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Approaches in the Chemoprevention of Breast Cancer

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Abstract

Nanotechnology in bioscience and therapeutics has advanced tremendously in this decade. Many nanoparticle formulations as well as passive and active targeted agents have been developed and proved effective preclinically in proof-of-concept models of different cancers.Many of these formulations use polymer nanoparticles, liposomes, bubkyballs, fullerenes, carbon nanotubes, dendrimers, isotope tags, and PEG compounds. In effect, nanoparticle formulations have become the norm in chemoprevention. In this paper we review nanoformulations of bioactive compounds that have been tested for their potential mechanistic antiproliferative activity in breast cancer. We also discuss the possibility of enhancing the activity of these compounds using different innovative bioconjugation methods.

Keywords: Breast cancer; Chemoprevention; Mammography

Introduction

Chemoprevention in breast cancer originally referred to the use of natural or synthetic compounds to reverse, suppress, or prevent molecular or histologic premalignant lesions from progressing to invasive cancer [1]. The idea of chemoprevention derives from our understanding of multistep carcinogenesis, in which there is a gradual but noticeable accumulation of both genotypic and phenotypic alterations. Some of these alterations may acquire a genetic advantage to transmit transgenerationally. Arresting one or several of these steps might be effective in preventing the genetic alterations that predispose to cancer. In many cancers researchers have identified typical intermediate biomarkers in patient populations that impose genetic changes during multistep carcinogenesis. Although breast cancer has no immediate precursors or biomarkers for effective early detection, some benign breast lesions have the potential to transform into cancer. They are categorized as atypical ductal hyperplasia, lobular carcinoma *in situ* (LCIS), and ductal carcinoma *in situ* (DCIS) [2]. Those benign conditions are very important in the prevention of breast cancer because they are associated with increased risk of invasive breast cancer. Apart from premalignant lesions, biomarkers have been proposed as irrelevant risk models. Although very few biomarkers are identified in breast cancer, some paved the way for the development of theranostics (Table1).

Nanotechnology Applications in Breast Cancer

The global incidence and mortality rate of breast cancer remain high despite increased understanding of the molecular mechanisms and the advent of novel therapies. The field of nanotechnology is poised to bring major changes in medical diagnostics, prevention, and treatment of breast cancer. Breast cancer detection involves clinical and self-examination followed by radiography as well as invasive biopsy for the histological confirmation of invasive disease [3]. With the advent of mammography the probability of early detection has increased dramatically, resulting in a 30% reduction in breast cancer mortality in women age 50–69 [4]. Mammography is a noninvasive procedure and may increase the survival rate for metastatic breast cancer. However, the survival rate of stage IV breast cancer patients is still below 15%, so effective therapies against invasive breast cancer are needed.

Nanotechnology and breast cancer diagnosis

Magnetic resonance imaging (MRI): Numerous nano carriers have been used to carry diagnostic agents for breast cancer imaging. Some of these carriers are under extensive research and development, especially those used in gamma-scintigraphy, MRI, computed tomography (CT), and sonography [5,6]. Accurate medical diagnostic imaging techniques require adequate intensity of signals coming from the tumor tissue, which differentiate the tumor from the surrounding area of tissue and the rest of the body.

Liposomes and micelle: Liposomes and micelles have been used as contrast agents as well as drug delivery agents for imaging and therapy, respectively. Water-soluble drugs and contrast agents are encapsulated utilizing liposomes, while water-insoluble agents are encapsulated by micelles. The crucial feature of micelles is their amphiphilic nature, which confers an ability to form a hydrophilic corona and hydrophobic core with a size distribution between 5 and 100nm [7]. Loading capacity of the hydrophobic core, micelle concentration, and size are important factors for encapsulation of pharmaceuticals and contrast agents. In preparing contrast agents for diagnosis using gamma and MR imaging it is particularly important to incorporate these agents into the aqueous interior or membrane of the liposomes or adsorb the contract agents to already prepared liposomes or to the lipid bilayer of the already prepared liposomes. Ion channels or transporters may also be used to incorporate into lipid bilayer of the preformed liposomes. It is difficult to enhance the signal from a metal contrast agent incorporated in a liposome or micelle; however, a research group has shown that this can be overcome by using polychelating amphiphilic polymers (PAP) [8]. PAP is a polymer with multiple chelating groups that increase the

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number of bound reporter metal atoms per vesicle and decrease dosage without compromising signal intensity. Adding specific targeted moieties to the liposomes also could improve the targeting of contrast agents designed for breast cancer imaging. Another research group has recently reported monoclonal antibody to 2C5 (mAb2C5) that can specifically detect tumor cells, leaving the normal cells behind [9]. It is claimed that these liposomes are capable of specifically delivering diagnostic moieties to various tumors with short image acquisition time. Another group has showed PEGylated immunoliposomes labeled with ^{99}Tc, surface conjugated with F fragment of GAH mAb, could target human gastric cancer in a murine model [10]. Some other studies investigating immunotargeted liposomes for MR imaging enhanced their contrast using gadopentetate dimeglumine (Gd-complex) [11]. MRI signal amplification is also achieved by combining PAP and Gd moietiesin mAb2C5-modified antibodies [12]. Superior *in vivo* tumor accumulation of mAb2C5 in mouse models of murine Lewis lung carcinoma has been achieved by modified PAP-containing pegylated liposomes, enabling faster detection of the solid tumors [13]. Use of primary and secondary antibodies for increasing the contrast has also been tested. Typically in this inverse imaging technique, patients will receive first antitumor antibody systemically for tumor imaging. This is followed by a second antibody, encapsulated in liposomes directed against the first antibody, which enhances reticuloendothelial (RES) clearance of the first antibody, enabling distinction between normal and tumor tissues [14]. This technology has stability issues with its secondary antibody and needs to be further refined for clinical diagnostic use.

Quantum dots: Quantum dots (QD) became powerful tools to improve molecular imaging and diagnostics as a result of their unique photophysical properties [15-17]. The unique features of QD are resistance to photo bleaching high signal intensity, fluorescence resonance energy transfer (FRET), and enhanced binding affinity to the target. The photostability of QD enables them to stay in the cells for longer periods of time compared with conventional organic dyes [18]. Many studies have shown the application of QD-based FRET in biological systems. QDs as FRET donors have two significant advantages over organic fluorophores: size-tuned emission and ability to attach different dye molecules per QD to improve FRET efficiency [19]. However, it's blinking nature, limited use as FRET acceptors, size variations and high signal-to-background ratio when used in bioluminescence resonance energy transfer (BRET) limited their use in biological applications [20,21]. Targeted *in vivo* imaging has been demonstrated using QD-conjugated peptides to image tumor vasculature [22]. In these studies integrin $\alpha_5\beta_3$ was the prime target since it is overexpressed on tumor vasculature, but a later integrin $\alpha_5\beta_3$ antagonist (QD-RGD) containing peptides was successfully used for tumor targeting and subsequent imaging by intravital microscopy [23]. Different tissues have different relaxation times, which results in a contrast in MR imaging. Often this contrast may not be sufficient for an accurate clinical diagnosis. In such circumstances QDs can be used as dual modality agents to increase the imaging contrast of MR or fluorescence-based imaging, Bakalova et al. [24], showed that the hydrophobic layer between the QD and the silica shell can be employed for integrating hydrophobic paramagnetic substances for dual modality MR/optical imaging. Radionuclide-based imaging (PET and SPECT) is found to be superior in terms of high sensitivity and penetration when compared to MR images. Vascular targeting using Cd125mTe/ZnS QDs has been studied for *in vivo* targeting with SPECT/CT imaging, tissue autoradiography, and in biodistribution and availability studies [25]. Translation of QD into clinical applications of PET imaging was first noted by [26] Cai et al., 2007, who demonstrated a QD-based dual modality probe for optical/PET imaging. They showed that cyclic RGD peptides and 1,4,7,10-tetraazacyclododecane-N,N',N'', N'''-tetra acetic acid (DOTA)were conjugated to NIR QD as chelators and labeled with ^{64}Cu for integrin $\alpha_5\beta_3$- targeted dual modality optical/PET imaging. They found that the majority of the dual modality agent retained in the tumor was specifically in its vasculature. Another group has investigated phospholipid-QD micelles labeled with ^{18}F for PET imaging in a murine system. These micelles were found to be well distributed throughout the body with prolonged half-life and slow reticuloendothelial uptake [27]. Altogether, QD micelles, liposomes, and polymer encapsulation formulations can work as PET/MR/optical imaging agents because they show high sensitivity, soft-tissue contrast, and high quantitation capacity. However, several obstacles remain to fully developing QD-based multimodality imaging agents; they must be examined carefully for targeting efficacy, toxicity, RES clearance, and cost effectiveness.

Dendrimers: Several studies have optimized dendrimer biodistribution and pharmacokinetics thorough careful modification of particle size, surface modifications, permeability across vascular wall, and RES escape, making them promising agents for future diagnostic imaging. The branching pattern of dendrimer molecules creates numerous functional groups that are readily available for chemical modification for numerous applications including binding of peptides, antibodies, specific ligands, and imaging agents. The branching pattern also provides ample interior space in the dendrimer molecule to carry therapeutic payloads [28,29]. Dendrimer-based contrast agents in medical imaging offer different advantages over conventional agents, including desirable blood pool properties with longer circulation and retention times and lymphatic retention [30]. Dendrimer–iron oxide for cell tracking, gadolinium, and Gd- chelators for contrast agents have been tested elaborately [31]. Dendrimer-based MR contrast agents have been demonstrated in the functional assessment of organs. Functional kidney imaging can be performed with dendrimer-based contrast agents (G2 DAB/PPI) to assess renal function [32,33]. These macromolecular dendrimers have prolonged intravascular half-life and plasma distribution abilities, which make them superior blood-pool-enhancing agents for quantitative characterization of tissues and blood vessels in tumors, tumor angiogenesis, and ischemic injury [34,35]. Folic acid-coated fluorescein isothiocyanate (FITC labeled) G5 dendrimers were used to target cancer cells and monitored by optical imaging in a study by Shi et al. [35]. Another group has used G5-PAMAM dendrimers conjugated with FITC that binds with peptide motifs to detect tumor angiogenesis and endothelial cell proliferation [36,37]. Lucarelli et al. [38], have used new approaches for lymphatic imaging.

Polymer nanoparticles: Synthetic biocompatible polymers are studied extensively for noninvasive imaging applications including MRI, optical imaging, and multimodality imaging. Polymeric imaging agents have enhanced plasma half-lives, prolonged stability minimal toxicity, decreased nonspecific binding, and improved passive and active targeting. Polymers also provide multifunctional and multimodality cancer imaging opportunities [39,40]. The ideal polymeric contrast agents in the diagnostics will have minimal or no toxicity because they degrade and clear from the body after the imaging is completed Poly L-glutamic acid (PG) is well known for its biocompatibility, biodegradability, and water solubility [41]. PG conjugated with gadolinium chelate (PG-DTPA-Gd) has been developed as an MRI

contrast agent [42]. This group demonstrated that PG-DTPA-Gd would be degraded by cysteine proteases within 24h in the presence of cathepsin B. Li's group further developed this PG-DTPA-Gd and demonstrated that these agents will accumulate in the necrotic tissue of the tumor due to its co localization with macrophages. PG-DO3A-Gd-Mce_6 conjugated with PEG reduced nonspecific liver uptake to improve its efficacy as contrast enhanced MRI-guided photodynamic therapy. These agents can efficiently perceive changes in the tissue distribution of polymer conjugates and geode site directed irradiation of target tissues [43].

Other polymers including poly L-lysine, N-(2 hydroxypropyl) methylacrilamide (HPMA), and poly (ethylene) oxide were demonstrated for MRI, optical, nuclear, and multimodality imaging applications. Our laboratory showed for the first time that poly lactic co-glycolicacid (PLGA) nanoparticles conjugated with hyaluronic acid increased the therapeutic benefit and enhanced optical imaging properties [44]. CD44 is the receptor for hyaluronic acid (HA). Targeting anticancer drugs using HA nanoparticles may facilitate the selective cellular uptake by tumor cells through CD44 receptor-mediated endocytosis. This study also warrants that endothelium of the tumor is densely vascularized and enhanced EPR effect may exist in the tumor vasculature; the resultant interstitial pressure will be very high to prevent nanoparticle uptake without an active targeting ligand. We have also developed PLGA-PEG nanoparticles that target or modulate estrogen (ERβ) receptors. Diagnosis and cancer treatment have been tremendously improved with recent developments in polymer nanotechnology applications. Future investigation in this area will make an impact on human cancer therapy and real monitoring of the treatment efficacy. However, more studies are needed to address the immunoreactivity of these particles as diagnostic as well as therapeutic agents.

Bioactive from Fruits and Vegetables for Breast Cancer Management

Botanicals have been used for the treatment of cancer historically. These bioactive may be useful in the prevention of cancer, including breast cancer. Many epidemiological studies suggest that a reduced risk of cancer is associated with high consumption of vegetables and fruits. Active ingredients or bioactive of these fruits and vegetables have immense value formodulating the activity of cancer chemotherapeutics and chemopreventive agents. Many of these phytochemicals have been shown to increase absorption of chemotherapeutic agents and have enhanced bioavailability, safety, and cost-effectiveness.

Recent studies have found that baicalin dose-dependently inhibits breast cancer (MDA-MB-231) cell migration and invasion in vitro and suppresses the tumor growth and the pulmonary metastasis in MDA-MB-231 breast cancer xenograft model [44]. Wang et al. [44] found that baicalin suppresses the p38 mitogen-activated protein kinase (MAPK) phosphorylation and expression, reduces MMP-2, MMP-9, uPA and uPAR expressions, and MDA-MB-231 cell invasion when compared to p38MAPK inhibitor SB203580 or combined with SB203580. Another study revealed that isoliquiritigenin extracted from licorice attenuated the expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), key molecular targets to prevent tumor metastasis [45]. Epithelial-mesenchymal transition (EMT) plays a critical role in cancer progression and in maintaining cancer stem cell properties and hence is emerging as a therapeutic target for inhibiting the progression of cancer cells. Recent studies by Ismail et al. [46], have investigated the role of 2'-Hydroxycinnamaldehyde, a compound originally isolated from cruciferous vegetables, in suppressing breast cancer metastasis by nuclear translocalization of GSK-3β via modulating Snail, which results in the transcriptional up-regulation of E-cadherin [46].

Curcumin, a natural compound extracted from *Curcuma longa*, an ingredient in Indian food preparations, has been shown to limit the metastatic potential of adenocarcinoma cell lines by shifting the expression of adhesion molecules and the organization and stiffness of the cell cytoskeleton [47]. Chemotherapy patients undergo various oxidative and nitrative stresses; this oxidative/nitrative stress in plasma obtained from breast cancer patients may induce changes in hemostatic activity, which may contribute to thrombosis in these patients. One research group has revealed in their study that extract of *Aroniamelanocarpa* (Chokeberry) may be a promising new source of bioactive antioxidant natural compounds to alleviate oxidative/nitrative stress induced by chemotherapy in breast cancer patients [48]. Another study showed recently that garlic-derived compounds such as such as diallyl disulfide (DADS) suppress breast cancer by the activation of metabolizing enzymes that detoxify carcinogens, the suppression of DNA adduct formation, the inhibition of the production of reactive oxygen species, the regulation of cell-cycle arrest, and the induction of apoptosis [49]. Another study shows a different mechanism of action of allium compounds in that they increase in the intracellular level of reactive oxygen species (ROS). Here diallyltrisulfide-induced antiproliferative activity is mediated by the generation of ROS and subsequent activation of the ASK1-JNK-Bim signal transduction pathway in human breast carcinoma MDA-MB-231 cells [50]. However,

Sample source	Biomarkers
Nipple aspirate	Lipophilin B
Nipple aspirate	Beta globulin
Nipple aspirate	Vitamin D binding protein
Serum	HER2
Nipple aspirate	Alpha-2 HS glycoprotein
Serum	CA-15-3
Serum	HSP90
Serum	p53
Nipple aspirate	Hemopexin
Serum	BRCA1, BRCA2
Serum	Estrogen receptor
Serum	Androgen receptor
Serum	Progesterone receptor
Tissue	Stem cells (in developmental phase)
Blood	Circulating tumor cells (in metastasis)
Tissue	Microtubule associated protein
Tissue	Topoisomerase
Tissue	Thymidine phosphorylase
Tissue	Beta tubulin
Tissue	Hyaluronic acid receptor
Tissue	Folic acid receptor
Tissue	MUC gene variants

Table 1: Established and investigational biomarkers of breast cancer.

diallyltrisulphide exerts its biological activity through induction of pro-apoptotic Bax protein, and p53 protein expression was up-regulated and translocation to nucleus in MCF-7 breast cancer cells, and also decreasing the percent of cells in G(2)/M and inducing apoptotic cell death [51]. Natural dietary agents and bioactive such as polyphenols, alkaloids, and phenolics have great impact in preventing and treating a wide variety of diseases including breast cancer. However, use of neutraceuticals has limited impact in the treatment of breast cancer chemoprevention evident from the literature. This might be because of their reduced bioavailability due to stability issues or unknown parameters such as undesired interaction with metabolic enzymes. Modern technologies such as nanoencapsulations and conjugation chemistry could help to enhance stability and bioavailability of these hidden gems of nature.

Empowerment of bioactive

Nano encapsulation: Encapsulation techniques using polymers, liposomes, or dendrimers are commonly used in breast cancer treatment. Rationally designed nanoparticles will be independent and show selectivity at the pharmacological site. These well-designed nanoparticles may act as drug carriers to deliver active agents to tumors and protect the drug from inactivation or leaking during its trajectory to the target tissue. Many biodegradable polymers used to deliver chemotherapeutics include poly (alkyl cyanoacrylates), poly (methylidenemalonate), polylactic acid, poly glycolic acid, and poly caprolactone [52]. Many of these polymers were surface conjugated with specific receptors/ligands and antibodies and showed promising target specificity in various preclinical and clinical studies. Plant secondary metabolites such as camptothecins were encapsulated with methoxy poly (ethyleneglycol) -poly (D, L- lactic acid) and administered intravenously in rats. They showed longer plasma retention and higher tumor localization when compared to parent camptothecin [53]. Other plant-derived microtubule stabilizing agents were successfully formulated to increase camptothecins' pharmacodynamics characteristics and stability and to minimize its undesirable side effects such as neurotoxicity, myelosuppression, and allergic reactions by cremophor EL (polyethoxylated castor oil) and Tween (polysorbate)-80. The same strategy has also been used in anthracylins and epipodophyllotoxins [54,55]. Poly ethylene glycol-coated nanoparticles of paclitaxel, surface conjugated with transferrin, significantly increased the tumor regression in xenograft murine tumor models. This formulation demonstrated marked delay in the blood clearance of the drug compared with intact paclitaxel intravenous injections [56]. Polymers for gene delivery include dendrimers, acrylate polymers, polylysine and chitosan polymers [57,58]. Bioavailability of natural compounds could increase by covalently linked antibodies, tumor vascular markers such as VEGF-R, EGF-R and others and permeation enhancing agents. Another class of targeting ligands includes carbohydrate moieties expressed by specific tissues like asialoglycoprotein by liver, as a galactose ligand, which is overexpressed in metastatic liver cancers [59]. Overall, nanotechnology can offer various methods for improving the pharmacological properties of natural bioactive compounds and pave the way from bench to bedside.

Probe	Imaging technique
Air, argon, nitrogen	Ultrasonography
Gd, Mn, Iron oxide, polymers	MRI
^{11}C, ^{18}F, ^{15}O,	PET
^{11}In, ^{99}Tc, ^{67}Ga	Gamma-scintigraphy
I, Br, Ba	CT

Table 2: Diagnostic imaging probes used in different medical imaging techniques.

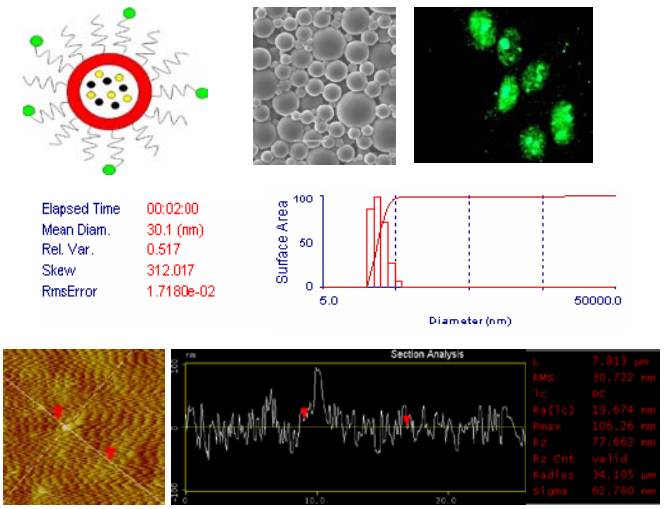

Figure 1: Polymer nanoparticle characterization for optimization foruse as contrast agents in optical imaging. The nanoparticles are decorated with FITC and internalization in breast cancer (MCF-7) cells. Characterization techniques used are scanning electron microscopy (SEM), DLS, and atomic force microscopy (AFM).

Application	Mediator	Conjugation technique
Activation of enzymes	Antibody	NHS-Maleimide conjugation
Activation of enzymes	Antibody	2-Iminothiolane conjugation
Activation of enzymes	Antibody	Glutaraldehyde mediated conjugation
Attaching thiol reactive groups	Dendrimers	NHS-PEG-Maleimide conjugation
Coupling glycoproteins	Dendrimers	Reductive amination
Iodine incorporation	Small molecules	Iodination using Chloramine-T
Coupling to hydrazide particles	Nanoparticles	Carbodiimide reaction
Antigen /hapten conjugation	Liposomes	Simple mixing with specific buffers
Antibody-liposome conjugate	Liposome	Sulfhdryl residue coupling or reductive amination
Liposome-mAb conjugation	Liposome	NHS ester of palmitic acid

Table 3: Specific reactions used for the modification of small molecules, antibody, dendrimeror nanoparticlesfor targeted drug delivery.

No.	Name	ΔG in kcal/mol
1	Exemestane	-103.69
2	Formestane	-100.09
3	Letrozole	-52.68
4	Anastrozole	-49.67
5	Fadrozole	-46.96
6	Phyllanthine	-88.54
7	Secrunine	-83.34
8	Gentiopicrin	-81.47

Table 4: Binding free energies of some AIs and selected plant secondary metabolites.

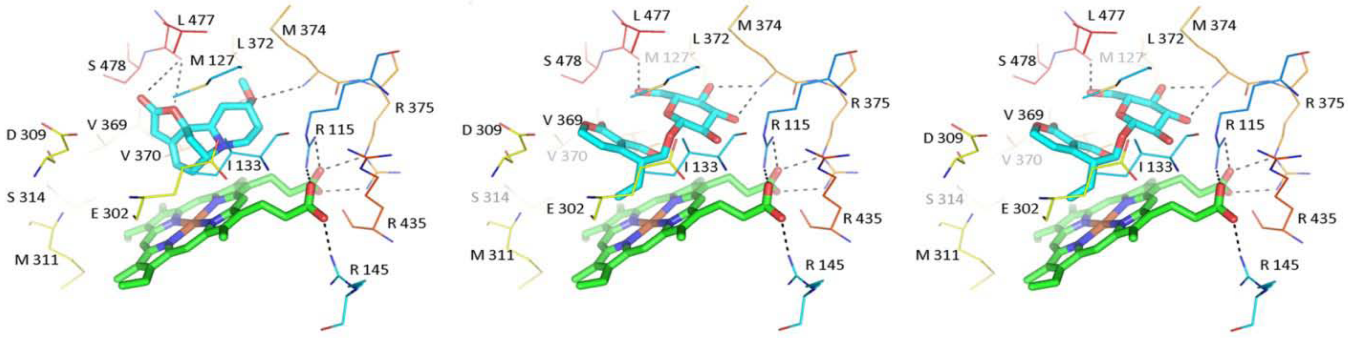

Figure 2: Binding of (A) Phyllanthine (B) Secrunine and (C) Gentiopicrin in the active site of aromatase. Hydrogen bonds are shown by dotted lines. Porphyrine ring (green) and surrounding amino acids were also shown in the figure.

Conjugation- techniques

Different types of chemical conjugation techniques can improve physiochemical and biological properties of the bioactive compounds. One of the popular types of chemical conjugation techniques involving zero-length crosslinkers like carbodiimides forms conjugates between two protein molecules, a peptide and protein, oligonucleotide and protein, or between a bioactive compound and its surface-encapsulated nanoparticles or shells based on the selection of water-soluble or water-insoluble carbodiimides. The specific interaction with avidin and biotin can also be utilized for detection or targeting systems using bioactive. Complex glycans on glycoproteins or bioactives can be modified with biotinylation reagents. Some of these techniques include modifying sialic acids on glycans by reduced amination with a biocytinhydrazide [60]. Conjugation of antibodies to protein or small molecule of small molecule encapsulated nanoparticles is critically important for many applications including therapeutics and diagnostics. Many of the natural bioactive can also be modified for better biological targeting and to enhance their bioavailability by antibody conjugation.

In silico modeling

Computational biology and bioinformatics have a significant role in the drug discovery process. The involvement of these two disciplines helps a lot in the drug discovery process. The rational drug-designing approaches not only speedup the process but also help to identify novel compounds. Computer-assisted molecular modeling and docking is a key approach in computational biology and bioinformatics. By using *in silico* molecular docking method one can deduce the predominant binding modes of a ligand with a protein of known three-dimensional structure. Docking method also helps to screen a large set of compounds, rank the compoundsbased on their binding free energies and propose structural hypotheses of how the compounds can inhibit the target.

Recently, a greater importance has been given to the identification of novel leads and alternative medicines that deal with cancer management. Several *in silico* based studies have been conducted on natural compounds to identify their anti-cancerous activities. One such approach was to identify the novel secondary metabolites as aromatase enzyme inhibitors. This enzyme (EC 1.14.14.1) is located in the endoplasmic reticulum of estrogen-producing cells that converts androgens to estrogens. The enzyme is 503 amino acid residues long and a prosthetic heme group is found to attach in its active site. It was already proved that aromatase inhibitor (AI) can be used in breast cancer therapy. Several *in silico* studies have been carried out to prove the efficacy of the aromatase inhibitors. Derivatives of androstenedione has been proved against aromatase by molecular modeling and docking studies and QSAR studies was also carried out to identify the physicochemical characteristics of potential AI [3]. In order to identify the AI with higher selectivity, Suvannang et al. [61] reported that the binding mode of all generations of AI drugs by means of molecular docking. From their studies it was reported that residues like F134, F221, W224, A306, A307, D309, T310, M374, S478, V370, L372 and L477 are important for inhibitor binding.

In another study, different plant secondary metabolites were collected and their activity towards the enzyme was deduced for the identification of novel AI. The binding mode and free energy of binding of some known AI (FDA approved drugs) were also compared with that of the secondary metabolites. The studies concluded that plant secondary metabolites like phyllanthine, secrunine and gentiopicrin can be AI. The binding free energies and binding modes of these inhibitors arereported in Table 4 and Figure 2.

Conclusion

There is a considerable interest in diet-derived natural compounds and bioactive to prevent disease conditions like breast cancer. Numerous natural compounds have been identified and studied in detail; however, very few compounds have found their way to bedside in modern medicine. We believe the reason for this might be early metabolic activation and biotransformation that reduced the activity of the compounds in circulation to get a systemic effect. In this paper we have presented different thoughts on improving the activity of natural compounds using different cutting-edge technologies. Careful consideration of these approaches may benefit the future research and use of natural products for the chemoprevention.

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