Review Article

New Insights into the Role of Plant Product Diosgenin and its Nanoformulation in Breast Cancer

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Abstract

Naturally occurring plant derived steroidal saponins play a remarkable role to combat various diseases, especially cancer. Diosgenin is a steroidal saponin, which has various properties including antimicrobial, antiviral, anti-inflammatory, anti-diabetic, hypercholesterolemia, and as well as anti-cancer activities. Diosgenin is associated with the inhibition of the actin polymerization,Cdc42 activation and Vav2 phosphorylation. Thus, this makes it a potential therapeutic agent against the human breast cancer. Generally, site-specific and controlled drug release increases the efficacy of the drug. This can be achieved by designing nano-based drug delivery system for diosgenin. Nano-based drug delivery system not only reduces rapid administration to overcome unfavorable side effects, but also helpsto increase the therapeutic value by reducing the toxicity and increasing the bioavailability.The present reviewmainly deals with the therapeutic effects of diosgenin on breast cancer and nano-based drug delivery systems for diosgenin, and it also highlights the feasibility of their use as a potential future candidate for enhancing anti-cancer activity in overcoming problems associated with the plant based medicines.

Keywords: Diosgenin; breast cancer; nanoparticles; steroidal saponins; nanocarriers

Introduction

Several medicinal herbs, as well as certain plant derivatives play a significant role in the primary health care system. Various plants offer the major source of drugs used traditionally in various complementary and alternative medicines (CAM), including the age-old ayurvedic, homoeopathic and as well as herbal medicine practices for the treatment of several diseases. According to World Health Organization report, population of about 80% still relies on the conventional medicine for the primary health care.[1] The initial pharmacologically-active compound recorded was morphine, which had been isolated from the opium. The natural products and traditional medicines have made a fruitful contribution towards the advanced medicine.[2] Plant-based drugs are found to be safer than the synthetic drugs, as they have fewer chemicals and have insignificant or no side-effects. In recent years, major advancements in the plant-derived therapeutic agents are being sought through the development of new classes of bioactive molecules like steroids, terpenoids, tannins, carotenoids, flavonoids, alkaloids, and glycosides targeted for combating various diseases. Naturally derived drugs encapsulated in nanocarriers can be considered as the novel treatment strategy for effective treatment and minimized side-effects. The present review aims to deal with such bio-active molecules, where most of them are still under clinical studies or preclinical trials, which are mainly focusing on breast cancer. The main advantages of these nanosystems are to protect the drug from rapid degradation after systemic distribution and to target cancer cells using ligands to increase the cellular uptake. Thus, this review focuses on the role of nanocarriers loaded with naturally derived drugs. It also highlights the delivery of naturally derived chemotherapeutic drugs using nanocarriers for the treatment of breast cancer.

Diosgenin: A steroidal saponin as an anti-cancerous agent

Diosgenin, ((25R)-5α–spirosten-3β-ol) is a steroid sapogenin found in various plants, including Dioscorea species, Fenugreek, and Costus. Diosgenin is extracted from yams, fenugreek and costus species.[3] Diosgenin possesses several interesting biological functions such as antimicrobial,[4] antiviral,[5] anti-inflammatory, anti-diabetic,[6] hypercholesterolemia[7] and it alleviates gastrointestinal ailments. It has shown to deploy anti-cancer effects against a broadrange of tumor cells including in colorectal cancer,[8] osteosarcoma[9] and leukemia.[10] The mechanisms include activation of p53 and caspase-3,[11] inhibition of the nuclear factor kappa light chain-enhancer of activated B cells (NF-kB),[12] C-X-C motif chemokine receptor-3 (CXCR3), and induction of Ca2+ release.[13] The effects of diosgenin in the prevention and treatment of diseases have recently received considerable attention[14] with a particular interest in the use of steroidal saponins (aglycone) as anti-cancer compounds. It was first isolated by Takeo Tsukamoto in 1936 from Dioscorea tokoro.[15]

It is used as a raw material for more than 60% of the materialistic synthesis of cortisone, progesterone, pregnenolone, and other steroids as well.[16] Saponins have been delineated to play a significant role in the lipid and glucose balance,[17] prevention of fat deposition in adipocytes and also in stimulation of growth hormones released from the pituitary.[18] Various studies have particularly linked diosgenin with the cancer prevention.[19] Diosgenin is imperative for the inhibition or activation of key proteins (bcl-2 and caspase-3) by mediating apoptosis in human colon cancer cells. The chemo-preventive role against bone cancer through the growth suppression and apoptosis induction in the cancer cells has also been identified.[20] Further research are now being undertaken to study the molecular pathways involved in the mechanism of diosgenin as an anti-cancer agent to treat breast cancer. Diosgenin is used in pharmaceutical industries as the important precursor for the synthesis of steroids. Due to the lack of appropriate enzymes involved in steroid hormone biosynthesis, mammals are unable to convert this diosgenin into important steroidal metabolites. It is reported to have anti-proliferative properties against the following cell lines, HeLa (cervical cancer),[21] HEL, K562 (erythroleukemia),[22] osteosarcoma 1547,[23] HepG2, C3A, HUH-7 (hepatocellular carcinoma),[24] and MCF-7 (breast cancer).[25]

Most of the studies state that diosgenin can induce apoptosis and may act as an anti-neoplastic agent. It has also been shown to inhibit multiplication of the HT-29 human colon cancer cells and induce apoptotic activity via the intrinsic pathway by modulation of caspase-3 and Bcl-2 expressions in vitro.[26] The anti-cancer activity was also exhibited by suppressing the fatty acid synthetase expression in HER2 protein which was seen to be overexpressed in breast cancer by suppressing 3-hydroxy-3-methylglutaryl CoA reductase in HCT-116 protein from human colon carcinoma.[27] Varying apoptotic mechanisms have been observed as induction through G2/M cell cycle arrest and as well as p53-independent p21 is seen to be up-regulated in HeLa cells.[28]

The pro-apoptotic mechanism of diosgenin involves the activation of caspase-3 in HeLa cells.[29] The anti-proliferative effects of diosgenin were found to be demonstrated through the p53-dependent apoptotic mechanism in melanoma M4Beu cells and laryngocarcinoma HEp-2 cells.[30] Many investigators have reported diosgenin as an initiator of cell cycle arrest in G1 phase and then apoptosis which was demonstrated in the human osteosarcoma 1547 cell line by increasing the tumor suppressing p53 expression.[24] In this regard, its pro-apoptotic activity was found to be higher than that of the two structurally similar plant steroids, tigogenin and hecogenin.[9]

In this context, other scientists also demonstrated that diosgenin inhibits the proliferation of leukemia cell line through cell cycle G2/M arrest and as well as apoptosis with the disruption of Ca2+homeostasis and mitochondrial dysfunction.[31] Further, it not only produces the cytotoxic effect on human chronic myeloid leukemia cells (K562 and BaF3-WT) butalso induces autophagy accompanied by the reactive oxygen species (ROS) generation and inhibition of mammalian target of rapamycin (mTOR) signaling pathway.

On the other hand, diosgenin formulated with the nanoparticles and its site of action is to elevate its pharmacological bioavailability. Moreover, diosgenin functionalized iron oxide nanoparticles as well as hollow manganese ferrite nanocarriers encapsulating tamoxifen and diosgenin were developed as potential therapeutic tools against breast cancer.[32] Li et al.[33] reported that organized, characterized and evaluated nanoparticle based on poly (ethylene glycol) diosgenin conjugates for co-delivery of anti-proliferative compounds as a much promising drug delivery system for cancer therapy.

Origin and structure of Diosgenin

Diosgenin is normally found in seeds of fenugreek (Trigonella foenum graecum Linn) and also in the root tubers of wild yams (Dioscorea villosa Linn). The botanical usage of fenugreek seeds is found in the Egyptian Ebers papyrus (c. 1500 BC) to instigate childbirth.[34] During the Hippocrates (5th century

BC) periods, Dioscorides (1st century AD) were used for the treatment of gynecological inflammation. The breakthrough of this diosgenin has found to be important in novel drug treatment and it is also widely used as an herbal product [35]. Structurally, diosgenin ($C_{27}H_{42}O_3$) is a spirostanol saponin with a molecular weight of 414.62 g/mol. A hydrophilic sugar moiety attached to hydrophobic steroid aglycone of triterpene group with a spiroketal side chain attached at position 16 and 17 of the sterane along with the double bond at 5-6. It has a hydroxyl group at 3rd position where they are mostly found to be combined with sugars, creating the compounds more water soluble and saponaceous.[36] The chief active constituents of diosgenin are steroidal sapogenin of about 4 – 6 % and its glycosides are epismilagenin,smilagenin,and β-isomer yommogenin (Figure 1).

Medicinal uses of Diosgenin

Steroidal saponins have a large number of commercial in pharmaceutical sectors due to their different physicochemical and biological properties. It is having more health beneficial applications and prevention against the cardiovascular diseases, colon cancer, and climacteric syndromes .[37] For oral contraceptives, the steroidal metabolite imparts 50% of the raw material for manufacturer.[38] It is used to instigate apoptosis in cancer cells and also to decrease high blood pressure.[39] Recent studies have found that it has been used in conventional medicine as an anti-hypercholesterolemia, anti-hypertriacylglycerolimia, anti-diabetic, anti-hyperglycemic agent and leukemia.[40] It is considered as natural surfactants in cleansing the products, cosmetics and also in shower gels, shampoos, hair conditioners and lotions, foam baths, liquid soaps, mouth washes, baby care products and toothpastes.[41] It is also found to treat urethral and renal infections in China. It has the ability to reduce post-menopausal symptoms.[42] It can also be used as a good anti-spasmodic and coughs for muscular spasms.

The therapeutics used for breast cancer causes severe drug reactions in addition to the therapeutic outcomes.[38] Several therapeutic agents that are employed for breast cancer treatments are:

a. Alkylating agents: cyclophosphamide
b. Anti-metabolite: methotrexate, 5-fluorouracil and capacitabine
c. Natural product: paclitaxel, vinorelbine, doxorubicin.
d. Hormone and antagonist: letrozole, tamoxifen, and anastrazole.
e. Miscellaneous: lapatinib, trastuzumab.

Generally, all chemotherapeutic drugs have side effects. The side effects include loss of hair, nausea, poor appetite,or vomiting. Traditional medicinal plants have served its less side effects and anti-cancer agents for ages due to the rich diversity of phytochemicals. Further, diosgenin is used in Indian as well as Chinese conventional medicine to combat its anti-cancer, analgesic, antioxidant, and anti-inflammatory properties.[43, 44]

Micro determination of Diosgenin from fenugreek

Fenugreek is isolated and extracted by the pharmaceutical industries to serve as a raw material for the manufacture of hormonal and therapeutic drugs. In this connection, polysaccharides form the mucilage (galactomannan) present in the plant and it also has many applications in pharmaceutical, cosmetics, paint and paper industries.[45] It is an interesting fact that the fenugreek seed is one of the most commonly used spice in everyday life for seasoning in soups and curries.[46] In Indian sub-continent, fenugreek is widely used as a part of traditional medicinal practices and it is an efficient stimulant which promotes lactation in post-partum women and animals.[47]

The fenugreek extract and its oil are known to possess antibacterial, anti-diabetic, hepatoprotective and anti-cancer activities. Apart from these, they are also used as a hypocholesterolemic agent, lactation aid and gastric stimulant. It is used as a food stabilizer, adhesive and also as an emulsifying agent because of its high fiber, protein and gum content. The protein of fenugreek is found to be more soluble at alkaline pH.[48]

Effect of Diosgenin on breast cancer cells

Breast cancer is one of the leading causes of mortality in women worldwide. The rates of breast cancer mortality are high in developing countries due to unavailability of mammography for the routine screening and late diagnosis. The current treatment of breast cancer includes chemotherapy, radiation therapy and surgery but these options tend to show more adverse effects that restrict their usage. The main objective of this breast cancer research is to identify and characterize the entities or molecules that might reduce the risk of development of breast cancer in humans. The natural and synthetic compounds have been identified to have a cancer chemo preventive value.[49] Many classes of natural and synthetic compounds are still being investigated in the clinical trials as cancer preventive substances for extreme malignancies.[50]

The cytotoxic effects of several chemicals and as well as natural substances on the malignant tumor cells in culture have been considerably studied as a initial screening for the anti-tumor activities by many research groups.[51] The repression of cell proliferation encouraged by diosgenin is due to the induction of cell death (Figure 2). Doxorubicin (DOX) is a Food and Drug Administration (FDA) approved chemotherapeutic drug used in treatment of breast cancer. DOX is an anthracycline drug that inhibits topoisomerase-II-mediated deoxy ribonucleic acid (DNA) repair and it leads to cell apoptosis. However, drug-induced cancer resistance and DOX-mediated cardiotoxicity are the two major limitations for it clinical use.

Diosgenin affects the cell proliferation on MCF-7[52] cells. This clearly indicates that it strongly inhibits the MCF-7 cells in culture and displays its anti-proliferative and cytotoxic nature. Depletion of blood reduced glutathione (GSH) leading to elevated accumulation of lipid peroxides and loss of cell viability[53,54] suggests that decreased GSH level may initiate redox imbalance in breast cancer cells and thus subsequently induces apoptosis. In several studies, diosgenin lowers the level of glycoproteins which confirms the anti-metastatic activity of the drug. Since, it has already been demonstrated to inhibit tumor growth, the present studies supports its anti-cancer properties.[54] Hence, using diosgenin in nanocarriers will enhance the efficacy of the drug on drug resistant breast cancer.

Role of nanocarriers in chemotherapy

Presently, nanotechnology has a revolutionary impact on health care and medicine having theragnostic (diagnostic and therapeutic) applications in various diseases such as cancer, cardiovascular diseases and infectious diseases.[55] Eventhough it has theragnostic properties, there are few disadvantages and risks associated with its applications. It is still in the developmental stage, so it is indeed worth exploring, considering its wide-ranging advantages, which include reduction in degree of invasiveness, reduced side-effects, less intake frequency, sensitivity and site-specificity etc (Figure 3).

This requires two basic components- a polymer (consisting of hydrophobic end and hydrophilic tail) and a drug (Figure 4). During the formation of nano-droplets, the hydrophobic end is arranged towards the inner side and hydrophilic tail is projected outwards. The main objective of targeted cancer therapy is to deliver the chemo-therapeutic drugs directly to the cancer cells, so that the normal cells are not or less affected. Nanoparticles allow exquisite modification, such that the binding mechanism comes with ease when it binds to the cancer cell membranes, the micro-environment, or to cytoplasmic or nuclear receptor sites.[56]

In general, American Society of Clinical Oncology (ASCO) recommends that people with the metastatic breast cancer, receive only one effective drug at a time because it is very much less likely to cause severe side effects, which may improve a patient's quality of life and usually does not influence survival.[57] Combinational chemotherapy is an approach towards prevention of mutation and resistance presented by cancerous cells against the drugs. Nanoparticles-enabled delivery of chemo-therapeutics may facilitate high dose of drug delivery to the intended site, offering reduced off-target toxicity compared to the conventional treatment.

Drug administration: Conventional approach (vs) application of nanocarriers

Chemotherapy involves use of several drugs to destroy cancer cells for controlling cancer progression, therebyminimizing or alleviating cancer associated symptoms. Since some medicinal plants are rich in compounds with anti-cancer potentials, administration of these compounds in combination with orthodox chemotherapeutic drugs has been reported to be more effective than administering a single drug.[58] Possible chemotherapeutic regimens include cyclophosphamide, methotrexate, 5-fluorouracil, and doxorubicin. However, the choice of specific compounds depends on many factors such as type of tumor, stage of the disease, age of the patient and the tolerance capability of the patient.[59]

The most advanced chemotherapeutic agents do not differentiate between the normal cells and the cancer cells efficiently which leads to non-specific distribution of drug in the body and causes systemic toxicity as well as extreme effects. This phenomenon reduces the efficient dose of the drugs reaching the target cells and causes sub-optimal results due to excessive toxicity.[1] Some of thecommon possible side effects include bone marrow suppression, gastrointestinal problems (vomiting, nausea, and diarrhea), mouth sores, hair loss, and alopecia.[2,60]Application of nanotechnology can be a solution for non-specific distribution of drugs and utilizing naturally derived drugs like diosgenin can highly reduce the chance of side-effects.

Drug coated nanocarriers

Drugs coated with nanocarriers have gained a lot of attention in the field of chemotherapy as nanoparticles have an exceptional potential in effective drug delivery. The nanocarriers that are

utilized as drug delivery vehicles are generally lesser than 100 nm in atleast one dimension and it consists of various biodegradable materials such as natural and synthetic polymers, lipids, and metals.[61] Recently, the cancer chemo- preventive potential of naturally occurring compounds has been of great interest and thus they are preferred to treat various diseases. This makes it an emerging area in the field of pharmacology. [62]

For most therapeutic substances, only a portion of medication extends towards the affected organ, such as in chemotherapy, where roughly 99% of the drugs administered do not reach the tumor site that affects the pharmacokinetics property of the drug.[63] The most commonly used nanocarriers include polymers, micelles, liposomes, carbon-based materials, and other agents.[64]

A nanoparticle complex may be designed to include the following components (Figure 5).

a. Surface ligands- help in attachment of the nanoparticles to the specific cells.

b. Imaging probe- helps in visualizing and tracking the nanoparticle.

c. Outer envelope- protects the drug within it and increases the bioavailability; circulation times and slows down the clearance from body.

d. Linker molecules- Triggers the release of drug when encountered by the oncomarkers which is referred to as a signature of the cancer cells.[65]

Although these targeted therapies have shown promising efficiency when compared to the traditional chemotherapy drugs, there are still some limitations in their delivery. In order to overcome these problems, the development of novel nanomaterials and nanocarriers are imperative for cancer detection, diagnosis and treatment.[66] In addition to the general side effects, particular side effects result from certain drugs, for example DOX shows cardio toxic effects.[67] Some of the clinically approved nanomedicines which are being used for the treatment of breast cancer with the details of their formulations and limitationshave been shown in [Table 1, 2].

Mechanism of nanocarriers in drug delivery

The action of drug coated nanocarriers begins right from the blood stream after intravenous administration to the patients. But due to its ability in sensitizing the tumor markers, it can easily recognize the affected tissue. Tumor markers are the substances that are only found in elevated levels in cancerous cells. This helps in differentiating the cancer cells from normal cells.[68] The nanocarriers are designed to have targeting ligands on its surface that binds with the cancer markers on surface of the cancer cells. Oncomarkers are the receptors to which the nanoparticle conjugates. Once the nano particle gets conjugated, the nano-carriers penetrate inside the cancerous cells. Subsequently, when nanocarriers encounter most of the markers found inside the cancerous cells, the protective shell opens and releases the drug within it. This results in the destruction of only the cancer cells which is the ultimate goal of all cancer therapies (Figure 6).

Introduction to HLA nano particles

Hyaluronic acid (HA) is a linear high molecular weight natural biopolymer which consists of repeat-ingalternating residues of β-D (1 3) glucuronic acid and the β-D (1 4)-N-acetylglucosamine. Molecular weight of HA ranges from hundreds to millions of Daltons. Studies on thermal degradation and stability of sodiumhyaluronate of molecular weights between 0.4 and 2.3 MDa in solidstate showed that the biopolymer depolymerization is decreased atneutral pH and low temperatures.[64] Therefore, solid formulations based on HA should remain stable and not depolymerized ifstored properly at low temperatures over moderate times (1–12months). However, HA is a biodegradable polymer,which is gradually degraded by enzymes hyaluronidases in mammals, invertebrates (insects, crustaceans), and some pathogenicfungi and bacteria.

Increased efficacy of nanoformulated Diosgenin

Developing a site-specific drug delivery system is one of the challenges that are currently addressed. Single drug therapies for cancer are often substandard and may not provide long term clinical benefits. A limitation of multi-drug use is the varying pharmacokinetics of different drugs. Diosgenin functionalized iron oxide nanoparticles (IONPs) is considered to be a potential chemotherapeutic drug which has the least or almost no side-effects; its efficacy depends on various factors that mainly includes immune parameters and site-specificity. Therefore, nanoformulated diosgenin offers a great benefit for drug delivery to overcome limitations in the conventional chemotherapy. Although, concerned effort is required to overcome all the challenges, successful delivery of these plant derived chemotherapeutics coated with nano-carriers have the potential to provide effective combination treatments for the cancer patients.[69]

Role of nanotechnology in nutraceuticals

Nanoparticles have advanced pharmacological effects compared with the therapeutic entities. The active intracellular delivery, developed pharmacokinetics and pharmacodynamic of drug nanoparticles depend on several factors including their size and the surface properties.[70] Selective therapies such as angiogenesis inhibitors, vascular disrupting agents, estrogens and as well as HER-2-targeted therapies have been developed to cure cancer. These approaches have increased the patient survival because of the therapeutic efficacy.[71]

In this current scenario, plant derived products are obtained in nanoparticle form for improvement of their pharmacokinetic and pharmacodynamic profile. Nanoparticles measure approximately 1-1000 nm in dimension and exhibits properties different from their macro scale counterparts.[72] The nanoformulation of phytoceuticals leads to a high surface area-to-volume ratio, enhancement in solubility and bioavailability, reticuloendothelial system (RES) uptake, enhanced permeability and retention (EPR) effect, improvement in tissue distribution of macrophages, sustained release, enhanced physicochemical stability, and so on.[73] Singh (2004) reported that liposomal formulation of glycosides like oleandrin, digoxin and digitoxin for the protein-stabilized nanoparticle (PSL) formulation is used for treating cell proliferation and reducing toxicity and also has the ability to deliver drugs to the tumor sites. This PSL nanoparticle formulation consists of a mixture of egg phosphatidylcholine (EPC), hydrogenated soya phosphatidylcholine (HSPC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylenositol (PI), monosialogangolioside, and spingomyelin (SPM), with digitalis glycoside. It is also used to treat cancer and other diseases such as diabetes and cardiac disorders in humans and mammals. This report was stated to be an effective method to reduce the growth of cancer or to reduce the incidence of metastasis, inflammation and arthritis in animals.[74] esai (2007) reported a method to treat proliferative diseases such as cancer by providing a combination therapy comprising of an effective amount of taxane in a nanoparticle form with albumin as a carrier, as first therapy, and use of radiation, surgery, administration of chemotherapeutic agents or a combination as second therapy. A combination of paclitaxel and albumin nanoparticles called abraxane was found to be effective for various cancers such as metastatic breast cancer, prostate cancer, malignant melanoma, carcinoma of the cervix, ovarian cancer.[75] Einbond and Redenti (2007) invented a pharmaceutical composition that contained a physiologically effective dose of nanoparticle triterpene glycoside or triterpene complex nanoparticles, which were liposome-encapsulated complex compounds or exosome-encapsulated compounds used to treat or prevent cancer and acted as a chemopreventive or chemotherapy agents for breast cancer[76] [Figure 7].

Discussion

It is important to note that according to the WHO estimates; more than 80% of population in the developing nations depends on the conventional medicine. Plant products are important sources of bioactive compounds and are considered to be one of the most successful discoveries of modern medicine. In recent years, the natural dietary agent has drawn a great deal of attention from both scientist communities and as well as the common people because of the potential ability to suppress cancer as well as to reduce the risk of cancer. Several different classes of active natural products have been documented. Traditional chemotherapy is extremely toxic to cancer cells as well as the normal cells. The controlled drug delivery has been shown to elevate the therapeutic index of drugs by expanding their localization to specific tissues, organs, or cells.[77] These approaches tend to decrease potential side effects by leaving normal sensitive cells unharmed. In the past decade, tremendous advancement has been made towards making nanoparticle-based therapeutic products and formulations commercially available. In 2006, European technological observatory survey displayed that more than 150 pharmaceutical companies were developing nanoscale therapeutics.[78] Nanocarriers have the potential to modify modern drugs by increasing their efficacy, stability, and solubility; decreasing their toxicity and sustaining their release. The combined use of two or more drugs is a widely adopted clinical practice and often displays much better therapeutic efficacy than that of the single drug. Targeted delivery of mixed anti-cancer drugs using these nanocarriers may find the widespread application in biomedicine.

Diosgenin is reported to have anti-cancer properties against various cell lines by the mechanism of inhibition of tumor cell growth by arresting the cell cycle and inducing apoptotic activities. Commercially, it is employed as the raw material for the synthesis of steroids of different kinds. It can be concluded that the diosgenin significantly ameliorates the alterations in carbohydrate metabolism, lipid profile and adenosine tri phosphatases (ATPases) during treatment through quenching free radicals and thereby suppressing key enzymes of gluconeogenesis, lipids and ATPases to attenuate progression of malignant cells. The idealistic cancer treatment destroying only the cancer cells without affecting the normal cells can be now obtained by the application of nanomedicine in the cancer treatment. But the response

ofbody's biochemical pathway towards these nano-medicine and the consequences of the application of these designed drugs into the system, still remains to be a question. However, the advancing technologies and ongoing research in the field of nanomedicine can give a ray of hope in achieving a complete cure for cancer. Therefore, this review reveals that the combination of nanotechnology and natural drugs can provide a very useful tool in designing future drug delivery system. In conclusion, nanocarriers encapsulated with diosgenin can be considered as a novel therapy for breast cancer metastasis and increase the chances of patient's survival rate.

Abbreviations

WHO- World Health Organization; ASCO- American Society of Clinical Oncology; NF-kB- Nuclear factor kappa-light-chain-enhancer of activated B cells; CXCR3- C-X-C motif chemokine receptor 3; DOX- Doxorubicin; FDA- Food and Drug Administration; DNA- Deoxy ribonucleic acid; GSH- Blood reduced glutathione; IONPs- Iron oxide nanoparticles; RES- Reticuloendothelial system; EPR- Enhanced permeability and retention; PSL- Protein-stabilized nanoparticle; EPC- Egg phosphatidylcholine; HSPC- Hydrogenated soya phosphatidylcholine; PE- Phosphatidylethanolamine; PG- Phosphatidylglycerol; PI- Phosphatidylinositol; SPM- Spingomyelin; ATP- Adenosine tri phosphatases

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JAJ, APS designed and wrote the manuscript.

Conflicts of interests:

No potential conflicts of interest were disclosed.

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