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Man vs Cancer: Garlic, as a Nature's Gift to Human, in the Form of Natural Nanomedicine for Breast Cancer Treatment

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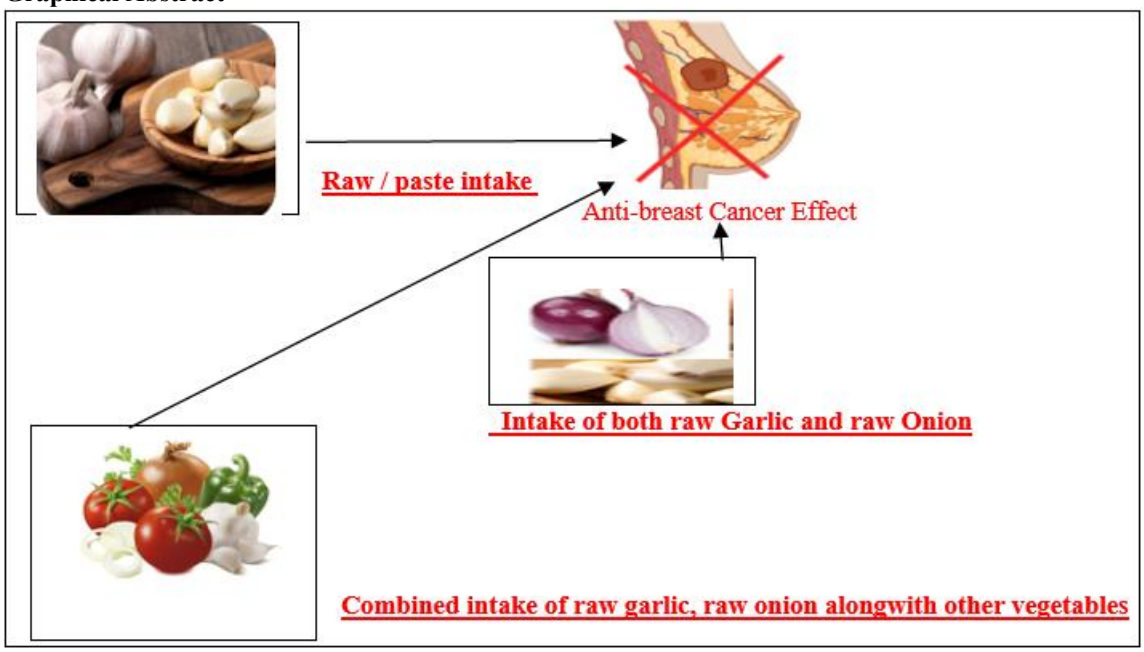
Abstract: ***Breast cancer is a disease in which malignant (cancer) cells form in the tissue of the breast. A world survey indicates the cancer occurrence in the breast is the foremost in women. Although surgery and chemotherapy remain the definitive treatment for the breast cancer, but green synthesis method offer the scientists for a low cost an d eco-friendly preventive method for breast cancer. Ancient peoples used plants, raw vegetables for the treatment of human diseases including cancers. They did not know present day advanced nanotechnology but were aware of such a green synthesis mechanism that were useful to human cancer treatment. Garlic is the best vegetable with promising potential to the best cancer treatment. Investigational results show as evidence the intake of direct eating garlic bulbs with other food or garlic paste form (waiting more than 15 minutes after doing it) reduce a woman's risk of breast cancer when taken every day basis. In addition, eating of raw onion and garlic every day offers an anti-cancer effect against breast cancers. Even, intake of raw garlic, onion alongwith other vegetables i.e. the combination of all these either in direct eating or in the form of paste both will be effective in protecting the woman's breast cancer. It is suggested that eating raw onion and garlic everyday may reduce woman's risk of getting breast cancer by 67% . Further clinical test may improve the protective power against the breast cancer.***

Keywords: Breast cancer, tumor, garlic, onion, TNBC, Medicinal plant

Graphical Abstract



1. Introduction

Developing breast cancer is not your or anyone's fault. Feeling guilty, or telling yourself that breast cancer happened because of something you or anyone else did, is not productive.

The general view of cancer among the common people is that cancer can spread to other organ in the human body although it grows locally and gradually making it as a complex disease. Breast cancer today has become a recent survey of cancer [1] indicates the realistic scenario of breast cancer as:

a) its incident rate is increasing year by year;
b) approximately more than 3 lakhs new cases were reported in 2024;
c) female occupied the first place of 32 % of the total number of new cases.

From the above it can easily be assumed that breast cancer treatment needs a priority i.e. cancer treatment is becoming increasingly crucial in developing nations as well as growing cancer in the aging population.

The traditional cancer treatment is based on the state of sub-type of cancer and how much it has been spread outside of the breast to lymph nodes (stage II & III) or to the other parts of the body (stage IV):

- Surgery to remove the breast tumor
- Radiation to reduce recurrence risk in the breast and surrounding tissues
- Medicines to kill the cancer cells and prevent spreading

In the case of surgery → removal of just the cancerous tissue or the whole breast i.e. Lymph nodes are removed at the time of cancer surgery for invasive cancers. In the case of medicines → to treat cancers that are selected based on the biological properties of the cancer as per determined by special tests.

Presently, "green extracted nano-medicine" is likely a preference i.e. gold nanoparticles and plant extracts to treat meta-static breast cancer through this treatment has shown promising results in preclinic studies and initial human clinical trials as an adjuvant therapy. It is to be noted that research suggests the nano-medicine is not an outright alternative to surgery for breast cancer but is a promising adjacent therapy that basically enhances the effectiveness and reduces the side effects of conventional treatments like chemotherapy, radiation and surgery.

What is breast Cancer

Breast cancer is a disease in which malignant (cancer) cells form in the tissue of the breast. In general, breast cancer is a disease in which abnormal breast cells grow out of control and form tumors. This cancer's cells begin inside the milk ducts and / or the milk producing lobules of the breast (see fig1). In this early stage it is not life threatening if it can be detected in the earliest form (i. situ).

Sign and Symptoms

In fact, most people will not experience any symptoms when cancer is still early but when it is more advanced then symptoms of breast cancer appears in the form of:

a) A breast lump or thickening, often without pain.
b) A change in size, shape and appearance of the breast
c) Dimpling, redness, pitting or other changes in the skin
d) Change in nipple appearance or the skin surrounding the nipple (areola)
e) Abnormal or bloody fluid from the nipple

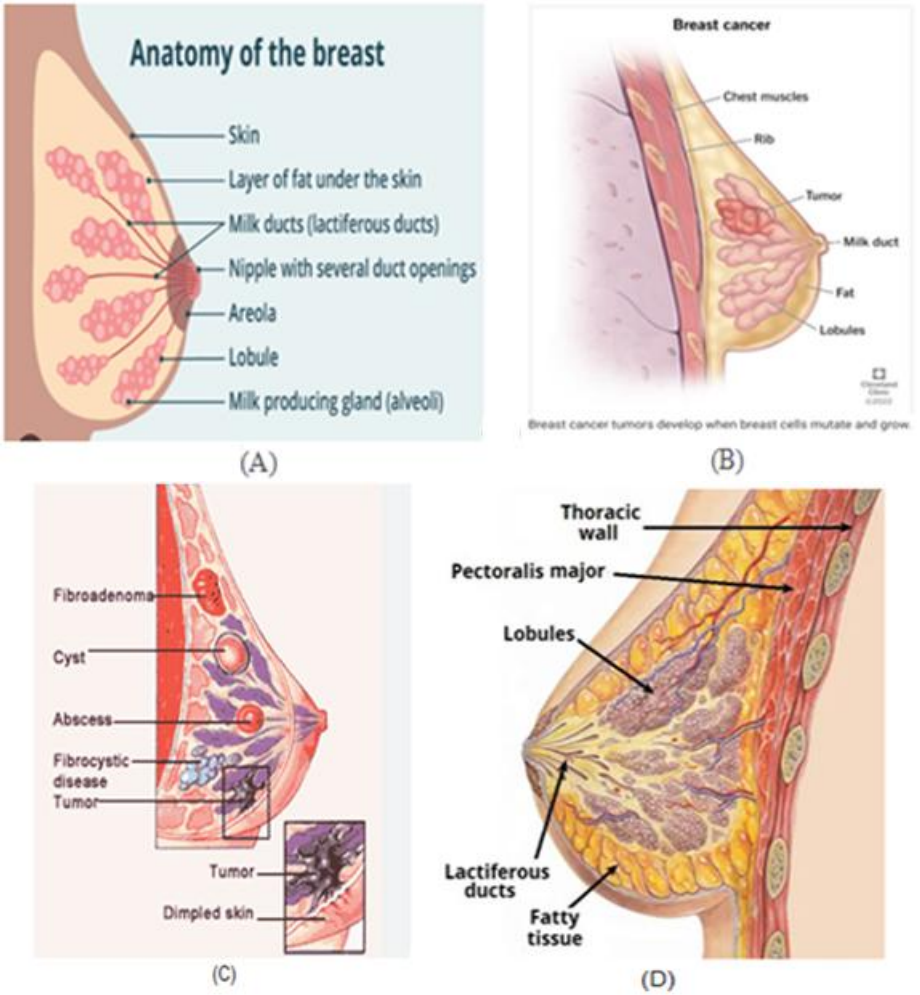


Figure 1: Schematic diagram showing the structure of female breast under state of (A) normal, (B) with tumor, (C) with enlarge tumor, and (D) cross sectional side views (Courtesy: Wikipedia commons)

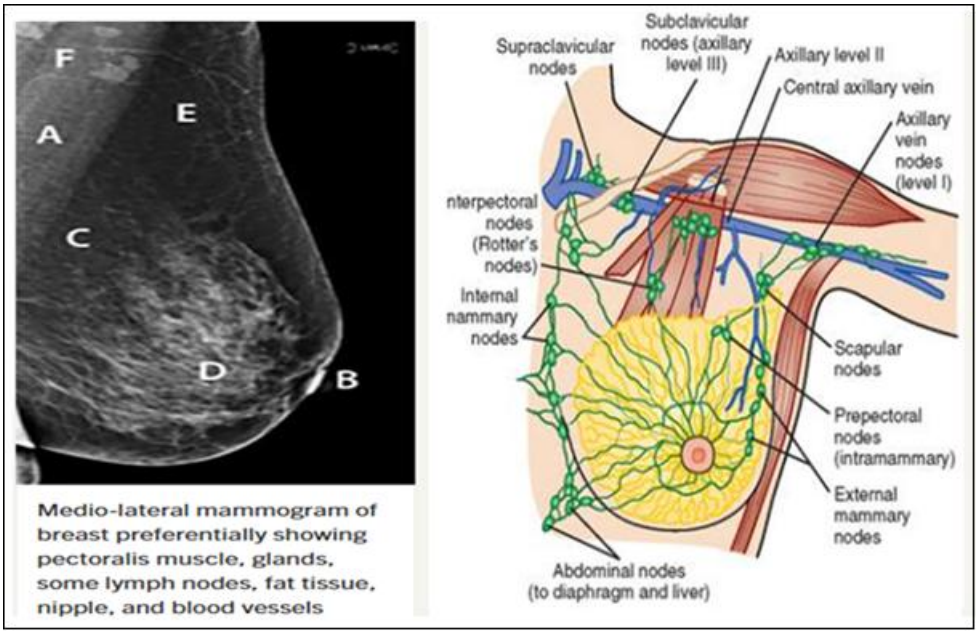


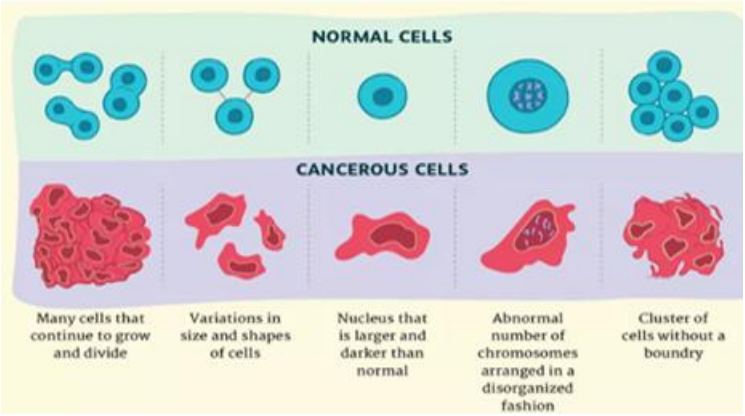
Figure 2: (Left) Ultrasonography image of breast and **(Right)** schematic diagram showing nodes at various location inside the breast (Courtesy and copyright © Prof. Iram Dubin) *Lymphatic Drainage schematic illustration rendering by Iram Dubin*

Type of Breast Cancer

Cancer cells differ from normal cells in key ways i.e. they grow uncontrollably, ignore cellular signals, evade the immune system, and fail to perform necessary bodily functions. Based on our present understanding in these distinctions i.e. clarity about how cancer develops and acts within the body, breast cancer is mainly divided into:

- ***Ductal Carcinoma In Situ (DCIS***) → it is non- invasive, i.e. stage 0 breast cancer that has not spread into other tissue or lymph nodes. DCIS is highly treatable.
- ***Invasive Ductal Carcinoma (IDC)*** → it is invasive breast cancer that began in the milk ducts and that has spread into surrounding breast tissue or area of the body.
- ***Invasive Lobular Carcinoma (ILC)*** → This ILC is invasive breast cancer that began in the milk gland (lobules) and has spread into surrounding breast tissue or areas of the body.
- ***Tripple Negative Breast Cancer (TNBC)***→ This type breast cancer is a rare but aggressive type that lacks the receptors commonly found in other types, impacting treatment options.
- ***Inflammatory Breast Cancer (IBC)***→This type breast cancer is also a rare but aggressive as well as fast growing and affects the skin of the breast, often causing a distinct rash.
- ***Metastatic Breast Cancer (MBC)*** → This is a stage 4 breast cancer that has spread from the breast into other areas of the body, particularly bones, liver, and brain.
- ***Lobular Carcinoma in Situ (LCIS)***→ It is "Not a Breast Cancer", but is a risk factor having a chance for developing breast cancer. So, it is a condition where abnormal cells are found in the breast lobules.
- ***Other Type*** → This includes *modullary carcinoma, tubular carcinoma, Paget's disease of the breast, angiosarcoma, and more.*

Types of Cells involved in Breast Cancer and their structure



(A)

Figure 3: (A) Schematic diagram showing a difference of cancer affected cells from the normal cells (from ref. [2]) (B) different types of cancer affected cell's structure as observed Prof. Chris Bakal (adopted from ref. [3], Courtesy and copyright Dr C. Bakal)

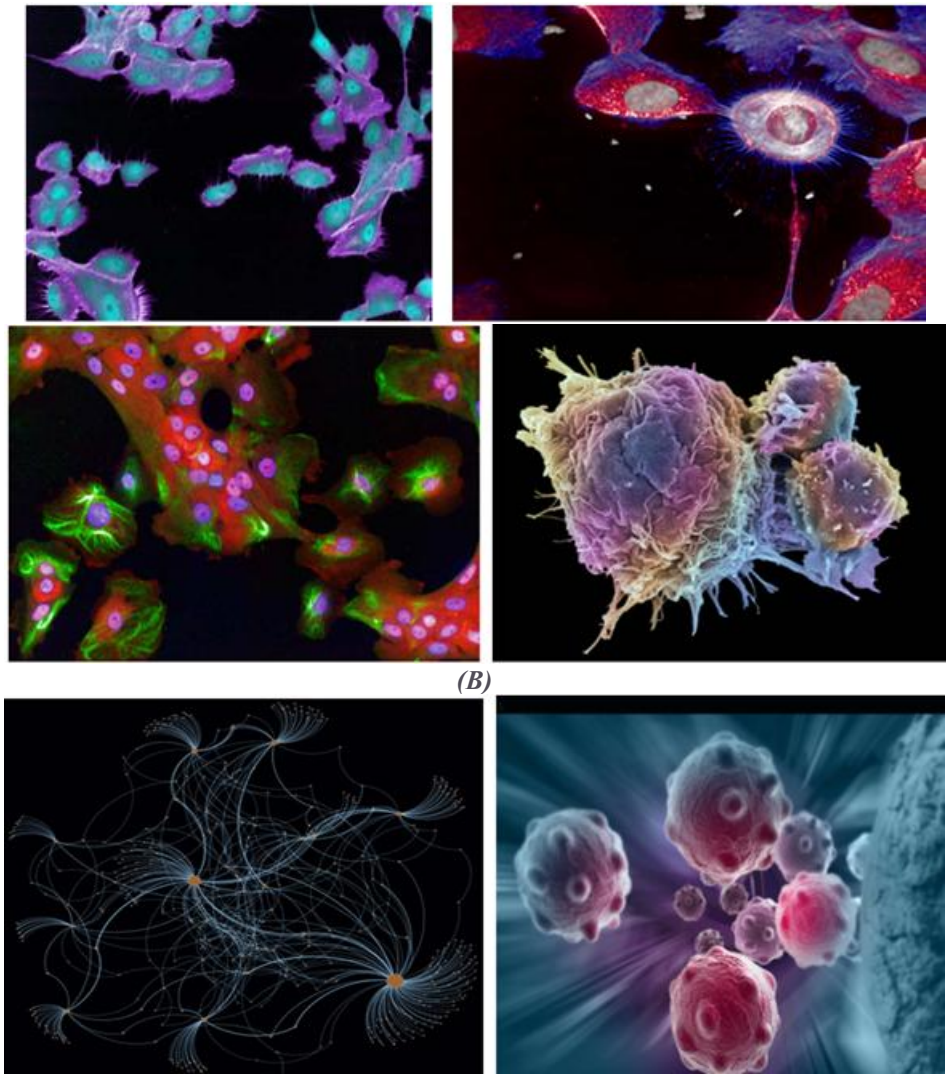


Figure 4: (Left) representation of the mapping of the connection of genetic data with the shape of cancer affected cells, (**Courtesy and Copyright** © Dr Chris Bakal**), (Right)** Shape of the cancer affected cells as per 3D simulation study as obtained by Dr Nicole Fawcett, 2015. Courtesy and Copyright © Dr Fawcett)

In the pathological view the following cells that make up the breast cancer:

a) Ductal cells → Ductal breast cancer (also called ductal carcinoma) is the most common type breast cancer is associated with these cells. This type of cancer starts in the ductal cells in the lining of a milk duct that can carry breast milk to the nipple.
b) Lobular cells → The lobular breast cancer (also called lobular carcinoma) in the lobules of the breast. These lobules make breast milk and then carry this milk to the nipple through the connected ducts.
c) Connective tissue cells → Connective tissue that includes the muscle, fat and blood vessels. Thus, rarely cancer in the breast is associated or made up of the connective tissue cells. Note that, cancer that begins in these connective tissues called "soft tissue sarcoma". For example —rare breast sarcomas like "angiosarcoma", "leiomyosaccoma".
d) Lymphatic System cells →Lymphoma cancer starts in the cells of the lymphatic system. It is also very rare that lymphoma cancer starts in the lymphatic system cells in the breast.

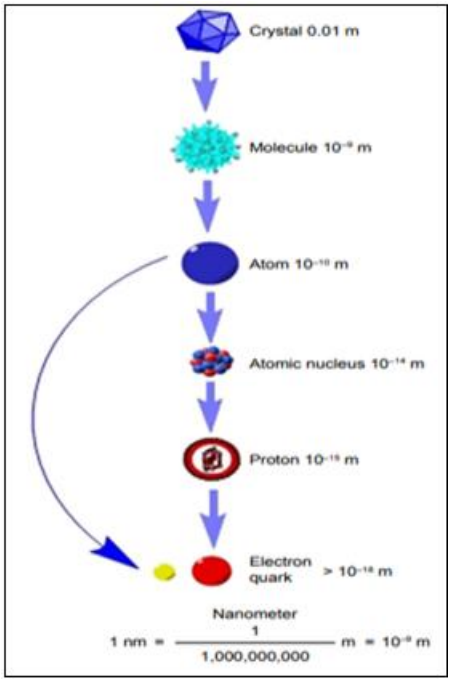


Figure 4: Shows the size of nano-particle as viewing in measuring scale

Why Nanoparticles are needed

What is Nano-particle and Nanotechnology

The prefix ":nano" comes from the Greek word meaning something very very small, which is depicted as one thousand millionth of a meter i.e. 10^{-9} m.

"Nano-technology" is a general term used for designing and making anything applicable, depending on the specific structure at the nanoscale ranging from (1 to 100) nm. Thus, the term "nanomaterials" means the considered materials are with at least one external dimension that covers the measuring angle 100nm or less. Due to their very very small in sizes, the nanomaterials may be in the form of (a) particles, tubes, rods or fibre, (b) the bulk form of the same compositions with different physicochemical potentials [4,5] as well as may behave differently aster entering the human, particularly in the blood cells [6].

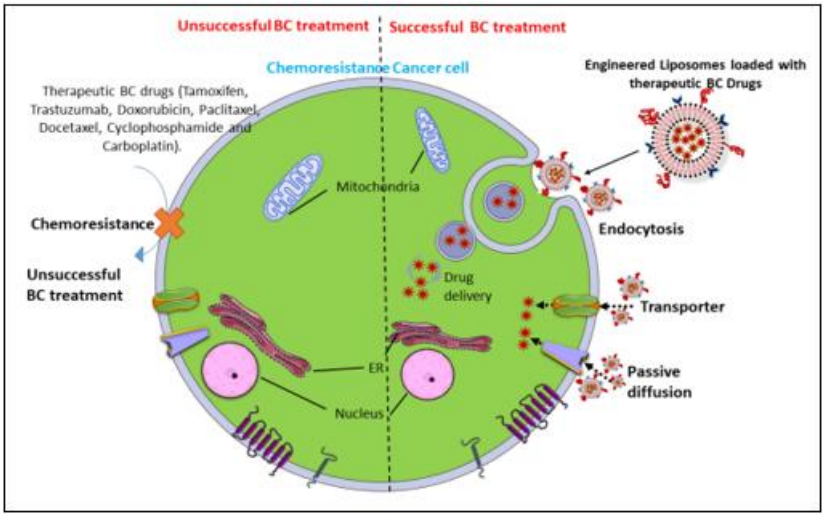


Figure 5: Drug uptake pathways in chemoresistant BC cells. Therapeutic BC drugs-loaded liposomes enter chemoresistant cancer cells through different mechanisms, viz., endocytosis, passive diffusion, and plasma membrane transporters. The application of nanoformulations improves drug-specific targeting, cell interaction, and direct uptake into BC cells.(adopted from ref. Ganesan et al.2021 [10])

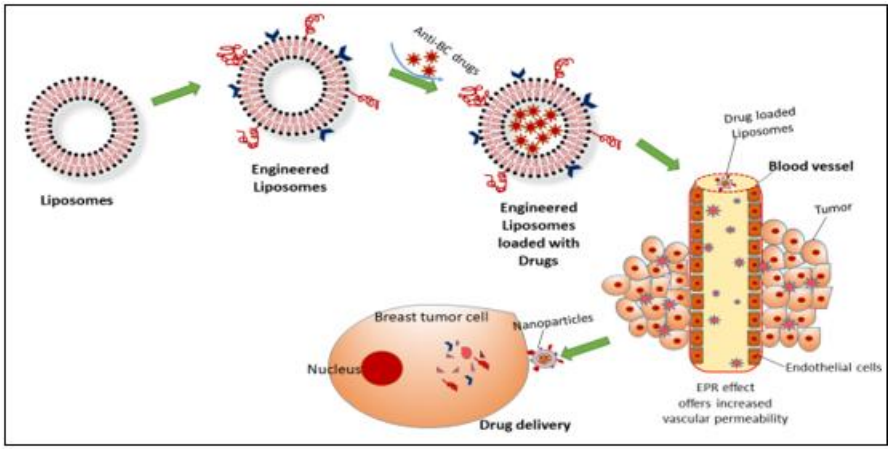


Figure 6: shows the mechanism of engineered liposomes loaded with therapeutic breast cancer drugs into the breast tumors. Note that the passive tissue targeting is succeeded by the extravasation of nanoparticles through increased vascular permeability of the tumor (EPR effect). Active cellular targeting can be attained by functioned liposomes of NPs with ligands that promote cell-specific recognition and attachment. Based on the cellular penetration, NPs can release their contents close to the target (adopted from ref. Ganesan et al 2021 [10]).

As the nanoparticles are, generally, within the size ranging 1 – 100 nm and have either active or passive targeting capability for drug delivery system (DDS), i.e. can increase the drug concentration inside the rumor and resulting reduces systematic toxicity in healthy tissues compared to the conventional mechanisms of breast cancer treatments (see figure 5). Not only that, it has been established from several investigations [7,8] regarding the benefits of nanoparticles in drug delivery systems for breast cancer therapy with regard to

a) Water dispersion, biocompatibility, biodegradability, stability,
b) Key responses to nanoparticles at the level of cells and tissues.
c) Nanoparticles, in particular liposomes which are bilayered phospholipids, are capable to exhibit their effectiveness when encapsulated both hydrophobic and hydrophilic drugs. This means that engineered liposomes have special potential to preserve the drug (until they are disturbed) and capable to promote the sustained delivery of drug formulation.

d) The most significant functional property is that these liposomes can easily be accumulated in the cancer cell resulting which an increase in the selectivity of the drug function, leading to diminishing toxicity is possible [9,10].

Traditional methods, Post-surgery problems and Potential of Nanoparticles

The realistic scenario is that most patients undergo a surgical procedure depending on various factors like patient's preference, identified type of breast cancer, tumor size and location, etc. But the commonly selected option is breast conserving surgery (so called lumpectomy) which involves removing the tumor and alongwith some surrounding healthy tissue as well as removal of nearby lymph nodes for checking purpose about the spread of cancer. Another alternative option is the removal of the entire breast along with lymph nodes.

As an addition, patient may opt for breast reconstruction by utilizing non-breast tissue or implant to create a new breast. In fact, to circumvent the non-specific harm to healthy tissues arises from conventional cancer treatments such as radiotherapy, chemotherapy and immunotherapy [11]. In this context, nanotechnology i.e. in particular nanoparticles as multifunctional nanocarriers have potentials for selectively improving drug delivery and retention towards exploiting (a) the discrepancies between tumor and normal tissues, (b) the tumor microenvironment such as abnormal temperature gradients, reductive conditions, mild acidity, hypoxia and over expressed proteins and enzymes. Thus, use of engineered nanoparticles for targeted cancer therapy, including breast cancer, showing a new hope as a growing field of research for cancer treatment. In other words, nanoparticles, therefore, provide us a promising potential in breast cancer treatment [12-14].

Different types of Nanoparticles / Nanomaterials used in Breast Cancer

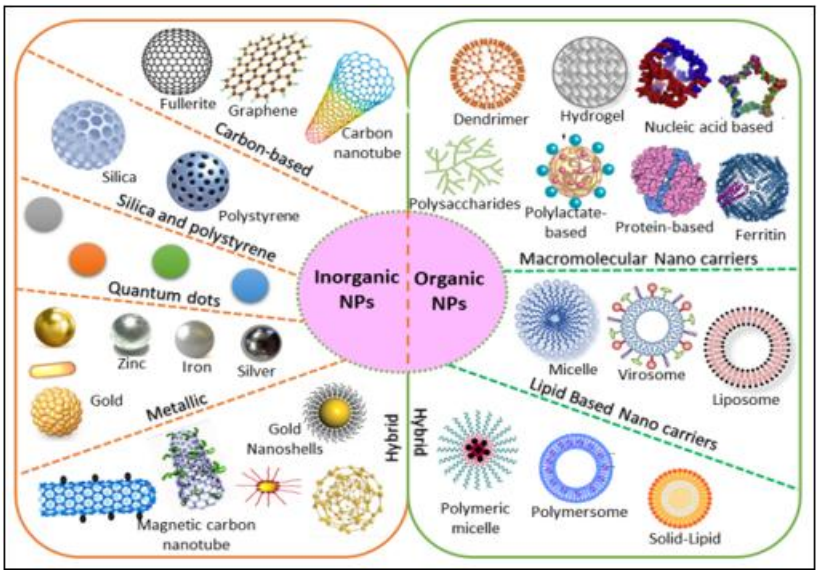


Figure 7: Representation of different engineered nano-particles used in breast cancer therapy (adopted from ref. Ganesan et al [10])

Challenges in post-surgical care for breast cancer involves ensuring effective pain management, reducing inflammation, preventing infections, and facilitating tissue healing. Effective drug delivery is crucial for managing these post-surgical effects. Various nano- particles including liposomes, dendriomers, polymeric nanoparticles, metallic nanoparticles, solid lipid nanoparticles and calcium phosphate nanoclusters have unique properties that can be applicable for promoting tissue regeneration, preventing infections and improving implant integration in post-orthodontic cares [15-17].

Green Synthesis Nanoparticles

Figure 7 shows different types of nanoparticles are used in the treatment of breast cancer. These nanoparticles can be synthesized from many different methods such as (i) electro-chemical, (ii) micro-emulsion, (iii) cell membrane, (iv) sublimation, (v) sedimentation, (vi) liquid phase, (vii) chemical precipitation methods [18,19]. But all these methods are expensive, environmentally unfriendly. On the other side, as an alternate, green synthesis method of using plant extracts becoming popular for biosynthesis of nanoparticles. Because this green synthesis method is an easy, cheap, and environmentally friendly [20]. Not only that, used plants are easily available in our surroundings and these are capable to transform inorganic, metals into metal nanoparticles through the reductive capacities of the metabolites (such as terpenoids, alkaloids, polythenol, tournins, etc). Nanoparticles with sizes ranging (10 – 100) nm show immense promising potential for the treatment of breast cancers [21,22]. In addition due to their minute size these particles possess a unique physical and chemical properties that can be easily modified. This means that using these nanoparticles as carrier of therapeutic drugs directly to cancer cell offers minimum harm to healthy cells [23].

Historical Background

In ancient cultures of India, China, the Mediterrarean and North Africa garlic consumption has been associated with medicinal properties which is capable to reduce the risk of carcinogenesis in breast cancer as well as other cancers like pancreatic cancer and esophageal cancer [24,25]. Garlic

contains S-allyl cysteine, diallyl disulfide and other compounds that are effective as anticancer in cellular models [26,27], particularly in the inhibition of cell proliferation, changes in enzyme activity, and immune regulation [28,29]. The significance of active ingredients in garlic oil (i.e. mainly a family of organosulfur molecules which have potential of selectively increase redox stress in cancer cells leading to apoptosis and death [30].

Garlic intake and Green Nano-particle extraction

Garlic have long been classified as a vegetable and used both for cooking and medicine. As a root vegetable garlic contains allicin, i.e. a protecting sulfur compound that inhibits cancer progression. Even, eating garlic frequently lowers the risk of colorectal cancer as well as reduces other cancers. Garlic contains many sulfides, including one of which is alliin, but when garlic bulbs are crashed then alliin is converted to another compound allicin. This allicin seems to be one of the main active compounds that gives (i) odor, (ii) anti-oxidant, (iii) health benefits.

Intake of Raw Garlic with other vegetables

Garlic (Allium Sativum L.) is endowed with various pharmacological attributed such as antimicrobial, antitumor, hypoglycemic and hypolipidemic anticancer activities. The consumption of garlic provides strong protection against cancer risk, absence of considerable toxicity, and active metabolites are probably play crucial roles in the killing of cancerous cells. Even garlic contains several bioactive molecules with anti-cancerous actions which include diallyltrisulfide, allicin, diallyldisulfide, and allylmercaptan [31].

Investigational / Observational Findings

Investigation- 1

In a case study of 314 women with aged (30 – 79) yrs with breast cancer and 346 women control in the form of sofrito in Puerto Rico Gauri Desai et al [32] attempted to find a correlation between intake of garlic, onion with daily food and breast cancer. Their observed results indicated that

a) for moderate intake / consumption of garlic and onion shows inverse association with breast cancer;
b) for high consumption of garlic and onion indicates protective against breast cancer compared to low consumptions of garlic and onion.

This means consuming high amounts of onion and garlic may have a protective effect against breast cancer, i.e. the association of onion and garlic consumption with breast cancer has been inconsistent (adjusted odds ratio (OR) were observed as 0.51, 0.49, and 0.47 with 95% confident level for low, medium and high intake, respectively). Although women with breast cancer were slightly older than controls at 58.7 yrs vs 54.1 yrs and women have fewer children.

Their conclusion was- "***our study provides evidence that the consumption of onion and garlic is associated with reduced risk of breast cancer***" with the need of further prospective studies and clinical trials in order to understand the real scenario of the use of onion and garlic in breast cancer prevention.

Investigation -2

As the breast cancer is a highly heterogeneous disease, it exhibits both in morphology, prognosis, and response to therapy. Based on both histopathelogical and molecular characteristics breast cancer primarily be classified under expression levels as "estrogen receptor (ER)", "progesterone receptor (PR), and human epidermal growth factor receptor2 (HER2) while subgroups are typically referred to as triple negative up to 10% associated with "ER+" and "HER2+". Thus, triple negative breast cancer (TNBC) again subdivided into various molecular subtypes showing different level of gene and protein expression with various metabolic and epigenomic profiles which are still not yet clear.

In order to search the role of garlic on the features of breast cancer cells, in particular the breast cancer derived MCF7 and MDA-MB 231 cell lines Brugnoli et al [33] studied heterogeneity associated variable effects of he anti-tumoral activity of garlic extract in breast cancer cells with the established triple negative breast cancer (TNBC) cell lines (taken from patient derived Xenografts (PDXs) and found a revealing subtype-dependent effects on (i) morphology, (ii) cell cycle, and (iii) invasive potentials which are correlated with the peculiar "***down modulation***" of Akt signaling, a crucial regulator in solid tumor. It means that although this observational results first demonstrate that the effect of garlic on TNBC breast cancer are not unique but hints the gaining of more precise knowledge of the mechanism activated by the natural compound (i.e. garlic extract) in each tumor is possible.

Investigation-3

Garlic, having numerous sulfur-containing compound and other bioactive constituents, shows promising potential of anticancer. In a long-period (between 1991 and 2004) conducted a series of case control study in the north-east of France (Lorraine) Chllier et al [34] observed the facts:

a) for each case, one specific control was matched for age (+/- 3 yrs) and the socio-economic status.
b) For the 6-day food diary accounting total caloric intake and established risk factors, the breast cancer risk was decreased when the consumption of fibre (p-value for trend = 0.03), and garlic and onions (p value for trend <10 (-6)) increased.
c) Intake of unsaturated fat could lower the risk of breast cancer in the same group (p value for trend = 0.03)

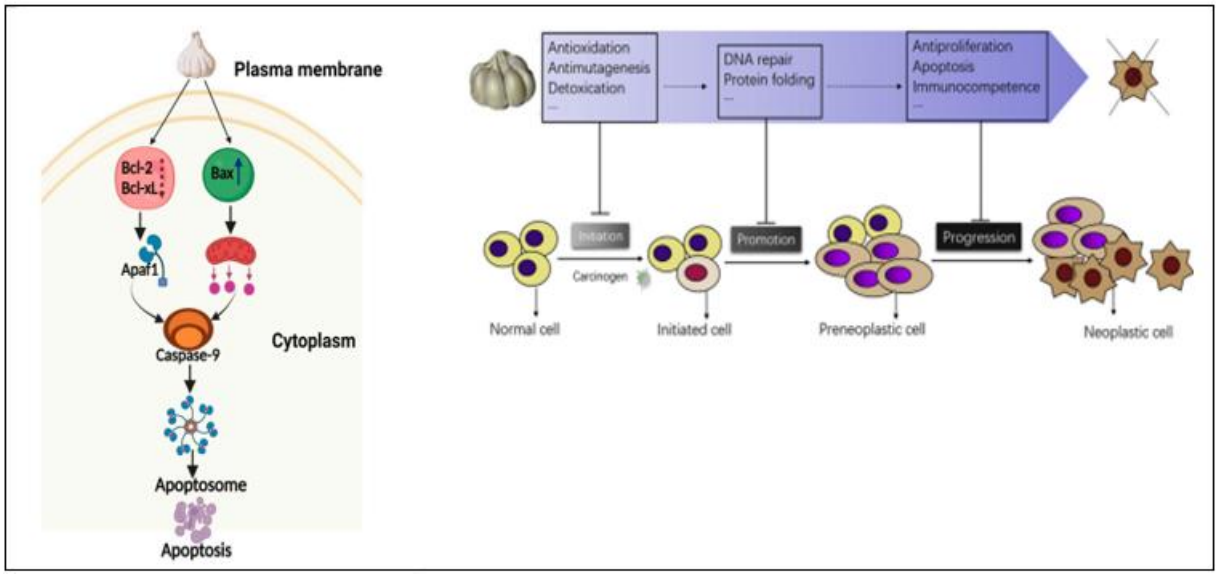


Figure 8: (Left) shows the possible pathway as proposed by Panday etal 2023 [34] for garlic (having sulfogenic components) that induces apoptosis in the breast cancer (for details see the text of same ref [35]). (**Right)** representation of the different stages of cancer progression and the corresponding anti-carcinogenic effect of garlic bioactive compound. Note that at initial stage blocking phytochemicals prevents the bioactivation of carcigens through antioxidation, then antimutagenesis and detoxication. (adopted from Zhang et al. 2020[36] and for details see the same ref. [36])

2. Conclusion

Breast cancer remains the most prevalent cancer among women worldwide, turns into a formidable global health challenge and ultimately driving an urgent need for innovative approaches to (a) diagnosis, and (b) treatment. Nanoparticles play a pivotal role in breast cancer management through advanced approaches which included targeted therapy, imaging and personalized medicine.

In ancient time (more than 5000 years ago) people had used natural remedies extensively to cure human illness and at present, research is going on towards the ancient methods for understanding how that can be applicable in modern time breast cancer treatment. Early diagnosis or surgical removal of tumor offers a best hope to the breast cancer patients. Intake of raw garlic as well as its extracted derivatives are found to be highly effective in suppressing the growth of breast cancer cells (see figure 8). The real mechanism, associated with the garlic, behind the growth suppression includes various processes such as activation of metabolizing enzymes inhibition of reactive oxygen species (ROS) generation, DNA adduct formation, control of cell cycles, and apoptosis induction, etc. Organosulfur compounds of garlic exhibit their capacities (i) to encourage cell death, (ii) prevent breast cancer formation and slow the growth of cancerous cells. Clinical trials show its effectiveness against the MCF-7 cell lines i.e. depending on concentration of garlic extract MCF-7 cell variation reduces. For example, 5 gm of crushed garlic (raw) enhanced the expression of several gene like proto-oncogene- juno, the aryl hydrocarbon receptor, nuclear translocator, etc.

In a clinical test it has been found that garlic components are multifaceted and comprise activation of genes associated with immunity. Not only that, garlic supplements were reported beneficial for (benign) breast cancer patients.

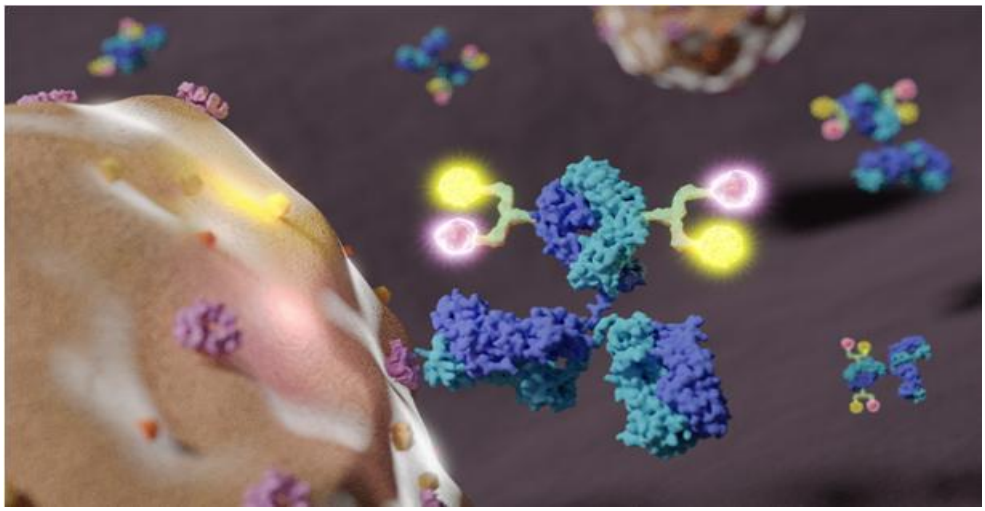


Figure 9: Schematic diagram showing how antibody-drug conjugates (marked by bright yellow-violet colour) are effective in fighting breast cancer as suggested by Yamazaki et al 2021 [37] (adopted from ref. [38])

Recently Yamazaki et al proposed a new technique, so called antibody-drug conjugate (ADC), for the breast cancer treatment. In this treatment both antibody and drug applied into the tumor cells so that a struggle begins heterogeneously among the tumor cell populations and that kills the cancer cells more effectively as evidence indicated by low levels of HER2.

This proposed treatment has a similarity with the treatment of combined intake of raw garlic, onion with other vegetables. In this case, garlic and onion provides the allicin as a protecting sulfur compounds for inhibiting cancer progression while other such as fibre (used as mentioned in investigation-3) provides antibody whose confirmation requires further clinical tests and laboratory studies. It is to be noted that although vegetables do not directly contain human antibodies, but they are crucial for providing the nutrients (vitamins, minerals, and antioxidants) needed for the body to produce antibodies and maintain a strong immune system. In this context, fibre plays an important role as offering antibody that is essential for maintaining a healthy gut microbiome, as well as strongly linking to immune system regulation.

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Conflict of Interest
The author do not have any conflict of interest.

Data Availability
Data sharing is not applicable as no data sets were analyzed.

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