(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume3, Issue 6, Page No: 147-162
November-December 2020

From Inception of Herbal Medicine to an Ideal Perception of Therapeutic Agent: Rhododendron as a Therapeutic Agent – A Review

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Type of Publication: Review
Conflicts of Interest: Nil

ABSTRACT

Breast cancer is the second leading cause of cancer death in women all over the world. Despite advanced treatment modalities, the systemic toxicity remains a major side effect resulting into patient morbidity and mortality despite many technological breakthroughs, even the best breast cancer treatments available today are not 100% effective. Chemotherapy has improved, but many drugs still do not reach the tumor site at effective doses and are often associated with high systemic toxicity and poor pharmacokinetics. Moreover, for many malignancies, diagnosis is obtainable only in metastatic stages of development, reducing the overall effectiveness of treatment. The choice of available treatments depends on tumor characteristics such as biomarkers, tumor size, metastatic disease, ligands, and antigen or endocrine receptor expression. Combined with surgical resection, chemotherapy and radiation remain the first line of treatment for patients with cancer. Even with these treatments, however, cancer continues to have high fatality rates and current therapeutic modalities have yet to significantly improve the often dismal prognosis of this disease. Nanotechnology is a highly focused approach, which may provide more effective and less toxic treatment when compared to chemotherapy. The Nanoparticles (NP) plays a vital role and it can conjugate with various drugs by different methods to deliver drugs to the target site. The NP surface is designed with ligands to get affinity towards specific cells and co-polymers to get protection from immune cells. The nanoparticles conjugated drug can ultimately recognize the site and join to the target and enter to the cell by receptor mediated endocytosis. Then NPs are able to release drugs controllably to cure diseases. Rhododendron is one of the naturally occurring plants which possess various health benefits, such as prevention and treatment of diseases associated with heart, dysentery, diarrhea, detoxification, inflammation, fever, constipation, bronchitis, asthma and cancer.

Keywords: NIL

INTRODUCTION

Breast cancer is the most common invasive cancer in women and the second leading cause of cancer death in women after lung cancer. Breast cancer is a type of cancer in which cells present in the breast grow out of control in breast tissue which change and divide uncontrolled, typically resulting in a lump or mass. Most breast cancers begin in the lobules (milk glands) or in the ducts that connect the lobules to the nipple. Breast cancer can spread outside the breast through blood vessels and lymph vessels. When breast cancer spreads to other parts of the body, it is said to have metastasized. Breast cancer cells usually form a tumor that can often be seen on an x-ray or felt as a lump.

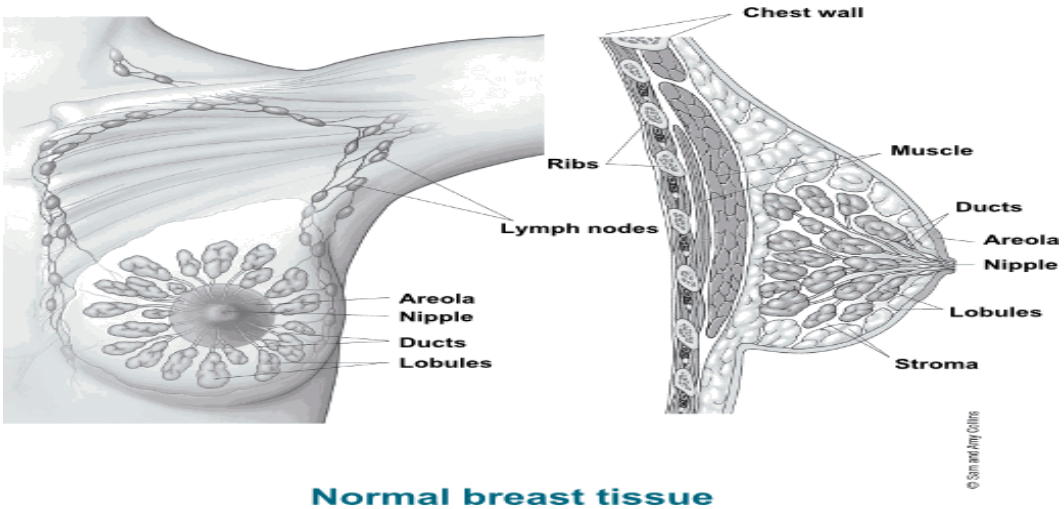

Figure: Normal Breast Tissue

STAGES OF BREAST CANCER (5)

The stages of cancer are decided according to the size of the tumor and whether it has spread to lymph nodes or other parts of the body.

The stages are as follows:

Stage 0: Known as ductal carcinoma in situ (DCIS) in which the cells are limited to within the ducts and have not invaded surrounding tissues.

Stage 1: At this stage, the tumor measures up to 2 centimeters (cm) across. It has not affected and lymph nodes, or there are small groups of cancer cells in the lymph nodes.

Stage 2: The tumor is 2 cm across, and it has started to spread to nearby nodes, or is 2–5 cm across and has not spread to the lymph nodes.

Stage 3: The tumor is up to 5 cm across, and it has spread to several lymph nodes or the tumor is larger than 5 cm and has spread to a few lymph nodes.

Stage 4: The cancer has spread to distant organs, most often the bones, liver, brain, or lungs.

RISK FACTORS (6)

1. Age

The risk of breast cancer increases with age. At 20 years, the chance of developing breast cancer in the next decade is 0.06%. By the age of 70 years, this figure goes up to 3.84%.

2. Genetics

Women who carry certain mutations in the BRCA1 and BRCA2 genes have a higher chance of developing breast cancer, ovarian cancer, or both. If a close relative has or has had breast cancer, a person's chance of developing breast cancer increases.

3. A history of breast cancer or breast lumps

Women who have previously had breast cancer are more likely to have it again than those who have no history of the disease. Having some types of noncancerous breast lump increases the chance of developing cancer later on.

4. Dense breast tissue

Women with denser breasts are more likely to receive a diagnosis of breast cancer.

5. Estrogen exposure and breastfeeding

Breastfeeding for over 1 year appears to reduce the risk of breast cancer. Extended exposure to estrogen appears to increase the risk of breast cancer. This could be due to a person starting their

periods earlier or entering menopause at a later than average age.

6. Body weight

Women who become overweight or develop obesity after menopause may also have a higher chance of developing breast cancer, possibly due to increased estrogen levels.

7. Alcohol consumption

A higher rate of regular alcohol consumption appears to play a role in breast cancer development. According to the National Cancer Institute (NCI), studies have consistently found that women who consume alcohol have a higher risk of breast cancer than those who do not.

Radiation exposure

Undergoing radiation treatment for a different cancer may increase the risk of developing breast cancer later in life.

8. Hormone treatments

According to the NCI, studies have shown that oral contraceptives may Slightly increase the risk of breast cancer. According to the ACS, studies have found that hormone replacement therapy (HRT), specifically estrogen-progesterone therapy (EPT), is related to an increased risk of breast cancer.

9. Cosmetic implants and breast cancer survival

A 2013 review found that women with cosmetic breast implants who received a diagnosis of breast cancer also had a higher risk of dying from the disease.

TYPES OF BREAST CANCER (6)

Breast cancer can be invasive or noninvasive.

Invasive breast cancer occurs when the cancer cells break out from inside the lobules or ducts and invade nearby tissue.

Noninvasive breast cancer does not go beyond the milk ducts or lobules in the breast. Most breast cancers start in the ducts or lobes and are called ductal carcinoma or lobular carcinoma:

Ductal carcinoma: These cancers start in the cells lining the milk ducts and make up the majority of breast cancers.

- **Ductal carcinoma in situ (DCIS).** This is cancer that is located only in the duct.
- **Invasive or infiltrating ductal carcinoma.** This is cancer that has spread outside of the duct.

Invasive lobular carcinoma: This is cancer that starts in the lobules.

Less common types of breast cancer include:

Medullary

Mucinous

Tubular

Metaplastic

Papillary

Inflammatory breast cancer is a faster-growing type of cancer that accounts for about 1% to 5% of all breast cancers.

Paget's disease is a type of cancer that begins in the ducts of the nipple. Although it is usually in situ, it can also be an invasive cancer.

SIGNS AND SYMPTOMS (7)

1. A lump that feels like a hard knot or a thickening in the breast or under the arm. It is important to feel the same area in the other breast to make sure the change is not a part of healthy breast tissue in that area.
2. Change in the size or shape of the breast.
3. Nipple discharge that occurs suddenly, is bloody, or occurs in only 1 breast.
4. Physical changes, such as a nipple turned inward or a sore in the nipple area.
5. Skin irritation or changes, such as puckering, dimpling, scaliness, or new creases.
6. Warm, red, swollen breasts with or without a rash with dimpling resembling the skin of an orange, called "peau d'orange"
7. Pain in the breast, particularly breast pain that does

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not go away.

DIAGNOSIS OF BREAST CANCER (3)

Breast exam

The doctor will check the breasts for lumps and other symptoms. During the examination, the person may need to sit or stand with their arms in different positions, such as above their head or by their sides.

Imaging tests

Several tests can help detect breast cancer:

Mammogram: This is a type of X-ray that doctors commonly use during an initial breast cancer screening. It produces images that can help a doctor detect any lumps or abnormalities.

Ultrasound: This scan uses sound waves to help a doctor differentiate between a solid mass and a fluid-filled cyst.

MRI: Magnetic Resonance Imaging (MRI) combines different images of the breast to help a doctor identify cancer or other abnormalities.

Biopsy

In a biopsy, samples of tissue are extracted and are sent for laboratory analysis.

HOW BREAST CANCER SPREADS (8)

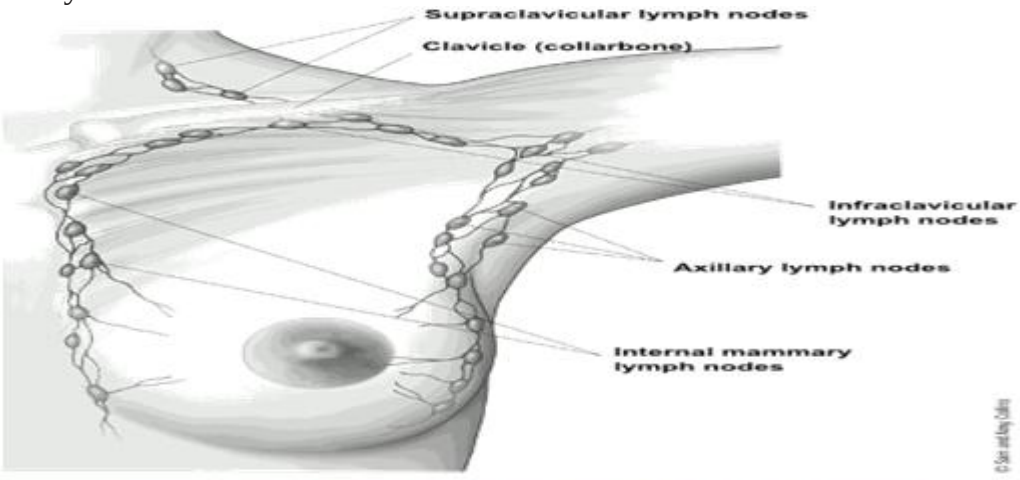
Breast cancer can spread when the cancer cells get into the blood or lymph system and are carried to other parts of the body.

The lymph system is a network of lymph (or lymphatic) vessels found throughout the body that connects lymph nodes (small bean-shaped collections of immune system cells). The clear fluid inside the lymph vessels, called lymph, contains tissue by-products and waste material, as well as immune system cells. The lymph vessels carry lymph fluid away from the breast. In the case of breast cancer, cancer cells can enter those lymph vessels and start to grow in lymph nodes. Most of the lymph vessels of the breast drain into:

Lymph nodes under the arm (axillary nodes)

Lymph nodes around the collar bone (supraclavicular [above the collar bone] and infraclavicular [below the collar bone] lymph nodes)

Lymph nodes inside the chest near the breast bone (internal mammary lymph nodes).



Lymph nodes in relation to the breast

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If cancer cells have spread to your lymph nodes, there is a higher chance that the cells could have traveled through the lymph system and spread (metastasized) to other parts of your body. The more lymph nodes with breast cancer cells, the more likely it is that the cancer may be found in other organs.

INTRODUCTON TO NANOPARTICLES (9, 10)

Nanoparticles are solid colloidal particles consisting of macromolecular substances that vary in size from 1nm to 100nm. The drug which is obtained is dissolved, entrapped, and adsorbed attached or encapsulated into the nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can show different properties and can release different characteristics for the encapsulated therapeutic agent.

(Matrix systems) (Reservior systems)

On the basis of preparation there are 2 types of nanoparticles, that is nanospheres and nanocapsules. Nanospheres have a monolithic type of structure, in which the active compound is dispersed actively in the surface or adsorbed into the surface of its carrier matrix. Nanocapsules form a membrane-like structure with the active compound trapped into the "heart" of its structure or adsorbed on the membrane surface. However, it is hard to classify a nanoparticles complex in to nanospheres or nanocapsules type.

As we know the Nanoparticles are used worldwide to elevate the pharmacokinetic and pharmacodynamics of drug molecules. Many researchers have proved the ability of nanoparticles in improving the bioavailability of drugs with low solubility while delivered via oral, transdermal, intravenous, and pulmonary. On the other hand, the improvement of the amount of drugs in systemic will increase the risk of side effects occurrence until the possibility of achieving toxic level. To achieve an optimum therapy results it is essential that the compatibility between nanoparticles dosage form and target tissue is obtained. In order to introduce a new drug delivery system in the market the foremost requirement is guarantee of target therapy achievement.

MAGNETIC NANOPARTICLES

Magnetic nanoparticles (MNPs) possess unique properties, which make them highly attractive to medical applications. These properties include their high surface to volume ratio, their quantum properties and their ability to carry other compounds due to their small size (11). MNPs are widely abundant in biological systems,

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ranging from geomagnetic navigational aids in migratory species to ferritin which is the most common iron storage protein and which contains up to 3000 ferric ions in a paramagnetic oxyhydroxide core [12]. The Microscopic origin of magnetic properties in matter lies in the orbital, and spin motions of electrons whose spin and angular momentum are associated with magnetic moment [13].

NANOCARRIERS USED FOR HERBAL BIOACTIVES IN BREAST CANCER [14, 15]

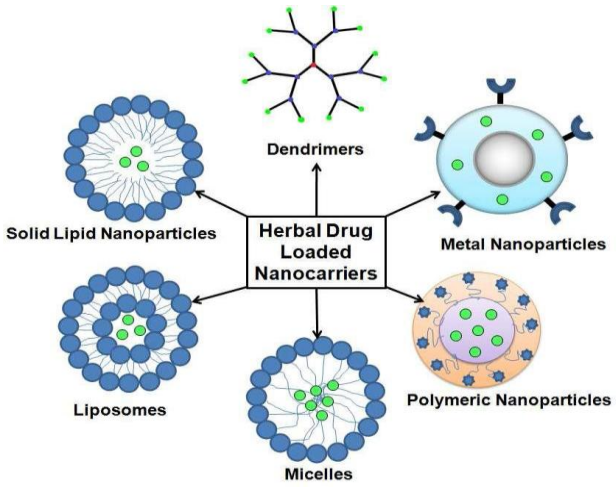

Fig: Different Nanocarriers Used for The Delivery of Herbal Bioactives.

In Breast Cancer Liposomes are composed of concentric lipid bilayers, separated by an aqueous medium. Hydrophobic herbal anticancer drugs are encapsulated in the lipid bilayer and are important for the delivery of herbal drugs due to the properties like amphiphilicity, biocompatibility and iodegradability. They have been widely studied for the delivery of various herbal bioactive components including curcumin [16], vincristine, topotecan [17], quercitine [18], thymoquinone[19], shikonin [20], berberin [21] and artemisinin [22].

Polymeric nanoparticles are mostly made from natural biodegradable polymers and fall in the size range of 10-1000 nm in diameter. Various polymeric nanocarriers consisting of PEG, PLGA, PCL, pluronic have been used for efficient delivery and uptake of herbal drugs by breast cancer cells. Activity of a novel docetaxel-loaded poly (ε-caprolactone)/pluronic F68 nanoparticles has been seen to overcome multidrug resistance in breast cancer treatment. They used docetaxel-resistant human breast cancer cell line, MCF-7 TAX30 [23]. PLGA nanoparticles stabilized with cationic surfactant is used for the oral delivery of paclitaxel to treat chemically-induced breast cancer in Sprague Dawley rats[24]. Camptothecin was combined with hydrophobically modified glycol chitosan (HGC) and its activity was observed in mice injected with MDA-MB-231 breast cancer cells [25].

Micelles are spherical aggregates with the hydrophilic regions in contact with surrounding solvent and hydrophobic drug in the micelle centre. The experiment was performed in which gambogic acid was entrapped in micelles and analyzed its activity in breast cancer cell line, MCF-7[26].

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Solid lipid nanoparticles (SLNs) are lipids containing colloidal carrier system with better stability of anticancer drugs. SLNs are made from lipids, which remain in solid state at room and body temperature. They have a size ranging from 50-1000 nm. SLNs were used for the enhanced antitumor activity of oridonin and tryptanthrin in breast cancer cell line, MCF-7 [27, 28].

Dendrimers are branched macromolecules with a simple core unit. The branching structure allows them to be conjugated to targeting molecules, imaging agents, and drugs. Shikonin was attached to dendrimers and its anticancer activity was observed in breast cancer cell line MCF-7 [29].

Metal nanoparticles such as iron oxide and gold have been extensively explored for their drug loading capacities and additional physico-chemical and optical properties in the regulation of breast cancer. Besides chemical synthesis, gold nanoparticles can also be synthesized by using plant extracts in one-step green synthesis process. By this method, the nanoparticles get coated with various bioactives present in the extract that endows them with various properties including anticancer activity [30, 31].

Nano-carriers Used for the Delivery of Herbal Bioactive Drugs in Breast Cancer

NATURAL BIOACTIVES WITH ANTICANCER ACTIVITY	**PLANT SOURCE**	**CELL LINE/ ANIMAL MODELS**	**NANOCARRIERS**
Curcumin	*Curcuma longa*	MCF-7, MDAMB-231, SKBR-3, Tumor models in mice	Iron oxide nanoparticles, polymeric nanoparticles, liposomes
Thymoquinone	*Nigella sativa*	MCF-7 and T47D	Liposomes
Shikonin	*Lithospermum erythrorhizon*	MCF-7	Liposomes, dendrimers
Berberin	*Coptidis Rhizoma*	Breast cancer stem cells	Liposomes
Artemisinin	*Artemisia annua*	Breast cancer cell line	Pegylated nanoliposomes

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Docetaxel	plants of the genus Taxus (yews)	Docetaxel resistant human breast cancer cell line, MCF-7 TAX30	Polymeric nanoparticles (PCL/Pluronic F68 nanoparticle)
		(MDA-MB-435)	
Camptothecin	*Camptotheca acuminata*	Mice injected with MDAMB-231	Hydrophobically modified Glycol Chitosan (HGC)
Gambogic acid	*Garcinia hanburyi*	MCF-7	Micelles
Oridonin	Rab*dosia rubescens*	MCF-7	(SLNs)
Tryptanthrin	*Isatis tinctoria*	MCF-7	Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), and Lipid Emulsions (LEs)
Vitamin C	*Allium cepa*	MCF-7	Gold nanoparticles
paclitaxel	*Taxus brevifolia*	MCF-7	GMO-MNPs
Gallic acid	gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants	MCF-7	Iron oxide- Chitosan-Gallic acid (FCG)
Silibinin	*Silybum marianum*	T47D	PLGA-PEGFe3O4
Cinnamaldehyde	*Cinnamomum zeylanicum*	MCF-7, MDAMB-231	PF127-Glycine-Fe3O4

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Noscapine	plants of the Papaveraceae family	SK-BR-3	Human Serum Albumin (HSA) nanoparticles

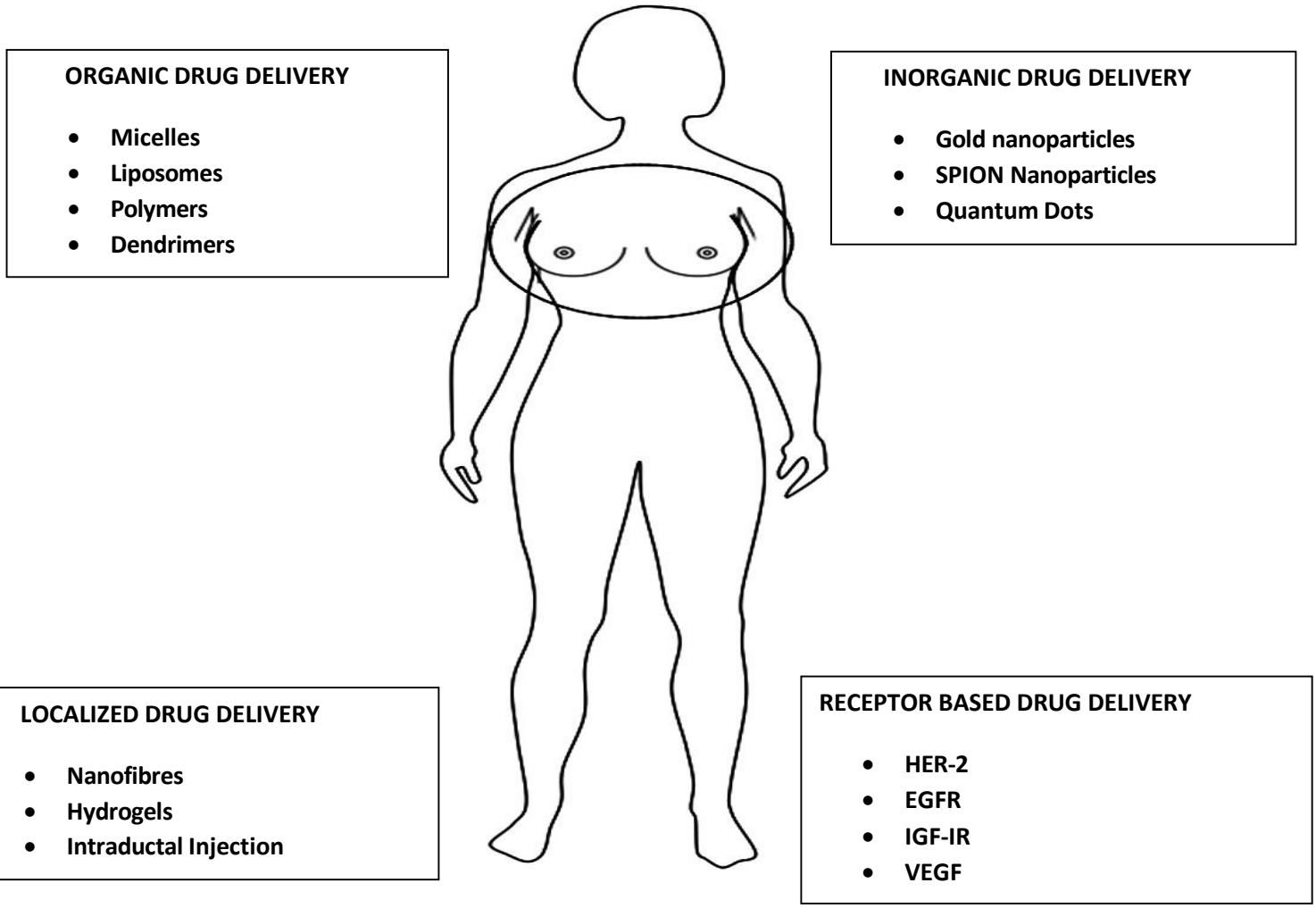

Figure 1: Drug delivery systems for breast cancer.

Abbreviations: SPIO, superparamagnetic iron oxide; HER-2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; IGF-IR, insulin-like growth factor I receptor; VE GFR, vascular endothelial growth factor receptor.

INTRODUCTION TO RHODODENDRON

Rhododendron plant species has a multifunctional activity. It gives many therapeutic benefits. It is a plant of Himalaya region like Kashmir, Bhutan, Uttrakhand, and Himachal. Originally espied in north intermediate India the plant is organize in the Himalayas in distinction to Kashmir to Bhutan & in the cliff of Assam & Manipur at elevation of 1200-400 m. Rhododendron is a hedge enough wing shrub up to 14 m in elevation & 2.4 m in circumference [32]. It flourishes at mountain of 4500 to 10,500 ft. & flourishes up to 40 to 50 ft

large frequently reap over 100 ft. It is also known as "burans" and "laligurans". It is a gift of our nature as medicinal agents most of the years it is take care of our mankind. Rhododendron species is a bundle of variable characteristics like firmness, flower, leaf, size. Multinational, more on 35000 plants species have been used for medicinal purpose. Community of the nature having two hits spot of bawdiest. The genus Rhododendron, having about 72 species, 20 sub species and 19 varieties in India, is mainly distributed in the Eastern Himalayas, during Rhododendron arboreum is the only local species found in Western Ghats. Rhododendron species influence the Guinness Record for World Largest Rhododendron & is extensively attractive for its remedial welfare & commercial value. The epithetical engaging blossom behind its religious understanding, it is treated religious & allow in place of worship for flower purposes. Flourishing fall is in distinction to March-September manner deepened glowing or maroon to faded salmon flower. The flower adopt shiny (sandy) to intermediate (loamy) soil & desire kind of humid & sour soil. It can develop in semi shadow (light woodland) or no shadow, lack shelter from heated afternoon sunlight so requires a place in the grassy shack or nursery. (33)

RHODODENDRON USES:

I- Anti-inflammatory and Anti-nociceptive activity

The ethyl extract fraction of Rhododendron arboretum showed significant anti-inflammatory and anti-nociceptive potential in animal models. Oral administration of Rhododendron arboreum extract (EERA) (100, 200 and 400 mg/kg) exhibited dose Hyperoside, Quercetin, Rutin, Coumaric Acid Epifridilenol dependent and significant anti-inflammatory activity in arachidonic induced hind paw edema ($p<0.01$), cotton pellet granuloma model of inflammation ($p<0.01$) and Freund's adjuvant-induced paw arthritis ($p<0.01$). A significant ($p<0.05$) anti-nociceptive activity was evidenced in mice, protection in acetic acid-induced writhing. EERA at the dose of 100, 200 and 400 mg/kg exhibited significant ($p<0.001$) resistance against analgesymeter induced pain in mice. The hot plate reaction time was increased at a dose of 100, 200 and 400 mg/kg significantly ($p<0.001$). The anti-inflammatory or nociceptive effect of the extract may be due to the presence of flavonoids (hyperin), tannins, saponins and other phytochemicals present either as single or in combination. The significant level of anti-inflammatory activity of the ethyl acetate extract could be attributed to high amount of flavonoids present in the extract.(34)

II- Hepatoprotective activity

The ethyl acetate fraction of Rhododendron arboretum exhibited significant hepatoprotective potential against carbon tetrachloride (CCl4)-induced liver damage in preventive and curative models. Fraction at a dose of 100, 200, and 400 mg/kg was administered orally once daily for 14 days in CCl4-treated groups (II, III, IV, V and VI). The serum levels of glutamic oxaloacetic transaminase (SGOT), glutamate pyruvate transaminase (SGPT), alkaline phosphatase (SALP), γ- glutamyltransferase (γ-GT), and bilirubin were estimated along with activities of glutathione S-transferase (GST), glutathione reductase, hepatic malondialdehyde formation, and glutathione content. The substantially elevated serum enzymatic activities of SGOT, SGPT, SALP, γ-GT, and bilirubin due to CCl4 treatment were restored toward normal in a dose-dependent manner. Meanwhile, the decreased activities of GST and glutathione reductase were also restored toward normal. In addition, ethyl acetate fraction also significantly prevented the elevation of hepatic malondialdehyde formation and depletion of reduced glutathione content in the liver of CCl4 - intoxicated rats in a dose-dependent manner.(35)

III- Anti-Diarrhoeal Activity

The ethyl acetate fraction of Rhododendron arboretum (flowers) showed potent antidiarrhoeal activity. A simple sensitive high performance thin layer chromatography (HPTLC) method was used for the determination of hyperin in EFRA. The standardized fraction was investigated for castor oil, magnesium sulfate-induced diarrhoea,

measurement of gastrointestinal transit using charcoal and castor oil-induced enteropooling. The concentration of hyperin in flowers of R. arboreum was found to be 0.148% by HPTLC. Oral administration of EFRA at 100, 200 and 400 mg/kg exhibited dose-dependent and significant (P<0.05-0.001) antidiarrhoeal potential in castor oil and magnesium sulfateinduced diarrhoea. EFRA at doses of 100, 200 and 400 mg/kg also

produced significant (P<0.05-0.001) dose-dependent reduction in propulsive movement in castor oil-induced gastrointestinal transit using charcoal meal in rats. EFRA was found to possess an anti enteropooling in castor oil-induced experimental animals by reducing both weight and volume of intestinal content significantly. The results showed that EFRA could, in a dose dependent manner, reduce castor oil-induced diarrhoea as well as the number of diarrhoeal faeces and total weight of faeces, which could be taken as antidiarrhoeal activities. The ethyl acetate fraction of R. arboreum flowers was also found to reduce magnesium sulfate-induced diarrhoea significantly which could be due to increased absorption of water and electrolytes. The EFRA suppressed the propulsive movement or gastrointestinal transit of charcoal meal which clearly indicates that extract may be capable of reducing the frequency of stools in diarrhoeal conditions. The extract inhibits gastrointestinal motility in diarrhoea through anticholinergic effect. EFRA was found to possess an antienteropooling in castor oil-induced experimental animals by reducing both weight and volume of intestinal content. Phytochemical screening revealed the presence of numerous constituents such as flavonoids, saponins, tannins, phytosterols, reducing sugars and phenolic compounds. Hence tannins, reducing sugars and sterols may be responsible for mechanism of antidiarrhoeal activity of EFRA (36)

IV- Anti-Diabetic Activity

Anti-diabetic activity was examined in (Rhododendron arboreum Sm) flower and active compounds were isolated from it. Aqueous methanolic extract of the flower of Laligurans was found to show inhibitory activity on the rat intestinal α-glucosidase. Both the water-soluble and ethyl acetate-soluble portions from the aqueous methanolic extract showed inhibitory activities on α- glucosidase, demonstrating higher activity by the ethyl acetatesoluble portion. From the ethyl acetate-soluble portion, α- glucosidase inhibitor quercetin-3-O-β-D-galactopyranoside (hyperin) was isolated through enzyme-assay guided separation. The isolated compound showed a dose dependent α-glucosidase inhibitory activity with IC50 values of 1.66 mM and 0.76 mM for sucrase and maltase, respectively. This study revealed that flower contains antidiabetic potential which property might be helpful to develop medicinal preparations, nutraceutical or functional food for diabetes and its complications.(37)

V- Antioxidant or Adaptogenic activity

The ethanolic extract of Rhododendron arboreum showed significant adaptogenic property as by mitigating the effect of acute and chronic stress induced biochemical and physiological perturbation. The study was conducted on mice and rats. Anoxia stress tolerance, swimming endurance, immobilization stress models were used for the evaluation of adaptogenic activity. Concomitant treatment with ethanolic extract at doses 250 and 500 mg/kg, showed marked increase in anoxia stress tolerance and swimming endurance time as compared to control group. Similarly, pre-treatment with extract showed marked decrease in blood glucose, cholesterol, triglycerides level as compared to stress control group in immobilization stress. Weights of liver and adrenal glands are markedly decreased, but no weight changes in spleen and testes were observed.(38)Flavonoids isolated from the leaves of R. arboreum were found to have potent antioxidant property.(39)

ANTI-CANCER ACTIVITY OF RHODODENDRON LUTEUM FLOWER EXTRACTS ON NON-TRANSFORMED AND TRANSFORMED CELL LINES (40)

Anti-cancer activity was observed in non transformed and transformed cell lines which were

treated by various organic extracts (ethyl acetate, hexane and methanol) obtained from different flower parts of R. luteum or DMSO for 48 h in in vitro conditions. Cytotoxic activity measurement was achieved by the MTT method. The results obtained from this study showed that ethyl acetate extracts derived from the sepals, petals and buds illustrated significant anti-proliferative effects on the HT29 colorectal cancer cell line. The IC50 values that were determined for sepal, petal and bud ethyl acetate extracts were 133.2 µg/ml, 459.3 µg/ml and 159.94 µg/ml, respectively in comparison to the ARPE-19 IC50 values which were 266.6 µg/mL, 800 µg/ml and 366.65 µg/ml, respectively. The difference between the non-transformed ARPE-19 and transformed HT-29 cell lines was statistically significant ($p<0.05$). In consequence, the results from this study suggest that different organic extracts from R. luteum may have selective effects on different cancer cells and offer a potential for usage as anticancer agents for colorectal cancer.

ACTIVITY OF DIFFERENT SPECIES OF RHODODENDRON ON CANCER

Rhododendron species have shown that the 70% ethanolic extract of Rhododendron brachycarpum leaves has a cytotoxic effect on human lung (A549), stomach (AGS), breast (MCF-7) and liver (Hep3B) cancer cell lines [41]. It is reported that different fractions of the methanolic extract of Rhododendron formosanum leaves exhibit cytotoxic effect in human lung cancer cells by inducing apoptosis[42]. In addition to that the aqueous extract of Rhododendron ponticum flowers exhibits cytotoxic effects on human prostate cancer (PC3 and DU145) cell lines. Studies have also investigated the antiproliferative activity of various compounds isolated from Rhododendron species [43]. It is also reported that grayanotoxin I isolated compound from Rhododendron brachycarpum has a strong antiproliferative effect in human lung, ovarian, melanoma, colon and glioblastoma cancer cells [44]. It is reported that ferruginenes C isolated from Rhododendron ferrugineum exhibits a cytotoxic effect on human acute promyelocytic leukemia, cervix, and breast cancer cells [45]. It is reported that hyperin isolated from Manchurian Rhododendron leaf exhibits antiproliferative effect in human endometrial cancer cells through mitochondrial apoptosis pathway [46]. It is reported that 15-oxoursolic acid isolated from Rhododendron arboreum exhibits cytotoxic effect on human renal, liver, lung, and ovarian cancer cells [47].Recently, researchers reported that the aqueous extract of Rhododendron ponticum flowers exhibits cytotoxic effect on the glioma cells [48]

MEDICINAL USES OF DIFFERENT PARTS OF RHODODENDRON

SPECIES	PARTS USED	USES
	Fresh Flowers	In treatment of hill diarrhea & dysentery
	Dried Flowers	Taken with ghee after frying
	Fresh & Dried Corolla	Take when fish bones stuck in the gullet

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R. arboreum Sm.	Leaves	Used as poultice in high fever and headache.
	Leaf Decoction	Used in treating chronic rheumatism, syphilis and sciatica
R. campanulatum D. Don	Powdered dried leaves	Used as snuff after mixing with tobacco leave to cure Hemicarinia and colds
	Dried twigs and wood in powdered form	In treatment of chronic fevers
R. anthopogon D. Don	Decoction of leaves	In treatment of Catarrh; also in treating cold, cough, chronic bronchitis and asthma; administered to produce sneezing.
	Decoction of leaves and flowers	In treating indigestion and lung infection.
	Dried flowers in powdered forms	Mixed with oil and used in massage in post delivery complications
R. anthopogon D. Don(particularly subsp. Hypenanthum {Balf. f.}Cullen)	Powdered dried leaves and young shoots	Eaten with butter in Leucorrhoea and Gonorrhoea
R. lepidotum Wall.ex G. Don	Bark	Drinks made are supposed to be purgative

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CONCLUSION:

The shortcomings of conventional cancer treatments and the increasing acceptance of herbal drugs have resulted into the need of novel strategies for improvement of the herbal bioactives. Nano-formulations of herbal chemopreventive agents such as curcumin, taxol, wogonin, silibinin, gambogic acid, gallic acid, artemisinin, tetraandrine, cinnamaldehyde and many more have been developed that possess enhanced anticancer activity. Researchers are focusing on managing breast cancer by effectively utilizing nanoscale technologies to boost the anticancer potential of herbal drugs. This approach offers additional benefits to the herbal drugs including enhanced therapeutic efficacy, prolonged half-life, improved solubility, reduced potential immunogenicity and sustained drug release. These nano-herbal formulations have a potential to open up a new era of chemotherapeutic agents for breast cancer management.

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