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Anacardium Occidentale-Derived Nanoparticles as a Biocompatible Targeted Therapy for Breast Cancer Cells

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Abstract:- Breast cancer is a global health burden and therefore necessitates a continued exploration for new therapeutic mediators. In current scenario, nanotechnology has developed an interest in the application of nanoparticles in treating cancer. The need for new therapeutic agents against one of the global health burdens, breast cancer, is continuous. Nanoparticle application using nanotechnology for cancers has received increased interest in recent years. This review critically analyzes the bioactive compounds of *Anacardium occidentale*, commonly known as cashew, and their synthesized nanoparticles in relation to activities on cell lines responsible for breast cancer. These facts describe the phytochemical make-up of *Anacardium occidentale*'s, approaches for nanoparticles synthesis, and their modes of action with respect to tumor cells; and implications for the elaboration of future approaches to the treatment of cancer.

Keywords:- *Phytochemicals. Anacardium Occidentale, Nanoparticles, Breast Cancer Cell Line.*

I. INTRODUCTION

Presently, breast cancer is one of the important and serious forms of cancers affecting millions of people in the world and has been regarded as a key challenge in the field of public health internationally. Though there are recent advances in diagnostic techniques and treatment modalities such as chemotherapy, radiation, surgery and targeted therapies, the morbidity as well as mortality rates associated with breast cancer remain alarmingly high.

The limitations of conventional treatments—such as drug resistance, nonspecific toxicity, and adverse side effects—have sparked the ongoing search for novel, more effective therapeutic strategies.

The phytochemicals obtained from natural sources and herbs have become increasingly popular nowadays, due to their bioactive potency, comprising anticancer, anti-inflammatory, and anti-oxidative influences. The herbs and the patterns of their utilization work in multi-directional ways, which are depicted in Fig. 1 [1].

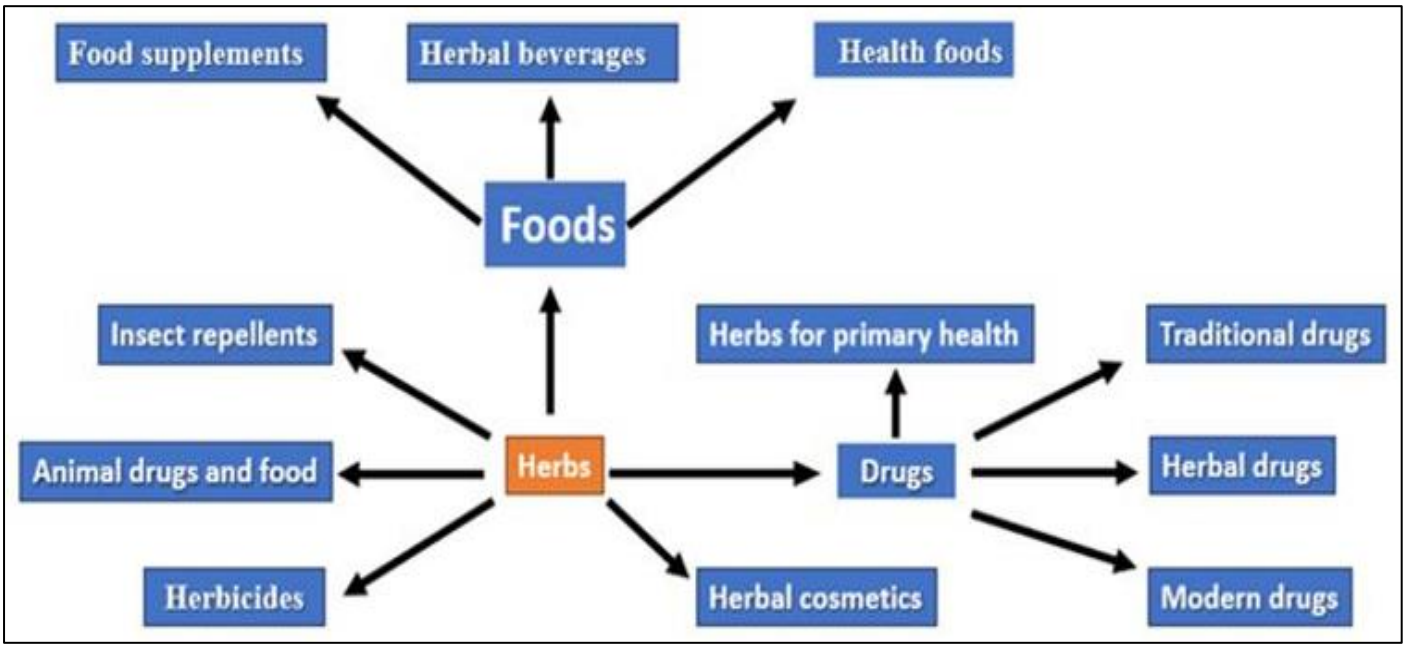

Fig 1 Pattern of Herbal Utilization

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Anacardium occidentale, commonly referred to as the cashew tree, has been reported to possess several medicinal properties. Historically used in traditional medicine, extracts from various parts of *A. occidentale* exhibit promising pharmacological activities, including antitumor effects. Recent studies suggest that bioactive compounds from *A. occidentale* can check malignancy or cell proliferation, induce programme cell death (apoptosis), and regulate key molecular routes associated with metastasis and tumor development, particularly cutting-edge breast cancer cells.

Nanotechnology has revolutionized cancer treatment by offering novel methods for drug delivery, enhancing the bioavailability, stability, and targeted delivery of therapeutic agents. The application of nanoparticles to deliver phytochemicals, such as those derived from *A. occidentale*, represents a promising frontier in breast cancer therapy.

Nano-formulated compounds can improve drug solubility, enhance permeability, and provide controlled release at tumor locations, thus increasing curative efficacy while curtailing side effects.

This review aims to deliver a all-inclusive overview of the anticancer potential of *Anacardium occidentale*, with a particular focus on its nano-formulated applications in breast cancer treatment. We will explore the phytochemical profile of *A. occidentale*, its mechanisms of action against breast cancer, and the emerging role of nanotechnology in optimizing its therapeutic effects. By synthesizing the current evidence, this review seeks to highlight the potential of nano-formulated *A. occidentale* as a novel, targeted method in the combat against breast cancer, offering insights into future research directions and clinical applications.

➢ *Plant Profile of Anacardium Occidentale Linn.*

Anacardium occidentale, accredited as the cashew tree, is a affiliate of the family Anacardiaceae with evergreen characteristics. The plant has been cherished for its various phytochemicals, which give benefits to health: antioxidant, anti-inflammatory, and anticancer effects. This evergreen usually measures 10-12 meters in stature with a trunk diameter of up to 30 cm, bearing waxy leaves, dark green in color, reaching up to 25 cm in length. Flowers are white or pink in cluster forms, and flowering starts after 3 to 5 years. The root system is extensive, with the taproot being very conspicuous. Quite importantly, the cashew tree bears cashew apples, i.e., fleshy, pear-shaped fruits, and underneath grows a kidney-shaped nut (Fig. 2) containing gum like resin containing toxic acid (Anacardic Acid) until processed [2].

Fig 2 Schematic Diagram of Anacardium Occidentale Plant with (A) Flower and Matured Fruits, (B) Green Leaves.

➢ *Taxonomy.*

Being from the family Anacardiaceae, which includes mango and poison ivy, *Anacardium occidentale* was named by Carl Linnaeus in 1753-a naming priority that underlines its wide use and ecological relevance [3]. The hierarchy in classification is as follows: The taxonomic hierarchy is as follows:

- Species: *Anacardium occidentale*
- Family: Anacardiaceae
- Kingdom: Plantae
- Genus: Anacardium
- Order: Sapindales

➢ *Phytochemistry of Anacardium Occidentale.*

Recent research underscores the health benefits of phytochemicals from parts of *Anacardium occidentale*, particularly phenolic compounds, which help prevent infectious and degenerative diseases, inflammation, and allergies. These compounds, categorized into phenolic acids, flavonoids, stilbenes, and tannins, act as antioxidants and

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metal ion chelators, combating free radicals and preventing lipid oxidation [4].

- *Cashew Leaves:*

Leaves have high rich in alkaloids (39.90%) [specifically flavonoids (15.38 mg/g), tannins (2.00 mg/g and saponins], with excellent anti-oxidant and anti-inflammatory activities [4]. They also help to lower cholesterol levels and are traditionally used in managing diabetes and hypertension [5].

- *Cashew Bark:*

Bark has a high content of tannins which exhibits antimicrobial action [5]. Traditionally used for astringent properties and treatment of ulcers, against bacteria such as *Staphylococcus aureus* and *Escherichia coli* [4].

- *Cashew Nuts:*

It has high nutrient value with monounsaturated fats (41.66–44.70%) [beneficial for heart health], protein (21 - 23%), and essential vitamins and minerals (iron, zinc, B12, B8, K1) [5]. Bioactive compounds like phenol (107 mg/100 g) and flavonoids (63.7 mg/100 g) act as antioxidant and anti-inflammatory agents [6] as well as high proportions of other antioxidants like vitamin E and phytochemicals, therefore accounting for anti-inflammatory activity [4].

- *Cashew Apples:*

Bioactive molecules like vitamin C and antioxidants, which contribute to immunity and may be anti-cancerous. Traditionally consumed as juice and management of gastrointestinal problems [4].

- *Overall Therapeutic Effects:*

Cashew leaves, barks, and nuts exhibited a number of bioactive activities, which include anti-diabetic, anti-inflammatory, and antioxidant activities [5]. Some extracts exhibited action against bacteria resistant to conventional antibiotics, thus further establishing the plant's pharmaceutical usefulness [4].

➢ *Medicinal Properties of Anacardium Occidentale.*

Anacardium occidentale medicinally, is one of the most beneficial plants due to its bioactive principles present in the leaves, which include phenolic acids, flavonoids, and tannins exhibiting striking antioxidant, antibacterial, and anti-inflammatory activity, adding to analgesic properties. Cashew extracts have been reported to inhibit some enzymes like cyclooxygenase, taking part in pain-inducing prostaglandin synthesis. It also impacts inflammatory routes like NF-κB and MAPK, inhibiting pain as well as inflammation. In animal models too, cashew extracts have supported evidence of helping in reducing inflammation and pain-related behaviors [6].

The plant also possesses very potent antimicrobial action, considering its rich composition of active principles like anacardic acid. Anacardic acid is particularly powerful against many noxious microorganisms, including bacteria like Staphylococcus aureus and Escherichia coli. Cashew extracts have also been shown to affect fungi such as Candida albicans and thus are useful in the treatment of infections. [7, 8].

Regarding the antimycotic activity, *Anacardium occidentale* has been found quite potent against a wide range of fungi, causing diseases in plants and humans. Cashew nutshell liquid or CNSL contains a great amount of phenolic compounds such as cardanol and Anacardic acid, exhibiting high efficacy in antifungal activity. Cashew extracts have been studied to prevent fungi like Fusarium solani and Aspergillus niger. The mode of antifungal action by this plant includes disruption of fungal cell walls, causing dehydration and subsequent collapse of the fungal cells. Overall, cashew extracts are known for their wide medicinal applications, especially within traditional medicine [9, 10].

- *Wound Healing Activity:*

Tannins, flavonoids, and saponins present in the leaves of *Anacardium occidentale* (cashew tree) provide wound-healing properties and can accelerate the rate of tissue repair by anti-inflammatory and anti-oxidant properties. Recently, a herbal ointment was made using ethanolic cashew leaf extract and tested on animals; it indeed proved promising. In fact, the extract enhanced collagen synthesis and angiogenesis, thus promoting wound healing. An excised wound model, for example, reduced the time required for healing to 13 days compared with 20 days for an untreated wound. In other incised wounds, higher tensile strength indicative of better collagen formation and integrity of the wounds treated with the herbal ointment was produced [11, 12].

- *Anti-Diarrhoeal Activity:*

Anti-diarrheal activities are exhibited by the various tannins, flavonoids, and Anacardic acids expressed from secondary metabolites of *Anacardium occidentale*. Thus, antimicrobial and anti-inflammatory activities of secondary metabolites provide anti-diarrheal agents for the management of diarrhoea and reduce gastrointestinal irritation. Cashew leaf and stem bark extracts have been mentioned to delay gastrointestinal motility as well as to inhibit muscarinic receptors, contributing to lessening the symptoms of diarrhoea. In the studies, the ethyl acetate fraction from cashew stem bark was especially effective in reducing the severity of induced diarrhoea in animal models. The astringent effect of tannins present in the extracts helps reduce intestinal secretions and increase water absorption, hence offering therapeutic benefits for diarrhoea, especially of bacterial origin [13].

- *Anti-Pyretic Activity:*

Traditionally, *Anacardium occidentale* was prescribed for reducing fever, especially in tropical areas. The active principles of the plant, like Flavonoids, Tannins, and Anacardic acid have anti-inflammatory properties to reduce fever. Experimental studies reveal cashew tree extracts diminish fever in animal models by inhibiting pro-inflammatory cytokines responsible for raising the body temperature during the feverish state of the animal body [4, 14].

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- *Anti-Ophidian Activity:*

The bark extract of this tree acts most effectively by inhibiting the toxic enzymes that are essential for phospholipase, protease, and hyaluronidase, which are responsible for the local tissue damage, inflammation, and bleeding disorders induced in the victim's body as a result of venom of a snake. Studies have shown that the bark extract is able to neutralize such venom-induced effects through the inhibition of these enzymes, which interact with the venom components in a way like to mimic mitigation of their toxic effects on the body. The efficacy of venom neutralization was dose-dependent; therefore, the higher the concentration, the better the neutralization. Phytochemicals present in the bark are terpenoids, flavonoids, and saponins, which can interact with the venom proteins, inhibit their deleterious effects, and hence could be an alternative treatment to conventional antivenoms. Besides anti-venom properties, *Anacardium occidentale* also possesses potent cytotoxic activity, or, more specifically, anti-cancer. Studies have reported that isolated compounds from leaves and bark have activities against certain cancer cells, particularly HL-60 and HCT-116 cell lines, with lower normal cell toxicity. This occurs through the stimulation of oxidative stress and apoptosis by generating reactive oxygen species in cancerous cells. Among these, one compound, pentagalloylglucose, showed selective toxicity against the HeLa cancer cells without affecting normal cells and emerged as a potent candidate for natural chemotherapeutic agents [15, 16].

- *Anthelmintic Activity:*

The antiparasitic activity of *Anacardium occidentale* against intestinal parasites has been studied by many authors. A high order of activity against parasites such as Ascaris and Trichuris has been detected from the extracts obtained from its nuts and shells. Bhaduri and Sanyal (1952), in one of the early studies, showed that cashew nutshell oil brought about reduction in egg count of parasites in infected patients [17]. Recent in vitro studies confirmed the effectiveness of different cashew extracts, such as ether extracts, which were potent against parasites like Hymenolepis nana, while hydroalcoholic extracts inhibited the egg hatching of Haemonchus contortus. Two key compounds, cardol diene and 2-methylcardol diene, isolated from cashew's ethanolic extract, killed Schistosoma mansoni parasites at certain concentrations [18, 19]. These phytochemicals of the plant are saponins and tannins, which act by disrupting cellular functions of the parasites, resulting in paralysis of the parasites and ultimately their death. Cashew extracts were found to be lowly toxic, hence safe for the treatment of helminthic infections [17].

- *Antidiabetic Activity:*

Cashew also has a lot of potential in controlling of diabetes due to its activity in respect of blood sugar management. Ethanolic extracts from leaves and bark have been reported to reveal excellent anti-hyperglycemic activities in diabetic models. For example, methanolic extracts reduced blood glucose in diabetic rats and even simulated the regeneration of pancreatic beta cells responsible for insulin secretion. Cashew exerts hypoglycemic effects through its bioactive compounds, which are saponins, flavonoids, and tannins, increasing insulin secretion and enhancing glucose metabolism [20]. In comparative studies, cashew extracts derived from leaves, nuts, and bark-assisted in lowering blood glucose levels; among them, nuts extract proved to be the most active. The treatment also improved pancreatic histology by preservation of the insulin-producing cells. These results point towards cashew as a potential herbal remedy for diabetes with minimum toxicity at therapeutic doses [21].

II. BREAST CANCER

Global and Indian Context Nowadays, it is considered to be one of the most prevalent health hazards globally, and breast cancer may be expected to afflict one in eight women over the course of their lives. It accounts for 25% of all cancers in females and was the second most commonly diagnosed cancer worldwide in 2022, with an estimated 2.3 million cases [22]. It has been one of the leading causes of mortality among cancers at different sites in developing countries. In India, also, the incidence rates of breast cancer have gone up; it has now become the most common cancer in women, with an estimated 103,819 cases reported over 2022–23 years [23]. The incidence of breast cancer in India also follows the trend observed in many parts of the world. The need for early detection, awareness, and better treatments is being pursued aggressively. New cases of cancer were 1.39 million in the year 2020, with about 40% comprised of breast and cervical cancers among females. The mortalities from breast cancer are very high in the country (98,337 deaths in 2022 among the registered cases) [24]. Advances in the treatment and screening have considerably reduced mortality rates in countries such as the US; much more is yet to be done to control this malady [25, 26].

➢ *Key Points about Breast Cancer:*

- **Types:** The disease most commonly originates in one of two types of breast tissues, ductal carcinoma, starting within the milk ducts, and lobular carcinoma, within the lobules. Other forms include Paget's disease (nipple and areola with red, scaly rash) as well as inflammatory breast cancer (orange peel skin with redness, swelling & enlargement and pain).
- **Risk Factors:** The important risk factors are females; increasing age above 40 years, family history, genetic mutations such as BRCA1 and BRCA2 genes, obesity, and other lifestyle habits including consumption of alcohol and lack of exercise. [27].
- **Symptoms:** The most frequent symptoms include dimpling or redness of skin with uncommon nipple discharge, a lump or bulge in the breast and changes in the shape or size of the breast [27].
- **Diagnosis:** The age factor for survival is greatly improved with an early diagnosis. Techniques of diagnosis include mammography, ultrasound, and biopsy according to [28].

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- **Management:** Primarily is based on nature of cancer, phase or stage of the cancer, and the entire health status of the patient. These include surgical intervention that may be in the form of either a lumpectomy or mastectomy with or without radiation and chemotherapy, hormone therapy, and biologic therapies with target specific delivery [26, 27].

➢ *Effects of Anacardium Occidentale on Breast Cancer.*

Most studies conducted with *A. occidentale* in the context of breast cancer remain at a preclinical stage and have demonstrated good cytotoxic activity against the disease by reducing tumor size in vitro and in vivo studies, respectively [29]. *Anacardium occidentale* is one of , 71 plant species included in the National List of Medicinal Plants of Interest to the Unified Health System developed by the Brazilian Government in 2009 [30]. Phytochemical studies on *A. occidentale* species have shown the presence of eleven classes of different bioactive components, although Anacardic acid (AA), Cardanol and Tannins are primarily responsible for the pharmacological actions of the plant. Effective anti-inflammatory activity has also been attributed to these through popular use and based on data from the literature [31, 32, 33, 34]. AA alone constitutes about 90% of the cashew nutshell liquid (CNSL), and the remaining part is constituted by AA-related compounds such as cardanol, cardol and 2-methyl cardol [33]. Cashew nutshell liquid contains phenolic lipids (anacardic, cardanol, cardol, and 2-methyl-cardol), of which Anacardic acid (AA) accounts for about 76.93% [35]. Anacardic acid (AA) is a yellow liquid partially miscible in alcohol and ether but nearly immiscible in water. Chemically, AA has a high anti-proliferation effect on MCF-10A, MCF-7, MDA-MB-231 breast cancer cells [33], which is a mixture of several closely related organic compounds each consisting of a salicylic acid substituted with saturated or unsaturated alkyl chain that has 15–17 carbon with chemical class of Pentadecane aliphatic chain containing Hydroxyl carboxyl acid [34]. On the other hand, cardanol and cardol are the phenolic components that are less effective in all sorts of biological activity exhibited by AA.

AA linked to anti-inflammatory, anti-oxidative, anti-microbial and anti-carcinogenic activities [36, 56]. It exhibits moderate cytotoxic activity on breast cell lines [37]. Moreover, treatment of different human cancer cell lines with Anacardic acid increases their sensitivity to ionising radiation [38]. Several mechanisms of action have been proposed for the anti-carcinogenic (specifically breast cancer) properties of this compound. It inhibits the histone acetyltransferase enzymes (HATs), inducing chromatin compaction and transcriptional activity reduction [38, 39, 40] and also modulates the nuclear factor-κB (NFKB), pathway which is involved in tumorigenesis, inflammation and radio sensitization processes [37].

➢ *Studies of AA or Anacardic Acid (Anacardium Occidentale L.) Role on Breast Cancer:*

- According Sung et al., 2008 [37], it was hypothesized that Anacardic acid or 6-nonadecylic salicylic acid may interfere with NF-κB activation associated with the promotion of apoptosis in cancer cells. It has been associated with several biological activities, which include anti cancer effects, anti-inflammation, and radio sensitization effects.
- More often, breast cancer depends upon estrogen signaling through Erα. Anacardic acid (AA) has been observed to be able to impede the growth of ERα-positive human breast cancer cells such as MCF-7 with less or little effect on ERα-negative cells. The active principle in the nut (Cashew) reduce the spread of ERα-positive breast cancer cells (human) significantly, viz. LCC9, MCF-7, and LY2 more effectively than the ERα-negative cells like MDA-MB-231 as well as MCF-10A, and the IC_{50} values for AA were notably lower in ERα-positive cells, suggesting these cells were more sensitive to Anacardic acid [41].
- Anti-metastatic efficacy of Anacardic acid or AA, especially in MCF-7 cell line of the breast cancer found as a strong inhibitor of EMT or epithelial to mesenchymal transition. AA significantly inhibits the proliferation of MCF-7 cells stimulated by vascular endothelial growth factor (VEGF) with targeted suppression of angiogenesis targeting growth factor (blood vessels endothelium) signaling routes, particularly in the influence of cells over-expressing gene [42].
- AA is known to impede the growth of breast cancer cells and depolarize OXPHOS or mitochondrial oxidative phosphorylation. Several cell lines of breast cancer were studied: MCF-7, sensitive to the endocrine; LCC9, LY2-resistant to the endocrine; and MDA-MB-231, triple-negative. These findings highlight the fact that Anacardic acid acts as a mitochondrially targeting antitumor agent against breast cancer in particular [43].
- Anti-cancer potential of Anacardic acid against MDA-MB-231, the model cell line of TNBC, emphasizes the stimulation of cell cycle arrest, supression of cell count and growth, , stoppage of invasion and migration, and induction of apoptosis by AA. These anticancer effects of AA are attributed to the regulation of heat shock protein 90 (Hsp90) and ERS-related molecules. TNBC is considered to comprise 10-15% of all cases of breast cancer, characterized by aggressive behaviour that conveys a bad prognosis. Hsp90 is a molecular chaperone that stabilizes many oncoproteins and is overexpressed in a number of cancers, including TNBC. Anacardic Acid [AA] was previously identified to have potent inhibition activity of the Hsp 90 ATPase. In this study, it is pointed out that AA inhibits (at an IC_{50} of 19.7 μM) the proliferation of MDA-MB-231 cells line [44].
- It was observed with a focus on estrogen receptor α-positive MCF-7 (luminal A) cells, triple-negative breast cancer or TNBC/basal B or MDA-MB-231 cells, MDA-MB-468, HCC1806, BT-20 cells, and all basal TNBC/A integrated metabolomics and transcriptomics analyses are used to elucidate the way through which AA, inhibit cancer cell growth and cancer cell viability without influencing primary breast epithelial cells as well as

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significantly inhibits the viability of all tested breast cancer cell lines [45].

- Another study examined that, cashew extracts have a potent cytotoxic effect against breast cancer cells (MCF7) by primarily inducing cell cycle check at G2/M phase followed by pre G1 apoptosis initiation as established by a significant intensification of apoptotic cells [46].

➢ *Studies of Cardanol (Anacardium Occidentale) on Breast Cancer:*

Another bioactive constituent of cashew nutshell oil is cardanol, which has been explored against some cancer cell lines (including breast cancer) for cytotoxic activity. Cashew nutshell oil formulations, such as emulsions, were found to significantly inhibit the spread of breast cancer cells (human). Some studies pointed out the effectiveness against MCF-7 cells, one of the most common models in studies of breast cancer [4, 47].

➢ *Mechanisms of Action in Breast Cancer.*

- *By Induction of Apoptosis:*

The compounds extracted from *Anacardium occidentale* have been shown to induce programmed cell death in breast cancer cells. Of critical importance, evasion of apoptosis has emerged as one of the hallmarks of the progression of carcinomas. Anacardic acid plays an significant role in the control of gene products linked with cell multiplication, invasion, survival and inflammation; it thus acts as a potent inhibitor of the NF-κB signaling pathway and may be responsible for its anti-inflammatory as well as anti-cancer features. It potentiates appoptotic pathway and limit tumor cell production and invasion by inhibiting IKK activation, preventing IκBα degradation, and down-regulating NF-κB regulated gene products [47].

Various studies have shown that some caspase enzymes, vital in the apoptotic process, could be activated by anacardic acids. A research carried out by Zhao et al. (2018), showed that dose dependent treatment with Anacardic acid enhanced the apoptotic markers in human MCF-7 (*in vitro*), due to its possible use as a chemotherapy agent. AA controls key molecules linked to Hsp90 and ERS, which are - Heat shock protein 70 (Hsp70), Cyclin-dependent kinase 4 (CDK-4), GRP78 or glucose-regulated protein 78, , B-cell leukemia/lymphoma 2 protein (Bcl-2), Matrix metallopeptidase 9 (MMP-9) and Induced myeloid leukemia cell differentiation protein (Mcl-1). The compound inhibits cell invasion and migration through down-regulation of MMP-9 and vimentin with increased expression of E-cadherin [44]. Wu et al. (1997) reported that the increased populations of apoptotic cells were significantly higher as compared to the necrotic cells where the late apoptosis events surpassed the early ones. This pro-apoptotic potential is brought about by the TPCs and TFC present in these extracts, which are known to induce apoptosis and inhibit DNA replication (48). Gene expression analysis indicated that the treated cancer cell lines down-regulated CDK4 and up-regulated the CDKN2A gene. It infers that the phenolic and flavonoid contents causes cell cycle inhibition which has been regarded as one of the most influential effect to end cancerous cells by cell cycle arrest (at G1 phase) through activation of cyclin dependent kinase inhibitors. It is well documented that passage through the cell cycle completes the cellular growth and proliferation of mammalian cells. Besides, [49].

- *By Inhibition of Cell Proliferation:*

Cell proliferation associated with tumor growth, which is one of the most important hallmark in cancer study. In fact, extracts from *Anacardium occidentale* have been reported to exert inhibitory effects on the proliferative spread of breast cancer cells. This action might be due to anacardic acid modulated signaling pathways which effects in proliferation and life span of cancer cell, such as the mTOR/PI3K/Akt pathway. Reguengo et al. (2022) demonstrated that extracts of *Anacardium occidentale* reduced the viability of breast cancer cells through modulatory supression of these pathways, which also indicating antiproliferative potency [50].

Indeed, Anacardic acid or AA is a potent inhibitor of the activities of histone acetyltransferase enzymes. Though it directly has no effect on DNA transcription, as an potent modulator and inhibitor of p300 and p300/CBP-associated factor (PCAF) (39), it powerfully inhibits HAT- induced transcription (chromatin templates).

By inhibiting ERα-DNA binding and consequently reducing the transcription of target genes, Anacardic acid induces cell cycle arrest (at G1 phase) and endorses proapoptotic routes in ERα-positive cells without affecting the stability of ERα protein levels. Computational molecular docking studies designated that AA interrelates with the DNA binding domain of ERα, suggesting a direct mechanism of action interfering with the ability of ERα to bind to DNA [41].

Anacardic acid (AA) triggers the modulatory expression of the epithelial marker (E-cadherin) and suppresses mesenchymal markers Twist and Snail. It also suppresses VEGF-induced signaling pathways by inhibitory modulation of the phosphorylation process of the MAP kinases ERK and JNK as well as through impeding the translocation of Sp1, a transcription factor [42].

In the cell lines, established from the tumors of the breast, AA concentration and cell line-dependently inhibited mitochondrial respiration; it increased basal oxygen consumption rate or OCR in MDA-MB-231 cells, LY2, LCC9, and MCF7. The action of AA was uncoupling in OXPHOS and could be classified as a mitocan. It was noted that in MCF-7 cells, the increase in basal oxygen consumption rate due to increased reserve capacity and proton leak was caused by a concentration-dependent increase in ATP-associated OCR and an surge in proton leak in LCC9 cells. This findings suggest that AA reduces ATP-associated oxygen consumption rate and reserve capability of mitochondria while increasing proton leak and indicating mitochondrial toxicity especially in MCF-7 cells [43].

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Overall, Anacardic acid or AA alone exhibits anti-cancer properties via numerous such pathways, which include:

Metabolic pathways (Glutathione, Alanine, Lipid and Glutamate metabolism), the Gene expression pathway (especially mTORC1 signaling system), the citric acid cycle and pentose phosphate pathway, which are important regulators of cancer cell proliferation and metabolism [45].

Phenolics contained in *Anacardium occidentale* have been reported to exhibit potency against cancer through antioxidant action. They neutralize the free radicals, hence reducing oxidative cell injury. These antioxidative properties also play a part in the protection against DNA mutations and other cellular damage to prevent cancer [51]. Chronic inflammation is also an important factor in the beginning and expansion of cancer, in which breast cancer also included. *Anacardium occidentale* extracts have been found to inhibit numerous inflammatory mediators such as prostaglandins and cytokines-particularly in cashew nuts. These compounds help to inhibit the inflammatory atmosphere that sustains tumor growth, as evidenced by both *in vitro* and *in vivo* models [52].

III. NANOTECHNOLOGY

Nanotechnology is the most advanced area of research in the present scenario. Sustainable, green nanotechnology with green chemistry and biogenic synthesis of different medicinal products are taking more deliberation instead of typical traditional chemical synthesis and procedures. Green Nano-technology and green chemistry, the two different practices of science, are used in combination to generate biologically synthesized metal nanoparticles [53].

Nanomaterials can be described as those materials which have at least one dimension (less than 100 nanometers). Nanomaterials exhibit different physical and chemical properties, including higher strength, lighter weight, higher reactivity, improved electrical conductivity, etc., all of which make many applications very feasible in a wide range of fields. Nanomaterials or nano-particles can be prepared through both chemical and physical techniques, most of which have potential hazards. One of the main challenges in the field of nanotechnology involves the development of environmentally benign synthesizing methods for stable, metal-based nanomaterials with diverse sizes, shapes, and different chemical compositions [54].

Two techniques generally considered as basic methods (Fig. 3), top down and bottom up [55]. Metallic nanoparticles are extensively cast-off in science due to their nano or small size and excellent properties. Researchers focus on creating mono-dispersed nanoparticles for biosensing, bio-labelling, and therapeutics. These nanoparticles have antibacterial, antifungal, and antioxidant properties, improving medicine by combating antibiotic resistance and enhancing targeted drug delivery.

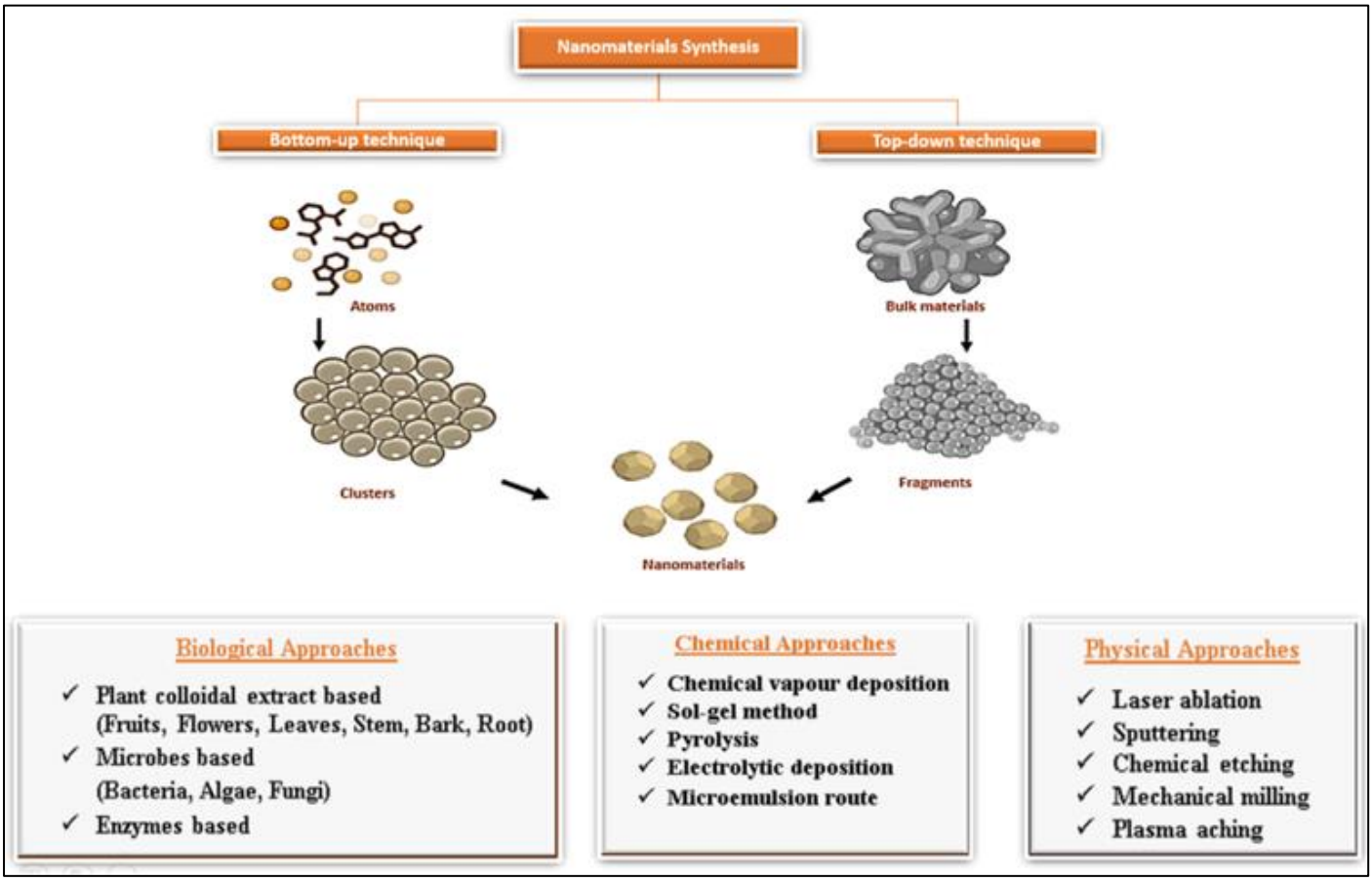

Fig 3 Basic Methods of Nanomaterials Synthesis

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The bioactive compounds (extracted from plant) perform as the top reducing agent for the reduction of metal ions to metal nanoparticles with distinct size, shapes and significant anti-inflammatory, antioxidant and microbial efficacy [56]. Biomolecules, microorganisms, and plant extracts were used for the synthesis of inorganic nanoparticles that further stabilized these nanoparticles and imparted medicinal properties to them.

Reaction conditions are pH and temperature dependent, which affect their size and shape. Noble metallic nanoparticles have applications in non-invasive diagnostics, enhancing medical imaging, and detecting genetic mutations owing to strong light absorption and multi-functionality. Because of encapsulation, the drug molecules are shielded by the nanoparticles from degradation, which in turn enhances the bioavailability of drugs and reduces toxicity due to the effective clearance of the drug.

Cancer is stared as the most frequent reason of death worldwide; in which the most frequent types being those of breast, lung, colon, and rectum. Standard chemotherapy drugs also face some limitations such as poor solubility, nonspecificity, and drug resistance. Targeted delivery is enhanced by nanoparticles, due to the toxic nature of chemotherapy drugs, offering optimal dosage and receptor binding. That's why, biodegradable polymeric nanoparticles have added worth in chemotherapy, while the natural materials like cellulose and chitin provide targeted drug delivery. There are different kinds (Fig. 4) of nanomaterials available for different scientific applications, such as in drug delivery systems [55], including micelles, dendrimers, liposomes, and polymeric nanoparticles etc., which are often made to improve stability and biocompatibility. The latest application example was lipid nanoparticles, which are under research study for mRNA vaccine delivery, including COVID-19 vaccines.

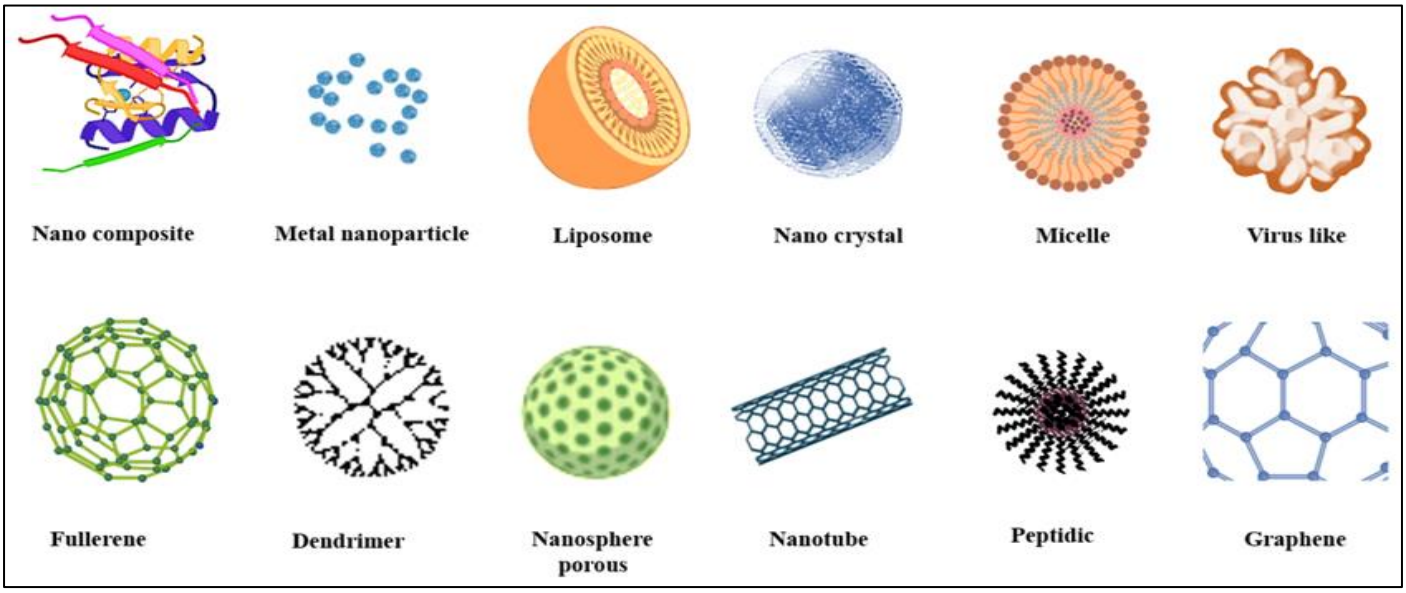

Fig 4 Schematic Diagram of Different types of Nano-Materials or Particles used in Drug Delivery and other Scientific Procedures.

- *Recent Researches on Anacardium Occidentale Nanoparticles and its Activity against Breast Cancer Cells.*

Nanotechnology can assist in the combination therapy that will help treat breast cancer. Doxorubicin is a chemotherapeutic agent that affects the G0/G1 and G2 checkpoints of the tumor cell cycle, which are primarily regulated by the tumor suppressor protein p53, and was reportedly able to reduce cell proliferation via G2/M phase arrest through a decrease in cell viability [57]. Thirumurugan, Blessy and Karthikeyan (2018) investigated the toxicity of different coatings of silver and platinum metal nanoparticles against MCF-7 breast cancer cells and estimated an IC_{50}, which showed that the potency effect is very similar to

Doxorubicin [58]. Huo et al. (2013) proposed that due to the cell-permeable nature, the drug-loaded nanoparticles show enhanced transport of drugs across cell membranes in the case of cancerous cells. Green synthesis of such noble metal nanoparticles by using root, stem , bark or leaf extract from plants as a reducing agent provides an ecofriendly, highly competent technique for their production [59].

Cashew gum is derived from *Anacardium occidentale* and has been pointed out for its huge potential in pharmaceutical dosage form applications. Cashew gum nanoparticles have been found with low polydispersity and tunable average sizes depending on the oil content. As a consequence, the nanoparticles have shown higher encapsulation efficiencies (99.9%); and their payload capacity also amplified with increasing oil content of nanoparticles [60]. Release of oil has followed Korsmeyer-Peppas kinetics model and hence exhibited controlled release properties. Though cashew gum nanoparticles do not present toxicity in distinct cell lines, cashew nutshell oil (CNSL) showed a weak tumor-promoting effect in a murine model [61]. This therefore means that formulation of delivery systems based on *Anacardium occidentale* has to take into consideration components and formulations with due care.

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A current study exhibited that nanoemulsions of cashew nutshell liquid (CNSL) exhibited potent cytotoxicity against MCF-7 (human breast cancer cell line). Treatment of the cells with nanoemulsion led to the loss of viability due to cell death by programmed cell death and/or by necrosis, shown from the typical morphological modifications in both cytoplasmic and nuclear structures of the MCF-7 cells, indicating target-specific killing. IC_{50} after 48 hrs of treatment was 88±14.2 µl/ml [62].

Anacardic acid (AA), Pequi oil and docetaxel (DTX) formulated cutting-edge nanoemulsion amplified antitumor properties while minimizing toxic effects stated by Loureiro, 2021 [60, 70]. On combining PDTX and PAA there is a significant morphological change: increased lysosomal and mitochondrial membrane permeability, G2/M cell cycle arrest, phosphatidylserine exposure. This work underlines the potential of pequi oil nanoemulsions as transporters for docetaxel and anacardic acid, improving their antitumor activities counter to breast cancer cells and especially in the management of triple-negative types of the disease.

According to Sunderam (2019), AuNPs or gold nanoparticles derived from the colloidal extract of leaf of *Anacardium occidentale* exhibited selective cytotoxicity to MCF-7 cancer cells. The results indicated that the viability of green-based AuNPs was 74.47% in Peripheral Blood Mononuclear Cells and 23.56% feasibility or viability in MCF-7 cell lines at a extreme concentration of 100 µg/ml, thus indicating a strong cytotoxic effect on cancer cells in comparision with normal control cells which is probably due to the generation of reactive oxygen species (ROS) by the gold nanoparticles (AuNPs) [63].

The effectiveness of cashew gum nanocomposite CG-CuNPs with an average size of approximately 10 nm was also uncovered by another study, and it showed its strong cytotoxic effect on the mouse mammary tumor (4T1 cell line). Amorim et al. (2019), conducted a cytotoxicity assay on murine macrophages (BALB/c), where the toxicity of CG-CuNPs is lower than that of CuSO4·5H2O. The viability assays explore that a 0.250-mM concentration of CG-CuNPs inhibited the growth of 4T1 LUC mouse mammary tumor cells and murine fibroblast cells NIH 3T3 by 70% over a period of 24 hours [64]. Chan et al. (2023) also demostrated that cashew shoot extract has cytotoxic effect against breast cancer, specifically on MDA-MB-231 cells with IC_{50} of 81.1 µg/ml and less cytotoxic for HT-29 and HepG2 [67].

➢ *Mechanisms of action of Anacardium Occidentale Nanoparticles (AONPs) on Breast Cancer Cells.*

- *By Inhibition of Cell Viability:*

It was observed that, the cytotoxicity potency of AONPs on various kinds of breast cancer cell lines, especially on MDA-MB-231 and MCF-7 highly effective. Treatment of AONPs resulted in a concentration-dependent decrease in the viability of cells and their IC_{50} value was significantly lower compared to the IC_{50} values of standard chemotherapeutic agents. This kind of anti-proliferative effect is considered to originate from the boosted absorbency and retention effect associated with nanoparticles [63, 67, 70].

- *By Induction of Apoptosis:*

The reasons for other different anticancer potentials of AONPs may be explained by its induction of apoptosis in cancerous cells. AONPs were known to cause activation of caspases 3 and 9, indicative of triggering the apoptotic cascade. Moreover, the analysis of expressed proteins indicated decrease in anti-apoptotic protein Bcl-2 and a upregulation of Bax, confirming that AONPs triggered apoptosis through the induction of mitochondrial pathways [68, 70].

- *By Molecular Mechanisms:*

✓ *Cell Cycle Arrest:*

To induce cell cycle arrest led to a significantly higher population of the cell phase in G2/M correlating to reduced expressions of cyclins and CDKs considered as basic regulators of cell cycle progression and which supressed by nanoparticles. It is this arrest that contributes to the inhibition of proliferation of tumor cells [69, 70].

Some studies work purport that, purified cashew nut-shell liquid, containing Cardanol, Anacardic acid and Methylcardol among others, inhibits the proliferation of cells, interferes with mitosis causing abnormalities in spindles, and then induces apoptosis in cancerous cells [65] by antioxidant action of iCNSL. This may further enhance DNA from reactive oxygen species damage and, hence its anti-cancer effect [66].

✓ *Oxidative Stress:*

The generation of reactive oxygen species or ROS is another important mechanism by which AONPs exert their anticancer effect. Studies are of the view that AONPs increase ROS generation significantly, giving rise to oxidative stress and thus favoring the generation of apoptosis. In a comparative study of AONP-treated breast cancer tissues shows increased levels of lipid peroxidation markers, therefore indicating that the death of malignant cells is mediated through oxidative stress [43, 70].

✓ *Inhibition of Metastasis:*

AONPs may also inhibit metastatic functions in breast cancer cells by modulating protein expression associated with the invasion and migration of cells. Treatment with AONPs down-regulated the expression of MMPs or matrix metalloproteinase that are considered crucial for degradation of the extracellular matrix and migration of the tumor cells. It is such a step showing the possible therapeutic role of AONPs in inhibiting metastasis of tumors [43, 70, 71].

✓ *Modulation of Signaling Pathways:*

Many signaling pathways, which are considered major players in the process of tumor development, have been implicated in the mode of action of AONPs. More specifically, the NF-kB pathway, which is major in the inflammation process and in tumorigenesis, has been

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reported to be down-regulated after treatment with AONPs. Such a study was seen to suppress the activation of NF-kB, with a consequent reduction in the expression of pro-inflammatory cytokines, and further suggested that AONPs might reduce the inflammatory milieu that promotes tumor growth [72].

IV. FUTURE PROSPECTS

Research and ethical implications on the use of targeted delivery systems made using *Anacardium occidentale* nanoparticles among MCF-7 and other breast cancer cells. The addressing of the issues identified in this study has the following other significant prospects:

- *Improved Treatment Outcome:*

The considerations for future cancer treatment have the highest regard for the treatment outcomes of cancer diseases. The efficiency of the therapeutic agents in targeting the cancer cells may be enhanced by using *Anacardium occidentale* nanoparticles to design targeted delivery systems that increase the bioavailability of the active compound. These could in turn enhance the efficacy of potent anticancer therapies if not their associated side effects.

- *Nano-based Drug Delivery Systems:*

It is worth noting that the use of AONPs in creating versatile drug delivery systems is one of the possibilities. These nanoparticles can be engineered to carry not only the active phytochemicals from *Anacardium occidentale* but also other chemotherapeutic agents, leading to synergistic effects against cancer cells. Targeting MCF-7 and other breast cancer cells, specifically through surface modifications could further enhance precision medicine approaches, minimizing damage to healthy cells.

- *Synergy with Conventional Therapies:*

At present, clinical trials are being undertaken that assess the incorporation of therapies such as chemotherapy or radiotherapy with AONPs. It can be expected that this will help improve cancer treatment chimera. Concerning the treatment of MCF-7 and other breast cancer cells, which is rather aggressive and very resistant to many drugs, where multi-drug resistance profiles can be quite useful. This approach may also result in lowering the amount of traditional medicinal therapy required for treatment, thereby minimizing its harmful effects.

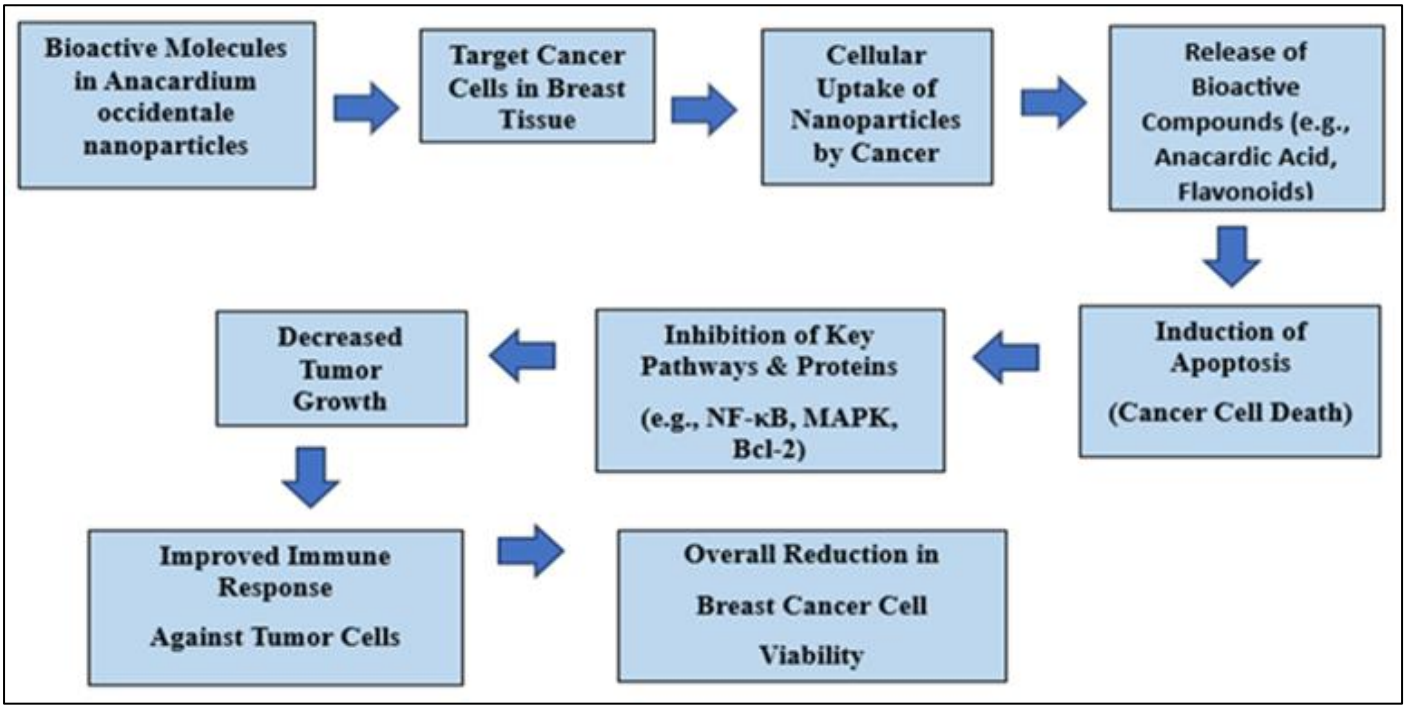

Fig 5 Summerization of Proposed Mechanism of Bioactive Molecules of Anacardium Occidentale Nanoparticles on Breast Cancer Cell.

- *Exploration of Molecular Mechanisms:*

There is a need for more in-depth study of molecular mechanisms of action on how AONPs promote apoptosis and impede MCF-7 and other breast cancer cell growth as they could unveil other molecular pathways that may be beneficial for therapeutic use. A summerized mechanism of anticancer efficacy of *Anacardium occidentale* and its nanoparticles (AONPs) on breast cancer cells depicted in Fig. 5. This understanding can also shape the architecture of new molecular targets for the treatment of cancers which could help develop drugs which would not be possible to develop using the existing principles of chemotherapeutics.

- *Personalized Medicine Approaches:*

Most AONPS strategies can thus permit the provision of treatment based on the genetic makeup of the patient in tune with growing practices of personalized medicines, particularly in AONPs. The next stage after completing the

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research could be practical - to search for the biomarkers that will help to determine the responsiveness to *Anacardium occidentale*-based therapy in breast cancer patients to build personalized approaches to treatment.

- *Preclinical and Clinical Studies:*

To put therapeutic claims for any AONPs into practice, it is required to undergo extensive preclinical studies, randomized controlled trials in animals. Studies should also include assessment of AONPs toxicity, biocompatibility and pharmacokinetics besides efficacy. In case of a favorable preclinical outcome, the appropriate next stage of development would include clinical testing of the safety and efficiency of the nanoparticles in patients. The success of these industrial applications may conceivably promote the acceptance of these agents in the mechanism of treating cancer patients.

- *Development of Eco-Friendly Nanotechnology:*

The development of synthesized AONPs has the potential to advance green nanotechnology as bioinspired nanoparticles provide a safer alternative to their chemically engineered counterparts. This is in line with the worldwide campaigns that seek to minimize the adverse effects of Nanotechnology on the environment, rendering it more viable and less prohibitive.

- *Scope of Study:*

This review will work on AONPs' potency in other cancers, for instance, ovarian, lung, or colon, stringing the fact that they work on MCF -7 and other breast cancer cells now. So, these nanoparticles in different cancer types can make their use and not limit breast cancer.

- *Combining AONPs with Biologics:*

Another area of research which is quite likely to be beneficial is the application of AONPs along with treatments which help increase patient's immunity to cancer aggressiveness. To bring even more equilibrium, anthropogenic products have been developed, which allow combining, for example, cytotoxic drugs with the delivery of molecules capable of stimulating immune response.

- *Patent and Commercialization Opportunities:*

With the advancement of research, another trend that can be observed is the potential development of AONPs patents for cancer treatment leading to possible commercialization. There may be investment by biotechnology and pharmaceutical companies in bringing AONP-based treatment that would reform cancer treatment by introducing a new class of anti-cancer drugs which relies on nanotechnology for efficient cancer treatment.

Overall, the use of *Anacardium occidentale* nanoparticles for the management of MCF-7 breast cancer cells is encouraging. If the knowledge gained in the understanding of the underlying mechanisms, drug delivery, and combination with other current and future treatment options is achieved, such therapy can one day alter the course of cancer into a chronic manageable illness.

V. CONCLUSION

To sum up, the use of nanoparticles derived from *Anacardium occidentale* is an innovative strategy that could be beneficial in treating MCF-7 breast cancer cells. The other therapeutic compounds of *A. occidentale*, when made into nanoparticles, have increased bioavailability, targeted delivery, reduced system toxicity, thereby increasing the therapeutic efficacy. In initial experiments, these nanoparticles were found to be potent cytotoxic against the MCF-7 cell or other breast cancer cell line and effective in the inhibition of cancer cell growth as well as the induction of programmed cell death. However, though the data points are encouraging, further research of this kind is warranted to decipher fully the mechanisms of action involved, the appropriate dosage, and clinical safety and efficacy over a period of time. This could add to existing breast cancer treatment modalities or better still provide an alternative therapy for the disease.

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