

Drug Delivery of Natural Products Through Nanocarriers for Effective Breast Cancer Therapy: A Comprehensive Review of Literature

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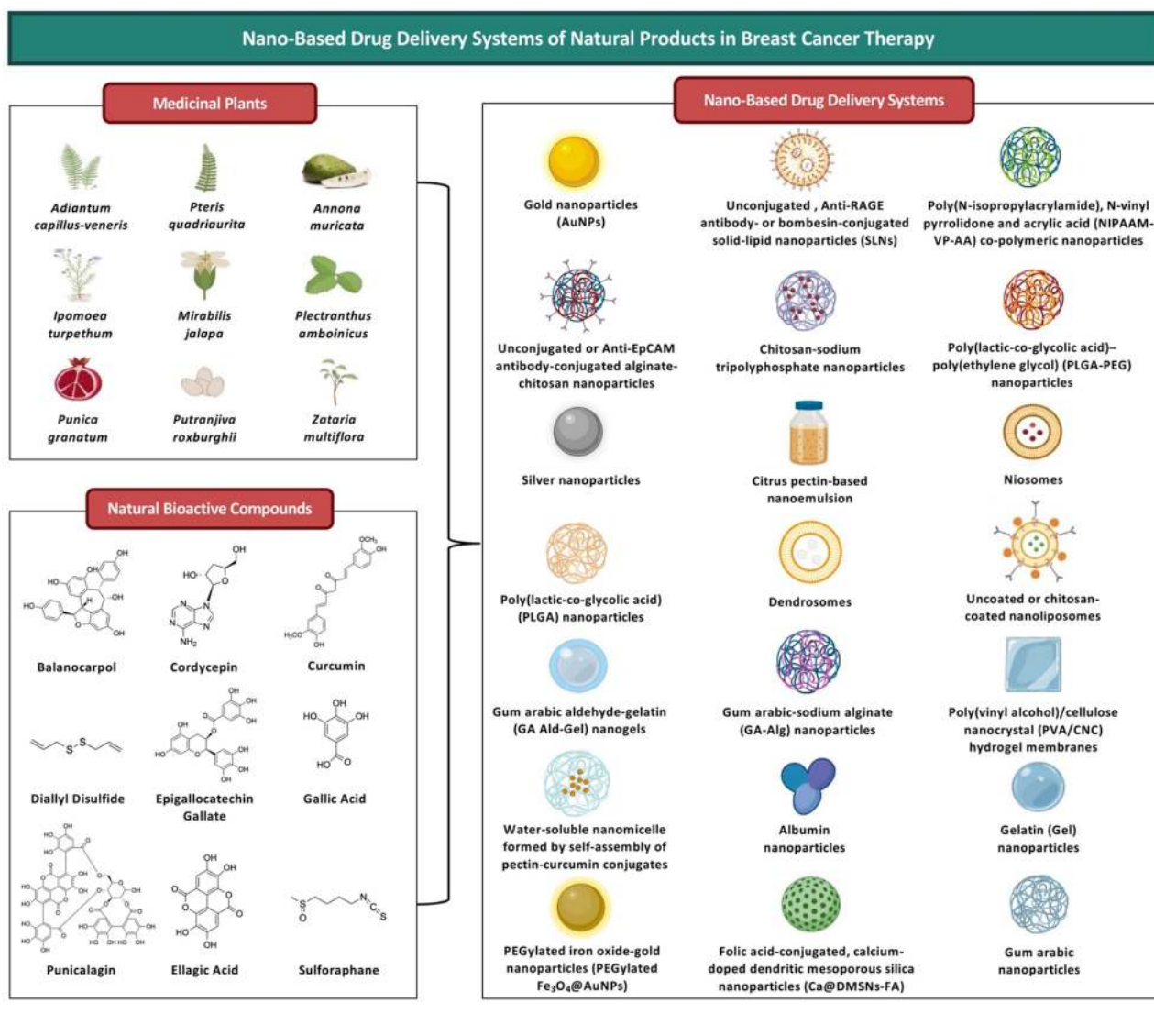
Abstract: Despite recent advances in the diagnosis and treatment of breast cancer (BC), it remains a global health issue affecting millions of women annually. Poor prognosis in BC patients is often linked to drug resistance as well as the lack of effective therapeutic options for metastatic and triple-negative BC. In response to these unmet needs, extensive research efforts have been devoted to exploring the anti-BC potentials of natural products owing to their multi-target mechanisms of action and good safety profiles. Various medicinal plant extracts/essential oils and natural bioactive compounds have demonstrated anti-cancer activities in preclinical BC models. Despite the promising preclinical results, however, the clinical translation of natural products has often been hindered by their poor stability, aqueous solubility and bioavailability. There have been attempts to overcome these limitations, particularly via the use of nano-based drug delivery systems (NDDSs). This review highlights the tumour targeting mechanisms of NDDSs, the advantages and disadvantages of the major classes of NDDSs and their current clinical status in BC treatment. Besides, it also discusses the proposed anti-BC mechanisms and nanoformulations of nine medicinal plants' extracts/essential oils and nine natural bioactive compounds; selected via the screening of various scientific databases, including PubMed, Scopus and Google Scholar, based on the following keywords: "Natural Product AND Nanoparticle AND Breast Cancer". Overall, these nanoformulations exhibit improved anti-cancer efficacy against preclinical BC models, with some demonstrating biocompatibility with normal cell lines and mouse models. Further clinical studies are, however, warranted to ascertain their efficacy and biocompatibility in humans.

Keywords: breast cancer, drug delivery, molecular mechanisms, nanoparticles, natural products, phytomedicine

Introduction

Breast cancer (BC) has been recognised as a global health issue, as it is the most common type of cancer and the major cause of cancer death in women.¹ In 2020, BC recorded high global incidence (2,261,419 cases) and mortality (684,996 deaths) rates.² Advancements in technology (eg, mammography, ultrasound, magnetic resonance imaging, computerised tomography and positron emission tomography) have enabled the early detection of BC.³ Nevertheless, approximately 30% of patients with early-stage BC eventually relapse with metastases.^{4,5} Metastatic BC is considered to be largely incurable, with a 5-year survival rate of only 26% despite currently available treatment options.⁶

Graphical Abstract



BC is a disease of heterogenous nature.⁷ Based on the receptor expression status, BC can primarily be categorised into three major subtypes, including luminal A/B, human epidermal growth factor receptor 2 (HER2)-enriched and triple-negative subtypes⁷ (Figure 1). Different BC subtypes exhibit distinct biological features, with variabilities in their prognosis and treatment response.⁸ In particular, triple-negative breast cancer (TNBC) is associated with worse prognosis, more aggressive behaviour, lack of validated molecular targets and limited therapeutic options (ie, chemotherapy), thereby rendering its management challenging.^{9,10}

A multimodal approach is often employed for BC treatment, whereby a combination of surgery, radiotherapy, endocrine therapy, HER2-targeted therapy or chemotherapy may be included in the treatment plan depending on the stage and subtype of BC as well as the tolerance of patients.¹¹ Table 1 summarises the typical systemic therapeutic options for the three major BC subtypes.^{12,13} However, there have been reports of resistance to endocrine therapy, HER2-targeted therapy and chemotherapy clinically.¹⁴ Both drug resistance and the lack of effective therapeutic options for metastatic BC and TNBC represent the major obstacles in treating BC. Therefore, BC remains a medical area with unmet needs and has attracted

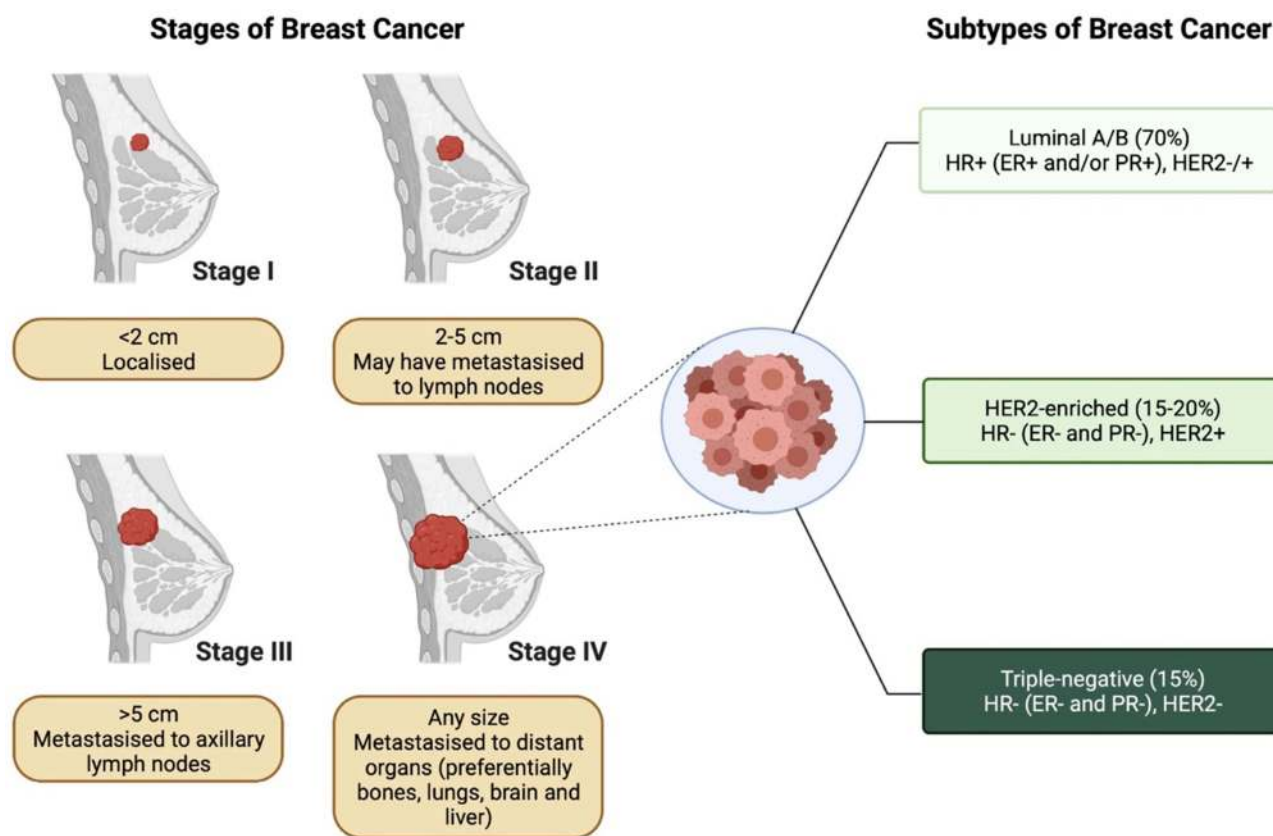


Figure 1 Stages and subtypes of breast cancer.

Note: Created with BioRender.com.

Abbreviations: ER, Estrogen receptor; HER2, Human epidermal growth factor receptor 2; HR, hormone receptor; PR, progesterone receptor.

researches into the discovery of novel anti-BC drugs that offer higher efficacy with minimal toxicity.

Historically, different forms of natural products (eg, oils, potions, remedies and traditional medicines) have been used to treat various diseases and injuries.¹⁵ The medicinal properties of natural products have subsequently attracted attention into identifying the bioactive compound(s) of interest, making natural products a vital source for drug discovery in various therapeutic areas, especially in cancer and infectious diseases.¹⁶ For instance, the majority (>60%) of clinically available anti-cancer drugs are natural product-derived.¹⁷ Of these drugs, paclitaxel from *Taxus brevifolia*, vinca alkaloids from *Catharanthus rosea*, etoposide from *Podophyllum peltatum* as well as topotecan and irinotecan from *Camptotheca acuminata* represent some of the most effective chemotherapeutic agents in clinics.¹⁷ There was a decline in the pursuit of natural product-based drug discovery by the pharmaceutical industry in the 1990s, mainly due to challenges in high-throughput screening, bioactive compound identification and synthesis as well as lead optimisation.¹⁶ However, recent technological advancements have helped to address these

challenges and thereby revitalised the industry's interest to re-explore natural products as a potential source of new drugs.¹⁶

Natural products are often tested for desired bioactivities in the form of extracts.¹⁸ Extracts demonstrating the bioactivity of interest are then subjected to fractionation for the isolation and identification of bioactive compound(s).¹⁸ Plants, in particular, represent a natural source that has been heavily explored for their anti-cancer potentials.¹⁹ Studies have reported anti-cancer activities of various plant extracts and isolated phytochemicals, which are the biologically active non-nutritive plant chemicals, in preclinical BC models.^{20,21} More recently, studies have also suggested the potential of using essential oils to treat various cancers, including BC.^{22,23} Essential oils, which are produced and secreted by specialised secretory structures of plants, are complex mixtures of lipophilic and volatile plant secondary metabolites.^{24,25} Natural extracts, essential oils and their bioactive compounds are known to exhibit multi-target mechanisms of action with minimal side effects, of which would be advantageous for cancer treatment.^{22,26}

Table 1 Systemic Therapeutic Options for Three Major Breast Cancer Subtypes

	Luminal A/B	HER2-Enriched	Triple-Negative	References
Endocrine Therapy -Selective estrogen-receptor modulators (SERMs; eg, tamoxifen) -Aromatase inhibitors (AIs; eg, exemestane, anastrozole and letrozole)	-Used in all patients	-Used only in patients with HR-positive breast tumours	-N/A	[13]
HER2-targeted Therapy -Trastuzumab ± pertuzumab	-N/A	-Used in all patients	-N/A	[13]
Chemotherapy -Cyclophosphamide + methotrexate + 5-fluorouracil (CMF) -Doxorubicin + cyclophosphamide (AC) -5-Fluorouracil + epirubicin + cyclophosphamide (FEC) -Cyclophosphamide + doxorubicin + 5-fluorouracil (CAF or FAC) -Doxorubicin + cyclophosphamide + paclitaxel (AC-T) -Docetaxel + cyclophosphamide (TC)	-Used only in some patients	-Used in all patients	-Used in all patients	[12,13]

Despite the promising preclinical findings, the physico-chemical properties of natural products generally lead to poor stability, aqueous solubility and bioavailability, all of which can hinder their clinical application.^{24,27} Additionally, the clinical application of essential oils has also been challenged by their high volatility, high sensitivity to environmental conditions (eg, high temperature, light and oxygen), low stability and high lipophilicity.^{24,25} Attempts made in trying to resolve these limitations are considered promising, especially through the use of nano-based drug delivery systems (NDDSs).^{28–31}

This review first describes the tumour targeting mechanisms of NDDSs, and summarises the major classes of NDDSs by highlighting their advantages, disadvantages and current clinical status in BC treatment. Thereafter, the anti-BC mechanisms of selected natural products (including extracts, essential oils and natural bioactive compounds) and their nanoformulations that have demonstrated preclinical anti-BC activities are discussed.

The Tumour Targeting Mechanisms of Nano-Based Drug Delivery Systems

NDDSs represent a rapidly developing area of science, where nanoscale materials are utilised as carriers for delivering drugs to their sites of action.³² The use of NDDSs for drug delivery can enhance the bioavailability of poorly water-soluble drugs, enable the co-delivery of multiple drugs, provide targeted drug delivery, protect normal cells from drug toxicity and prolong drug action.^{32–34}

Targeted drug delivery to tumours is of the utmost importance to enhance the efficacy of anti-cancer drugs while minimising their systemic toxicity, and it may be achieved by NDDSs via passive and active targeting mechanisms (Figure 2).^{35,36}

The Passive Tumour Targeting Mechanism

Passive tumour targeting generally depends on a phenomenon called the enhanced permeation and retention (EPR) effect.³³ Tumour angiogenesis is stimulated in response to the needs of tumours for nutrients, oxygen and waste excretion.³⁷ However, the new tumour vasculature exhibits both structural and functional abnormalities.³⁷ For instance, the newly formed blood vessels surrounding tumours are leaky (with pore sizes ranging from 100 nm to 2 µm), thus allowing for enhanced permeation of NDDSs.³⁸ Moreover, tumours also lack normal lymphatic drainage system, leading to enhanced retention of these NDDSs.³⁸ Overall, the EPR effect can improve the specificity of drug delivery to tumours over normal tissues by approximately 20–30%.³³ However, NDDSs must (1) have reasonable stability in the blood circulation and (2) be able to avoid clearance by the reticuloendothelial system (RES) and sequestration by the mononuclear phagocyte system (MPS) in order to reach the tumours and achieve the EPR effect.³⁹ These two challenges have specifically been addressed via the PEGylation of NDDSs, which can improve their hydrophilicity and decrease their immunogenicity.³³

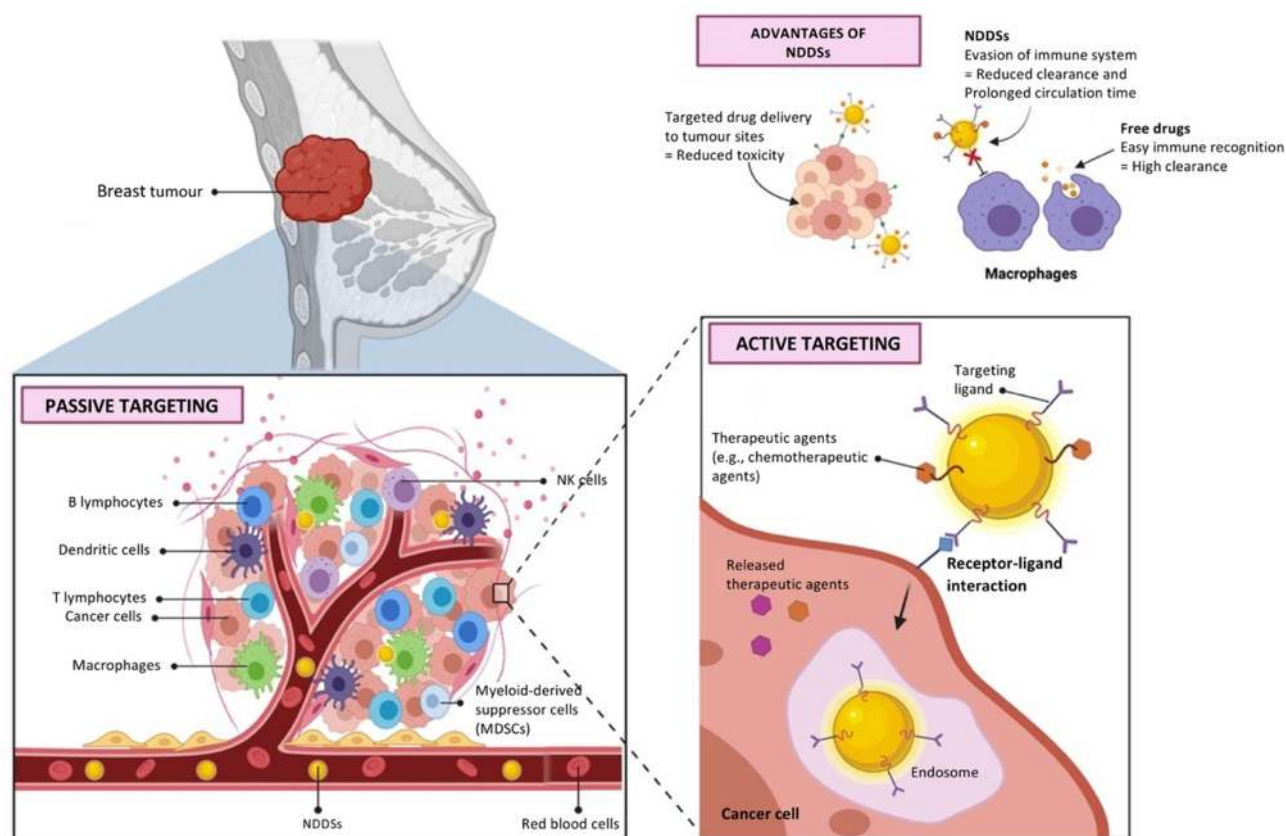


Figure 2 Passive and active targeting mechanisms of nano-based drug delivery systems to tumours.

Notes: Created with BioRender.com. Data from Byrne et al³⁵ and Rosenblum et al.³⁶

Abbreviation: NDDSs, nano-based drug delivery systems.

The Active Tumour Targeting Mechanism

Following the tumour accumulation of NDDSs through the EPR effect, drug efficiency can be further improved via active tumour targeting.³³ Active tumour targeting is achieved by binding on the NDDS surface of any ligands that interact with receptors that are overexpressed on the surface of cancer cells.³⁹ This action increases the affinity of NDDSs for cancer cells and may enhance their uptake by cancer cells via receptor-mediated endocytosis.^{33,40} Interestingly, NDDSs have also been actively targeted to tumour microenvironment (TME),⁴⁰ tumour endothelial cells⁴¹ and organelles of tumour cells⁴² for cancer therapy.

The Major Classes of Nano-Based Drug Delivery Systems Evaluated for Breast Cancer Therapy

The use of NDDSs for cancer therapy is promising, as NDDSs have demonstrated potentials in enhancing the efficacy of anti-cancer drugs, reducing their toxicity to normal cells and overcoming drug resistance.⁴³ NDDSs

can generally be grouped into three different categories, namely organic, inorganic and hybrid (made of ≥ 2 types of nanomaterials) NDDSs.³³ Several major classes of NDDSs have been investigated for the delivery of anti-BC agents⁴⁴ (Figure 3). Each of these NDDS classes is associated with certain advantages and disadvantages (Table 2), thus reflecting the importance of selecting the most appropriate delivery system for a particular drug.

The Organic Nano-Based Drug Delivery Systems

The Carbon-Based Nanocarriers

The capability of carbon atoms to undergo sp -, sp^2 - and sp^3 -hybridisation explains the existence of multiple carbon allotropes.⁴⁵ In addition to the three naturally occurring carbon allotropes (ie, amorphous carbon, diamond and graphite), several synthetic carbon allotropes (eg, carbon nanotubes, carbon nanocones, carbon nanohorns, fullerene, graphene and nanodiamond) have also been developed.⁴⁵ In recent years, carbon-based nanocarriers have been extensively exploited for different biomedical

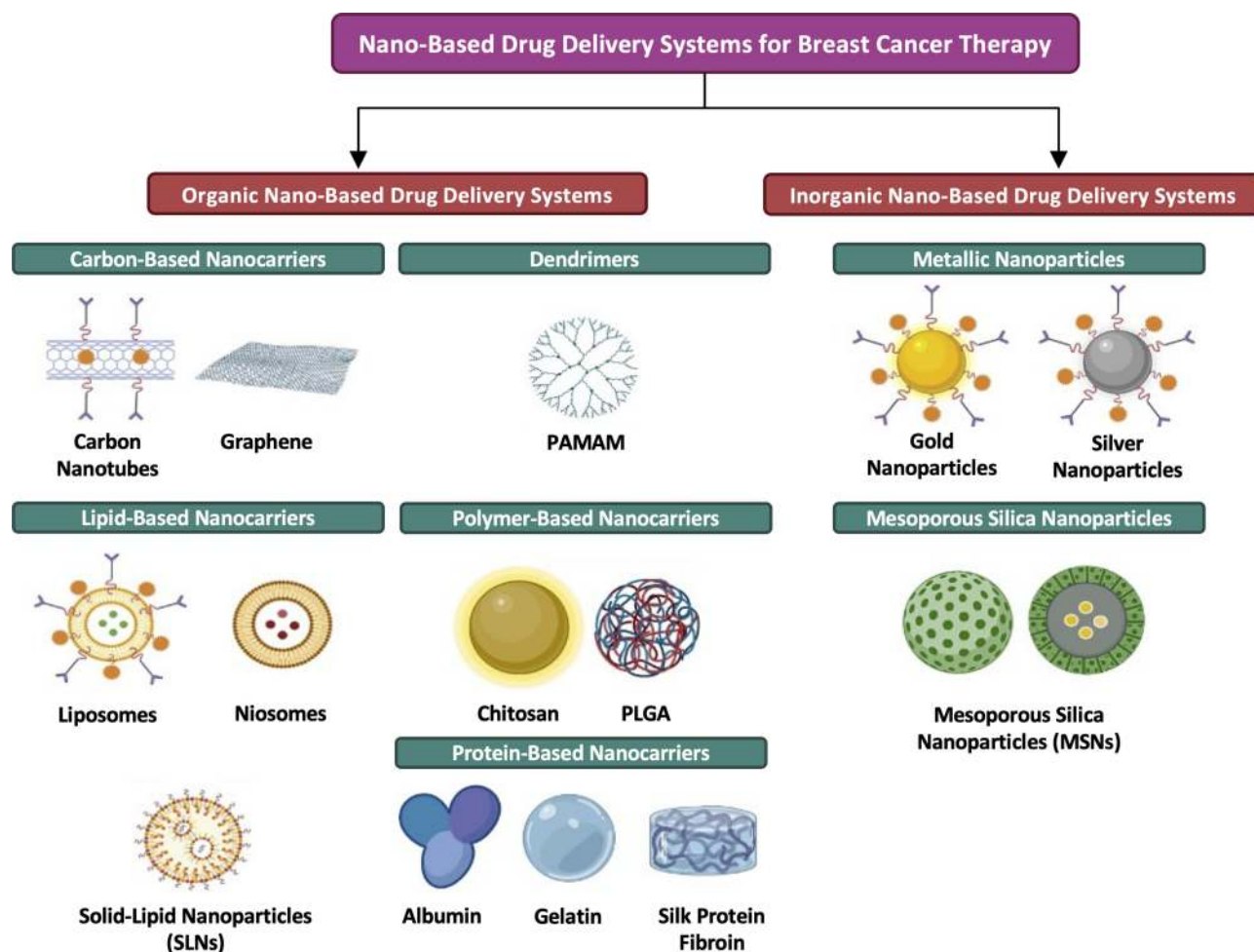


Figure 3 Major classes of nano-based drug delivery systems for breast cancer therapy.

Note: Created with BioRender.com.

Abbreviations: PAMAM, poly(amidoamine); PLGA, poly(lactic-co-glycolic acid).

applications (eg, bio-sensing and drug delivery) owing to their unique profiles of chemical and physical properties (eg, electrical and thermal conductivity, mechanical strength, optical properties and structural diversity).^{46,47} Moreover, other aspects of carbon-based nanocarriers such as their large surface area, high chemical stability, preferential tumour accumulation and high cellular entry have also made them potentially promising as drug carriers in cancer treatment.⁴⁸

An activated carbon nanoparticle-epirubicin suspension was developed and tested clinically as regional lymphatic chemotherapy in BC patients.⁴⁹ It was reported that BC patients subjected to regional injection of activated carbon nanoparticle-epirubicin suspension had higher epirubicin concentration in the lymph nodes and lower plasma epirubicin concentration than those subjected to intravenous injection of free epirubicin, indicating that this nanoformulation

can improve the therapeutic efficacy of epirubicin while minimising its systemic toxicities. This nanoformulation is also capable of releasing epirubicin slowly in the lymph nodes, which may prolong its chemotherapeutic action. Further development of carbon-based nanocarriers is, however, often hindered by controversies surrounding their inherent toxicities.⁴⁸

The Dendrimers

Dendrimers are three-dimensional polymeric macromolecules that are characterised by their well-organised and highly branched structures.⁵⁰ A typical dendrimer consists of a symmetric central core, together with an inner shell and an outer shell.⁵¹ The precise molecular weight, biocompatibility, monodispersity, high aqueous solubility, high biological barrier penetrability and polyvalency of dendrimers have contributed to their extensive biomedical

Table 2 Advantages and Disadvantages of Major Classes of Nano-Based Drug Delivery Systems and Their Current Clinical Status for Breast Cancer Treatment

	Advantages	Disadvantages	Clinically Evaluated Examples for Breast Cancer Treatment	References
Organic Nano-based Drug Delivery Systems				
Carbon-based Nanocarriers	<ul style="list-style-type: none"> -Electrical and thermal conductivity -Mechanical strength -Optical properties -Structural diversity -Large surface area -High chemical stability -Preferential tumour accumulation -High cellular entry 	<ul style="list-style-type: none"> -Inherent toxicities 	<ul style="list-style-type: none"> -Activated carbon nanoparticle-epirubicin suspension ●N/A 	[46-49]
Dendrimers	<ul style="list-style-type: none"> -Precise molecular weight -Biocompatibility -Monodispersity -High aqueous solubility -High biological barrier penetrability -Polyvalency for versatile functionalisation 	<ul style="list-style-type: none"> -Cationic dendrimers ●Toxicities 	<ul style="list-style-type: none"> -PEGylated PLL dendrimer-based nanoformulation of docetaxel (DEP® docetaxel) ●Phase II -PEGylated PLL dendrimer-based nanoformulation of SN-38 (DEP® irinotecan) ●Phase II 	[50,52,56-58]
Lipid-based Nanocarriers	<ul style="list-style-type: none"> -Ease of preparation -Large-scale and low-cost production -Biocompatibility -Biodegradability -Targetability -High stability -High drug loading capacity -Capability to incorporate both hydrophobic and hydrophilic drugs 	<ul style="list-style-type: none"> -Liposomes ●Difficulties with large-scale manufacturing, sterilisation and stability -Niosomes ●Polydispersity of currently commercially available non-ionic surfactants -Solid lipid nanoparticles ●Low drug loading capacity and risk of drug expulsion 	<ul style="list-style-type: none"> -PEGylated liposomal doxorubicin (Doxil®) ●Approved -Liposomal cytarabine (Depocyt®) ●Approved; Phase III for leptomeningeal metastasis from breast cancer 	[59-61,63-69,78]
Polymer-based Nanocarriers	<ul style="list-style-type: none"> -Natural polymers ●Better biocompatibility and biodegradability -Synthetic polymers ●Abundantly present ●Better thermal stability and mechanical properties ●Can be more easily processed to achieve desired pore size and scaffold geometry 	<ul style="list-style-type: none"> -Natural polymers ●Poor thermal stability and mechanical properties -Synthetic polymers ●Impurities that can affect biocompatibility 	<ul style="list-style-type: none"> -mPEG-PDLLA micellar formulation of paclitaxel (Genexol-PN®) ●Approved -PGA-paclitaxel (Opaxio™) ●Phase III; Phase II for metastatic breast cancer 	[81,82,87-90]

(Continued)

Table 2 (Continued).

Advantages	Disadvantages	Clinically Evaluated Examples for Breast Cancer Treatment	References
<ul style="list-style-type: none"> -Biocompatibility -Biodegradability -Easy synthesis and nanoparticle size control -Cost-effectiveness -High stability -Amenability to surface modification 	<ul style="list-style-type: none"> -Albumin ●High cost -Collagen ●Risk of prion transmission from animal sources -Ferritin ●High cost -Gelatin ●Risk of prion transmission from animal sources ●Low mechanical strength ●Fast degradation -Gliadin ●Fast degradation ●Large nanoparticle size -Legumin ●Low yield -Protamine ●Low yield -Silk protein fibroin ●Slow degradation -Silk protein sericin ●Low yield 	<ul style="list-style-type: none"> -Nanoparticle albumin-bound paclitaxel (Abraxane[®]) ●Approved -Nanoparticle albumin-bound rapamycin (ABI-009) ●Phase II; Phase I for advanced breast cancer 	<p>[93,94,96–100]</p>
Inorganic Nano-based Drug Delivery Systems			
Metallic Nanoparticles	<ul style="list-style-type: none"> -Unique catalytic, electrical, magnetic, optical and thermal properties -Simple surface chemistry and functionalisation -Easy synthesis -High drug loading capacity -Large surface area-to-volume ratio 	<ul style="list-style-type: none"> -Toxicities -Low stability -Low biocompatibility 	<ul style="list-style-type: none"> -Colloidal gold-bound tumour necrosis factor (Aurimmune[™]) ●Phase I <p>[39,102,107,109–111]</p>
Mesoporous Silica Nanoparticles	<ul style="list-style-type: none"> -Simple fabrication -Tunable particle size and shape -Large internal pore volume and surface area -High drug loading capacity -Good stability -Good biocompatibility -Easy surface modification and functionalisation -Capability to incorporate both hydrophilic and hydrophobic drugs 	<ul style="list-style-type: none"> -Toxicities 	<p>-N/A</p> <p>[112–115,121–123]</p>

Abbreviation: mPEG-PDLLA, monomethoxy-poly(ethylene glycol)-block-poly(D,L-lactide).

and therapeutic applications (eg, imaging, gene therapy and drug delivery).^{50,52} The exploitation of dendrimers for drug delivery dates back to the late 1990s.⁵³ In fact, dendrimers have been considered to be multi-functional drug carriers, as they can enhance the solubility, dissolution, adsorption, bioavailability, stability and efficacy of drugs as well as enable controlled drug release and targeted drug delivery.^{52,53}

Various types of dendrimers have been investigated as drug carriers in oncology, including dendrimer based on 2,2-bis(hydroxymethyl) propionic acid, melamine-based dendrimer, poly(amidoamine) (PAMAM) dendrimer, poly(glycerol-succinic acid) dendrimer, poly(propylene imine) (PPI) dendrimer, 5-aminolevulinic acid (ALA)-containing dendrimer and poly-L-lysine (PLL) dendrimer.^{54,55} However, while neutral and anionic dendrimers are usually non-toxic, cationic dendrimers often confer high toxicity.⁵⁶ Cationic dendrimers tend to interact with negatively charged biological membranes, which can consequently lead to membrane integrity disruption, cytosolic protein leakage and eventually cell lysis.⁵⁰ It has been reported that the surface modification of dendrimers (eg, PEGylation) can mask their charge(s) and thereby reduce their toxicities.⁵⁵

A PEGylated PLL dendrimer-based nanoformulation of docetaxel demonstrated superiority over conventional docetaxel in terms of efficacy, safety and pharmacokinetics in the Phase I trial, in which patients with advanced brain, breast, cervical, gastro-oesophageal, lung, pancreatic, prostate and renal cancers were enrolled.⁵⁷ Based on the positive Phase I results, nanoformulated docetaxel has been advanced to Phase II.⁵⁷ Similarly, a PEGylated PLL dendrimer-based nanoformulation of SN-38 has also progressed to Phase II following the observation of improved anti-cancer efficacy and safety as compared to conventional irinotecan in breast, colorectal and pancreatic cancer patients in the Phase I component of its Phase I/II trial.⁵⁸

The Lipid-Based Nanocarriers

Lipid-based nanocarriers (eg, liposomes, niosomes and solid-lipid nanoparticles [SLNs]) have attracted considerable attention in drug delivery owing to their ease of preparation, large-scale and low-cost production, biocompatibility, biodegradability, targetability, high stability and high drug loading capacity.^{59,60} Additionally, they can also prolong drug action by enabling controlled drug release and extending drug half-life.⁶⁰ 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.⁶⁰

Liposomes are the first generation of lipid-based nanocarriers developed for drug delivery.⁶¹ They are spherical lipid vesicles consisting of an aqueous core that is surrounded by at least one phospholipid bilayer.⁶² Due to the amphipathic nature of phospholipids, liposomes are capable of loading both hydrophobic and hydrophilic drugs into the lipid bilayer and the aqueous internal compartments, respectively.^{59,61} In 1995, PEGylated liposomal doxorubicin was approved by the US Food and Drug Administration (FDA) for the treatment of AIDS-related Kaposi's sarcoma, making it the first FDA-approved nanomedicine.⁶³ It is currently also indicated for the clinical treatment of recurrent ovarian cancer, metastatic BC and multiple myeloma.⁶⁴ In all settings, PEGylated liposomal doxorubicin has shown reduced cardiotoxicity in comparison to free doxorubicin.⁶³ Liposomal cytarabine obtained FDA approval for the intrathecal treatment of lymphomatous meningitis in 1999.⁶⁵ Since then, a number of clinical trials have been underway to establish the effectiveness of liposomal cytarabine in other cancer types.⁶⁶ It was found in a Phase III trial that systemic therapy plus intrathecal liposomal cytarabine resulted in better median progression-free survival than systemic therapy alone (3.8 vs 2.2 months) in BC patients with newly diagnosed leptomeningeal metastasis.⁶⁷ Nonetheless, the development of liposomal nanoformulation is limited by difficulties with large-scale manufacturing, sterilisation and stability.⁶⁸

Niosomes are spherical vesicles with closed bilayer structures that arise from the self-clustering of cholesterol and non-ionic surfactants in aqueous media.⁵⁹ They have similar structures and physical-chemical properties as liposomes, and can also load both hydrophobic and hydrophilic drugs.^{68,69} In contrast to liposomes, however, niosomes require simpler fabrication methods, lower production costs and possess greater stability.⁶⁸ Therefore, niosomes have been proposed as an alternative to liposomal delivery of anti-cancer drugs.⁵⁹ Niosomal nanoformulations of cisplatin,⁷⁰ doxorubicin⁷¹ and tamoxifen citrate⁷² have been reported to possess higher anti-cancer efficacy than their free drugs in preclinical BC models, but none of these has been advanced to clinical trials to date. One disadvantage of niosomes is that their currently

commercially available non-ionic surfactants (ie, Spans and Tweens) are all polydisperse.⁶⁹

SLNs, a relatively new colloidal drug delivery system, are made of lipid matrices that remain in a solid state at physiological temperatures.⁶⁰ Similar to liposomes and niosomes, SLNs are also capable of incorporating both hydrophobic and hydrophilic drugs.⁶⁰ However, they are superior to liposomes in terms of reproducibility, feasibility of large-scale production, stability and entrapment efficiency for hydrophobic drugs.⁷³ Although no SLN-based nanoformulation of anti-cancer drugs has been clinically studied for BC treatment to date, there have been preclinical reports of the anti-BC activities of doxorubicin,⁷⁴ methotrexate,⁷⁵ paclitaxel⁷⁶ and tamoxifen⁷⁷ loaded SLNs. However, SLNs are associated with several drawbacks, including low drug loading capacity and risk of drug expulsion due to crystallisation during storage.⁷⁸

The Polymer-Based Nanocarriers

In general, polymer-based nanocarriers are able to protect drugs from rapid metabolism and clearance by RES, liver and kidney as well as offer targeted delivery and sustained release of drugs.⁷⁹ They can be prepared from either natural or synthetic polymers.⁸⁰ As opposed to natural polymers, synthetic polymers are abundantly present, possess better thermal stability and mechanical properties and can be more easily processed to achieve desired pore size and scaffold geometry.⁸¹ However, synthetic polymers often come with impurities that can affect their biocompatibility, while natural polymers generally offer better biocompatibility and biodegradability.⁸² In recent years, semi-synthetic polymers, which are derived from the modification of natural polymers via blending, crosslinking or grafting with synthetic polymers, have been introduced.⁸² They exhibit combined advantageous properties of both natural and synthetic polymers and thus are a highly promising type of nanomaterial for drug delivery.⁸¹

Polysaccharides represent a class of natural polymer that has been extensively exploited for drug delivery.⁸³ They can be obtained naturally from algal (eg, alginate), animal (eg, chitosan, chondroitin and hyaluronic acid), plant (eg, pectin, cellulose and gum arabic) and microbial (eg, dextran, xanthan gum and hyaluronic acid) origins,^{84,85} among which alginate, chitosan, dextran and hyaluronic acid have been most frequently utilised for delivering anti-cancer drugs.⁸³ Various synthetic polymers have also been exploited for the preparation of NDDSs, including hydrophobic polymers such as poly(lactic-co-glycolic acid) (PLGA), poly

(lactic acid) (PLA) and polycaprolactone (PCL) as well as hydrophilic polymers such as poly(ethylene glycol) (PEG), poly(glutamic acid) (PGA), poly(ethyleneimine) (PEI), poly(acrylamide) (PAM) and poly(vinyl alcohol) (PVA).^{84,86}

Polymer-based nanoformulations of various chemotherapeutic agents have also been clinically tested for BC treatment. In a Phase III trial, a monomethoxy-poly(ethylene glycol)-block-poly(D,L-lactide) (mPEG-PDLLA) micellar formulation of paclitaxel was found to offer superior clinical efficacy (ie, objective response rate of 39.1% vs 24.3%) and manageable toxicities in comparison to conventional paclitaxel in patients with recurrent or metastatic HER2-negative BC.⁸⁷ This micellar formulation of paclitaxel is now on the South Korean market for treating metastatic BC, non-small cell lung cancer (NSCLC) and ovarian cancer.⁸⁸ Another nanoformulation, PGA-paclitaxel, has also been evaluated in Phase II trials for the treatment of BC, NSCLC and ovarian cancer.⁸⁹ Specifically, a Phase II trial reported that the combination of PGA-paclitaxel plus capecitabine showed significant efficacy and reasonable tolerability in metastatic BC patients.⁹⁰ Notably, PGA-paclitaxel have been advanced to Phase III trials for the treatment of NSCLC and advanced ovarian cancer.⁸⁹

The Protein-Based Nanocarriers

Protein-based nanocarriers consist of multiple protein subunits that can undergo spontaneous and precise self-association to form nanocarriers with internal hollow cavities.⁹¹ Over the past few years, there has been a rapid expansion in the practical applications (eg, biocatalysis, diagnostic imaging, drug delivery and vaccine development) of protein-based nanocarriers owing to their unique properties.⁹² In addition to being biocompatible and biodegradable, protein-based nanocarriers also offer other advantages such as ease of synthesis and size control, cost-effectiveness, high stability, amenability to surface modification for targeted drug delivery and ability to provide controlled drug release.^{93,94} However, nanocarriers derived from different proteins have been associated with certain disadvantages such as high cost (eg, albumin and ferritin), risk of prion transmission from animal sources (eg, collagen and gelatin), low mechanical strength (eg, gelatin), slow degradation (eg, silk protein fibroin), fast degradation (eg, gelatin and gliadin), large nanoparticle size (eg, gliadin) and low yield (eg, legumin, protamine and silk protein sericin).^{93,94}

The most extensive use of protein-based nanocarriers as NDDSs has been seen in oncology. There has been a

heavy focus particularly on albumin nanocarriers, as albumin has been reported to preferentially accumulate in solid tumours.⁹⁵ For example, nanoparticle albumin-bound paclitaxel that demonstrated greater anti-cancer efficacy and lower toxicity than conventional paclitaxel in both preclinical and clinical studies successfully obtained FDA approval for the treatment of metastatic BC in 2005.^{96,97} In a Phase I trial, nanoparticle albumin-bound rapamycin also showed preliminary evidence of response and stable disease as well as acceptable tolerability in patients with advanced non-hematologic cancers, including BC.⁹⁸ It is currently being tested in Phase II trials, either alone or in combination with other therapies, for the treatment of various cancers such as high-grade glioma, newly diagnosed glioblastoma⁹⁹ and advanced malignant perivascular epithelioid cell tumour.¹⁰⁰

The Inorganic Nano-Based Drug Delivery Systems

The Metallic Nanoparticles

Metallic nanoparticles are colloidal particles with diameters ranging from 10 to 1000 nm.¹⁰¹ They are known for their unique catalytic, electrical, magnetic, optical and thermal properties, simple surface chemistry and functionalisation as well as ease of synthesis.¹⁰² These features have led to the extensive investigation of metallic nanoparticles in a wide range of biomedical applications (eg, diagnostic testing, imaging, radiotherapy enhancement, thermal ablation as well as gene and drug delivery), rendering them multi-purpose.¹⁰²

Metallic nanoparticles are associated with both intrinsic and extrinsic anti-cancer effects.¹⁰² For instance, several metallic nanoparticles (eg, silver, gold, cerium oxide, copper oxide, iron oxide, titanium oxide, titanium dioxide and zinc oxide) have been reported to mediate intrinsic anti-cancer activities via different mechanisms.^{103,104} The extrinsic anti-cancer activities of metallic nanoparticles are seen in targeted hyperthermic therapy.¹⁰⁵ For example, a thermal therapy product based on iron oxide nanoparticles has been approved by the European Medicines Agency (EMA) to treat glioblastoma.¹⁰⁶ Following the direct injection of aqueous iron oxide nanoparticle dispersion into the tumour, an alternating magnetic field is applied to generate heat for killing the cancer cells.¹⁰⁶

Besides being useful as anti-cancer agents, metallic nanoparticles can also be utilised as NDDSs for anti-cancer drugs. They have high drug loading capacity and possess a large surface area-to-volume ratio that facilitates chemical

modification.¹⁰⁷ Moreover, superparamagnetic metallic nanoparticles (eg, iron oxide) can also enable site-specific delivery of drugs via the application of an external magnetic field.¹⁰⁸ A metallic nanoformulation, colloidal gold-bound tumour necrosis factor, has completed Phase I trials in patients with different cancers, including BC.¹⁰⁹ It could be administered at doses that exceeded the maximum tolerated dose of native tumour necrosis factor while showing reasonable tolerability and tumour targetability.¹¹⁰ However, some metallic nanoparticles have been associated with toxicities even though the metals used are relatively inert (eg, gold, silver and copper), as well as with low stability and biocompatibility.^{39,111}

The Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) are silica materials with a highly ordered porosity of 2 to 50 nm in diameter.¹¹² They have emerged as an ideal NDDS owing to their unique properties, including simple fabrication, tunable particle size and shape, large internal pore volume and surface area giving rise to high drug loading capacity, good stability, good biocompatibility, easy surface modification and functionalisation as well as capability to incorporate both hydrophilic and hydrophobic drugs.^{112–115}

The first introduction of MSNs as NDDSs dates back to 2001 when Vallet-Regí et al¹¹⁶ successfully encapsulated an anti-inflammatory drug (ie, ibuprofen) into MSNs. Considerable research efforts have since been devoted to the development of MSNs for treating various diseases, particularly cancer.¹¹³ MSN-based nanoformulations of various chemotherapeutic agents (eg, doxorubicin¹¹⁷ and epirubicin¹¹⁸) and nucleic acids (eg, siPlk1 plus miR-200c¹¹⁹ and HER2-targeted siRNA¹²⁰) have demonstrated anti-BC effects preclinically. However, the clinical translation of MSNs may be limited by its reported toxicities (eg, cardiotoxicity, pulmonary toxicity, renal toxicity and genotoxicity).^{121–123}

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

Extracts/essential oils of certain medicinal plants contain a cocktail of bioactive compounds that exert anti-BC activities via different mechanisms of action (Table 3). These bioactive compounds may exhibit synergistic effects, thereby allowing the extracts and essential oils to exhibit

Table 3 Proposed Anti-Breast Cancer Mechanisms of Medicinal Plant Extracts or Essential Oils in Preclinical Breast Cancer Models

Plant Botanical Name	Plant Common Name	Extract/ Essential Oil	Cell Models/Animals (Sex)	Mechanisms of Action	References
<i>Adiantum capillus-veneris</i>	Southern maidenhair fern	Leaf extract	-MCF-7 cell line -BT-47 cell line	<ul style="list-style-type: none"> -Modulation of proliferation markers • ↓ PCNA level -Modulation of cell cycle regulators • ↓ Cyclin D1 and CDK4 levels • ↑ p21 level and nuclear relative to cytosolic p21 -Induction of mitochondrial apoptotic pathway • ↑ Bax/Bcl-2 ratio • ↓ $\Delta\Psi_m$ • ↑ Caspase-9 and -3 levels • ↑ Cytosolic relative to mitochondrial cytochrome c 	[136]
<i>Pteris quadriaurita</i>	Striped brake fern				
<i>Annona muricata</i>	Soursop, Guanábana, Graviola or Omustatfeli/Ekitafele	Leaf extract	-Mice bearing 4T1 xenografts (female)	<ul style="list-style-type: none"> -Regulation of immune system • ↑ White blood cell, T cell and natural killer cell populations -Reduction of inflammation • ↓ NO and MDA 	[151]
		Leaf extract	-BT-20 cell line	<ul style="list-style-type: none"> -Suppression of EGFR signalling pathway • ↓ EGFR phosphorylation -Suppression of MAPK signalling pathway • ↓ MAPK phosphorylation -Suppression of PI3K/AKT signalling pathway • ↓ AKT phosphorylation -Suppression of NF-κB signalling pathway • ↓ NF-κB p65 level -Modulation of cell cycle regulators • ↓ Cyclin D1 level 	[153]
		Leaf extract	-MCF-7 cell line	<ul style="list-style-type: none"> -Stimulation of ROS generation • ↑ Intracellular ROS level -Induction of caspase-dependent apoptosis • ↑ Caspase-3 level 	[154]
<i>Ipomoea turpethum/ Operculina turpethum</i>	Transparent wood rose	Stem extract	-Rats bearing DMBA-induced breast tumours (female)	<ul style="list-style-type: none"> -Antioxidant activity • ↓ Lipid peroxidation activity • ↑ SOD, CAT, GPx, GSH, vitamin C and vitamin E levels 	[159]

<i>Mirabilis jalapa</i>	Four o'clock flower	N/A	-N/A	-N/A	N/A
<i>Plectranthus amboinicus</i>	Indian borage	Leaf extract	-MBA-MB-231 cell line	-Induction of caspase-dependent apoptosis ● ↑ Caspase-3 and -7 activities	[171]
<i>Punica granatum</i>	Pomegranate	Fruit extract	-MDA-MB-231 cell line -SUM-149 cell line	-Suppression of NF-κB signalling pathway ● ↓ Constitutive NF-κB activity ● ↓ NF-κB p50 and p65 levels ● ↓ IκBα phosphorylation -Downregulation of Rho GTPases ● ↓ RhoA and RhoC levels -Modulation of cellular eicosanoid profile ● MDA-MB-231: ↑ PGE ₂ and ↓ 15-HETE levels ● SUM-149: ↓ LTB ₄ , 12-HETE and 15-HETE levels	[184]
		Peel extract	-MDA-MB-231 cell line	-Modulation of metastasis-related markers ● ↑ ICAM-1 level ● ↓ MMP-9, fibronectin and VEGF levels	[185]
		Peel extract	-MDA-MB-231 cell line	-Modulation of EMT markers ● ↓ Mesenchymal markers (vimentin and ZEB1) ● ↑ Epithelial markers (E-cadherin) -Suppression of β-catenin signalling pathway ● ↓ β-catenin level	[186]
		Fruit extract	-MCF-7 cell line	-Downregulation of DNA repair genes ● ↓ MRE11, RAD50, NBS1, RAD51, BRCA1, BRCA2, BRCC3 and MSH6 levels -Induction of DNA double-strand breaks	[187]
		Fruit extract	-MCF-7 cell line -MDA-MB-231 cell line	-Anti-estrogenic activity ● ↓ Estradiol binding to ER ● ↓ ER-mediated gene expression via ERE ● ↓ Estrogen responsive gene expression (ERα, pS2 and PR)	[188]
<i>Putranjiva roxburghii</i> / <i>Drypetes roxburghii</i>	"Amulet-Plant or Wild Olive or Child-Life-Tree"	N/A	-N/A	-N/A	N/A

(Continued)

Table 3 (Continued).

Plant Botanical Name	Plant Common Name	Extract/ Essential Oil	Cell Models/Animals (Sex)	Mechanisms of Action	References
<i>Zataria multiflora</i>	Avishan-e-Shirazi	Essential oil	-MDA-MB-231 cell line	<ul style="list-style-type: none"> -Stimulation of ROS generation •↓ Intracellular ROS level -Intercalation between DNA strands -Induction of DNA damage •↑ 8-oxoguanine formation •↑ DNA migration -Induction of mitochondrial apoptotic pathway •↓ $\Delta\Psi_m$ •↑ Caspase-3 activity 	[198]

Notes: ↑, increased; ↓, decreased.

Abbreviations: Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; BRCA1/2, Breast cancer gene 1/2; BRCC3, BRCA1/BRCA2-containing complex subunit 3; CAT, catalase; CDK4, cyclin-dependent kinase 4; DMBA, 7,12-dimethylbenz(a)anthracene; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; ER α , estrogen receptor- α ; ERE, estrogen response element; GPs, glutathione peroxidase; GSH, glutathione; ICAM-1, intercellular adhesion molecule-1; IxBr, inhibitor kappa B- α ; LT β , leukotriene B $_4$; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MMP-9, matrix metalloproteinase-9; MSH6, MutS homolog 6; NBS1, Nibrin; NF- κ B, nuclear factor-kappa B; NO, nitric oxide; PCNA, proliferating cell nuclear antigen; PGE $_2$, prostaglandin E $_2$; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; PR, progesterone receptor; ROS, reactive oxygen species; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor; ZEB1, zinc finger E-box binding homeobox 1; 12/15-HETE, 12/15-hydroxyeicosatetraenoic acid; $\Delta\Psi_m$, mitochondrial membrane potential.

higher anti-cancer activities than a single bioactive compound.¹²⁴ However, the clinical use of extracts and essential oils in cancer treatment is often limited by their poor bioavailability.^{24,27} In line with this, multiple studies have developed nanoformulations for medicinal plant extracts/essential oils that have demonstrated anti-BC potentials preclinically but could not be translated clinically due to bioavailability issues (Table 4).

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

Adiantum capillus-veneris, or southern maidenhair fern, is a type of herb generally cultivated in temperate and tropical regions.¹²⁵ It is widely distributed in America, Europe, Atlantic coast as far as Ireland, southern Alpine valley regions, Australia and Iran.¹²⁵ Traditionally, *A. capillus-veneris* is utilised either as a single herbal medicine or in multi-herbal formulations to treat human diseases such as bronchial disorders, cold, cough, fever, hepatitis, jaundice, skin disorders and tumours.^{125,126} Its therapeutic potential is further reflected by a range of reported pharmacological activities, including anti-diabetic,¹²⁷ anti-inflammatory,¹²⁸ antimicrobial,¹²⁹ antinociceptive,¹³⁰ hypocholesterolemic,¹³¹ wound healing,¹³² antioxidant and anti-cancer¹³³ activities.

Pteris, one of the largest fern genera, consists of approximately 200–250 species.¹³⁴ *Pteris* spp. are widely distributed on all continents except Antarctica. They have been used by humans as ornamental plants, arsenic hyper-accumulators, food, spices and medicines.^{134,135} Importantly, *Pteris* is known to be rich in *ent*-kaurane diterpenoids, a compound class whose members often possess good anti-cancer activity.¹³⁵ For example, *Pteris quadriaurita* (striped brake fern) has been reported to exhibit anti-cancer activity¹³⁶ in addition to anti-bacterial, anti-fungal, anti-haemolytic and antioxidant activities.¹³⁷

The methanolic leaf extracts of both *A. capillus-veneris* and *P. quadriaurita* have demonstrated anti-cancer activities against BC cell lines.¹³⁶ In the same study, the researchers synthesised gold nanoparticles (AuNPs) from these extracts and evaluated the effects of the resulting AuNPs on MCF-7 and BT-47 BC cell lines. Only *P. quadriaurita* AuNPs were found to possess greater cytotoxicity against MCF-7 cells than its free extract (IC₅₀ values of 9 μ g/mL vs 380 μ g/mL). Nonetheless, subsequent gene and protein expression analyses revealed that MCF-7 and BT-47 cells treated with *A. capillus-veneris* and *P. quadriaurita* AuNPs had a more significant

Table 4 A Summary of Preclinical Studies Evaluating the Anti-Breast Cancer Potentials of Nanoformulated Medicinal Plant Extracts or Essential Oils

Plant Botanical Name	Plant Parts	Type of Extract	Type of Nanoformulation	Cell Models/ Animals (Sex)	Doses	IC ₅₀ Value (Treatment Duration)	Key Observations	Biocompatibility (IC ₅₀ Value)	Detected Compounds	References
<i>Adiantum capillus-veneris</i>	Leaves	Methanol	-Gold nanoparticles	-MCF-7 cell line -BT-47 cell line	-0–600 µg/mL	-500 µg/mL (24 h) -382 µg/mL (24 h)	↔ Cytotoxicity ^a -↑ Anti-proliferative activity ^a -↓ Cell cycle arrest-inducing activity ^a -↑ Pro-apoptotic activity ^a	-N/A	-1,2,3,5-cyclohexanetetrol, (1.alpha.,2.beta.,3.alpha.,5.beta.) -Sorbitol -3-O-methyl-D-glucose -1,3,4,6-dimethylene-D-glycero-D-mannoheptitol -3,7,11,15-tetramethyl-2-hexadecen-1-ol -Phytol -Hexadecanoic acid, methyl ester -N-hexadecanoic acid -8,11-octadecadienoic acid, methyl ester -17-octadecynoic acid, methyl ester -9,12-octadecadienyl chloride, (Z,Z)- -Octadecanoic acid -Squalene -Lupeol -DL-alpha-tocopherol -Octasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl -Olean-12-en-28-oic acid, 3,16,21-trihydroxy-gamma-lactone, (3.beta.,16) -Stigmasta-5,22-dien-3-ol, acetate, (3.beta.)- -Olean-13 (18)-ene -7,22-ergostadienone -Lupan-3-ol, acetate -Stigmasta-4,22-diene	[136]

(Continued)

Table 4 (Continued).

Plant Botanical Name	Plant Parts	Type of Extract	Type of Nanoformulation	Cell Models/ Animals (Sex)	Doses	IC ₅₀ Value (Treatment Duration)	Key Observations	Biocompatibility (IC ₅₀ Value)	Detected Compounds	References
<i>Pteris quadriaurita</i>	Leaves	Methanol	-Gold nanoparticles	-MCF-7 cell line -BT-47 cell line	-0–125 µg/mL -0–500 µg/mL	-9 µg/mL (24 h) -460 µg/mL (24 h)	-↑ Cytotoxicity ^a -↑ Anti-proliferative activity ^a -↑ Cell cycle arrest-inducing activity ^a -↑ Pro-apoptotic activity ^a	-N/A	-Phytol -2-pentadecanone, 6,10,14-trimethyl- -1,4-eicosadiene -Hexadecanoic acid, methyl ester -1-hexadecen-3-ol, 3,5,11,15-tetramethyl- -N-hexadecanoic acid -Linoleic acid ethyl ester -9,12-octadecadienyl chloride, (Z,Z)- -Octadecanoic acid, methyl ester -(R)-(-)-14-methyl-8-hexadecyn-1-ol -Octadecanoic acid -5,8,11,14,17-eicosapentaenoic acid -Palmitoyl chloride -4,8,12,16-tetramethylheptadecan-4-olide -1,3,5-trisilacyclohexane -Heptacosane -Eicosane, 9-octyl- -lindan, 1-methyl-3-nonyl- -Heptasiloxane, hexadecamethyl- -2H-1-Benzopyran-6-ol, 3,4-dihydro-2,8-dimethyl-2-(4,8,12-trimethyltridecyl)- -Octasiloxane, 1,1,3,3,5,5,7,9,9,11,11,13,13,15,15-hexadecamethyl- -Cholesta-4,6-dien-3-ol, (3.beta.)- -Stigmastan-3,5-diene -DL-alpha-tocopherol -Octasiloxane, 1,1,3,3,5,5,7,9,9,11,11,13,13,15,15-hexadecamethyl- -Olean-13(18)-ene	[136]

<i>Annona muricata</i>	Fruits	Ethanol	-Solid lipid nanoparticles	-MCF-7 cell line	-6.25–100 µg/mL	-12 µg/mL (24 h)	-↑ Cytotoxicity ^a -↑ Pro-apoptotic activity ^a	-N/A	-Alkaloids -Cardiac glycosides -Flavonoids -Phenols -Reducing sugars -Steroids -Terpenoids	[155]
	Peels	Deionised distilled water	-Silver nanoparticles	-A549 cell line	-25 µg/mL -17.34 µg/mL	-17.34 µg/mL (N/A)	-↓ Cell proliferation ^b -↑ Cell apoptosis ^b -↑ p53 expression ^b	-Normal HBL breast epithelial cell line (N/A)	-N/A	[156]
<i>Ipomoea turpethum/Operculina turpethum</i>	Roots	Ethanol	-Poly(N-isopropylacrylamide), N-vinyl pyrrolidone and acrylic acid co-polymeric nanoparticles	-MCF-7 cell line -MDA-MB-231 cell line ^c	-100–500 µg/mL	-221.81 µg/mL (24 h) -171.13 µg/mL (24 h)	-↑ Cytotoxicity ^a -↓ Cell proliferation ^b -↑ Cell apoptosis ^b -↑ Nuclear condensation ^b -↑ Cell accumulation in G0/G1 phase ^b	-N/A	-N/A	[161]
<i>Mirabilis jalapa</i>	Leaves	RIP	-Alginate-chitosan nanoparticles -Anti-EpCAM antibody-conjugated alginate-chitosan nanoparticles	-T47D cell line	-0–16.67 µg/mL	-14.87 µg/mL (3 h) -13.27 µg/mL (3 h)	-↑ Cytotoxicity ^a -↑ Cancer cell selectivity ^a	-Normal Vero kidney cell line (27.84 µg/mL for unconjugated and 33.62 µg/mL for conjugated)	-38% proteins	[167]
<i>Plectranthus amboinicus</i>	Leaves	Ethanol	-Chitosan-sodium tripolyphosphate nanoparticles	-T47D cell line	-15.625–500 µg/mL	-89.166 µg/mL (24 h)	-↓ Cell viability ^b -↑ Cell proliferation (24 h) ^b -↓ Cell proliferation (48, 72 h) ^b -↑ Cell apoptosis ^b	-N/A	-N/A	[175]
<i>Punica granatum</i>	Fruits	N/A	-Poly(lactic-co-glycolic acid)-poly(ethylene glycol) nanoparticles -Solid lipid nanoparticles	-MCF-7 cell line -HS578T cell line ^c	-0–30 µg/mL	-19.36 ± 3.70 µg/mL (96 h) -29.17 ± 7.60 µg/mL (96 h)	-↑ Growth-inhibitory activity ^a	-N/A	-Punicalagin -Ellagic acid	[189]
				-MCF-7 cell line	-1–500 µg/mL	-1.05 µg/mL (24 h)	-↑ Cytotoxicity ^a	-Normal HFB-4 melanocyte cell line (19.34 µg/mL)	-N/A	[190]

(Continued)

Table 4 (Continued).

Plant Botanical Name	Plant Parts	Type of Extract	Type of Nanoformulation	Cell Models/ Animals (Sex)	Doses	IC ₅₀ Value (Treatment Duration)	Key Observations	Biocompatibility (IC ₅₀ Value)	Detected Compounds	References
<i>Putranjiva roxburghii</i> <i>Drypetes roxburghii</i>	Seeds	Deionised water	-Silver nanoparticles	-MDA-MB-231 cell line ^c	-0.0097–10 mg/mL	-0.26 mg/mL (24 h)	-↑ Cytotoxicity ^a -↑ Cell apoptosis ^b -↑ DNA fragmentation ^b	-Peripheral blood mononuclear cells (N/A)	-N/A	[196]
		Distilled water					-MCF-7 cell line			
<i>Zataria multiflora</i>	N/A	Essential oil	-Citrus pectin-based nanoemulsion	-MCF-7 cell line -MDA-MB-231 cell line ^c -T47D cell line -MDA-MB-231 spheroids ^c	-0–250 µg/mL	-5.38 µg/mL (72 h) -20.4 µg/mL (72 h) -0.0016 µg/mL (72 h) -65.5 µg/mL (48 h)	-↑ Anti-proliferative activity ^a -↑ Cell apoptosis ^b -↑ Cell accumulation in G2/M phase (MDA-MB-231 cells) or S phase (MDA-MB-231 spheroids) ^b	-Normal L929 fibroblast cell line (N/A)	-N/A	[205]

Notes: ↑, increased; ↓, decreased; ↔, no significant change; ^aIndicates changes in comparison to free extract treatment; ^bIndicates changes in comparison to untreated controls; ^cRepresents triple-negative breast cancer models. **Abbreviations:** DNA, deoxyribonucleic acid; EpCAM, epithelial cell adhesion molecule; RIP, ribosome-inactivating protein.

reduction in the protein level of proliferating cell nuclear antigen (PCNA; ie, a proliferation marker) than those treated with free extracts. A more significant reduction in the mRNA and protein levels of cyclin D1 and the protein level of cyclin-dependent kinase (CDK)4, as well as a more significant increase in the mRNA level of p21 (ie, a CDK inhibitor) and the protein level of nuclear p21 relative to cytosolic p21 were also observed. Moreover, both *A. capillus-veneris* and *P. quadriaurita* extracts and their AuNPs also induced apoptosis in MCF-7 and BT-47 cells, as evidenced by a significant increase in the number of TUNEL- and Annexin V-positive cells. Apoptosis was further confirmed to be mediated by the mitochondrial apoptotic pathway, as indicated by a drop in mitochondrial membrane potential ($\Delta\Psi_m$); a significant increase in the mRNA and protein levels of Bcl-2-associated X protein (Bax; ie, a pro-apoptotic protein) and the protein levels of caspase-9 (ie, an initiator caspase of the mitochondrial apoptotic pathway), caspase-3 (ie, an effector caspase) and cytosolic cytochrome c relative to mitochondrial cytochrome c; as well as a significant decrease in the mRNA and protein levels of B-cell lymphoma 2 (Bcl-2; ie, an anti-apoptotic protein). Importantly, AuNPs induced greater changes in the expression of the abovementioned apoptotic markers than their free extracts. Taken together, these findings suggest that the formulation of *A. capillus-veneris* and *P. quadriaurita* extracts into AuNPs can improve their anti-proliferative, cell cycle arrest-inducing and pro-apoptotic activities against BC cells.

The *Annona muricata* Extracts

Annona muricata is a fruit tree widely cultivated in the tropical regions of Central and South America, Western, Central and Eastern Africa as well as Southeast Asia.¹³⁸ It is known by a range of common names at different places, including Soursop (English), Guanábana (Latin American Spanish), Graviola (Portuguese) and Omusitafeli/Ekitafeli (Uganda).¹³⁸ Traditionally, different parts of *A. muricata* such as fruits, leaves, seeds, flowers, bark and roots have been used to treat cancer, diabetes, malaria, parasitic infections and stomach ache, etc.^{138,139} More recent studies have discovered various pharmacological activities of *A. muricata* extracts, including anti-arthritic,¹⁴⁰ anti-convulsant,¹⁴¹ anti-diabetic,¹⁴² anti-hypertensive,¹⁴³ antioxidant,¹⁴⁴ anti-parasitic,¹⁴⁵ hypolipidemic,¹⁴⁶ wound healing,¹⁴⁷ gastroprotective,¹⁴⁸ hepatoprotective,¹⁴⁹ anti-inflammatory and analgesic¹⁵⁰ activities. In particular, extracts prepared from *A. muricata* leaves, fruits and seeds have demonstrated

both in vitro and in vivo anti-BC activities.^{151–154} These anti-BC activities have been linked to the regulation of immune system, the reduction of inflammation, the suppression of various signalling pathways (eg, epidermal growth factor receptor [EGFR], mitogen-activated protein kinase [MAPK], phosphoinositide 3-kinase/protein kinase B [PI3K/AKT] and nuclear factor-kappa B [NF- κ B]), the modulation of cell cycle regulators, as well as the stimulation of ROS generation and consequent induction of caspase-dependent apoptosis.^{151,153,154}

Sabapati et al¹⁵⁵ loaded *A. muricata* ethanolic fruit extract into SLNs and found that extract-loaded SLNs caused a greater dose-dependent reduction in MCF-7 cell viability than the free extract (IC₅₀ values of 12 μ g/mL vs 30 μ g/mL). Flow cytometric analysis of Annexin V-FITC-stained cells further showed that extract-loaded SLNs could induce a significantly higher percentage of apoptotic MCF-7 cell death than the free extract (86.0% vs 71.34%). Interestingly, void SLNs did not elicit significant cytotoxicity against MCF-7 cells. Collectively, these findings indicate that SLNs are biocompatible NDDSs capable of enhancing the cytotoxicity and pro-apoptotic activity of *A. muricata* extract against BC cells.

In another study, Jabir et al¹⁵⁶ reported the green synthesis of silver nanoparticles using silver nitrate solution and *A. muricata* aqueous peel extract. The resulting silver nanoparticles (AMSNPs) elicited a significant, time-dependent anti-proliferative effect on AMJ-13 BC cell line (IC₅₀ = 17.34 μ g/mL) but had a less significant effect on normal HBL breast epithelial cell line. This anti-proliferative activity of AMSNPs was linked to the induction of apoptosis via p53 signalling, as evidenced by the observations of disrupted membrane integrity and lysosomal vacuoles, increased percentage of sub-G1 phase corresponding to apoptotic cells, $\Delta\Psi_m$ loss and upregulated p53 expression in treated AMJ-13 cells. However, the study did not compare the anti-BC effect of AMSNPs with that of free *A. muricata* aqueous peel extract.

The *Ipomoea turpethum* Extracts

Ipomoea turpethum (or *Operculina turpethum*), commonly known as “transparent wood rose”, can be found in many countries such as Africa, America, Bangladesh, China, India, Madagascar, Mauritania, Pakistan, Philippines and Sri Lanka.^{157,158} It is one of the medicinal plants that have been employed in the Ayurvedic medicine for treating bronchitis, cancer, cervical lymphadenitis, chronic gout, constipation, dysmenorrhea, fever, fistulas, hemorrhoids, herpes,

induced lacrimation, inflammation, jaundice, neurological disorders, obesity, skin disorders and ulcers.^{157,158} Additionally, *I. turpethum* extracts (ie, from stems, roots, aerial and whole part) have also demonstrated anti-cancer potentials in preclinical BC models.^{159,160} One study further showed that the anti-BC activities of *I. turpethum* stem extract are mediated, at least partly, via its antioxidant activity.¹⁵⁹

Similarly, Mughees et al¹⁶¹ found that *I. turpethum* ethanolic extracts prepared from different plant parts (ie, flowers, leaves, roots, aerial and whole part) demonstrated significant cytotoxicities against both MCF-7 and MDA-MB-231 BC cell lines. The root extract that exhibited the greatest cytotoxicity (IC₅₀ values of 452.35 µg/mL for MCF-7 cells and 310 µg/mL for MDA-MB-231 cells) was subsequently loaded into poly (N-isopropylacrylamide) (NIPAAm; for temperature sensitivity), N-vinyl pyrrolidone (VP; for temperature sensitivity) and acrylic acid (AA; for pH sensitivity) co-polymeric nanoparticles. The TME is generally more acidic and has a higher temperature than normal tissues owing to the excessive lactic acid produced from enhanced glycolysis and the secretion of pyrogenic substances by tumour cells.¹⁶² Intriguingly, the NIPAAm-VP-AA double-triggered nanoparticle system takes advantage of these TME characteristics for targeted delivery of loaded root extract to the tumour sites.¹⁶¹ Expectedly, it was observed that this nanoformulation exerted greater cytotoxicity than the free root extract (ie, IC₅₀ values of 221.81 µg/mL for MCF-7 cells and 171.13 µg/mL for MDA-MB-231 cells). Moreover, IC₅₀ concentrations of this nanoformulation also markedly reduced MCF-7 (from 99.2% to 57.7%) and MDA-MB-231 (from 99.3% to 55.4%) cell proliferation; as well as significantly increased the percentage of early and late apoptotic MCF-7 (from 2.2% to 3.4% and from 4.1% to 9.2% respectively) and MDA-MB-231 (from 6.3% to 14.7% and from 4.5% to 7.3% respectively) cells, the condensation of nuclear chromatin and the accumulation of MCF-7 (from 50.7% to 63.4%) and MDA-MB-231 (from 57.9% to 81.3%) cell populations in G0/G1 phase. These observations collectively indicate that the NIPAAm-VP-AA co-polymeric nanoparticle-based nanoformulation can enhance the cytotoxicity of *I. turpethum* extract as well as exert anti-proliferative, pro-apoptotic and cell cycle arrest-inducing activities against BC cells.

The *Mirabilis jalapa* Extracts

Mirabilis jalapa (four o'clock flower), a medicinal plant that can be found in Brazil, India and Mexico, has been used traditionally in the treatment of abscess, boils, bruises,

diarrhoea, inflammation, pain, piles, ulcers, urticaria and wounds.¹⁶³ It has been reported to contain ribosome-inactivating proteins (RIPs).¹⁶³ RIPs are a family of proteins with *N*-glycosidase activity that catalyses the removal of a single adenine from ribosomal ribonucleic acid, thereby leading to protein synthesis inhibition.¹⁶⁴ They play a key role in defending plants against attacks from pathogens and insects.¹⁶⁵ Interestingly, RIPs isolated from *M. jalapa* leaves have demonstrated cytotoxicity against T47D BC cell line.¹⁶⁶ However, more needs to be done to fully elucidate the anti-BC mechanism(s) of RIPs.

As proteins are subjected to rapid enzymatic degradation following oral administration and have poor membrane permeability, Wicaksono et al¹⁶⁷ formulated a RIP extract of *M. jalapa* leaves (RIP-MJ) into anti-EpCAM antibody-conjugated alginate-chitosan nanoparticles. Epithelial cell adhesion molecule (EpCAM) is a transmembrane glycoprotein that is lowly expressed in normal breast tissues but becomes overexpressed in breast carcinomas.¹⁶⁸ As such, conjugation of nanoparticles with anti-EpCAM antibody enables active breast tumour targeting. For instance, anti-EpCAM antibody-conjugated and unconjugated RIP-MJ nanoparticles elicited greater cytotoxicity against T47D cells than free RIP-MJ (IC₅₀ values of 13.27 µg/mL and 14.87 µg/mL vs 1842.03 µg/mL).¹⁶⁷ Interestingly, while free RIP-MJ had a lower IC₅₀ value in normal Vero kidney cells than in T47D cells (1387.87 µg/mL vs 1842.03 µg/mL), the opposite was observed for anti-EpCAM antibody-conjugated (IC₅₀ values of 33.62 µg/mL vs 13.27 µg/mL) and unconjugated (IC₅₀ values of 27.84 µg/mL vs 14.87 µg/mL) RIP-MJ nanoparticles. These findings collectively suggest that the use of NDDS and targeting ligand can improve both the cytotoxicity and the selectivity of RIP-MJ against BC cells.

The *Plectranthus amboinicus* Extracts

Plectranthus amboinicus, commonly known as Indian borage, is an Asian native plant that can also be found in the Americas.¹⁶⁹ It has been used in Brazil to treat various medical conditions such as inflammation and cancer.¹⁷⁰ In particular, its leaves have been reported to contain compounds with anti-cancer activities (eg, cinaminics, essential oils, flavonoids and terpene derivatives).¹⁶⁹ Unsurprisingly, preclinical studies focussing on *P. amboinicus* leaf extract revealed its anti-BC activities.^{169–174} In one of these studies, the pro-apoptotic activity of *P. amboinicus* leaf extract was linked to the activation of caspase-3 and caspase-7.¹⁷¹

Hasibuan and Sumaiyah¹⁷⁵ loaded *P. amboinicus* ethanolic leaf extract into chitosan-sodium tripolyphosphate nanoparticles (PAEEN) and reported that 24 h of PAEEN treatment could cause a dose-dependent reduction in T47D cell viability ($IC_{50} = 89.166 \mu\text{g/mL}$). Interestingly, although T47D cell proliferation increased following 24 h of PAEEN treatment, a dose-dependent reduction in T47D cell proliferation was seen following 48 h and 72 h of PAEEN treatment. Subsequent flow cytometric analysis revealed that PAEEN could also induce apoptosis in T47D cells. However, the study did not compare these observed cytotoxic, anti-proliferative and pro-apoptotic activities of PAEEN with those of free *P. amboinicus* ethanolic leaf extract.

The *Punica granatum* Extracts

Punica granatum (pomegranate), a deciduous shrub native to Asian countries such as Iran and India, is also widely cultivated in Mediterranean countries, such as Egypt, Morocco, Spain, Tunisia and Turkey.^{176,177} The therapeutic potentials of various *P. granatum* parts (ie, bark, flowers, fruits, leaves, roots and seeds) have been recognised early and exploited in different traditional medicine systems (eg, Ayurveda, Chinese, Islamic and Persian) for treating diarrhoea, dysentery, heart choking, intense cough, jaundice, nasal bleeding, periodontitis, sore throat, spleen diseases, ulcers, etc.¹⁷⁸ These medicinal benefits of *P. granatum* are attributed to its pharmacological activities such as antimicrobial,¹⁷⁹ antioxidant,¹⁸⁰ wound healing,¹⁸¹ cardioprotective,¹⁸² anti-inflammatory and antinociceptive¹⁸³ activities. There has also been extensive preclinical evaluation of the potential utilisation of *P. granatum* fruit and peel extracts in BC treatment.^{184–188} Evidences from these studies suggested that the anti-BC activities of *P. granatum* extracts are mediated via the suppression of NF- κ B and β -catenin signalling pathways; the downregulation of Rho GTPases; the modulation of cellular eicosanoid profile, metastasis-related and epithelial-mesenchymal transition (EMT) markers; the downregulation of DNA repair genes and consequent induction of DNA double-strand breaks; and its anti-estrogenic activity.

Shirode et al¹⁸⁹ encapsulated *P. granatum* fruit extract into poly(lactic-co-glycolic acid)–poly(ethylene glycol) (PLGA-PEG) nanoparticles and reported that *P. granatum* extract-loaded nanoparticles induced a more significant reduction in MCF-7 and Hs578T BC cell growth than the free extract (IC_{50} values of $19.36 \pm 3.70 \mu\text{g/mL}$ vs $44.34 \pm 7.81 \mu\text{g/mL}$ in MCF-7 cells and $29.17 \pm 7.60 \mu\text{g/mL}$ vs

$61.93 \pm 16.11 \mu\text{g/mL}$ in Hs578T cells). Interestingly, void PLGA-PEG nanoparticles had no significant effect on MCF-7 and Hs578T cell growth. These observations collectively indicate that the PLGA-PEG nanoparticle system is biocompatible and capable of enhancing the growth-inhibitory activity of *P. granatum* extract against BC cells.

Besides, Badawi et al¹⁹⁰ loaded *P. granatum* fruit extract into SLNs and found that this nanoformulation significantly reduced MCF-7 cell viability to a greater extent than the free extract, with a 47-fold reduction in IC_{50} value ($1.05 \mu\text{g/mL}$ vs $49.2 \mu\text{g/mL}$). Similarly, void SLNs were observed to exhibit cytotoxicity against MCF-7 cells. The observed enhancement in cytotoxicity may thus, at least partly, be explained by the synergistic effect between *P. granatum* extract and SLNs. Importantly, *P. granatum* extract-loaded SLNs had a higher IC_{50} value in normal HFB-4 melanocytes than in MCF-7 cells ($19.34 \mu\text{g/mL}$ vs $1.05 \mu\text{g/mL}$), suggesting that this nanoformulation is BC cell-selective. Collectively, these observations suggest that SLNs can enhance the cytotoxicity of *P. granatum* extract against BC cells, possibly via synergism and improvement of BC cell selectivity.

The *Putranjiva roxburghii* Extracts

Putranjiva roxburghii (or *Drypetes roxburghii*), an evergreen tree native to India, is locally referred to as “Amulet-Plant or Wild Olive or Child-Life-Tree”.¹⁹¹ It is also widely distributed in Bangladesh, Myanmar, Nepal, Sri Lanka, Thailand, Papua New Guinea, Taiwan, the United States, Trinidad and Tobago.^{191,192} Traditionally, it has been used in Ayurveda for treating conditions such as azoospermia, burning sensation, hot swellings, eye disorders, smallpox as well as mouth and stomach ulcers.¹⁹² More recent studies have revealed the anti-BC, anti-epileptic, antioxidant, anti-inflammatory, antimicrobial, antinociceptive and anti-pyretic potentials of *P. roxburghii* leaf and seed extracts.^{193–195} However, further mechanistic studies are required to explain how *P. roxburghii* extracts exert these pharmacological activities.

Balkrishna et al¹⁹⁶ carried out the green synthesis of silver nanoparticles using silver nitrate solution and *P. roxburghii* aqueous seed extract. The study revealed that *P. roxburghii* silver nanoparticles (PJSNPs) could exert more potent cytotoxic effect on MDA-MB-231 cells than the free extract (IC_{50} values of 0.26 mg/mL vs 7.7 mg/mL). This promising finding may be attributed to the small size ($\sim 8 \pm 2 \text{ nm}$) and negative zeta potential (-26.71 mV) of PJSNPs, which can enhance both their bioavailability and cellular

uptake. Furthermore, IC_{50} concentration of PJSNPs also increased the percentage of apoptotic cells (69%) and induced DNA fragmentation in MDA-MB-231 cells. Notably, PJSNP treatment did not show marked cytotoxicity against peripheral blood mononuclear cells (PBMCs). Taken together, this nanoformulation can enhance the cytotoxicity of *P. roxburghii* extract and exert pro-apoptotic activity against BC cells while sparing toxicities against PBMCs. Another study by Nayaka et al¹⁹⁷ similarly reported the cytotoxicity of PJSNPs against MCF-7 cells ($IC_{50} = 72.32 \mu\text{g/mL}$).

The *Zataria multiflora* Essential Oils

Zataria multiflora, or Avishan-e-Shirazi, is a thyme-like plant that can be found extensively in Iran, Afghanistan and Pakistan.¹⁹⁸ It is not only a popular condimental plant but also a traditional medicinal plant that has been employed as anaesthetic, analgesic, anthelmintic, anti-diarrheal, antiseptic, anti-spasmodic, carminative, diaphoretic, diuretic, stimulant and vermifuge agents.¹⁹⁹ More recent studies have evaluated the pharmacological activities of *Z. multiflora* essential oil (ZEO), the constituents of which are dominated by oxygenated monoterpenes, monoterpene hydrocarbons and sesquiterpene hydrocarbons.²⁰⁰ Besides antimicrobial,²⁰¹ antioxidant,²⁰² anti-cholinesterase and anti-inflammatory²⁰³ activities, ZEO has also been reported to mediate potent anti-BC activities via the stimulation of ROS generation, the intercalation of DNA strands, the induction of DNA damage and the eventual induction of mitochondrial apoptotic pathway.^{198,204}

Salehi et al²⁰⁵ attempted to overcome the limitations hindering the clinical development of essential oils via the development of a citrus pectin-based nanoemulsion for ZEO (CP-ZEO NE). Both ZEO and CP-ZEO NE treatments dose-dependently decreased MCF-7, MDA-MB-231 and T47D cell proliferation but had no significant effect on the proliferation of normal L929 fibroblast cells. However, a reduced sensitivity to ZEO was observed in MDA-MB-231 and T47D cells 24 h following treatment, possibly due to the high volatility and low stability of ZEO. Interestingly, CP-ZEO NE preparation may have improved ZEO stability, as CP-ZEO NE-treated MCF-7, MDA-MB-231 and T47D cells demonstrated the highest sensitivity to CP-ZEO NE at 72 h. This finding is consistent with the lower IC_{50} values of CP-ZEO NE over ZEO at 72 h in MCF-7 (5.38 $\mu\text{g/mL}$ vs 33.1 $\mu\text{g/mL}$), MDA-MB-231 (20.4 $\mu\text{g/mL}$ vs 30.54 $\mu\text{g/mL}$) and T47D (0.0016 $\mu\text{g/mL}$ vs 37.03 $\mu\text{g/mL}$) cells. Similarly, CP-ZEO NE also

demonstrated greater anti-proliferative activity against MDA-MB-231 spheroids than ZEO, as reflected by a lower IC_{50} value after 48 h of treatment (65.5 $\mu\text{g/mL}$ vs 118.4 $\mu\text{g/mL}$). Moreover, CP-ZEO NE also showed pro-apoptotic activity against MCF-7, MDA-MB-231 and T47D cells, as evidenced by apoptosis-related morphological changes (eg, small, rounded, wrinkled and irregular cell shape, low-density and membrane blebbing); increased orange-red fluorescence, nuclear fragmentation and chromatin condensation in dual acridine orange/ethidium bromide (AO/EB) staining test; a DNA ladder pattern on agarose gel electrophoresis; increased number of TUNEL-positive cells; “Hedgehog tails” in comet assay; increased apoptotic cell population in Annexin V-FITC/PI staining; and increased percentage of sub-G1 phase corresponding to apoptotic cells. Pro-apoptotic activity of CP-ZEO NE was similarly observed in MDA-MB-231 spheroids. Additionally, CP-ZEO NE treatment also induced a G2/M phase arrest in MDA-MB-231 cells but a S phase arrest in MDA-MB-231 spheroids. Taken together, CP-ZEO NE is a biocompatible nanoformulation that is capable of enhancing the stability and anti-proliferative activity of ZEO as well as exerting pro-apoptotic and cell cycle arrest-inducing activities against BC cells and spheroids.

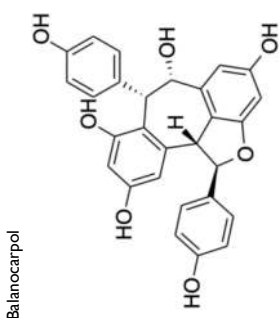
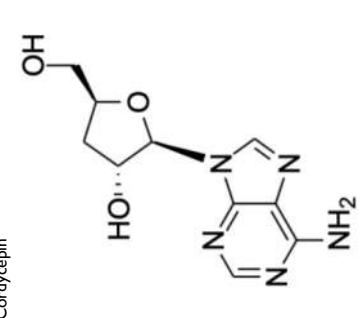
The Anti-Breast Cancer Mechanisms of Natural Bioactive Compounds and Anti-Breast Cancer Activities of Their Nanoformulations in Preclinical Models

A number of bioactive compounds isolated from natural sources have been proven to be effective in the treatment of human diseases, including cancer.²⁰⁶ Table 5 summarises the proposed anti-BC mechanisms of selected natural bioactive compounds. However, the clinical utilisation of natural bioactive compounds is often challenged by their low stability, poor aqueous solubility and low bioavailability.²⁰⁷ One approach to overcoming these challenges includes the exploitation of NDDSs (Table 6).

Balanocarpol

Balanocarpol, a resveratrol dimer, can be isolated from many *Hopea* spp., particularly *Hopea dryobalanoides* and *Hopea mengarawan* found in the Malaysian rain forest.^{208–210} Its anti-BC potential has been preclinically

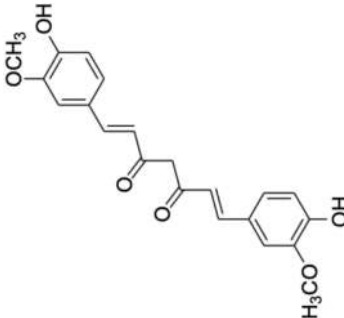
Table 5 Proposed Anti-Breast Cancer Mechanisms of Natural Bioactive Compounds in Preclinical Breast Cancer Models

Natural Bioactive Compound	Natural Sources	Cell Models/Animals (Sex)	Mechanisms of Action	References
Balanocarpol 	<i>Hopea</i> spp. such as <i>Hopea dryobalanoides</i> ("merawan mata kucing hitam") and <i>Hopea mangarawan</i> ("merawan hitam")	-MCF-7 cell line	-Inhibition of SK1 enzymatic activity and expression -Induction of PARP cleavage -Reduction of DNA synthesis	[209]
Cordycepin 	<i>Cordyceps</i> spp.	-MCF-7 cell line -MDA-MB-231 cell line	-Induction of autophagy-associated cell death ●↑ LC3II intensity ●↑ AVO and MDC-positive vacuole formation -Induction of mitochondrial apoptotic pathway ●↑ Mitochondrial translocation of Bax ●↑ Mitochondrial cytochrome c release ●↑ Cleaved caspase-3 and -9 levels ●↑ PARP cleavage	[215]
		-MCF-7 cell line	-Regulation of signalling pathways ●Hedgehog ●p53 ●Estrogen -Induction of caspase-dependent apoptosis ●↓ Bax/Bcl-2 ratio ●↑ Cleaved caspase-7, -8 and -9 levels ●↓ XIAP level	[216]

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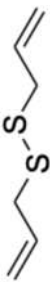
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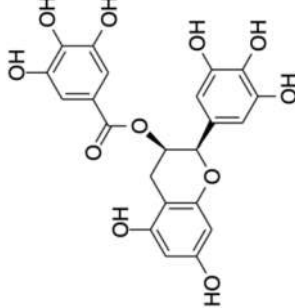
Natural Bioactive Compound	Natural Sources	Cell Models/Animals (Sex)	Mechanisms of Action	References
		<ul style="list-style-type: none"> -MCF-7 cell line -MDA-MB-231 cell line -MDA-MB-453 cell line -T47D cell line 	<ul style="list-style-type: none"> -Inhibition of RNA synthesis -Induction of DNA double-strand breaks ● ↑ γH2AX level -Induction of DNA damage response ● ↑ ATM and ATR phosphorylation -Inhibition of poly(ADP)riboseylation ● ↓ PARP activity 	[217]
		<ul style="list-style-type: none"> -MCF-7 cell line -MDA-MB-231 cell line 	<ul style="list-style-type: none"> -Induction of apoptosis ● Modulation of apoptosis-related proteins (↑ PUMA, FAS, DR4, DR5, cytochrome c and cleaved caspase-3 levels; ↓ Bcl-2, XIAP and PDGFR-α levels) -Modulation of EMT markers ● ↓ Mesenchymal markers (snail, slug, ZEB1 and N-cadherin) ● ↑ Epithelial markers (E-cadherin) -Suppression of hedgehog signalling pathway ● ↓ GLI1, GLI2 and SMO levels ● ↓ Nuclear translocation of GLI1/2 -Suppression of Notch signalling pathway ● ↓ NOTCH1, NOTCH3, JAGGED1 and HES1 levels ● ↓ Notch-dependent luciferase reporter activity 	[218]
		<ul style="list-style-type: none"> -MCF-7 cell line -MDA-MB-231 cell line -Mice bearing MCF-7 xenografts (male) 	<ul style="list-style-type: none"> -Stimulation of ROS generation ● ↑ Intracellular ROS level -Induction of caspase-dependent apoptosis ● ↑ Bax/Bcl-2 ratio ● ↓ ΔΨ_m ● ↑ Cleaved caspase-3, -8 and -9 levels 	[219]

<p>Curcumin</p>  <p>The image shows the chemical structure of Curcumin, a polyphenolic compound. It consists of two phenyl rings connected by a central heptadiene chain. The left phenyl ring has a methoxy group (-OCH₃) and a hydroxyl group (-OH) at the 3 and 4 positions, respectively. The right phenyl ring has a hydroxyl group (-OH) and a methoxy group (-OCH₃) at the 3 and 4 positions, respectively.</p>	<p><i>Curcuma longa</i> (turmeric)</p>	<p>-MDA-MB-231 /HER2 cell line</p>	<p>[230]</p> <ul style="list-style-type: none"> -Modulation of cell cycle regulators ● ↑ p27 level via ↓ Skp2 and HER2 levels ● ↓ Cyclin E, CDK2 and CDK4 levels -Induction of caspase-dependent apoptosis ● ↑ Bax/Bcl-2 ratio ● ↑ Cleaved caspase-3 level ● ↑ PARP cleavage -Suppression of PI3K/AKT signalling pathway ● ↓ AKT phosphorylation -Suppression of ERK signalling pathway ● ↓ ERK phosphorylation -Modulation of metastasis-related markers ● ↓ MMP-2 and MMP-9 levels
		<p>-MDA-MB-231 cell line -Mice bearing MDA-MB-231 xenografts (female)</p>	<p>[231]</p> <ul style="list-style-type: none"> -Activation of p53 signalling pathway ● ↑ p53 level -Inhibition of angiogenesis ● ↓ Microvessel formation -Suppression of NF-κB signalling pathway ● ↓ NF-κB activation ● ↓ NF-κB-regulated gene products (cyclin D1, p65 and PECAM-1)
		<p>-MCF-7 cell line -T47D cell line</p>	<p>[232]</p> <ul style="list-style-type: none"> -Modulation of cell cycle regulators ● ↓ CDC25 and CDK1 levels ● ↑ p21 level -Suppression of PI3K/AKT/mTOR signalling pathway ● ↓ AKT, mTOR and S6 phosphorylation -Induction of mitochondrial apoptotic pathway ● ↑ Bax/Bcl-2 ratio ● ↑ Cleaved caspase-3 level
		<p>-MCF-7 cell line -MDA-MB-231 cell line</p>	<p>[233]</p> <ul style="list-style-type: none"> -Suppression of β-catenin signalling pathway ● ↓ Dishevelled, β-catenin, cyclin D1 and slug levels ● ↑ GSK3β and E-cadherin levels

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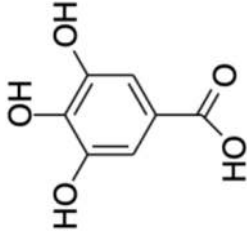
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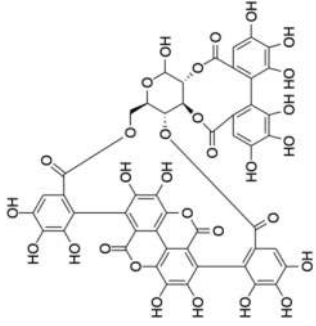
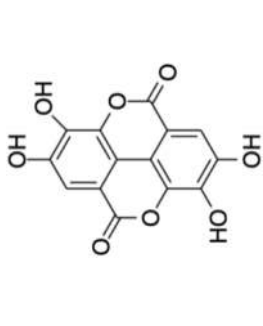
Natural Bioactive Compound	Natural Sources	Cell Models/Animals (Sex)	Mechanisms of Action	References
Diallyl disulfide 	<i>Allium sativum</i> (garlic)	-MCF-7 cell line -MDA-MB-231 cell line -BT-549 cell line -Mice bearing MDA-MB-231 xenografts (female)	-Induction of caspase-dependent apoptosis <ul style="list-style-type: none"> • ↑ Bax level • ↓ Bcl-2, Bcl-xL and Bcl-w levels • ↑ Caspase-3 activity -Induction of histone-H4 acetylation via inhibition of histone deacetylation -Induction of mitochondrial apoptotic pathway <ul style="list-style-type: none"> • ↑ Bax/Bcl2 ratio • ↑ Caspase-3 and -9 activities -Modulation of metastasis-related markers <ul style="list-style-type: none"> • ↓ MMP-9 level and activity • Modulation of EMT markers • ↓ Mesenchymal markers (vimentin, N-cadherin and snail) • ↓ Epithelial markers (E-cadherin) • Suppression of β-catenin signalling pathway • ↓ Active β-catenin level 	[256] [257]
		-MCF-7 cell line	-Induction of caspase-dependent apoptosis <ul style="list-style-type: none"> • ↑ Caspase-3 cleavage • ↑ PARP cleavage -Suppression of ERK signalling pathway <ul style="list-style-type: none"> • ↓ ERK phosphorylation -Activation of JNK signalling pathway <ul style="list-style-type: none"> • ↑ JNK phosphorylation -Activation of p38 signalling pathway <ul style="list-style-type: none"> • ↑ p38 phosphorylation 	[258]
		-MDA-MB-231 cell line -Mice bearing MDA-MB-231 xenografts (male)	-Modulation of miRNA expression <ul style="list-style-type: none"> • ↑ miR-34a level -Suppression of SRC/Ras/Ras/ERK signalling pathway <ul style="list-style-type: none"> • ↓ SRC level • ↓ Ras-GTP level • ↓ ERK1/2 phosphorylation 	[259]
		-Mice bearing MCF-7 xenografts (female) -Mice bearing MDA-MB-231 xenografts (female)	-Modulation of protein targets <ul style="list-style-type: none"> • ↓ MMP-9 and uPA levels • ↓ TTP level 	[260]

<p>Epigallocatechin gallate</p> 	<p><i>Camellia sinensis</i> (tea plant)</p>	<p>-MDA-MB-231 cell line -Hs578T cell line</p>	<p>-Induction of apoptosis <ul style="list-style-type: none"> ● ↑ Bax/Bcl-2 ratio ● ↑ PARP cleavage -Modulation of metastasis-related markers -Suppression of PI3K/AKT signalling pathway <ul style="list-style-type: none"> ● ↓ MMP-9 level ● ↓ AKT level and phosphorylation -Suppression of β-catenin signalling pathway <ul style="list-style-type: none"> ● ↓ β-catenin level -Inhibition of angiogenesis <ul style="list-style-type: none"> ● ↑ VEGF level (24 h); ↓ VEGF level (48 h and 72 h) </p>	<p>[267]</p>
		<p>-Mice bearing E0771 xenografts (female)</p>	<p>-Suppression of HIF-1α signalling pathway <ul style="list-style-type: none"> ● ↓ HIF-1α activation -Suppression of NF-κB signalling pathway <ul style="list-style-type: none"> ● ↓ NF-κB activation -Inhibition of angiogenesis <ul style="list-style-type: none"> ● ↓ VEGF level </p>	<p>[268]</p>
		<p>-4T1 cell line -Mice bearing 4T1 xenografts (female)</p>	<p>-Induction of mitochondrial and death receptor apoptotic pathways <ul style="list-style-type: none"> ● ↑ Pro-apoptotic genes (PUMA, caspase-3, -8, -9, FAS, FasL, Apaf1, Bax, Bad, cytochrome c, PTEN and Smac) ● ↓ Anti-apoptotic genes (survivin, Bcl-2, Bcl-xL and c-Myc) ● ↑ Caspase-3, -8 and -9 activities ● ↓ ΔΨ_m -Induction of autophagy <ul style="list-style-type: none"> ● ↑ Beclin1, ATG5 and LC3B levels (10 μM and 20 μM); ↑ Beclin1, ATG5 and ↓ LC3B levels (40 μM) -Inhibition of glucose metabolism <ul style="list-style-type: none"> ● ↓ Glucose uptake ● ↓ Lactic acid production ● ↓ ATP level ● ↓ Key glycolytic enzyme levels and activities (HK, PFK, LDH and PK) ● ↓ HIF-1α level ● ↓ GLUT1 level -Inhibition of angiogenesis <ul style="list-style-type: none"> ● ↓ VEGF level </p>	<p>[270]</p>

(Continued)


Table 5 (Continued).

Natural Bioactive Compound	Natural Sources	Cell Models/Animals (Sex)	Mechanisms of Action	References
Gallic acid 	A variety of medicinal plants and fruits such as <i>Quercus</i> spp. and <i>Punica</i> spp.	-MCF-7 cell line -Mice bearing MCF-7 xenografts (female)	-Induction of miR-25-dependent apoptosis ● ↓ miR-25 level ● ↑ Pro-caspase-3, -9 and PARP-1 levels	[271]
		-MCF-7 cell line -MDA-MB-231 cell line	-Inhibition of hTERT transcription ● ↓ DNMT and HAT activities ● ↓ Acetyl-H3, acetyl-H3K9, acetyl-H4 and dimethyl-H3K4 levels in hTERT promoter ● ↑ hTERT repressor (MAD1 and E2F-1) binding to hTERT promoter ● ↑ hTERT activator (c-Myc) binding to hTERT promoter	[272]
		-MCF-7 cell line	-Induction of mitochondrial apoptotic pathway via modulation of p53, Mcl-1 and p21 expression ● ↑ p53 level (3 h and 48 h) ● ↑ Mcl-1 level (48 h) ● ↓ p21 level (1 h, 2 h and 3 h); ↑ p21 level (48 h)	[277]
		-MDA-MB-231 cell line	-Activation of p38 signalling pathway ● ↑ p38 phosphorylation at threonine 180 and tyrosine 182 -Modulation of cell cycle regulators ● ↓ Cyclin D1, CDK4, cyclin E and CDK2 levels ● ↑ p21 and p27 levels -Induction of caspase-dependent apoptosis ● ↑ Cleaved caspase-3 and -9 levels ● ↑ PARP cleavage	[278]
		-MCF-7 cell line	-Modulation of cell cycle regulators ● ↓ Cyclin A, CDK2, cyclin B1 and cdc2/CDK1 levels ● ↑ p21 level ● ↑ p27 level via ↓ Skp2 level, Skp2-p27 association and p27 polyubiquitination	[279]
		-MCF-7/DOX cell line -MCF-7/DOX500 cell line	-Modulation of metastasis-related markers ● ↓ MMP-2 and -9 activities	[280]
		-MDA-MB-231 cell line	-Suppression of NF-κB signalling pathway ● Inhibition of classical NF-κB activation pathway via ↓ IKKα and IKKβ phosphorylation, IκB degradation, p65 nuclear translocation and NF-κB DNA binding ● Inhibition of parallel NF-κB activation pathway via ↓ MEK/ERK/p90RSK/MSK signalling and p65 phosphorylation ● ↓ NF-κB target gene expression (IL-6, IL-8, VEGF, Bcl-2, XIAP, COX-2 and CXCR4)	[281]

<p>Punicatagin</p> 	<p><i>Punica granatum</i> (pomegranate)</p>	<p>-MCF-7 cell line -MDA-MB-231 cell line</p>	<p>-Downregulation of GOLPH3 -Modulation of metastasis-related markers ● ↓ MMP-2 and -9 levels -Modulation of EMT markers ● ↓ Mesenchymal markers (N-cadherin) ● ↑ Epithelial markers (E-cadherin)</p>	<p>[293]</p>
<p>Ellagic acid</p> 		<p>-MCF-7 cell line -MDA-MB-231 cell line -Cancer stem cells derived from MDA-MB-231 cell line -BT-549 cell line -MMTV-PyMT mice (female)</p>	<p>-Antioxidant activity -Inhibition of oxidative DNA damage ● ↓ 4-OHE₂/CuCl₂-induced DNA adduct formation</p>	<p>[294]</p>
		<p>-Mice bearing MDA-MB-231 xenografts (female)</p>	<p>-Suppression of VEGFR2 and its downstream signalling pathways ● ↓ VEGFR-2, AKT and JNK phosphorylation -Inhibition of angiogenesis ● ↓ Tumor microvessel density</p>	<p>[297]</p>
		<p>-MCF-7 cell line -MCF-7 cell line -MDA-MB-231 cell line -Cancer stem cells derived from MDA-MB-231 cell line -BT-549 cell line -MMTV-PyMT mice (female)</p>	<p>-Regulation of TGF-β/Smads signalling pathway</p>	<p>[298]</p>
		<p>-MCF-7 cell line -MDA-MB-231 cell line -Cancer stem cells derived from MDA-MB-231 cell line -BT-549 cell line -MMTV-PyMT mice (female)</p>	<p>-Downregulation of ACTN4 -Suppression of β-catenin signalling pathway ● ↓ AKT and GSK3β phosphorylation ● ↓ β-catenin phosphorylation ● ↓ Cytosolic and nuclear β-catenin levels ● ↓ β-catenin transcription activity -Modulation of stem-like markers ● ↓ Nanog, c-Myc, Oct-4 and survivin levels -Modulation of cell cycle regulators ● ↓ Cyclin D1 level -Modulation of EMT markers ● ↓ Mesenchymal markers (snail, slug and ZEB1)</p>	<p>[299]</p>
		<p>-MCF-7 cell line -MDA-MB-231 cell line</p>	<p>-Modulation of cell cycle regulators ● ↓ CDK6 level and activity</p>	<p>[300]</p>

(Continued)

Table 5 (Continued).

Natural Bioactive Compound	Natural Sources	Cell Models/Animals (Sex)	Mechanisms of Action	References
 <p>Sulforaphane</p>	Cruciferous vegetables especially <i>Brassica oleracea</i> (broccoli)	-MCF-7 cell line -MDA-MB-231 cell line	-Targeting of heat shock response ● ↓ HSF1 level ● ↓ Heat shock proteins (HSP70 and 90) -Modulation of tumour suppressors ● MCF-7: ↑ p21 and p53 levels ● MDA-MB-231: ↑ p21 and ↑ p53 levels -Induction of caspase-dependent apoptosis ● ↑ Pro-apoptotic proteins (Apaf1, AIF, Bax and Bad) ● ↓ Anti-apoptotic proteins (Bcl-2) ● ↑ Mitochondrial cytochrome c release ● ↑ Caspase-3, -8 and -9 activities	[310]
		-MCF-7 cell line -MDA-MB-231 cell line -MDA-MB-468 cell line -SKBR3 cell line	-Suppression of PI3K/AKT/mTOR/S6K1 signalling pathway ● ↓ AKT phosphorylation at serine 473 ● ↓ S6K1 phosphorylation at threonine 389 -Induction of autophagy ● ↑ Membranous vacuole formation ● ↑ LC3II recruitment to autophagosomes -Inhibition of protein synthesis	[311]
		-MDA-MB-231 cell line -MDA-MB-468 cell line -MCF-10ACA1a cell line -MCF-7 cell line -BT-474 cell line	-Disruption of HDAC5-LSD1 axis ● ↓ HDAC5 level via ↓ USFI ● ↓ Deubiquitinase USP28 level, ↑ LSD1 polyubiquitination and ↓ LSD1 level -Upregulation of tumour suppressor genes ● ↑ CTDSP1, GLIPR1, CYLD, TPPI2, PPP2R1B, ISG15 and EGLN3 levels	[312]
		-MDA-MB-231 cell line	-Modulation of markers associated with aggressive phenotype ● ↓ PBR and POU5F1 levels ● ↓ EMT markers (vimentin and Twist1) ● ↓ Metastasis-related markers (MMP-7 and MMP-14) ● ↓ Pro-inflammatory cytokines (IL-1 β , IL-6, IL-4, TNF- α and IFN- γ) ● ↓ Pro-angiogenic growth factors (PDGF and VEGF)	[313]

Notes: ↑, increased; ↓, decreased.

Abbreviations: ACTN4, actinin alpha 4; AIF, apoptosis inducing factor; Apaf1, apoptotic protease activating factor 1; ATG5, autophagy related 5; ATM, ataxia-telangiectasia-mutated kinase; ATR, adenosine triphosphate; ATR, ataxia telangiectasia and Rad3-related kinase; AVO, acidic vesicular organelles; Bad, Bcl-2-associated agonist of cell death; Bax, Bcl-2-associated protein; Bcl-xL, B-cell lymphoma-extra large; Bcl-2, B-cell lymphoma 2; CDC25, cell division cycle 25 phosphatase; CDK1/2/4/6, cyclin-dependent kinase 1/2/4/6; COX-2, cyclooxygenase-2; CTDSP1, CTD small phosphatase-like; CXCR4, C-X-C chemokine receptor type 4; CYLD, cylindromatosis lysine 63 deubiquitinase; DNA, deoxyribonucleic acid; DNMT, DNA methyltransferase; DR4/5, death receptor 4/5; EGLN3, Egl-9 family hypoxia inducible factor 3; EMT, epithelial-mesenchymal transition; E2F-1, E2F transcription factor 1; FAS, Fas cell surface death receptor; FasL, Fas ligand; GLIPR1, GLI lysine-specific histone demethylase 1A; HER2, human epidermal growth factor receptor 2; HES1, hairy and enhancer of split 1; HIF-1 α , hypoxia-inducible factor-1 alpha; HK, hexokinase; HSF1, heat shock factor 1; HSP70/90, heat shock protein 70/90; hTERT, human telomerase reverse transcriptase; IFN- γ , interferon-gamma; IKK α / β , I κ B kinase alpha/beta; IL-1 β /4/6/8, interleukin-1 beta/4/6/8; ISG15, interferon-stimulated gene 15; I κ B, inhibitor of NF- κ B; JAGGED1, jagged canonical Notch ligand 1; JNK, c-Jun N-terminal kinase; LC3II/B, microtubule-associated protein 1 light chain 3 II/beta; LDH, lactic dehydrogenase; MADI, max dimerization protein 1; Mcl-1, myeloid-cell leukemia 1; MDC, monodansylcadaverine; MEK/ERK/PP0RSK/MSK, mitogen-activated protein kinase/extracellular signal-regulated kinase/p90 ribosomal S6 kinase/mitogen- and stress-activated kinase 3/6; MMP-2/7/9/14, matrix metalloproteinase 2/7/9/14; NF- κ B, nuclear factor-kappa B; NOTCH1/3, notch receptor 1/3; Oct-4, octamer-binding transcription factor-4; PARP, poly-ADP ribose polymerase; PBR, peripheral-type benzodiazepine receptor; PDGF, platelet derived growth factor; PDGFR- α , platelet derived growth factor receptor-alpha; PECAM-1, platelet and endothelial cell adhesion molecule-1; PFK, phosphofructokinase; PI3K/AKT/mTOR/S6K1, phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin/ribosomal protein S6 kinase 1; PK, pyruvate kinase; POU5F1, POU class 5 homeobox 1; PPP2R1B, protein phosphatase 2 scaffold subunit; Abeta; PTEN, phosphatase and tensin homologue deleted on chromosome 10; PUMA, p53 upregulated modulator of apoptosis; RNA, ribonucleic acid; ROS, reactive oxygen species; Skp2, S-phase kinase-associated protein 2; SKI, sphingosine kinase 1; SMO, smoothened; SRC/Ras/ERK, SRC/rat sarcoma virus/extracellular signal-regulated kinase; S6, p70 ribosomal S6 kinase; TPPI2, Tissue factor pathway inhibitor 2; TGF- β , Transforming growth factor-beta; TNF- α , Tumour necrosis factor-alpha; TTP, Tristetraprolin; Twist1, Twist family BHLH transcription factor 1; uPA, Urokinase-type plasminogen activator; USF1, Upstream transcription factor 1; USP28, Ubiquitin specific peptidase 28; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; XIAP, X-linked inhibitor of apoptosis protein; ZEB1, Zinc finger E-box binding homeobox 1; 4-OHE₂/CuCl₂, 4-hydroxyestradiol/Copper(II) chloride; γ H2AX, histone 2AX phosphorylation; Δ V_m, mitochondrial membrane potential.

Table 6 A Summary of Preclinical Studies Evaluating the Anti-Breast Cancer Potentials of Nanoformulated Natural Bioactive Compounds

Natural Bioactive Compound	Type of Nanoformulation	Cell Models/ Animals (Sex)	Doses	IC ₅₀ Value (Treatment Duration)	Key Observations	Biocompatibility (IC ₅₀ Value)	References
Balanocarpol	-Niosomes	-ZR-75-1 cell line	-1.6–196.6 μ M	-57.97 μ M (24 h)	- \uparrow Cytotoxicity ^a	-N/A	[210]
Cordycepin	-Poly(lactic-co-glycolic acid) nanoparticles	-MCF-7 cell line	-5–400 μ g/mL	-16.79 μ g/mL (24 h)	- \uparrow Cellular uptake ^a - \uparrow Cytotoxicity ^a - \downarrow Hemotoxicity ^a	-Rat red blood cells (N/A)	[227]
Curcumin	-Dendrosomes	-4T1 cell line ^d -Mice bearing 4T1 xenografts (female) ^d	-5–45 μ M -40–80 mg/kg (i.p.; 35 days)	-32.5 μ M (24 h) -25 μ M (48 h) -17.5 μ M (72 h)	- \uparrow Cytotoxicity ^a - \uparrow Anti-migratory activity ^a - \uparrow Anti-adhesive activity ^a - \uparrow Survival rates ^b - \downarrow Tumour incidence, volume and weight ^b - \downarrow Metastasis ^b - \downarrow NF- κ B, p105, MMP-9, VEGF COX-2 gene expression ^b	-Normal mouse embryonic fibroblastic cells (N/A) -Female mice bearing 4T1 xenografts (>80 mg/kg) caused hematotoxicity, hepatotoxicity and renal toxicity	[240]
	-Nanoliposomes derived from salmon, soya and rapeseed lecithins	-MCF-7 cell line	-5–20 μ M	-N/A	- \downarrow Cell index ^{a, b}	-N/A	[241]
	-Chitosan-coated nanoliposomes derived from salmon, soya and rapeseed lecithins	-MCF-7 cell line	-5–20 μ M	-N/A	- \uparrow Anti-proliferative activity ^c - \uparrow Encapsulation efficiency ^c	-N/A	[243]
	-Gum arabic aldehyde-gelatin nanogels	-MCF-7 cell line	-3.125–50 μ g/mL	-N/A	- \downarrow Cytotoxicity ^a	-Fresh human blood samples (N/A)	[244]
	-Gum arabic-sodium alginate nanoparticles	-MCF-7 cell line	-1.563–100 μ g/mL	-48.40 μ g/mL (24 h) -33.26 μ g/mL (48 h) -16.84 μ g/mL (72 h)	- \uparrow Cytotoxicity ^a	-N/A	[239]
	-Poly(vinyl alcohol)/cellulose nanocrystal hydrogel membranes	-MCF-7 cell line	-2–8 mg/mL	-N/A	- \uparrow Morphological changes ^b - \downarrow Cell viability ^b - \uparrow Cancer cell selectivity ^a	-Normal HFB-4 melanocyte cell line (N/A)	[246]

(Continued)

Table 6 (Continued).

Natural Bioactive Compound	Type of Nanoformulation	Cell Models/ Animals (Sex)	Doses	IC ₅₀ Value (Treatment Duration)	Key Observations	Biocompatibility (IC ₅₀ Value)	References
	-Water-soluble nanomicelle formed by self-assembly of pectin-curcumin conjugates	-MCF-7 cell line	-1–320 μ M	-12.0 \pm 3.0 μ M (48 h)	- \uparrow Cytotoxicity ^a - \uparrow Aqueous solubility ^a - \uparrow Stability ^a - \downarrow Renal toxicity ^a	-Normal 293A human kidney cell line (139.4 \pm 2.1 μ M)	[247]
	-Albumin nanoparticles	-MDA-MB-231 cell line ^d -Rats (male)	-20–120 μ M -10 mg (i.v.; day 1)	-N/A	- \uparrow Anti-proliferative activity ^a - \uparrow Nanoparticle accumulation in brain and lungs ^a	-N/A	[248]
	-Gelatin nanoparticles	-MCF-7 cell line	-0–140 μ g/mL	-648 μ g/mL (48 h)	- \downarrow Cell viability ^b	-N/A	[206]
	-PEGylated iron oxide-gold nanoparticles	-SKBR3 cell line	-0–15 μ M	-N/A	- \uparrow Cytotoxicity ^a - \uparrow Cell apoptosis ^b - \uparrow Bax gene expression ^b - \downarrow Bcl-2 gene expression ^b - \downarrow MMP-9 gene expression ^b	-N/A	[250]
	-Folic acid-conjugated, calcium-doped dendritic mesoporous silica nanoparticles	-MCF-7 cell line -Mice (female)	-5–20 μ M -30 mg/kg (i.p.; 1 h)	-N/A	- \uparrow Cellular uptake ^a - \uparrow Aqueous solubility ^a - \uparrow Cytotoxicity ^a - \uparrow Pro-apoptotic activity ^a - \uparrow Cell cycle arrest-inducing activity ^a - \uparrow Intracellular ROS generation ^a - \uparrow Caspase-3, caspase-9, cytochrome c, PARP, p53 and I κ B protein levels ^a - \downarrow Bcl-2, β -catenin, NF- κ B, p65, PI3K, pAKT and pmTOR protein levels ^a - \uparrow In vivo bioavailability ^a	-N/A	[252]

Diethyl disulfide	-Solid lipid nanoparticles	-MCF-7 cell line	-1.562–100 µM	-N/A	-N/A	-Normal MCF-10A human breast epithelial cell line (N/A)	[262]
	-Anti-RAGE antibody-conjugated solid lipid nanoparticles	-MDA-MB-231 cell line ^d	-1.562–100 µM	-N/A	-N/A	-N/A	[10]
Epigallocatechin gallate	-Solid lipid nanoparticles	-MDA-MB-231 cell line ^d	-10–100 µg/mL	-9.7 ± 0.6 µg/mL (24 h)	-N/A	-N/A	[273]
	-Bombesin-conjugated solid lipid nanoparticles	-MDA-MB-231 cell line ^d	-5–100 µg/mL	-3.2 ± 1.7 µg/mL (48 h)	-N/A	-N/A	[275]
Gallic acid	-Gum arabic-stabilised nanoparticles	-MCF-7 cell line -MDA-MB-231 cell line ^d	-1.563–100 µg/mL	-30 µg/mL (72 h) -44 µg/mL (72 h)	-N/A	-Normal MCF-10A human breast epithelial cell line (~340 µg/mL)	[288]
	-Poly(lactic-co-glycolic acid)-poly(ethylene glycol) nanoparticles	-MCF-7 cell line -Hs578T cell line ^d	-0–30 µg/mL	-7.5 µM (96 h) -4.1 µM (96 h) -50.5 µM (96 h) -83.5 µM (96 h)	-N/A	-N/A	[189]
Sulforaphane	-PEGylated iron oxide-gold nanoparticles	-SKBR3 cell line	-0–15 µM	-N/A	-N/A	-N/A	[250]

Notes: †, increased; ‡, decreased; ↔, no significant change; ^aIndicates changes in comparison to free extract treatment; ^bIndicates changes in comparison to untreated controls; ^cIndicates changes in comparison to uncoated/unconjugated nanoformulation counterpart; ^dRepresents triple-negative breast cancer models.

Abbreviations: Bad, Bcl-2-associated agonist of cell death; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; COX-2, cyclooxygenase-2; IκB, inhibitor of NF-κB; MMP-9, matrix metalloproteinase-9; NF-κB, nuclear factor-κB; B; pAKT, phosphorylated protein kinase B; PARP, poly-ADP ribose polymerase; P13K, phosphoinositide 3-kinase; pmTOR, phosphorylated mammalian target of rapamycin; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

established and linked to the inhibition of sphingosine kinase 1 (SK1) enzymatic activity and expression.²⁰⁹ SK1 catalyses the conversion of sphingosine to sphingosine-1-phosphate, the signalling of which has been implicated in cell survival, proliferation, migration and angiogenesis.^{211,212} SK1 overexpression has been correlated with drug resistance, worse prognosis and reduced overall survival in many cancers, thus making it a promising anti-cancer target.²¹¹ Additionally, balanocarpol's anti-BC potential has also been linked to the induction of poly-ADP ribose polymerase (PARP) cleavage and the reduction of DNA synthesis.²⁰⁹ However, its high toxicity, low aqueous solubility and poor bioavailability have greatly hindered its clinical translation.²¹⁰

To address the abovementioned limitations of balanocarpol, Obeid et al²¹⁰ encapsulated balanocarpol into niosomes comprising span 80 and cholesterol (1:1). It was found that void niosomes at doses below 625 µg/mL were not cytotoxic to A2780 ovarian cancer cells and ZR-75-1 BC cells. Therefore, 625 µg/mL niosome was used to deliver balanocarpol for ensuring any observed cytotoxicity was induced solely by balanocarpol. Balanocarpol-encapsulated niosomes exhibited significantly greater cytotoxicity against ZR-75-1 cells than free balanocarpol (IC₅₀ values of 57.97 µM vs >196.6 µM), indicating improved anti-BC efficacy.

Cordycepin

Cordyceps spp., an entomopathogenic fungus, is usually found in Asia, Europe and North America.²¹³ Cordycepin (3-deoxyadenosine), an adenosine analogue, is the main bioactive constituent of *Cordyceps* spp.²¹⁴ It has been extensively investigated for its pharmacological activities, including anti-BC,^{215–219} antimicrobial,²²⁰ anti-inflammatory,²²¹ analgesic,²²² hypoglycaemic,²²³ hypolipidemic²²⁴ and platelet inhibitory²²⁵ activities. As a nucleoside antagonist, cordycepin is known to exert anti-cancer effects principally by inhibiting RNA synthesis.²¹⁷ Further investigations into its anti-BC mechanisms have suggested that the induction of autophagy-associated cell death, mitochondrial apoptotic pathway and caspase-dependent apoptosis; the regulation of p53 and estrogen signalling pathways; the promotion of DNA double-strand breaks and DNA damage response; the inhibition of poly(ADP)ribosylation; the suppression of hedgehog and Notch signalling pathways; the modulation of EMT markers; and the stimulation of ROS generation are also involved.^{215–219} However, the clinical application of cordycepin has been hindered due to toxicity to normal

cells as well as poor bioavailability resulting from low aqueous solubility and rapid metabolism by adenosine deaminase.²²⁶

A study reported the encapsulation of cordycepin into PLGA nanoparticles (CPNPs) and observed that CPNPs had a higher uptake by MCF-7 cells than free cordycepin.²²⁷ This translated to a significantly greater cytotoxic effect of CPNPs on MCF-7 cells (IC₅₀ values of 16.79 µg/mL vs 47.84 µg/mL). In addition, CPNPs also enabled the sustained release of cordycepin (65% release in ten days), thus prolonging its anti-BC action. Importantly, while free cordycepin elicited hemolytic activity against rat red blood cells at 50 to 100 µg/mL, CPNPs of equivalent doses did not cause hemolysis. As opposed to free cordycepin, these findings suggest that CPNPs can exert marked and prolonged anti-BC activity at a non-hemotoxic concentration.

Curcumin

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a major natural polyphenol found in the rhizome of *Curcuma longa* (turmeric).²²⁸ It has shown benefits in diseases such as inflammatory conditions, kidney conditions, metabolic syndrome and pain, most of which have been attributed to its anti-inflammatory and antioxidant activities.²²⁸ Importantly, it has also demonstrated anti-cancer potentials both preclinically and clinically in oral,²²⁹ breast,^{230–233} colorectal,²³⁴ pancreatic,²³⁵ skin²³⁶ as well as head and neck²³⁷ cancers. Specifically, the anti-BC activities of curcumin have been linked to the modulation of cell cycle regulators and metastasis-related markers; the induction of caspase-dependent apoptosis and mitochondrial apoptotic pathway; the suppression of PI3K/AKT/mammalian target of rapamycin (mTOR), extracellular signal-regulated kinase (ERK), NF-κB and β-catenin signalling pathways; the activation of p53 signalling pathway; as well as the inhibition of angiogenesis.^{230–233} However, the clinical applicability of curcumin is challenged by its poor bioavailability resulting from low aqueous solubility, poor absorption, extensive metabolism, rapid degradation at physiological pH and rapid systemic elimination.^{238,239}

Different NDDS classes (eg, dendrosomes, liposomes, polymer-based nanocarriers, protein-based nanocarriers, metallic nanoparticles and MSNs) have been employed to overcome the poor bioavailability of curcumin. For example, Farhangi et al²⁴⁰ prepared dendrosomal curcumin (DNC) and tested its effects on both in vitro and in vivo metastatic BC models. While free curcumin caused

an obvious reduction in 4T1 cell viability only at 72 h, DNC dose- and time-dependently suppressed 4T1 cell viability from 24 to 72 h (IC_{50} values of 32.5 μ M at 24 h, 25 μ M at 48 h and 17.5 μ M at 72 h). Furthermore, DNC also dose-dependently elicited greater anti-migratory and anti-adhesive effects on 4T1 cells than free curcumin. Interestingly, DNC only demonstrated slight cytotoxic effects on normal mouse embryonic fibroblastic cells at high doses, indicating its biocompatible nature. When mice bearing 4T1 xenografts were subjected to intraperitoneal injection of DNC for seven days, it was found that doses up to 80 mg/kg were remarkably safe whereas 160 and 320 mg/kg DNC caused mild symptoms of hematotoxicity, hepatotoxicity and renal toxicity. These suggest that ≤ 80 mg/kg DNC may be more physiologically relevant in treating BC. In comparison to untreated controls, DNC-treated mice (40–80 mg/kg; 35 days) showed higher survival rates, lower tumour incidence, smaller tumour volume and tumour weight as well as lower incidence of metastasis. In addition, these mice also had lower mRNA levels of NF- κ B p105 and its downstream effectors (eg, matrix metalloproteinase [MMP]-9, vascular endothelial growth factor [VEGF] and cyclooxygenase-2 [COX-2]) in BC xenografts, brain, liver, lungs and spleen. Taken together, DNC is both biocompatible and capable of enhancing the anti-BC efficacy of curcumin, and its observed in vitro and in vivo anti-BC activities are likely correlated with the suppression of NF- κ B signalling.

Hasan et al²⁴¹ loaded curcumin into nanoliposomes derived from salmon, soya or rapeseed lecithins. While free curcumin, soya curcumin-loaded nanoliposomes and rapeseed curcumin-loaded nanoliposomes induced an obvious reduction in MCF-7 cell index only from 12 to 20 μ M, salmon curcumin-loaded nanoliposomes could significantly reduce MCF-7 cell index from 5 to 20 μ M. Interestingly, void salmon nanoliposomes were reported to exert greater anti-proliferative effect on MCF-7 cells than void soya and rapeseed nanoliposomes. Lipid profiling revealed that salmon lecithins uniquely contained a high proportion of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA),²⁴¹ both of which have previously been reported to possess anti-cancer potentials.²⁴² Collectively, these findings suggest that the observed higher anti-BC efficacy of salmon curcumin-loaded nanoliposomes may be partly attributed to the synergistic effect between EPA- and DHA-containing salmon nanoliposomes and curcumin. In another study, the same research group coated lecithin nanoliposomes with chitosan and found that

chitosan-coated curcumin-loaded nanoliposomes exhibited greater anti-proliferative activity against MCF-7 cells than their uncoated counterparts.²⁴³ This improvement in anti-BC efficacy offered by chitosan coating is potentially linked to enhanced permeation and encapsulation efficiency of nanoliposomes.

Besides, gum arabic-based nanoformulations have also been developed. For instance, a study reported the preparation of curcumin loaded-gum arabic aldehyde-gelatin (Cur/GA Ald-Gel) nanogels.²⁴⁴ In the study, free curcumin was found to significantly reduce MCF-7 cell viability from 3.125 to 50 μ g/mL. In contrast, Cur/GA Ald-Gel nanogels could only induce significant cytotoxic effects on MCF-7 cells from 12.5 to 50 μ g/mL, and these effects were less significant than those induced by equivalent doses of free curcumin. This lower in vitro anti-BC efficacy of Cur/GA Ald-Gel nanogels may be explained by the slow release of curcumin (ie, <65% during the treatment period of 24 h). Nonetheless, the nano-range size (452 ± 8 nm) of Cur/GA Ald-Gel nanogels may promote their in vivo tumour accumulation via the EPR effect, and their large negative zeta potential (-27 ± 4 mV) may confer good in vivo stability. Additionally, the release rate of curcumin was observed to be higher under an acidic condition (pH 5) than a neutral condition (pH 7.4), which is suggestive of preferential curcumin release at the tumour sites. Although Cur/GA Ald-Gel nanogels induced dose-dependent hemolysis, the observed percentages of hemolysis was <5%,²⁴⁴ thus classifying them as “hemocompatible” according to the ISO/TR 7406 standard.²⁴⁵ Overall, these findings suggest that although Cur/GA Ald-Gel nanogels did not demonstrate superior in vitro anti-BC efficacy as compared to free curcumin, they are hemocompatible and their nano-range size, large negative zeta potential and pH-dependent release property may lead to superior in vivo anti-BC efficacy. Another study reported the encapsulation of curcumin into gum arabic-sodium alginate (Cur/GA-Alg) nanoparticles.²³⁹ Cytotoxicity assay revealed that the IC_{50} values of Cur/GA-Alg nanoparticles against MCF-7 cells were consistently lower than those of free curcumin at 24 h (48.40 μ g/mL vs 68.20 μ g/mL), 48 h (33.26 μ g/mL vs 55.86 μ g/mL) and 72 h (16.84 μ g/mL vs 32.10 μ g/mL). Importantly, void GA-Alg nanoparticles showed no significant cytotoxicity against MCF-7 cells, indicating that this NDDS is capable of enhancing the anti-BC efficacy of curcumin while being biocompatible.

Poly(vinyl alcohol)/cellulose nanocrystal (PVA/CNC) hydrogel membranes, another type of polymer-based nanocarrier, have also been developed.²⁴⁶ Curcumin-loaded PVA/CNC hydrogel membranes were found to induce significant morphological changes (eg, cell shrinkage and increased apoptotic bodies) and dose-dependent reduction in viability in MCF-7 cells. Furthermore, while free curcumin demonstrated greater cytotoxicity in normal HFB-4 human melanocytes than in MCF-7 cells, curcumin-loaded PVA/CNC hydrogel membranes were not cytotoxic to HFB-4 cells. These findings collectively indicate that curcumin-loaded PVA/CNC hydrogel membranes are biocompatible and BC cell-selective. Another study reported a novel water-soluble nanomicelle that is formed via the self-assembly of pectin-curcumin conjugates, with hydrophobic curcumin sitting in the core and hydrophilic pectin polymer backbone forming the outer shell.²⁴⁷ It was observed that pectin-curcumin conjugates elicited greater cytotoxicity against MCF-7 cells than free curcumin (IC_{50} values of $12.0 \pm 3.0 \mu\text{M}$ vs $48.3 \pm 2.9 \mu\text{M}$). This enhancement in cytotoxicity is likely attributed to improved aqueous solubility and stability. Notably, pectin-curcumin conjugates also demonstrated lower cytotoxicity against normal 293A human kidney cells than free curcumin (IC_{50} values of $139.4 \pm 2.1 \mu\text{M}$ vs $70.7 \pm 1.5 \mu\text{M}$). Taken together, conjugation to pectin can enhance the anti-BC efficacy of curcumin (via solubility and stability improvement) while minimising its toxicity to normal cells.

Different protein-based nanoformulations of curcumin have also been developed. For example, Jithan et al²⁴⁸ developed curcumin-encapsulated albumin nanoparticles (CAENs) and found that CAENs (20–120 μM) exhibited greater anti-proliferative effect on MDA-MB-231 cells than free curcumin. This enhancement in anti-BC efficacy may be a result of enhanced dissolution rate and aqueous solubility. Furthermore, it was observed in rats following a single intravenous injection of 10 mg CAENs that CAENs tended to accumulate in brain and lungs, which are the common sites of BC metastases. These observations collectively reflect the potentials of CAENs in enhancing the anti-BC efficacy of curcumin and in treating metastatic BC. Metwally et al²⁰⁶ encapsulated curcumin into gelatin (Cur/Gel) nanoparticles and found that Cur/Gel nanoparticles exhibited cytotoxicity against MCF-7 cells after 48 h ($IC_{50} = 64.8 \mu\text{g/mL}$). This IC_{50} value is close to but higher than that of 48 h free curcumin treatment ($IC_{50} = 53.18 \mu\text{g/mL}$) observed in another study,²⁴⁹ which may be explained by the slow release of curcumin from nanoparticles (ie, only 40–60% after 48 h).²⁰⁶ Moreover, void Gel nanoparticles yielded a high IC_{50}

value of 2.9 mg/mL against MCF-7 cells. These findings collectively suggest that Gel nanoparticles are biocompatible and capable of prolonging curcumin action, although they do not significantly improve the anti-BC efficacy of curcumin.

Curcumin has also been encapsulated into metallic nanoparticles. In a study, curcumin-encapsulated PEGylated iron oxide-gold nanoparticles (Cur/PEGylated $\text{Fe}_3\text{O}_4@Au\text{NPs}$; 0–15 μM) elicited greater cytotoxicity against SKBR3 BC cells than free curcumin, possibly attributable to improved stability and preferential curcumin release under acidic conditions.²⁵⁰ Cur/PEGylated $\text{Fe}_3\text{O}_4@Au\text{NPs}$ also demonstrated pro-apoptotic activity against SKBR3 cells. Subsequent gene expression analysis linked this pro-apoptotic activity to Bax upregulation and Bcl-2 downregulation. Additionally, MMP-9 downregulation was also observed. Taken together, Cur/PEGylated $\text{Fe}_3\text{O}_4@Au\text{NPs}$ mediate enhanced cytotoxic effect on BC cells by upregulating Bax/Bcl-2 ratio and inducing apoptosis; and they may potentially inhibit BC cell migration by downregulating MMP-9.

Folic acid (FA) has a strong binding affinity for folate receptors, which are glycosylphosphatidylinositol-anchored membrane proteins often overexpressed in BC.²⁵¹ Therefore, J. Wang et al²⁵² loaded curcumin into calcium-doped dendritic MSNs conjugated with FA (Cur-Ca@DMSNs-FA) for achieving active BC cell targeting and facilitating cellular uptake of nanoparticles. In the study, Cur-Ca@DMSNs-FA demonstrated improved aqueous solubility and in vivo bioavailability as compared to free curcumin, and showed a remarkably higher curcumin release rate under acidic (80% in 0.5 h) than neutral (35% in 12 h) conditions. Unsurprisingly, it was further observed that Cur-Ca@DMSNs-FA (5–20 μM) exhibited more significant cytotoxicity (9% vs 33% cell viability), pro-apoptotic activity (25.85% vs 12.5% of total apoptosis ratio) and G2/M-phase arrest-inducing activity (41.07% vs 24.54% of cells in G2/M phase) against MCF-7 cells than comparable doses of free curcumin. Interestingly, void Ca@DMSNs-FA (320 $\mu\text{g/mL}$) was non-toxic to MCF-7 cells and had a hemolytic ratio of 4.38% (<5%). Taken together, this NDDS is biocompatible and capable of enhancing the anti-BC efficacy of curcumin via enhanced cellular uptake, improved aqueous solubility and bioavailability as well as pH-dependent curcumin release. The same study reported higher ROS production in MCF-7 cells treated with Cur-Ca@DMSNs-FA than those treated with free curcumin. Further protein expression analysis revealed that Cur-Ca@DMSNs-FA also

induced greater upregulation of caspase-3, caspase-9, cytochrome c, PARP, p53 and inhibitor of NF- κ B (I κ B); as well as greater downregulation of Bcl-2, β -catenin, NF- κ B p65, PI3K, phosphorylated AKT and phosphorylated mTOR in MCF-7 cells than free curcumin. Collectively, these findings linked the anti-BC activities of Cur-Ca@DMSNs-FA to the induction of oxidative stress and mitochondrial apoptotic pathway, as well as the suppression of PI3K/AKT/mTOR, β -catenin and NF- κ B signalling pathways.

Diallyl Disulfide

Allium sativum (garlic), native to Central Asia and north-eastern Iran, is now widely cultivated throughout the world.^{253,254} It has commonly been used as both a spice and a medicinal plant in treating bone diseases, cancer, cardiovascular diseases, diabetes, gastric diseases, hypertension, metabolic disorders, microbial infections, skin diseases, etc.^{253,254} These health benefits of *A. sativum* are attributed to its diverse range of bioactive compounds.²⁵⁵ Its major organosulfur compound, diallyl disulfide, has been reported to mediate anti-BC activities by inducing caspase-dependent apoptosis and mitochondrial apoptotic pathway, inhibiting histone deacetylation, modulating metastasis-related and EMT markers, suppressing β -catenin and SRC/rat sarcoma virus (Ras)/ERK signalling pathways, activating c-Jun N-terminal kinase (JNK) and p38 signalling pathways, upregulating miR-34a and tristetraproline (TTP) as well as downregulating urokinase-type plasminogen activator (uPA).^{256–260} Diallyl disulfide has also demonstrated superior anti-BC efficacy in comparison to conventional chemotherapeutic agents (eg, 5-fluorouracil and cyclophosphamide), thus suggesting its potential to be developed as an anti-BC agent.²⁶¹

Although the clinical translation of diallyl disulfide has been restricted by its low water solubility, poor bioavailability and short half-life, these problems have been tackled by NDDSs. Talluri et al²⁶² reported the loading of diallyl disulfide into SLNs (DADS-SLNs). DADS-SLNs were found to have higher uptake by MCF-7 cells than free diallyl disulfide. DADS-SLNs could also preferentially release diallyl disulfide under acidic conditions (pH 4.5) and enable sustained diallyl disulfide release up to 48 h. As expected, DADS-SLNs (1.562–100 μ M) were capable of eliciting greater cytotoxic and pro-apoptotic effects on MCF-7 cells than free diallyl disulfide. This enhancement in anti-BC efficacy was further reflected by changes in cellular oxidative status and apoptotic marker

expression. For instance, DADS-SLN-treated MCF-7 cells had higher ROS production; higher levels of pro-apoptotic proteins (eg, Bax, Bcl-2-associated agonist of cell death [Bad], caspase-3 and caspase-9); and lower level of anti-apoptotic protein (Bcl-2) than diallyl disulfide-treated MCF-7 cells. Importantly, DADS-SLNs were not cytotoxic to normal MCF-10A human breast epithelial cells. Taken together, this nanoformulation is biocompatible and capable of enhancing the anti-BC efficacy of diallyl disulfide by exhibiting enhanced cellular uptake as well as enabling both pH-dependent and sustained release of diallyl disulfide.

Receptor for advanced glycation end products (RAGE), a multi-ligand single transmembrane receptor belonging to the immunoglobulin superfamily, is frequently overexpressed in late-stage BC.²⁶³ Therefore, the same research group further conjugated DADS-SLNs with anti-RAGE antibody (RAGE-DADS-SLNs) to enable active BC cell targeting.¹⁰ As expected, RAGE-DADS-SLNs (1.562–100 μ M) exhibited significantly higher cellular uptake and cytotoxicity in MDA-MB-231 cells than DADS-SLNs. RAGE-DADS-SLNs also showed higher pro-apoptotic activity, as reflected by their ability to induce a greater increase in the level of pro-apoptotic protein (eg, caspase-9) and a greater decrease in the levels of anti-apoptotic proteins (eg, Bcl-2 and survivin) than DADS-SLNs. Furthermore, it has been reported that RAGE activation can lead to the stimulation of signalling pathways (eg, ras-related C3 botulinum toxin substrate 1 [Rac1], MAPK and NF- κ B) implicated in cell migration and invasion, thereby contributing to tumour progression.²⁶⁴ This indicates that the observed greater cytotoxicity and pro-apoptotic activity of RAGE-DADS-SLNs than DADS-SLNs may be the consequence of both cellular uptake enhancement and RAGE inhibition.¹⁰

Epigallocatechin Gallate

Green tea, one of the most widely consumed beverages worldwide, is obtained from the leaves of *Camellia sinensis* tea plant.²⁶⁵ Green tea consumption has long been associated with health-promoting properties in atherosclerosis, bacterial and viral infections, cancers of the breast, colon, oesophagus, kidney, lung, mouth, pancreas, small intestine and stomach, diabetes, heart diseases, liver diseases, obesity, etc.²⁶⁵ Epigallocatechin gallate (EGCG), the major green tea catechin, is believed to contribute to the majority of green tea-associated health benefits.²⁶⁶ Specifically, EGCG has been reported to mediate anti-BC effects preclinically via the modulation of metastasis-

related markers; the suppression of PI3K/AKT and β -catenin signalling pathways; the suppression of hypoxia-inducible factor-1 alpha (HIF-1 α) and NF- κ B signalling pathways and consequent inhibition of angiogenesis; the induction of mitochondrial apoptotic pathway, death receptor apoptotic pathway, miR-25-dependent apoptosis and autophagy; as well as the inhibition of glucose metabolism and human telomerase reverse transcriptase (hTERT) transcription.^{267–272} Despite these promising pre-clinical findings, the clinical application of EGCG is hindered due to its poor bioavailability and low stability at physiological pH.²⁷⁰

Radhakrishnan et al²⁷³ encapsulated EGCG (5% w/w) into SLNs, and found that this nanoformulation enabled sustained EGCG release (ie, >90% release in 24 h) and improved EGCG stability. Expectedly, EGCG-SLNs could induce a more significant dose-dependent reduction in MDA-MB-231 cell viability than free EGCG (IC₅₀ values of 9.7 ± 0.6 μ g/mL vs 78.9 ± 4.3 μ g/mL). Moreover, EGCG-SLNs also elicited greater pro-apoptotic activity against MDA-MB-231 cells than free EGCG, as evidenced by the observations of more extensive morphological changes (eg, cell shrinkage and elongated-to-spherical cell shape), nuclear shrinkage and apoptotic body formation in EGCG-SLN-treated MDA-MB-231 cells. Importantly, void SLNs (10–100 μ g/mL) lacked observable cytotoxicity against MDA-MB-231 cells, suggesting that this NDDS is biocompatible and capable of enhancing the anti-BC efficacy of EGCG via its sustained release and stability improvement.

Bombesin (BBN; a 14-amino acid peptide) is a natural ligand for gastrin-releasing peptide receptor, which is a G-protein coupled receptor that is overexpressed in various cancers, including BC.²⁷⁴ The same research group thus further conjugated EGCG-SLNs with BBN to achieve active BC cell targeting.²⁷⁵ In the study, increased cellular uptake of BBN-conjugated EGCG-SLNs relative to unconjugated EGCG-SLNs was observed. Consequently, BBN-conjugated EGCG-SLNs could exert greater cytotoxicity (IC₅₀ values of 3.2 ± 1.7 μ g/mL vs 6.9 ± 1.1 μ g/mL) and pro-apoptotic activity against MDA-MB-231 cells than unconjugated EGCG-SLNs. Although both EGCG-SLNs and BBN-conjugated EGCG-SLNs exhibited greater anti-migratory effect on MDA-MB-231 cells than pure EGCG, the effect of the latter was more intensive. Collectively, the results indicate that enhanced cellular uptake mediated by BBN conjugation can improve the anti-BC efficacy of EGCG-SLNs.

Gallic Acid

Gallic acid (3,4,5-trihydroxybenzoic acid), one of the most common plant phenolic acids, can be found in a variety of medicinal plants and fruits such as *Quercus* spp. and *Punica* spp.²⁷⁶ It has been associated with tremendous health benefits owing to the wide range of its pharmacological activities, including anti-BC,^{277–281} anti-inflammatory,²⁸² antimicrobial,²⁸³ antioxidant,²⁸⁴ cardioprotective,²⁸⁵ gastroprotective²⁸⁶ and neuroprotective²⁸⁷ activities. Specifically, the anti-BC activities of gallic acid have been linked to various mechanisms such as the modulation of p53, Mcl-1 and p21 expression and consequent induction of mitochondrial apoptotic pathway; the activation of p38 signalling pathway as well as consequent modulation of cell cycle regulators and induction of caspase-dependent apoptosis; the modulation of metastasis-related markers; as well as the suppression of NF- κ B signalling pathway and consequent downregulation of NF- κ B target genes signifying anti-inflammatory (ie, interleukin [IL]-6, IL-8 and COX-2), anti-angiogenic (ie, VEGF), pro-apoptotic (ie, Bcl-2 and X-linked inhibitor of apoptosis protein [XIAP]) and anti-metastatic (ie, C-X-C chemokine receptor type 4 [CXCR4]) effects.^{277–281} However, the therapeutic potential of gallic acid as an anti-BC agent is restricted by its low bioavailability resulting from poor absorption and rapid metabolism.²⁸⁸

Hassani et al²⁸⁸ reported the preparation of gum arabic-stabilised gallic acid nanoparticles (GANPs). It was observed that GANPs could exert more significant cytotoxicity against MCF-7 and MDA-MB-231 cells than free gallic acid, as well as retard the migratory capacity of MCF-7 and MDA-MB-231 cells. Interestingly, GANPs demonstrated differential cellular uptake in different BC cell lines, whereby a significantly higher uptake was seen in MCF-7 than MDA-MB-231 cells. This may potentially explain the greater cytotoxic and anti-migratory effects of GANPs on MCF-7 than MDA-MB-231 cells. Importantly, GANPs showed negligible cytotoxicity against normal MCF-10A human breast epithelial cells and preferentially released gallic acid under acidic condition (pH 4.8; 95.96%) rather than neutral condition (pH 7.4; 74.56%), reflecting the biocompatibility and BC cell selectivity of this nanoformulation.

In the same study, various in vitro antioxidant assays (ie, 2,2-diphenyl-1-picrylhydrazyl radical [DPPH], nitric oxide scavenging and β -carotene bleaching assays) consistently suggested that GANPs exhibited greater antioxidant activity than free gallic acid.²⁸⁸ This activity enhancement may partly

be attributed to the synergistic effect between gallic acid and gum arabic, both of which have previously been reported as potent antioxidants.^{284,289} Cancer cells are often in a pro-oxidative state.²⁹⁰ ROS is implicated in cancer initiation and progression as it can induce gene mutations and changes in various signalling pathways involved in cell differentiation, survival, growth, proliferation, protein synthesis and glucose metabolism.^{291,292} Using antioxidants to deplete cancer cells from these ROS-induced cellular events may thus have preventive and therapeutic effects. Taken together, GANPs are biocompatible and can improve the anti-BC efficacy of gallic acid by enhancing its BC cell selectivity and antioxidant activity.

Punicalagin and Ellagic Acid

Punicalagin [2,3-(S)-hexahydroxydiphenoyl-4,6-(S,S)-galloyl-D-glucose], the major *P. granatum* polyphenol, is an ellagitannin that has been reported to mediate anti-BC effects via the downregulation of golgi phosphoprotein 3 (GOLPH3) and consequent modulation of metastasis-related and EMT markers, as well as its antioxidant activity and consequent inhibition of oxidative DNA damage.^{293,294} However, ellagitannins are not absorbable in the gastrointestinal tract.²⁹⁵ They usually undergo physiological pH- and/or gut microbiota-facilitated hydrolysis in the stomach or small intestine to yield ellagic acid (2,3,7,8-tetrahydroxychromeno[5,4,3-cde]chromene-5,10-dione).²⁹⁵ Ellagic acid can be subjected to further metabolism by colonic microbiota to yield bioavailable urolithins.²⁹⁶ Similar to punicalagin, ellagic acid has demonstrated anti-BC activities preclinically, with the associated molecular mechanisms being the inhibition of angiogenesis via vascular endothelial growth factor receptor 2 (VEGFR2) signalling pathway suppression,²⁹⁷ the regulation of transforming growth factor-beta (TGF- β)/Smads signalling pathway;²⁹⁸ the suppression of β -catenin signalling pathway via actinin alpha 4 (ACTN4) downregulation and consequent downregulation of stem-like markers, cyclins and mesenchymal markers;²⁹⁹ as well as the inhibition of CDK6 expression and activity.³⁰⁰ However, the poor absorption and bioavailability of punicalagin and ellagic acid, together with the short elimination half-life of ellagic acid, can limit their in vivo anti-BC efficacies.^{301,302}

A polymer-based nanoformulation of punicalagin and ellagic acid has been reported by Shirode et al.¹⁸⁹ In the study, it was found that punicalagin- and ellagic acid-encapsulated PLGA-PEG nanoparticles could exert

significantly greater growth-inhibitory effects on MCF-7 and Hs578T cells than free punicalagin and ellagic acid. Interestingly, punicalagin-encapsulated PLGA-PEG nanoparticles were more potent than ellagic acid-encapsulated PLGA-PEG nanoparticles in both MCF-7 (IC₅₀ values of 7.5 μ M vs 50.5 μ M) and Hs578T (IC₅₀ values of 4.1 μ M vs 83.5 μ M) cell lines.

Sulforaphane

Sulforaphane [1-isothiocyanato-4-(methylsulfinyl)butane] is an isothiocyanate organosulfur compound that naturally occurs in the form of biologically inactive glucoraphanin in cruciferous vegetables, especially *Brassica oleracea* (broccoli).³⁰³ The conversion of glucoraphanin to sulforaphane occurs via myrosinase-catalysed hydrolysis and/or gut microbiota-mediated degradation.³⁰³ Sulforaphane has been extensively investigated for a range of pharmacological properties, including anti-aging,³⁰⁴ anti-inflammatory,³⁰⁵ antimicrobial,³⁰⁶ antioxidant,³⁰⁷ hypoglycemic³⁰⁸ and neuroprotective³⁰⁹ activities. Sulforaphane has also been pre-clinically recognised as a promising anti-BC candidate.^{310–313} Its anti-BC effects have been proposed to be mediated via the targeting of heat shock response and consequent modulation of tumour suppressors and induction of caspase-dependent apoptosis;³¹⁰ the suppression of PI3K/AKT/mTOR/ribosomal protein S6 kinase 1 (S6K1) signalling pathway and consequent induction of autophagy and inhibition of protein synthesis;³¹¹ the disruption of histone deacetylase 5-lysine-specific histone demethylase 1A (HDAC5-LSD1) axis and consequent upregulation of tumour suppressor genes;³¹² as well as the modulation of markers associated with aggressive phenotype (eg, downregulation of EMT markers, metastasis-related markers, pro-inflammatory cytokines and pro-angiogenic growth factors).³¹³ However, the industrialisation of sulforaphane has been hindered due to its low aqueous solubility as well as instability resulting from high sensitivity to light, pH, temperature and oxygen.³¹⁴

In a study, it was found that sulforaphane-encapsulated PEGylated Fe₃O₄@AuNPs (SF/PEGylated Fe₃O₄@AuNPs; 0–15 μ M) could exert greater cytotoxicity against SKBR3 cells than free sulforaphane, possibly due to enhanced stability of sulforaphane and its preferential release under acidic conditions provided by this nanoformulation.²⁵⁰ The cytotoxicity of SF/PEGylated Fe₃O₄@AuNPs against SKBR3 cells was mediated by apoptosis induction, whereby downregulation of Bcl-2 and upregulation of Bax were observed. The further observation of MMP-9 downregulation reflected the anti-migratory potential of SF/PEGylated

Fe₃O₄@AuNPs in SKBR3 cells. Collectively, these findings suggest that the encapsulation of sulforaphane into PEGylated Fe₃O₄@AuNPs can enhance its anti-BC efficacy, and this nanoformulation exhibits pro-apoptotic and anti-migratory activities against BC cells.

Future Perspectives

Plant-based natural products have long been recognised as a vital source of anti-cancer drugs. This review introduces nine selected medicinal plants, including *A. capillus-veneris*, *P. quadriaurita*, *A. muricata*, *I. turpethum*, *M. jalapa*, *P. amboinicus*, *P. granatum*, *P. roxburghii* and *Z. multiflora*, the extracts/essential oils of which have been evaluated for anti-BC potentials. Another nine natural bioactive compounds that have previously demonstrated anti-BC potentials, including balanocarpol, cordycepin, curcumin, diallyl disulfide, EGCG, gallic acid, punicalagin, ellagic acid and sulforaphane, have also been highlighted. Mechanistic studies have linked the anti-BC activities of these natural products to a wide range of molecular targets or mechanisms, including the modulation of angiogenesis, apoptotic pathways, autophagy, cell cycle regulators, cellular eicosanoid profile, DNA structure, synthesis, repair genes and damage response, EMT markers, enzymes, epigenetic mechanisms, glucose metabolism, heat shock response, immune system, inflammation, markers associated with aggressive phenotype, metastasis-related markers, miRNA, oxidative status, proliferation markers, protein synthesis, RNA synthesis, signalling pathways, stem-like markers and tumour suppressors. However, there is a lack of investigation into the anti-BC mechanisms of *I. turpethum*, *M. jalapa*, *P. amboinicus* and *P. roxburghii* extracts, which represents a future research direction to be addressed.

Although the abovementioned natural products have shown promising anti-BC activities in preclinical studies, they have not been advanced further into clinical settings. This may be attributed to their undesirable physicochemical properties, which may result in poor stability, aqueous solubility and bioavailability that can adversely influence their anti-BC efficacies in humans. There have been attempts to resolve these issues, particularly via the employment of NDDSs. Carbon-based nanocarriers, dendrimers, lipid-based nanocarriers, polymer-based nanocarriers, protein-based nanocarriers, metallic nanoparticles and MSNs represent the major classes of NDDSs that have been exploited for BC therapy. As each of these NDDS classes is associated with different advantages

and disadvantages, the selection of the best suited delivery system for a specific natural product is critical.

The development of nanoformulation has been reported for all selected natural products. In particular, curcumin has attracted the greatest research interests, where dendrosomes, liposomes, polymer-based nanocarriers, protein-based nanocarriers, metallic nanoparticles and MSNs have all been employed as NDDSs for curcumin. Generally, an enhancement in anti-BC efficacy and a reduction in toxicity to normal cells have been observed with nanoformulations as opposed to their free counterparts. These observed benefits are intensified when the surface of nanoformulations are conjugated with targeting ligands (eg, anti-RAGE antibody and BBN) to achieve active BC cell targeting. In addition, nanoformulations of curcumin (ie, Cur/GA Ald-Gel nanogels, Cur/PEGylated Fe₃O₄@AuNPs and Cur-Ca@DMSNs-FA), diallyl disulfide (ie, DADS-SLNs), gallic acid (ie, GANPs) and sulforaphane (ie, SF/PEGylated Fe₃O₄@AuNPs) also have the tendency to release encapsulated natural products under acidic conditions, which enables the targeting of breast tumours with acidic TME. Furthermore, nanoformulations of cordycepin (ie, CPNPs), curcumin (ie, Cur/GA Ald-Gel nanogels and Cur/Gel nanoparticles), diallyl disulfide (ie, DADS-SLNs) and EGCG (ie, EGCG-SLNs) exhibit sustained release properties, thus prolonging the anti-BC actions of these natural products. Notably, nanoformulated *I. turpethum* extract (ie, *I. turpethum* extract-loaded NIPAAM-VP-AA co-polymeric nanoparticles), *P. granatum* extract (ie, *P. granatum* extract-loaded PLGA-PEG nanoparticles), *P. roxburghii* extract (ie, PJSNPs) and ZEO (ie, CP-ZEO NE) as well as nanoformulated curcumin (ie, DNC and CEANs), diallyl disulfide (ie, DADS-SLNs and RAGE-DADS-SLNs), EGCG (ie, EGCG-SLNs and BBN-conjugated EGCG-SLNs), gallic acid (ie, GANPs), punicalagin and ellagic acid (ie, punicalagin and ellagic acid-encapsulated PLGA-PEG nanoparticles) have shown anti-cancer activities in preclinical TNBC models, and thus are highly promising for further development. Of note, in addition to the surface modification and release properties of nanoformulations mentioned above, other aspects such as the efficiency and cost of their preparation should also be considered to ensure the feasible development of these nanoformulations.

Despite the abovementioned promising preclinical findings, however, it is of the utmost importance to establish the biocompatibility or safety profiles of these nanoformulated natural products. While AMSNPs,

unconjugated and anti-EpCAM antibody-conjugated RIP-MJ nanoparticles, *P. granatum* extract-loaded SLNs, PJSNPs, CP-ZEO NE, CPNPs, DNC, Cur/GA Ald-Gel nanogels, curcumin-loaded PVA/CNC hydrogel membranes, pectin-curcumin conjugates, DADS-SLNs and GANPs have been confirmed to be biocompatible with preclinical models by current studies, further studies are required to ascertain the biocompatibility of other nanoformulations in preclinical models and subsequently, all nanoformulations in humans. Additionally, strategies that may further improve the functionality of nanoformulated natural products in humans should also be considered.³¹⁵

For example, nanoformulations could be tailored to be responsive to biological cues in the TME (eg, pH and redox status) or external cues (eg, magnetic field and ultrasound) for enhancing precision in the delivery and release of natural products. Moreover, the TME could also be reprogrammed to enhance the tumour accumulation of nanoformulations. For instance, passive and active tumour targeting of nanoformulations may be improved via the promotion of tumour vascular permeability and the upregulation of receptor expression, respectively. Furthermore, the development of nanoformulations with transcytosis capability may also facilitate deep tumour penetration. These represent some interesting aspects that may be important for the future development of more functional nanoformulated natural products.

Consent for Publication

The final version of the manuscript was reviewed by all the authors who consented to its submission and publication.

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All the authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval

of the version to be published; and agree to be accountable for all aspects of the work.

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