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Review Article

The Use Of Nanocarriers For The Delivery of Natural Ingredients As Drugs For Successful Breast Cancer Treatment: A Comprehensive Review of Literature

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ABSTRACT

Millions of women globally are impacted by breast cancer (BC) each year, despite recent improvements in diagnosis and treatment. Drug resistance and the dearth of viable
alternatives to therapy for metastatic and triple-negative BC are frequently linked with a poor outcome in BC patients. Because natural compounds have strong safety profiles and multi-target pathways of action, a lot of research has been done to discover their anti-BC potentials in response to these unmet demands. In preclinical BC models, a variety of natural bioactive substances including extracts from medicinal plants and essential oils have shown anti-cancer activity. However, despite the encouraging preclinical findings, the low stability, water solubility, and bioavailability of organic compounds have repeatedly prevented their clinical translation. There have been efforts to get outside of these limitations, particularly through the help of drug delivery systems based on nanotechnology (NDDSs).The approaches by which NDDSs target malignancies, the advantages and drawbacks of the main classes of NDDSs, and their present clinical role in the treatment of BC are all discussed in this study.likewise it covers the suggested anti-BC processes and the nanoformulations of nine natural bioactive compounds and extracts/essential oils from medicinal plants. Some of these nanoformulations show bio compatibility with healthy cell lines and rodents models, whereas others showed enhanced anti-cancer activity against preclinical BC models. However, additional clinical investigation is necessary for assessing the efficacy and biocompatibility in individuals.

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Introduction:

As the most common kind of cancer and the leading cause of cancer-related deaths in women, breast cancer (BC) has been recognised as a global health concern. BC had the largest global incidence rate (2,261,419 cases) and rate of mortality (684,996 deaths) in 2020. Early BC detection is now possible thanks to improvements in technology (such as mammography, ultrasound, magnetic resonance imaging, computational tomography, and positron

emission tomography). *Yang ZN, et al. 2017.* However, about 30% of individuals with early-stage BC experience a metastasized relapse. Despite current treatment options, metastatic BC has a 5-year survival rate of only 26%, making it generally incurable. One of the diverse diseases is BC. BC can be broadly divided into three subtypes corresponding on the receptor expression status: triple-negative, human epidermal growth factor receptor 2 (HER2)-enriched, and luminal A/B. With differences in prognosis and response to treatment, several BC subtypes have unique biological characteristics. Specifically, triple-negative breast cancer (TNBC) is difficult to manage since it is linked to a poorer prognosis, more aggressive behavior, a lack of confirmed molecular targets, and fewer treatment options (such as chemotherapy). When treating BC, a multimodal strategy is frequently used. Depending on the patient's tolerance and the stage and subtype of the disease, the treatment plan may involve a combination of surgery, radiation, endocrine therapy, HER2-targeted therapy, or chemotherapy. summarizes the common systemic treatment choices for the three main subtypes of BC. Clinical resistance to chemotherapy, HER2-targeted treatment, and endocrine therapy has been documented, however. The main treatment challenges for BC include medication resistance and the dearth of viable therapeutic alternatives for metastatic BC and TNBC. As a result, BC continues to be a medical field with unmet needs, which has drawn research into the development of new anti-BC medications that provide greater efficacy with lower toxicity. Oils, potions, cures, and traditional medicines are examples of natural goods that have been used historically to treat a variety of illnesses and wounds. Natural products are an essential source for drug development in many therapeutic fields, particularly in infectious diseases and cancer, since their medicinal qualities have drawn attention to the identification of the bioactive component or compounds of interest. For example, more than 60% of anti-cancer medications that are now on the market are derived from natural products. Some of the most successful chemotherapeutic medicines in clinical settings are *etoposide* from *Podophyllum peltatum, vinca* alkaloids from *Catharanthus rosea*, paclitaxel from *Taxus brevifolia*, and *topotecan* and *irinotecan* from *Camptotheca acuminata.* Due to difficulties with high-throughput screening, bioactive molecule identification and synthesis, and lead optimization, the pharmaceutical industry's efforts to find new drugs based on natural products waned in the 1990s. Recent technological developments have, however, assisted in resolving these issues and have rekindled corporate interest in reexamining natural ingredients as a possible source of novel medications. In the form of extracts, natural materials are frequently examined for desirable bioactivities. In order to isolate and identify the bioactive component or compounds, extracts exhibiting the desired bioactivity are further fractionated. One natural source that has been extensively studied for its potential to treat cancer is plants. Numerous plant extracts and extracted phytochemicals—the physiologically active non-nutritive plant chemicals—have been shown in preclinical BC models to have anti-cancer properties. Studies conducted more recently have also raised the possibility of treating BC and other malignancies with essential oils. Essential oils are complex combinations of volatile and lipophilic secondary metabolites that are generated and released by specialized plant secretory systems.Treatment for cancer would benefit from the multi-target modes of action and low side effects of natural extracts, essential oils, and their bioactive components. Although the preclinical results are encouraging, the physicochemical characteristics of natural compounds typically result in low stability, water solubility, and bioavailability, all of which can impede their clinical use. Due to their high volatility, high sensitivity to environmental factors (such as high temperatures, light, and oxygen), limited stability, and high lipophilicity, essential oils have also presented difficulties for therapeutic use and Efforts to address these constraints are viewed as encouraging, particularly when employing nano-based drug delivery systems (NDDSs).

This review first explains how NDDSs target tumors. It next summarizes the main classes of NDDSs, pointing out their benefits, drawbacks, and current clinical status in the treatment of BC. (*Sung H, Ferlay J, Siegel RL, et al 2021)* Following that, the anti-BC mechanisms of a few natural products—such as extracts, essential oils, and naturally occurring bioactive compounds—as well as their nanoformulations that have shown preclinical anti-BC properties are examined.

The Mechanisms by Which Nanotechnology-Based Drug Delivery Systems Target Tumors:

NDDSs are a fast-growing field of study in which medications are delivered to their areas of action using nanoscale materials as carriers. (*Wang L. 2017)* Drug delivery with NDDSs can increase the bioavailability of poorly water-soluble medications, allow for the co-administration of several medications, deliver

pharmaceuticals precisely, shield healthy cells from drug toxicity, and extend the duration of a medication's effects. to NDDSs can accomplish targeted drug delivery to tumors through passive and active targeting mechanisms, which is crucial for increasing the effectiveness of anti-cancer medications while reducing their systemic toxicity.

The Mechanism of Passive Tumor Targeting

Enhanced permeability and retention (EPR) is a characteristic that is typically the basis for passive tumor targeting. When tumors require oxygen, nutrients, and the removal of waste, tumor angiogenesis is triggered. Nevertheless, there are both structural and functional anomalies in the new tumor vasculature. For instance, NDDSs can more easily penetrate newly created blood arteries around tumors because they are leaky, with pore diameters ranging from 100 nm to 2 μM. (*Hattori M, Iwata H. 2018)* Additionally, tumors do not have a regular lymphatic drainage system, which makes these NDDSs more likely to be retained. In general, the EPR effect can increase drug delivery selectivity to tumors by 20–30% compared to normal tissues. To reach the tumors and produce the EPR effect, NDDSs must, however,

(1) Have a suitable level of stability in the blood circulation

(2) Be able to evade sequestration by the mononuclear phagocyte system (MPS) and clearance by the reticuloendothelial system (RES).

In particular, PEGylation of NDDSs has been used to resolve these two issues by increasing their hydrophilicity and lowering their immunogenicity.

The Active Targeting Mechanism for Tumors

Drug efficiency can be further enhanced by active tumor targeting after NDDS tumor formation via the EPR effect. Any ligand that interacts with receptors that are overexpressed on the surface of cancer cells can bind to the NDDS surface to accomplish active tumor targeting. By increasing their affinity for cancer cells, NDDSs may be more readily absorbed by cancer cells through receptor-mediated endocytosis. Interestingly, NDDSs have also been actively targeted for cancer therapy to the tumor microenvironment (TME), tumor endothelial cells, and tumor cell organelles.

The Principal Types of Nano-Based Drug Delivery Systems Assessed for Treatment of Breast Cancer

The potential of NDDSs to improve the effectiveness of anti-cancer medications, lessen their toxicity to healthy cells, and overcome drug resistance makes their application in cancer therapy exciting.In general, 43 NDDSs fall into one of three categories: hybrid (composed of at least two types of nanomaterials), inorganic, or organic. A number of significant NDDS classes have been studied for anti-BC agent delivery44. (*Jin X, Mu P. 2015).* The significance of choosing the best delivery method for a certain medication is demonstrated by the fact that each of these NDDS classes has specific benefits and drawbacks .

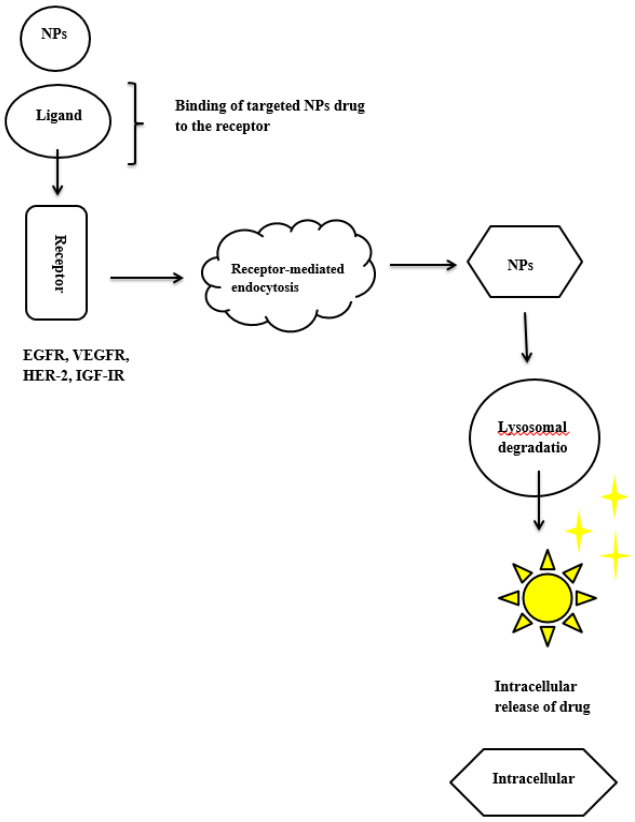
The Drug Delivery Systems Based on Organic Nanotechnology.

The Nanocarriers Made of Carbon:

The occurrence of several carbon allotropes can be explained by the ability of carbon atoms to undergo sp-, sp2-, and sp3-hybridization. A number of synthetic carbon allotropes, such as carbon nanotubes, carbon nanocones, carbon nanohorns, fullerene, graphene, and nanodiamonds, have been created in addition to the three naturally occurring carbon allotropes—amorphous carbon, diamond, and graphite.45 Due to their distinct chemical and physical profiles (such as electrical and thermal conductivity, mechanical strength, optical properties, and structural diversity), carbon-based nanocarriers have been widely used in recent years for a variety of biomedical applications (such as drug delivery and bio-sensing). Furthermore, other characteristics of carbon-based nanocarriers, like as high cellular entrance, preferential tumor accumulation, wide surface area, and high chemical stability, have also rendered them potentially promising as drug carriers in the treatment of cancer. (*Peart O. 2017).*

A suspension of epirubicin and activated carbon nanoparticles was created and clinically tested as a regional lymphatic chemotherapy for BC patients.49 Activated carbon nanoparticle-epirubicin suspension administered regionally to BC patients was found to increase the concentration of epirubicin in the lymph nodes and decrease the concentration of plasma epirubicin compared to those who received intravenous injections of free epirubicin. This suggests that the nanoformulation can enhance the therapeutic efficacy of epirubicin while reducing its systemic toxicities. Additionally, the delayed release of epirubicin in the lymph nodes by this nanoformulation may extend the chemotherapeutic effect. On the other hand, debates about the intrinsic toxicity of carbon-

based nanocarriers frequently impede their continued development. (*Dai X, Li T, Bai Z, et al 2015).*



The Dendrimers:

The well-organized and highly branching architectures of dendrimers, three-dimensional polymeric macromolecules, are their defining characteristics.Fifty A symmetric central core, an inner shell, and an outer shell make up a typical dendrimer. Numerous biomedical and therapeutic applications (such as imaging, gene therapy, and drug delivery) have been made possible by dendrimers' exact molecular weight, biocompatibility, monodispersity, high aqueous solubility, high biological barrier penetrability, and polyvalency. Since the late 1990s, dendrimers have been used to deliver drugs. In actuality, dendrimers have been regarded as multipurpose drug carriers since they can improve a drug's solubility, dissolution, adsorption, bioavailability, stability, and effectiveness in addition to facilitating targeted drug delivery and controlled drug release. (*Yersal O, Barutca S. 2014).*

Numerous dendrimers, such as those based on 2,2-bis(hydroxymethyl) propionic acid, melamine-based dendrimers, poly(amidoamine) (PAMAM) dendrimers, poly(glycerol-succinic acid) dendrimers, poly(propylene imine) (PPI) dendrimers, 5-aminolevulinic acid (ALA)-containing dendrimers, and poly-L-lysine (PLL) dendrimers have all been studied as drug carriers in oncology. Nevertheless, cationic dendrimers frequently impart considerable toxicity, whereas neutral and anionic dendrimers are typically non-toxic. Because cationic dendrimers have a tendency to interact with negatively charged biological membranes, they may cause cytosolic protein leakage, breakdown of membrane integrity, and ultimately cell lysis. According to reports, dendrimers' toxicities can be decreased by masking their charge or charges through surface modification (such as PEGylation).

Patients with advanced brain, breast, cervical, gastro-oesophageal, lung, pancreatic, prostate, and renal cancers were enrolled in the Phase I trial, where a PEGylated PLL dendrimer-based nanoformulation of docetaxel showed superiority over conventional docetaxel in terms of efficacy, safety, and pharmacokinetics. Phase II of nanoformulated docetaxel has been advanced due to the promising Phase I results. In a similar vein, SN-38's PEGylated PLL dendrimer-based nanoformulation has advanced to Phase II after Phase I of its Phase I/II trial showed better anti-cancer efficacy and safety than traditional irinotecan in patients with breast, colorectal, and pancreatic cancer.

The Nanocarriers Based on Lipids:

Because of their ease of preparation, biocompatibility, biodegradability, targetability, high stability, and high drug loading capacity, lipid-based nanocarriers—such as liposomes, niosomes, and solid-lipid nanoparticles [SLNs]—have garnered a lot of interest in the field of drug delivery. Additionally, they can also prolong drug action by enabling controlled drug release and extending drug half-life. Lipid-based nanocarriers are particularly considered to have revolutionised cancer treatment, as they have been reported to improve the efficacies of anti-cancer drugs as well as reduce their therapeutic doses, associated toxicities and drug resistance. (*Mehanna J, Haddad FG, Eid R, Lambertini M, Kourie HR.et al 2019).*

Developed for medication delivery, liposomes are the first generation of lipid-based nanocarriers. The aqueous center of these spherical lipid vesicles is encased in at least one phospholipid bilayer. Liposomes can load hydrophilic and hydrophobic drugs into the aqueous internal compartments and the lipid bilayer, respectively, as phospholipids are amphipathic. PEGylated liposomal doxorubicin became the first FDA-approved nanomedicine in 1995 when it was authorized by the US Food and Drug Administration (FDA) to treat AIDS-related Kaposi's

sarcoma. Multiple myeloma, metastatic BC, and recurrent ovarian cancer are currently also medically treated with it. Studies have demonstrated that PEGylated liposomal doxorubicin is less cardiotoxic than free doxorubicin in all contexts. In 1999, the FDA approved liposomal cytarabine for intrathecal therapy of lymphomatous meningitis. Since then, other clinical studies have been conducted to see whether liposomal cytarabine is useful in treating different kinds of cancer. In a Phase III trial, BC patients with newly diagnosed leptomeningeal metastases who received systemic therapy plus intrathecal liposomal cytarabine had a higher median progression-free survival (3.8 vs. 2.2 months) than those who received systemic therapy alone. However, issues with stability, sterilization, and large-scale manufacturing restrict the development of liposomal nanoformulation.

When non-ionic surfactants and cholesterol self-cluster in aqueous media, spherical vesicles with closed bilayer structures called niosomes are created. Their physical-chemical characteristics and architectures are comparable to those of liposomes, and they can carry both hydrophilic and hydrophobic medications. However, compared to liposomes, niosomes are more stable, need less complicated fabrication techniques, and have lower production costs. As a result, niosomes have been suggested as a substitute for liposomal delivery of medications that fight cancer. It has been claimed that niosomal nanoformulations of doxorubicin71, tamoxifen citrate72, and cisplatin70 exhibit greater anti-cancer activity than their free medicines in preclinical BC models; however, none of them have progressed to clinical trials thus far. The polydispersity of the non-ionic surfactants that are now marketed for niosomes, such as Spans and Tweens, is one of their drawbacks. Lipid matrices that maintain their solid state at physiological temperatures make up SLNs, a relatively recent colloidal drug delivery technology. SLNs can incorporate both hydrophobic and hydrophilic medicines, just like liposomes and niosomes. For hydrophobic medications, they outperform liposomes in terms of stability, entrapment efficiency, repeatability, and the viability of large-scale manufacture.There have been preclinical reports of the anti-BC activity of doxorubicin-,74 methotrexate-,75 paclitaxel-76 and tamoxifen-77 loaded SLNs, despite the fact that no SLN-based nanoformulation of anti-cancer medicines has been clinically tested for BC treatment to yet. Nevertheless, SLNs have a number of disadvantages, including as a low drug loading capacity and the potential for drug expulsion from crystallization during storage.

The Nanocarriers Based on Polymers:

In general, polymer-based nanocarriers can provide targeted drug administration and prolonged release while shielding medications from quick metabolism and removal by the liver, kidney, and RES. They can be made from synthetic or natural polymers. Synthetic polymers are more prevalent than natural polymers, have superior mechanical and thermal stability, and are easier to process to produce the appropriate pore size and scaffold shape. However, synthetic polymers often come with impurities that can affect their biocompatibility, while natural polymers generally offer better biocompatibility and biodegradability. The introduction of semi-synthetic polymers in recent years is the result of modifying natural polymers by grafting, crosslinking, or combining them with synthetic polymers. They are a particularly promising kind of nanomaterial for medication delivery because they combine the beneficial qualities of natural and synthetic polymers. (*Talluri SV, Pindiprolu SKSS, Chintamaneni PK, Tummala S, Nandha Kumar S et al 2017).*

One type of naturally occurring polymers that has been widely used for medication delivery is polysaccharides. Natural sources of these include algae (like alginate), animals (like chitosan, chondroitin, and hyaluronic acid), plants (like pectin, cellulose, and gum arabic), and microorganisms (like dextran, xanthan gum, and hyaluronic acid). Among these, hyaluronic acid, dextran, chitosan, and alginate have been used most commonly to deliver anti-cancer medications. Hydrophobic polymers like poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and polycaprolactone (PCL) as well as hydrophilic polymers like poly(ethylene glycol) (PEG), poly(glutamic acid) (PGA), poly(ethyleneimine) (PEI), poly(acrylamide) (PAM), and poly(vinyl alcohol) (PVA) have all been used to prepare NDDSs. Clinical trials have also been conducted on polymer-based nanoformulations of several chemotherapeutic drugs for the treatment of BC. In patients with recurrent or metastatic HER2-negative BC, a monomethoxy-poly(ethylene glycol)-block-poly(D,L-lactide) (mPEG-PDLLA) micellar formulation of paclitaxel gave better clinical efficacy (i.e., objective response rate of 39.1% vs. 24.3%) and manageable toxicities than conventional paclitaxel, according to a Phase III trial. The South Korean market currently offers this micellar version of paclitaxel for the

treatment of ovarian cancer, non-small cell lung cancer (NSCLC), and metastatic breast cancer. PGA-paclitaxel, another nanoformulation, has also been assessed in Phase II trials for the treatment of ovarian, NSCLC, and BC cancers. According to a Phase II trial, patients with metastatic BC who received PGA-paclitaxel + capecitabine had notable effectiveness and acceptable tolerability. For the treatment of advanced ovarian cancer and non-small cell lung cancer, PGA-paclitaxel has notably progressed to Phase III trials.

The Protein-Based Nanocarriers:

Multiple protein subunits that are capable of accurate and spontaneous self-association to create nanocarriers with internal hollow chambers make up protein-based nanocarriers. Protein-based nanocarriers' practical uses (such as biocatalysis, drug transport, diagnostic imaging, and vaccine development) have rapidly expanded in recent years due to their special qualities. Protein-based nanocarriers are not only biocompatible and biodegradable, but they also have other benefits such easy synthesis and size control, high stability, affordability, surface modification for targeted drug delivery, and controlled drug release. However, high cost (e.g., albumin and ferritin), risk of prion transmission from animal sources (e.g., collagen and gelatin), low mechanical strength (e.g., gelatin), slow degradation (e.g., silk protein fibroin), fast degradation (e.g., gelatin and gliadin), large nanoparticle size (e.g., gliadin), and low yield (e.g., legumin, protamine, and silk protein sericin) are some of the drawbacks of nanocarriers derived from various proteins. Oncology is the field that has used protein-based nanocarriers as NDDSs the most extensively. A lot of attention has been paid to albumin nanocarriers in particular since it has been shown that albumin preferentially accumulates in solid tumors. For example, in 2005, the FDA approved albumin-bound paclitaxel nanoparticles for the treatment of metastatic BC after they showed higher anti-cancer activity and lower toxicity than traditional paclitaxel in preclinical and clinical investigations. Nanoparticle albumin-bound rapamycin also shown good tolerability, stable disease, and early response in patients with advanced non-hematologic malignancies, including BC, in a Phase I trial. It is presently undergoing Phase II trials, either as a standalone treatment or in conjunction with other therapies, for various cancers including high-grade glioma and newly diagnosed glioblastoma and advanced malignant perivascular epithelioid cell tumour. (*Cheung KL et al 2020).*

The Inorganic Nano-Based Pharmaceutical Delivery Systems

The Nanoparticles of Metal:

Colloidal particles with diameters between 10 and 1000 nm are known as metallic nanoparticles. Sie sind bekannt für ihre einzigartigen katalytischen, elektrischen, magnetischen, optischen und thermischen Eigenschaften, die einfache Oberflächenchemie und Funktionalisierung sowie die leichte Synthese. Due to these characteristics, metallic nanoparticles have been thoroughly examined for various biomedical uses (such as diagnostic testing, imaging, enhancing radiotherapy, thermal ablation, and gene and drug delivery), making them versatile. (*Waks AG, Winer EP et al 2018).*

Metallic nanoparticles exhibit intrinsic and extrinsic anti-cancer properties. Zum Beispiel wurde berichtet, dass mehrere metallische Nanopartikel (z. B. Silber, Gold, Ceroxid, Kupferoxid, Eisenoxid, Titandioxid und Zinkoxid) intrinsische anti-krebsaktive Wirkungen durch unterschiedliche Mechanismen vermitteln. Targeted hyperthermic therapy demonstrates the extrinsic anti-cancer effects of metallic nanoparticles. A thermal therapy product utilizing iron oxide nanoparticles has received approval from the European Medicines Agency (EMA) for glioblastoma treatment. After directly injecting a dispersion of aqueous iron oxide nanoparticles into the tumor, an alternating magnetic field is applied to produce heat that will kill the cancer cells.

Metallic nanoparticles can serve dual purposes: they can act as anti-cancer agents themselves and as novel drug delivery systems for anti-cancer medications. Their large surface area-to-volume ratio allows for chemical modification, and they can load a significant amount of drugs. A colloidal gold-bound tumour necrosis factor, a metallic nanoformulation, has successfully finished Phase I trials in patients with various cancers, including BC. It could be given in doses higher than the maximum tolerated dose of native tumor necrosis factor, while still demonstrating reasonable tolerability and tumor targetability. Nevertheless, certain metallic nanoparticles have been linked to toxic effects, despite the metals used being relatively inert (such as gold, silver, and copper), as well as having low stability and biocompatibility. (*Anampa J, Makower D, Sparano JA. et al 2015).*

The Nanoparticles of Mesoporous Silica:

MSNs (mesoporous silica nanoparticles) are silica materials characterized by a highly ordered porosity

ranging from 2 to 50 nm in diameter. They have come to be regarded as an ideal NDDS due to their distinctive characteristics, such as easy fabrication, adjustable particle size and shape, high internal pore volume and surface area that results in a significant drug loading capacity, strong stability, good biocompatibility, straightforward surface modification and functionalization, and ability to accommodate both hydrophilic and hydrophobic drugs. (*Luque-Bolivar A, Pérez-Mora E, Villegas VE, Rondón-Lagos M. et al 2020).* MSNs were first introduced as NDDSs in 2001 when (Vallet-Regí et al) managed to successfully encapsulate an anti-inflammatory medication (specifically, ibuprofen) within MSNs. Since then, substantial research endeavors have focused on creating MSNs for the treatment of various diseases, especially cancer. Nanoformulations based on MSN of different chemotherapeutic agents (such as doxorubicin117 and epirubicin118) and nucleic acids (like siPlk1 plus miR-200c119 and HER2-targeted siRNA120) have shown preclinical anti-BC effects. Nonetheless, the clinical application of MSNs may be constrained by their reported toxic effects (such as cardiotoxicity, pulmonary toxicity, renal toxicity, and genotoxicity).

The Anti-Breast Cancer Properties of Medicinal Plant Extracts/Essential Oils and Their Nanoformulations in Preclinical Models

Extracts and essential oils from specific medicinal plants comprise a mix of bioactive compounds that demonstrate anti-BC effects through various mechanisms . The extracts and essential oils may demonstrate greater anti-cancer activities than individual bioactive compounds, due to the potential synergistic effects of these bioactive compounds.Nevertheless, extracts and essential oils are often limited in their clinical use for cancer treatment due to their poor bioavailability. In alignment with this, various research efforts have produced nanoformulations of medicinal plant extracts/essential oils that exhibit preclinical anti-BC potential but have not been successfully translated into clinical applications due to bioavailability challenges. (*Dias DA, Urban S, Roessner U et al 2012).*

The *Adiantum capillus-veneris* and *Pteris quadriaurita* Extracts:

The southern maidenhair fern, scientifically known as *Adiantum capillus-veneris*, is an herb that is typically grown in both temperate and tropical areas. It has a broad distribution across America, Europe, the Atlantic coast extending to Ireland, southern Alpine valley regions, Australia, and Iran. Traditionally, A. *capillus-veneris* is used either on its own or in combination with other herbs to address various human ailments, including bronchial disorders, colds, coughs, fevers, hepatitis, jaundice, skin conditions, and tumours. The range of reported pharmacological activities further reflects its therapeutic potential, including anti-diabetic,127 anti-inflammatory,128 antimicrobial,129 anti-nociceptive,130 hypocholesterolemic, 131 wound healing, 132 antioxidant, and anti-cancer 133 activities.

Pteris, which is among the largest genera of ferns, comprises about 200 to 250 species. species of Pteris are found across all continents, with the exception of Antarctica. Humans have utilized them as decorative plants, arsenic hyperaccumulators, food items, spices, and medicinal remedies. Notably, Pteris has a reputation for containing abundant ent-kaurane diterpenoids, a class of compounds whose constituents frequently exhibit strong anti-cancer properties. Pteris quadriaurita (striped brake fern) has been noted for its anti-cancer activity136, as well as its anti-bacterial, anti-fungal, anti-haemolytic, and antioxidant properties.one hundred thirty-seven. (*Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT et al 2021).* The leaf extracts of A. capillus-veneris and P. quadriaurita in methanol have shown anti-cancer effects on BC cell lines.136 In the same research, the authors created gold nanoparticles (AuNPs) from these extracts and assessed the impact of the resulting AuNPs on MCF-7 and BT-47 BC cell lines. Only P. quadriaurita AuNPs exhibited higher cytotoxicity against MCF-7 cells compared to its free extract, with IC50 values of 9 µg/mL and 380 µg/mL, respectively. However, subsequent analyses of gene and protein expression revealed that MCF-7 and BT-47 cells treated with A. capillus-veneris and P. quadriaurita AuNPs caused a more pronounced decrease in the protein level of proliferating cell nuclear antigen (PCNA; a marker of proliferation) compared to those treated with free extracts. It was also noted that the mRNA and protein levels of cyclin D1 and the protein level of cyclin-dependent kinase (CDK)4 decreased more significantly, while the mRNA level of p21 (a CDK inhibitor) increased more significantly, as did the protein level of nuclear p21 compared to cytosolic p21. Furthermore, extracts of A. capillus-veneris and P. quadriaurita, along with their AuNPs, triggered apoptosis in MCF-7 and BT-47 cells, as demonstrated by a notable rise in the number of TUNEL- and Annexin V-positive cells. As evidenced by a decrease in mitochondrial membrane potential ($\Delta\Psi m$), it was further corroborated that apoptosis was mediated by

the mitochondrial apoptotic pathway; an important elevation of the mRNA and protein levels of Bcl-2-associated X protein (Bax; a pro-apoptotic protein), as well as the protein levels of caspase-9 (an initiator caspase in the mitochondrial apoptotic pathway), caspase-3 (an effector caspase), and cytosolic cytochrome c compared to mitochondrial cytochrome c; along with a notable reduction in the mRNA and protein levels of B-cell lymphoma 2 (Bcl-2; das heißt, ein Protein, das gegen Apoptose wirkt). Crucially, AuNPs brought about more significant alterations in the expression of the aforementioned apoptotic markers than did their free extracts. All in all, these results indicate that the formulation of A. Incorporating capillus-veneris and P. quadriaurita extracts into AuNPs can enhance their ability to induce cell cycle arrest, exhibit anti-proliferative effects, and promote apoptosis in BC cells. (*Cragg GM, Pezzuto JM et al 2016).*

Extracts of Annona muricata:

The fruit tree Annona muricata is commonly grown in the tropical areas of Central and South America, Western, Central and Eastern Africa, and Southeast Asia. It is known by various common names in different regions, such as Soursop (in English), Guanábana (in Latin American Spanish), Graviola (in Portuguese), and Omusitafeli/Ekitafeli (in Uganda). Traditionally, various parts of A. muricata, including fruits, leaves, seeds, flowers, bark, and roots, have been utilized to address conditions such as cancer, diabetes, malaria, parasitic infections, and stomach pain. More recent studies have discovered various pharmacological activities of A. muricata extracts, including anti-arthritic, anti-convulsant, anti-diabetic, anti-hypertensive, antioxidant, anti-parasitic, hypolipidemic,wound healing, gastroprotective, hepatoprotective, anti-inflammatory and pain-relieving activities. Especially, extracts derived from the leaves, fruits, and seeds of A. muricata have shown anti-BC activities both in vitro and in vivo.

According to (Sabapati et al 155 2015), when A. muricata ethanolic fruit extract was incorporated into SLNs, the resulting extract-loaded SLNs exhibited a more significant dose-dependent decrease in MCF-7 cell viability compared to the free extract (with IC50 values of 12 µg/mL and 30 µg/mL, respectively). Cells stained with Annexin V-FITC were analyzed using flow cytometry, and the results revealed that extract-loaded SLNs caused a significantly greater percentage of MCF-7 cell apoptosis compared to the free extract (86.0% versus 71.34%). It is noteworthy that void SLNs did not provoke considerable cytotoxicity in MCF-7 cells. These findings suggest that SLNs are biocompatible NDDSs that can increase the cytotoxicity and pro-apoptotic activity of A. muricata extract on BC cells. (Jabir et al156) described the green synthesis of silver nanoparticles using a solution of silver nitrate and an aqueous extract of A. muricata peel in another study. The silver nanoparticles produced (AMSNPs) had a considerable anti-proliferative effect on the AMJ-13 BC cell line (IC50 = 17.34 µg/mL) that was dependent on time, but their effect on the normal HBL breast epithelial cell line was less significant. The anti-proliferative effect of AMSNPs was associated with the promotion of apoptosis through p53 signaling. This was demonstrated by findings such as compromised membrane integrity and lysosomal vacuoles, an increased sub-G1 phase percentage indicative of apoptotic cells, ΔΨm loss, and elevated p53 expression in AMJ-13 cells subjected to treatment. Nevertheless, the research did not assess how the anti-BC effects of AMSNPs and free Aqueous extract of A. muricata peel.

Extracts of Ipomoea Turpethum:

Ipomoea turpethum (or Operculina turpethum), widely referred to as the “transparent wood rose”, is found in various countries including Africa, America, Bangladesh, China, India, Madagascar, Mauritania, Pakistan, Philippines and Sri Lanka. This plant is among those used in Ayurvedic medicine to address ailments such as bronchitis, cancer, cervical lymphadenitis, chronic gout, constipation, dysmenorrhea, fever, fistulas, hemorrhoids, herpes, induced lacrimation, inflammation, jaundice, neurological disorders, obesity, skin disorders, and ulcers. Moreover, extracts of I. turpethum (from stems, roots, aerial parts, and whole specimens) have shown anti-cancer properties in preclinical breast cancer models.

In a similar vein, (Mughees et al.2018) observed that I. turpethum ethanolic extracts derived from various plant components (i.e., flowers, leaves, roots, aerial parts, and whole plant) exhibited considerable cytotoxic effects on both MCF-7 and MDA-MB- BC cell lines. The root extract with the highest cytotoxicity (IC50 values of 452.35 µg/mL for MCF-7 cells and 310 µg/mL for MDA-MB-231 cells) was then incorporated into poly (N-isopropylacrylamide) (NIPAAM; temperature-sensitive), N-vinyl pyrrolidone (VP; temperature-sensitive), and acrylic acid (AA; pH-sensitive) co-polymeric nanoparticles. Due to the excessive lactic acid produced from enhanced glycolysis and the secretion of pyrogenic

substances by tumor cells, the TME is generally more acidic and has a higher temperature than that of normal tissues. As expected, it was noted that this nanoformulation demonstrated greater cytotoxicity compared to the free root extract (specifically, IC50 values of 221. 81 µg/mL for MCF-7 cells and 171.13 µg/mL for MDA-MB-231 cells). Additionally, the IC50 concentrations of this nanoformulation led to a significant decrease in cell proliferation of MCF-7 (from 99.2% to 57.7%) and MDA-MB-231 (from 99.3% to 55.4%); it also led to a significant rise in the proportion of early and late apoptotic MCF-7 (2.2% → 3.4% and 4.1% → 9.2%, respectively) and MDA-MB-231 (6.3% → 14.7% and 4.5% → 7.3%, respectively) cells, as well as to the condensation of nuclear chromatin and an increase in the populations of MCF-7 (50.7% → 63.4%) and MDA-MB-231 (57.9% → 81.3%) cells in G0/G1 phase. All these observations suggest that the NIPAAM-VP-AA co-polymeric nanoparticle-based nanoformulation can boost the cytotoxic effects of I. turpethum extract and has anti-proliferative, pro-apoptotic, and cell cycle arrest-inducing activities against BC cells. (*Beutler JA et al 2009)*

Future Perspectives

Natural products derived from plants have been acknowledged for a long time as an essential supplier of anti-cancer medications. This review presents nine selected medicinal plants, namely A. capillus-veneris, P. quadriaurita, A. muricata, I. turpethum, M. jalapa, P. amboinicus, P. granatum, P. roxburghii and Z. multiflora, whose extracts/essential oils have been assessed for anti-BC potentials. Additionally, nine other natural bioactive compounds that have shown anti-BC potential in the past—balanocarpol, cordycepin, curcumin, diallyl disulfide, EGCG, gallic acid, punicalagin, ellagic acid, and sulforaphane—have been emphasized. Mechanistic studies have connected the anti-BC activities of these natural products to a diverse array of molecular targets or mechanisms, such as the modulation of angiogenesis, apoptotic pathways, autophagy, cell cycle regulators, cellular eicosanoid profile, DNA structure, synthesis and repair processes, damage response genes, EMT markers, enzymes, epigenetic mechanisms, glucose metabolism, heat shock response, immune system functions, inflammation processes, markers linked to aggressive phenotypes, metastasis-related markers, miRNA regulation, oxidative status changes, proliferation markers, protein and RNA synthesis processes, signaling pathways involvement, stem-like markers and tumor suppressors. Nonetheless, the anti-BC mechanisms of extracts from I. turpethum, M. jalapa, P. amboinicus, and P. roxburghii have not been thoroughly investigated, indicating a potential avenue for future research. Despite the fact that the natural products mentioned earlier have demonstrated encouraging anti-BC effects in preclinical research, they have not been progressed into clinical environments. This can be ascribed to their undesirable physicochemical characteristics, which can lead to poor stability, aqueous solubility, and bioavailability, negatively affecting their anti-BC efficacies in humans. Efforts have been made to address these problems, especially through the use of NDDSs. The main types of NDDSs used for BC therapy include carbon-based nanocarriers, dendrimers, lipid-based nanocarriers, polymer-based nanocarriers, protein-based nanocarriers, metallic nanoparticles, and MSNs. Since each of these NDDS classes has different benefits and drawbacks, choosing the most appropriate delivery system for a particular natural product is essential.

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