promise in combination therapies with immunotherapy or radiotherapy. These systems utilize plant-derived natural products like polysaccharides, phenols, and terpenoids to enhance drug delivery[113]. Herbal medicine, rich in antioxidants and anticancer components, can cause cancer cells to undergo apoptosis without endangering healthy cells, making them valuable in inflammation treatment [114]. Additionally, by improving immune function and modifying the tumor microenvironment, combining immunotherapy and chemotherapy with enzyme-sensitive tumor-targeting nano-drug delivery devices has shown synergistic anticancer effects [115]. Plant virus nanoparticles (PVNPs) have also emerged as potential candidates for cancer immunotherapy, acting as immune adjuvants and stabilizing cancer antigens for effective antitumor immune responses [116]. These advancements highlight The potential of methods based on plants in enhancing combination therapies for cancer treatment.

6.1.2 Personalized Medicine Approaches

Advancements in plant-based personalized medicine approaches in nano-drug delivery have shown significant promise in cancer treatment. Curcumin, quercetin, and resveratrol are examples of phytochemicals produced from plants that have anti-cancer properties but face limitations like poor bioavailability and low solubility [21,30]. Nanotechnology offers solutions by enhancing the delivery of these compounds through nanoscale

formulations, improving their efficacy in targeting cancer cells [88,117]. To optimize the impact of drugs on cancer cells while avoiding damage to normal tissue, plant-derived nanomaterials have been investigated for use in cancer therapy [118]. By combining herbal medicine with nanotechnology, the action of plant extracts can be potentiated, reducing side effects and improving treatment outcomes through targeted drug delivery. These advancements highlight the potential of personalized medicine approaches utilizing plant-based nano-drug delivery systems in improving cancer treatment efficacy.

Conclusion

Plant-based nanoparticles' potential as medication delivery systems for the medication of TNBC is discussed in the review study., a subtype known for its aggressiveness and limited treatment options. The introduction provides an overview of TNBC, highlighting its heterogeneity and challenges in treatment, including drug resistance and poor prognosis. It also introduces the concept of nanoparticles as potential solutions for drug delivery in TNBC therapy. The background section provides an overview of the history of nanoparticles in cancer therapy, emphasizing the advantages of plant-derived nanoparticles for improving drug delivery efficiency and reducing adverse effects. Various types of nanoparticles and their properties are discussed, with a focus on their potential applications in TNBC treatment.

Recent advancements in plant-based nanoparticles, including development and synthesis methods, characterization techniques, and functionalization strategies, are thoroughly reviewed. Green synthesis approaches, isolation and modification techniques are explored, along with their potential applications in drug delivery systems. Characterization techniques and evaluation methods for plant-based nanoparticles are discussed in detail, emphasizing their importance in optimizing drug delivery potential. The mechanisms of targeted drug delivery with plant-based nanoparticles are elucidated, focusing on both active and passive targeting mechanisms.

To demonstrate their therapeutic potential, applications of plant-based nanoparticles in TNBC treatment, including in vitro and in vivo research, are discussed. The use of plant-based nanoparticles in combination therapies and personalized medicine approaches is explored, showcasing their versatility and effectiveness in improving cancer treatment efficacy. The paper concludes with future directions and opportunities, emphasizing the need for further research in novel drug delivery strategies and personalized medicine approaches utilizing plant-based nanoparticles. The potential of combination therapies with immunotherapy or radiotherapy is highlighted, along with the importance of personalized medicine in improving cancer treatment outcomes. Overall, the review paper provides an extensive overview of the potential of plant-based nanoparticles in TNBC treatment, highlighting their versatility, effectiveness, and future prospects for improving cancer therapy.

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