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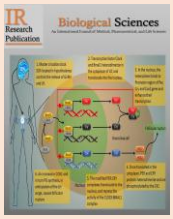

Review on herbal drugs nanonization for the treatment of breast cancer

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ABSTRACT

In the field of nanotechnology recent advances in phytomedicine are providing positive outcomes for cancer treatment due to increasing knowledge of the molecular mechanisms underlying cancer progression. Naturally occurring chemical compounds from herbal plants are known as phytochemicals, serve as vital resources for novel drugs, and are also sources for cancer therapy. With the application of nanotechnology of nanonization of herbal drugs, it will make the development of nanoherbal medicine possess high bioavailability, extended half-life, increased immune evasion and targeted ability at the tumor site, and good antitumor activity and eco-friendly which consequently will open a new era of herbal drug discovery. This review aims to highlight the potential of nanotechnology used with herbal plants, along with their pharmacologic action molecular or specific targets for the treatment of breast cancer.

Introduction

Breast cancer is the leading cause of death in women worldwide and is the second most common cause after lung cancer. It usually starts in the mammary glands [1]. The main risk factors for breast cancer are age, diet, high levels of hormones and environmental changes. Due to major advances in the medical field, the survival rate of breast cancer patients increases with early detection. But treatment leads to many side effects and reduces the quality of life of the cancer patient [2]. Common treatments for breast cancer include surgery, radiation therapy, and chemotherapy and hormone therapy. However, these are associated with more serious side effects that are more dangerous to the patient [3].The advent of nanotechnology is considered to be the biggest engineering innovation since the industrial revolution [4]. Nanoscale systems are also known as sub-micrometers, because particle diameters are, 1 µm. Today, the effective use of nanoparticles in combination with herbal constituents has shown significant improvements in the treatment process. Some examples are Curcumin, Cinnamaldehyde, Vincristine, Topotecan, Quercetin, Thymoquinone, Shikonin, Berberine, Artemisinin etc [5].

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Pathophysiology

Breast cancer is a multi-faceted disease that can have different predictions and respond to treatment differently despite the histological similarity,

Abbreviations: *PLGA-PEG- Poly Lactic-co-Glycolic Acid - poly glycolic acid, Fe3O4 - Iron Oxide, Fe2O3- Ferric Oxide, SiO2 - Silicon Dioxide, MCF 7- Michigan Cancer Foundation-7, MDA-MB-231- Metastatic Breast 231, PF127- Pluronic F127, HEK 293- Human Embryonic Kidney 293 cells, APS - Antiphospholipid Syndrome, SLNs- Solid Lipid Nanoparticles, NLCs- Nanostructured Lipid Carriers, LEs- Lipid Emulsions, PtNPs- Platinum Nanoparticles, AuNPs - Gold Nanoparticles, Zno- Zinc Oxide, PR- Progesterone Receptor, HER2- Human Epidermal Growth Factor Receptor 2.*

distance and stage. As with other types of human cancer, the development of breast carcinoma is likely to follow a multi-step process of activating oncogenes and a malignant tumor by the anti-methylation promoter. Hypermethylation is a basic process involved in developing malignant tumors, including breast cancer. This promoter methylation is not randomly distributed in carcinogenesis as much as possible but is genetically linked to a specific type of cancer. In breast cancer, several genes have been identified as methylated differently in certain histological subtypes. Invasive breast cancer will be molecularly subtyped based on its color response to rabbit monoclonal antibodies: Estrogen receptor (ER), Progesterone receptor (PR), and Her-2 neu antibodies; using fixed tissue blocks filled with paraffin [6].

Conventional treatments for breast cancer

The chemotherapeutic drugs Doxorubicin (DOX) is used for tumor growth suppression in various cancer. The toxicity associated with the use of DOX was found, like cardiotoxicity, myelosuppression, alopecia, mucositis, and alopecia. Cisplatin (CP) most potent compound among platinum agents and is used for breast cancer treatment. However, their clinical use is also limited by their side effect, which occurred with a high CP dose. Docetaxel limitation in the therapy of breast cancer is their large volume of distribution in systematic circulation may lead to toxicity to the vital organs and various toxicities like hematologic, neurologic, and physiological [7]. There are other treatment methodologies include hormonal supplements, surgery, radiation therapy, or Complementary or Alternative Medicine (CAM). With advances in the understanding of the cellular and molecular levels of carcinogenesis, chemoprevention has grown into a promising strategy for treating cancer [8]. In addition, the price of targeted drugs is so high that most patients cannot afford them. Immunotherapy is another new approach including cytokine infusions, cancer vaccines, and T-cell therapy. It can stimulate immune cells to enhance their anticancer activity [9].

Role of herbal plants in the treatment of breast cancer

Herbs were considered the most significant source of medicine from ancient India for the treatment of diseases. After this, the crude drugs were obtained from plants, animals, and marine sources. Since the 20th century, plants have been one of the major important sources of drugs rather than marine and animal sources [10]. The growing uses of herbal medicines because of their availability, efficiency, and fewer side effects. Plants have been the major source of medicine ever since the emergence of human civilization. Approximately one-third of all pharmaceuticals are obtained from plant origin, wherein microorganisms, fungi, and organic matters are also included. All over the world, over 60% of all pharmaceuticals are plant-based in modern as well as the traditional system of medicine [11].

Novel technology-based approaches for the treatment of breast cancer

Nanotechnology engineering and the production of materials using atomic and molecular elements are probable to benefit all medical fields, and oncology is the first and most beneficial to date. Nanotechnology usually refers to structures that can be up to a few hundred manometers in size and are developed by high-level or ground-based engineering of single parts [22]. Examples related to cancer Nanotechnologies include injectable drug delivery of NANOVECTORS such as LIPOSOMES targeted breast cancer treatment, Nano-sized Magnetic Resonance Imaging (MRI) antagonistic intraoperative imaging in the context of neuro-oncological interventions, nanoparticle-based methods to obtain high specificity for DNA and protein [23].

The National Cancer Institute in its 2004 commitment of $144 million toward the development of novel nanotechnologies for improving cancer mortality defined the path of opportunities in six areas including:

- Finding molecular changes responsible for disease pathogenesis
- Disease diagnosis and imaging
- Drug delivery and therapy
- Multifunctional systems for combined therapeutic and diagnostic applications
- Vehicles to report the in vivo efficacy of a therapeutic agent
- Nanoscale enabling technologies, which will accelerate scientific discovery and basic research.

Table 1. Various herbal plants used in cancer treatment.

S.NO.	Name of plant	Parts used	Activity	Reference
1	Urticadioica (Stinging nettle)	Leaves	Anti-proliferative activities	[12]
2	Curcuma longa Linn (Turmeric)	Rhizome	Inhibition of Ornithine Decarboxylase activity Antiproliferative, Antitumorigenic	[13]
3	Withania somnifera (Winter cherry)	root/leaf extract	Chemopreventive efficacy	[14]
4	Elettaria cardamomum (Cardamom)	cardamom oil	anti-proliferative activities, prevent the growth of cancer cells including breast cancer cells.	[15]
5	Echinacea (Estern purple coneflower)	Flowers	Cytotoxicity	[16]
6	Catharanthusroseus (sadabahar)	stem and leaf	growth inhibition effect of tumor cells	[17]
7	Podophyllum peltatum (Mayapple)	Roots	Immidiate cell growth was inhibited.	[18]
8	Rheum emodi (Rhubarb)	Rhizome	Cell migration inhibition efficiency	[19]
9	Taxusbrevifolia (Himalayan yeh)	bark, shoot, green and red arils, seed parts, young stems and needles	Blocks cancer cells growh by stopping celldivisions,resulting in cell death.	[20]
10	Campototheca acuminata (Happy tree)	Bark and stem	Cytotoxicity effect	[21]

The evolution of Nanotechnology continues to emerge, it is important that production processes, both in nanoparticle production and in combination with embedded nanoparticle products, incorporate sound natural, and non-polluting technologies. Several nanoparticle production processes currently use toxic chemicals either in the form of reducing salt to reduce the corresponding metal salts or as reinforcing agents to stop nanoparticles from mixing. Several new nanotechnology-based herbal remedies have been developed with active biopharmaceutical properties and desirable features targeted at them. This offers a few other ways to apply for treatment. Herbal pharmaceutical nanoparticles have many benefits, such as partial melting, improved bioavailability, increased absorption, reduced therapeutic dosages, and long-term drug treatment achievements compared to traditional medicine preparations [24].

Nanocarriers used for herbal bio-actives in breast cancer

Various herbal anticancer drugs such as curcumin, cinnamaldehyde, vincristine, topotecan, quercetin, thymoquinone, shikonin, berberine, artemisinin, silibinin, paclitaxel, camptothecin, oridonin, and tryptanthrin, etc., have been used against breast cancer. These drugs have been synthesized with a variety of nanocarriers including liposomes, micelles, polymeric nanoparticles, metal nanoparticles, dendrimers, and solid lipid nanoparticles (SLNs) for advanced breast cancer treatment [25]. Liposomes provide properties like amphiphilicity, biocompatibility, and biodegradability for herbal anticancer drugs including curcumin, vincristine, quercitin, thymoquinone, berberine, etc. Polymeric nanoparticles consisting of PEG, PLGA, PCL, and pluronic have been used for efficient delivery and uptake of herbal drugs by breast cancer cells. Dendrimer's branching structure allows them to be conjugated to target molecules, imaging agents, and drugs. Solid lipid nanoparticles (SLNs) are lipids containing a colloidal carrier system that offers the stability of anticancer drugs and antitumor activity [25]. In Table no.2, herbal nanoformulations have been shown which have anticancer activity against

Table 2. List of herbal nanoformulations for the treatment of breast cancer.

Natural bioactive having anti-cancer activity	Source	Family	Delivery system	Cell line	Reference
Curcumin	Curcuma Longa	Zingiberaceae	PLGA-PEG Nanoparticle, Fe_3O_4-SiO_2 Nanoparticles.	MCF-7	[26]
Mangiferin	Mangifera Indica	Anacardiaceae	Gold Nanoparticles	MDA-MB-231	[27, 28]
Aloe-emodin	Aloe Barbadensis Miller or Rheum Palmatum L	Liliaceae	PEG-LCNPS Nanoparticle	MCF-7	[29, 30]
Carum and thymoquinone	Carum Carvil	Apiaceae	Niosome Delivery System With Ergosterol	MCF7, MDA-MB-231	[31, 32]
Lawsone	Lawsonia Inermis	Lythraceae	Niosome	MCF-7	[33, 34]
Astragalus polysaccharide	Astragalus Membranaceus	Leguminosae	APS/AUNR/PLGA-PEG Nanoparticles	MCF-7, SK-BR-3 and MDA-MB-231 (16)	[35, 36, 37]
Ellagic acid	Alternanthera Sessilis	Amarantha ceae	Silver Nanoparticle	MCF-7	[38]
Tryptanthrin	Polygonum Tinctoriu	Polygonaceae	Solid Lipid Nanoparticles (SLNS), Nanostructured Lipid Carriers (NLCS), And Lipid Emulsions (IES)	MCF-7	[39, 40]
Artemisinic acid and alpha thujone	Artemisia Absinthium	Asteraceae	Polymeric Nanoparticles	MCF-7 and MDA, MB-231	[41, 42]
Baicalein	Scutellaria Baicalensis Georgi	Lamiaceae	Fe2O3 Magnetic Nanoparticles	R MDA-MB-231 CELLS and HBL-100	[43, 44]
Oak fruit hull (jaft)	Quercus Infectoria	Fagaceae	Silver Nanoparticle	MCF-7 CELLS	[45, 46]

Table 2. Continuous…

Natural bioactive having anti-cancer activity	Source	Family	Delivery system	Cell line	Reference
Andrographolide, neoandrographolid, 5, 7, 2′, 3′-tetramethoxy-flavanone, 5-hydroxy-7, 2′, 3′-trimethoxy-flavone, stigma sterols.	Andrographis Paniculata	Acanthaceae	Carbon Dots	MCF-7	[47]
Chikusetsusaponiniva methyl ester	Panax Japonicus	Araliaceae	Liposomal Nanoparticle	4T1 and MDA-MB 231	[48, 49]
Longan	Euphorbia Longana Lam.	Sapindaceae	Silver Nanoparticles	MCF-7	[50, 51]
A-hederin	Nigella Sativa L.	Ranunculaceae	Platinum Nanoparticles (Ns-Ptnps)	MDA-MB-231	[52]
Withanolide-a	Withaniasomnifera	Solanaceae	Gold Nanoparticles (Aunps)	SKBR-3	[53, 54]
Vinblastine and vincristine	Catharanthus Roseus	Apocynaceae	Copper Nanobiocomposite	MCF-7	[55]
Green tea catechin	Camellia Sinensis	Theaceae	Gold Nanoparticle	MCF-7	[56]
Alkaloids, carbohydrates, glycosides, saponins, proteins, amino acids, steroids, terpenoids, flavonoids, and phenols	Pterygota Alata (Roxb.)	Malvaceae	Gold Nanoparticle	MCF-7	[57, 58]
Alkaloid, tannins, terpenoids, steroids, and saponins	Phyllanthus Fraternus	Phyllanthaceae	Silver Nanaoparticle	MCF-7	[59]
Alkaloids, carbohydrates, flavonoids, glycosides, phenols, saponins, steroids, tannins and terpenoids	Coriandrum Sativum	Apiaceae	Silver Nanoparticle	MCF-7	[60]
Alkaloids, flavonoids, glycosides, saponins	Pedalium Murex Linn.	Pedaliaceae	Silver Nanoparticle	MCF-7	[61]

Table 2. Continuous…

Natural bioactive having anti-cancer activity	Source	Family	Delivery system	Cell line	Reference
Secoiridoids, flavonoids, alkaloids and sesquiterpenes	Jasminum Officinale L	Oleaceae	Silver Nanoparticle	MCF-7	[62]
Lipophilic phytochemicals and phenolic compounds.	Persea Americana	Lauraceae	Silver Nanoparticle	MCF-7	[63]
Polyphenolic component	Lippia Nodiflora	Verbenaceae	Silver Nanoparticle	MCF-7	[64]
Alkaloids, flavonoids, tannins, sterols and terpenes. Phytoconstituents such as chelerytherine, sarguinarine, protopine, optisine and berberine	Argemone Mexicana L	Papaveraceae	Gold Nanoparticle	MCF-7	[65]
Phenol and flavanoids	Pterolobium Hexapetalum	Cesalpiniaceae	Copper Oxide Nanoparticle	MDA-MB-231	[66]
Triterpenoids (arjunin, arjunic acid, arjungenin, arjunolic acid, terminic acid and terminoltin), flavonoids (arjunone, luteolin and baicalein), phenolic (gallic acid and catechin) and tannin (pyrocatechols, punicallin and castalagin)	Terminalia Arjuna	Combertaceae	Silver Nanoparticle	MCF-7	[67]
Iridoid lactones such as allamandin, plumericin, and plumierides	Allamanda Neriifolia Hook	Apocynaceae	Silver Nanoparticle	MCF-7	[68]
Alkaloids, flavonoids, amino acids, proteins, tannins, steroids, and terpenoids	Phyllanthus Madera spatensis L	Euphorbiaceae	Silver Nanoparticle	MCF-7	[69]

Table 2. Continuous…

Natural bioactive having anti-cancer activity	Source	Family	Delivery system	Cell line	Reference
Phenol, flavanoid, carbohydrate, protein	Sechium Edule	Cucurbitaceae	Zno Nanoparticle	MCF-7	[70, 71]
Tannins, flavonoids, steroids, glycosides, and alkaloids	Ziziphus Nummularia	Rhamnaceae	Gold Nanoparticle	T-47D	[72]
Flavonoids, terpenoids, glycosides, essential oil, furanocoumarins and unsaturated sterols	Deverra Tortuosa	Apiaceae	Zno Nanoparticle	MCF-7	[73]
Carbohydrates (reducing sugars), saponins, terpenoids/steroids, flavonoids, phenolic compounds, tannins, cardiac glycosids, proteins/ amino acids, alkaloids, and anthraquinones	Corchorus Olitorius	Tiliaceaea	Gold And Iron Oxide Nanoparticles	MCF- 7	[74]

various cancer cells. Further research in this area may lead to improved breast cancer management.

Conclusion

We studied the various herbal plants and their nanoformulations with delivery systems for the treatment of breast cancer. Natural drugs are showing the way for efficient drug delivery and depicted anticancer activity against MCF-7, MDA-MB-231, T-47D, SKBR-3, and hek293 cells. A better understanding of the biological processes and refinement of nanotechnology i.e., higher surface area, extended drug release, high encapsulation efficiency, biocompatibility, and cost-effectiveness will help to develop more compatible nanoformulation for the treatment of breast cancer. Decent participation among molecular biologists, a researcher from phytochemistry, and a researcher from formulation and clinicians could open the way for the treatment of cancer.

Contribution of authors

All the authors have contributed equally to designing, writing, and analyzing the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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