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Targeting Breast Cancer Using Phytoconstituents Nanomedical based Drug Delivery System

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Abstract

Breast cancer is one of the most common cancers in women globally. Treatment for breast cancer is better than prevention. Numerous biological factors can cause breast cancer, which makes treating it with chemotherapy and/or radiation therapy extremely challenging and often results in undesirable side effects. Plant extracts have been used to treat almost every illness for millennia, and breast cancer is no different. Herbal medicines are a dependable option for treating cancer because of their low toxicity. Additionally, because herbal treatments are easily accessible and reasonably priced, most women who have been diagnosed with breast cancer happily accept them. In both in vitro and in vivo investigations conducted over the past ten years, it has been discovered that several plants and the compounds present in them exhibit promising anticancer effects against breast cancer cells. Even while natural compounds show promising preclinical results, their poor stability, water solubility, and bioavailability typically hinder the clinical translation of these medications. Attempts have been made to overcome these limitations, particularly through the application of nano-based drug delivery systems (NDDSs).

Keywords: Breast cancer, Herbal remedies, Nanomedicine, Phytoconstituents, Targeted delivery

Introduction:

Cancer is one of the main causes of death worldwide [1,2]. It is estimated that 8 million people died from malignant diseases in 2008; by 2030, that figure is predicted to increase to 11 million [3]. Breast cancer is the most common malignancy in women and one of the main causes of death [4]. As a complicated disease, breast cancer can be caused by a wide range of factors. There are notable regional differences in the disease's prevalence, death, and survival rates, even though the illness is universal. Numerous factors, such as environment, genetics, way of life, and population structure, could be the source of these variances [5]. Due to changes in risk factors, the prevalence of breast cancer has increased and is still rising. While identifying individuals can reduce the occurrence of breast cancer, this approach has disadvantages such as increased costs, overdiagnosis, and side effects. The categorization of women according to their breast cancer risk factors can help with the development of customised screening programmes as well as the enhancement of risk-free practises. Breast cancer is the most common malignancy in women and the second most common disease overall [4]. This figure was 223,899 in South Central Asia and 107,545 in Southeast Asia [7]. Thanks to more people having access to screening programmes and treatment, the 5-year survival rate for breast cancer was 89% between 2005 and 2011 [13]. Scotland has a 1-year survival rate for breast cancer of 94.1%, while Italy has a 1-year survival rate of 97.1% [14]. Because they must wait a long time for a diagnosis and treatment, African women with breast cancer have a poor survival rate [15]. The age-standardized rate per 100,000 for breast cancer in different regions of the world is as follows: Out of 100, the scores for Western Europe were 96.0, North America was 91.6, Northern Europe was 89.4, Australia and New Zealand was 85.8, South-Central Asia was 28.2, and Eastern Asia was 27.0.Breast cancer claimed the lives of 166,685,000 persons globally in 2020,

affecting 2.3 million women. By the end of 2020, 7.8 million women had received a breast cancer diagnosis, making it the most frequent cancer worldwide [16]. Refer to Tables 1 and 2.

Table 1. Genes that have been changed in breast cancer.

List of genes altered in Breast Cancer				
ACVR1B	EGFR	HER2	PBRM1	RET
AKT1	EP300	IRAK4	PCGF2	SEPT9
ATM	ERBB2	ITCH	PIK3CA	TP53
BAP1	ERBB3	KMT2C	PIK3R1	TRAF5
BRCA1	ESR1	MAP2K4	PPM1L	WEE1
BRCA2	EXOC2	MAP3K1	PTEN	ZBED4
CBFB	EXT2	MDM2	PTGFR	ZNF226
CDH1	FBXO32	MUC16	FGFR2	
CDKN2A	FGFR1	NCOR1	RAS	
c-MYC	FGFR2	NEK2	RB1	

Numerous genes have been connected to the development of breast cancer. Tumour development and metastasis are partially attributed to abnormal amplification and changes in oncogene and anti-oncogene expression.

Table 2. benefits and drawbacks of various nanomaterials for treating breast cancer, as well as the state of ongoing clinical trials.

Nanocarriers	Targeted drug therapy		Clinical trials for breast cancer treatment
	Advantage	Disadvantage	
Solid–lipid nanoparticles	Good solubility and bioavailability due to organic makeup	Low drug-loading capacities	NA
	Better control of drug-release kinetic	Possibly containing other colloidal structures and complex physical state	
Liposome	Wide range of drug delivery applications	Cationic lipids cause toxicity	Liposome-annamycin Phase I/II (annamycin in lipid composition of DSPC, DSPG, and Tween for intravenous administration)
	Able to increase drug load and minimize undesired drug activity	Rapid degradation of the nanocarriers by MPS	
Polymeric	Versatility in terms of chemical composition	Degradation of the carrier	Nanoxel Phase 1 (paclitaxel in polymeric micelle)
Magnetic nanoparticle	Influenced by exterior magnetic field for guided therapy, imaging, and drug delivery	Potential material toxicity	NA
Quantum dots	Fluorescent properties for imaging and drug tracking	Potential material toxicity	NA
Carbon nanotubes	Able to penetrate and localize at cellular level for the delivery of chemotherapeutic and imaging agent	Potential material toxicity	NA

DSPC: Distearoylphosphatidylcholine; DSPG: Distearoyl phosphatidylglycerol.

Pathophysiology

Breast tumours usually start as ductal hyperproliferation and develop into benign tumours or even metastatic carcinomas when they are regularly triggered by various carcinogenic factors. Tumour microenvironments, including stromal effects and macrophages, play a critical role in the development and metastasis of breast cancer. Carcinogens could only cause stroma-only exposure in the rat mammary gland; neither extracellular matrix nor epithelial neoplasms could form [17]. Macrophages has the capacity to generate an inflammatory and mutagenic environment that promotes angiogenesis and enables cancer cells to withstand immunological rejection [18]. This is a very small population of cells that can develop from progenitor or stem cells found in healthy tissues. They are resistant to therapies like radiation and chemotherapy and have the ability to self-renew [21, 22]. Breast cancer stem cells, or bCSCs, were initially identified by Ai Hajj in 23. Immunocompromised animals injected with as few as 100 bCSCs were able to grow new tumours.

Genes linked to breast cancer

- **BRCA1/2**

Breast cancer-related genes 1 and 2 are the two well-known anti-oncogenes for breast cancer risk (BRCA1 and BRCA2). The loci for BRCA1 and BRCA2 are located on chromosomes 17q21 and 13q12, respectively. Both of them encode proteins that inhibit the growth of tumours. BRCA1 loss results in cell cycle checkpoint dysregulation, abnormal centrosome duplication, genetic damage, and ultimately apoptosis [29, 30]. "Pocket proteins" like as p130, p107, and the retinoblastoma molecule inhibit BRCA1 synthesis in an E2F-dependent manner. The BRCA1 gene has been found to create a loop between the introns, terminator regions, and promoter. This loop interacts with the gene's own promoter to regulate gene expression [31, 32]. The BRCA2 protein regulates recombinational repair in DNA double-strand breaks through interactions with RAD51 and DMC1 [33, 34]. High-grade invasive ductal carcinomas are more likely to be present in breast tumours with a luminal phenotype that are connected to BRCA2 [35]. A person's chance of getting breast cancer may increase dramatically if they inherit dangerous mutations in the BRCA1 or BRCA2 genes. Autosomal dominant inheritance is the mode of transmission for BRCA1/2 mutations, even in cases where the second allele is normal. Roughly 20–25% of hereditary breast cancers and 5–10% of all breast cancers are caused by BRCA1/2 mutations [36, 37].

- **HER2**

The human epidermal growth factor receptor 2, or c-erbB-2, is a major oncogene in breast cancer and is located on the long arm of human chromosome 17. The homolog of Neu in mice was initially identified in rat neuroblastoma cells treated to 3-methylcholanthrene. The main mechanisms that cause the HER2 gene to express are gene amplification and reorganisation. The HER2 protein, which is a member of the EGFR family of tyrosine kinases, forms heterodimers with Her3 and Her4, two other ligand-bound members of the EGFR family, to initiate downstream signalling pathways [39]. Normal mammary duct development is impaired in animal models of HER2 deletion. Overexpression of HER2, which is present in 20% of primary breast tumours and increases the number of cancer stem cells via PTEN/Akt/mTORC1 signalling, is indicative of poor clinical outcomes [40,41].

receptor for epithelial growth factor

EGFR, often referred to in live organisms as c-erbB-1 or Her1, is located on the short arm of chromosome 7. The tyrosine kinase family of glycoproteins found on the cell surface, including betacellulin, amphiregulin, TGF-, and EGF, binds to the EGFR protein to initiate its activation. In addition to promoting cell invasion, angiogenesis, and proliferation, the downstream signalling pathways of EGFR, including PI3K, Ras-Raf-MAPK, and JNK, also function to prevent apoptosis [42, 43]. Overexpression of the EGFR gene was found in approximately 30% of cases with inflammatory breast cancer, an exceptionally aggressive subtype of breast cancer. The prognosis for patients with IBC who test positive for EGFR is worse than that of patients who test negative for EGFR. In addition to lacking HER2 amplification, progesterone receptor (PR) expression, and oestrogen receptor (ER) expression, approximately half of cases of triple-negative breast cancer (TNBC) also exhibit overexpression of EGFR. Therefore, targeting the EGFR pathway may be a viable therapeutic for these malignant tumours [44].

- **Aging**

An important risk factor for breast cancer is getting older, which is strongly connected with the disease's prevalence (second only to sex). According to reports, women over 40 and 60 made up 99.3% and 71.2%, respectively, of all breast cancer-related deaths in the United States in 2016 [52]. Therefore, a screening mammography is required for women 40 years of age or older in advance.

- **Family history**

A family history of breast cancer is present in nearly one-fourth of cases. Women who have a mother or sister who has breast cancer are more likely to get breast cancer themselves. A UK cohort research involving over 113,000 women found that women with one first-degree family member who had breast cancer had a 1.75-fold higher chance of getting the disease than women without any affected relatives. Furthermore, women who have two or more first-degree relatives with the condition have a risk increase of 2.5 times or higher [53]. Part of the genetic susceptibility to breast cancer is caused by gene mutations associated to the disease, such as those in BRCA1 and BRCA2.

- **Reproductive factors**

Reproductive traits that may increase the risk of breast cancer include poor parity, late menopause, early menarche, and advanced age at first pregnancy. The chance of developing breast cancer rises by 3% for each year following menopause. Breast cancer risk is decreased by 5% or 10% for every extra birth or one-year menarche delay, respectively [14,54,55]. The risk ratio (HR) between late (35 years) and early (20 years) ages at first birth is 1.54, per a recent Norwegian cohort study [56]. There is a significant correlation between the ER status and reproductive factors. For example, the odds ratios (OR) for parity (0.7 vs. 0.9 for 3 births vs. nulliparae) and age at first birth vary between ER+ and ER-breast cancer [57].

- **Estrogen**

Both endogenous and exogenous oestrogens have been related to a higher risk of breast cancer. Ovarian excision can reduce the risk of breast cancer in premenopausal women since the ovary normally produces endogenous oestrogen [58]. The two main sources of exogenous oestrogen are oral contraceptives and hormone replacement therapy (HRT). Oral contraceptives have been widely used since the 1960s, and their formulations have been refined to reduce side effects. The OR is still higher than 1.5 for populations of African American women and Iranian women [59, 60]. However, there is no increased risk of breast cancer for women who stop taking oral contraceptives more than ten years later [14]. HRT entails administering exogenous oestrogen or other hormones to postmenopausal or menopausal women. Numerous studies have found a connection between the use of HRT and a higher risk of breast cancer. The UK's Million Women Study found that the relative risk (RR) difference between those who have never used HRT and those who now use it is 1.66 [61].

- **Lifestyle**

Breast cancer risk can be increased by modern lifestyle factors such as heavy alcohol consumption and food high in fat. Drinking alcohol can increase blood levels of estrogen-related hormones and activate the pathways leading to the oestrogen receptors. A meta-analysis based on 53 epidemiological studies found that every 35–44 g of alcohol used daily can raise the risk of breast cancer by 32%, and every 10 g of alcohol consumed daily can raise the risk by 7.1% [66,67]. The average Western diet is far too heavy in fat, and eating too much fat—especially saturated fat—is associated with a higher risk of death (RR = 1.3) and a worse prognosis for breast cancer patients [68]. Although the exact relationship between smoking and the development of breast cancer is still unknown, carcinogens from cigarettes have been detected in the breast fluid of non-lactating women. Additionally, women who drink and smoke have a greater risk of breast cancer (RR = 1.54) [69].

The current course of breast cancer treatment

Because the disease is being discovered earlier and earlier, we are seeing a greater number of patients with operable breast cancer. Radiation, excision of the axillary lymph nodes, mastectomy, or lumpectomy are among the operative treatments for breast cancer. In addition to surgical tumour removal, oncologists are increasingly recommending adjuvant therapy, which may include postoperative radiation, chemotherapy, and/or long-term tamoxifen (Nolvadex), an anti-estrogen medicine. Large tumours and positive axillary lymph nodes used to be the main criteria for adjuvant therapy in women. However, this is increasingly being prescribed for all women with breast cancer because we now know that, regrettably, a significant portion of patients, even those with no clinical signs of spread, such as patients with small neoplasms and those whose lymph nodes are found to be free of tumour cells, have already metastasized and will recur. Unfortunately, a recurrence of breast cancer always results in death. Thus, even while current salvage medicines can prolong life and achieve remissions in many individuals, the focus of treatment must clearly be on preventing recurrence.

- **Supplemental chemotherapy**

Breast cancer diagnosis and mastectomy are often made even more vulnerable by adjuvant chemotherapy side effects, which can be far more devastating to a woman's sexuality and to a marriage or relationship than the surgery itself. However, a "miracle cure" for breast cancer does not exist. Put another way, there is currently no medication that can either stop the cancerous cells from spreading or that can specifically eradicate breast cancer cells. Currently, we are still dependent on chemotherapeutic agents—which are toxic to all human cells but supposedly most lethal to rapidly multiplying cancerous cells—and general cellular poisons, as well as the manipulation of a woman's hormones to create an endocrine environment hostile to the tumour.

Using phytoconstituents to treat breast cancer

- **Flavonoids**

Numerous epidemiological studies have demonstrated the negative correlation between a diet high in fruits and vegetables and the incidence or development of cancer [76,77] (see Fig. 1). Flavonoids have received a lot of attention recently as possible ROS-targeting cancer treatment and prevention medications. Polyphenolic compounds called flavonoids are essential for protecting plants from oxidative stress, microbes, and UV radiation [78]. Flavonoids are defined by the International Union for Pure and Applied Chemistry (IUPAC) as compounds with a limited C6–C3–C6 carbon backbone. They are arranged as a phenyl ring (ring A) combined with a pyran ring (ring C), as mentioned in Fig. 2 [79], in addition to another phenyl ring (ring B) that is substituted at position 2 of ring C.

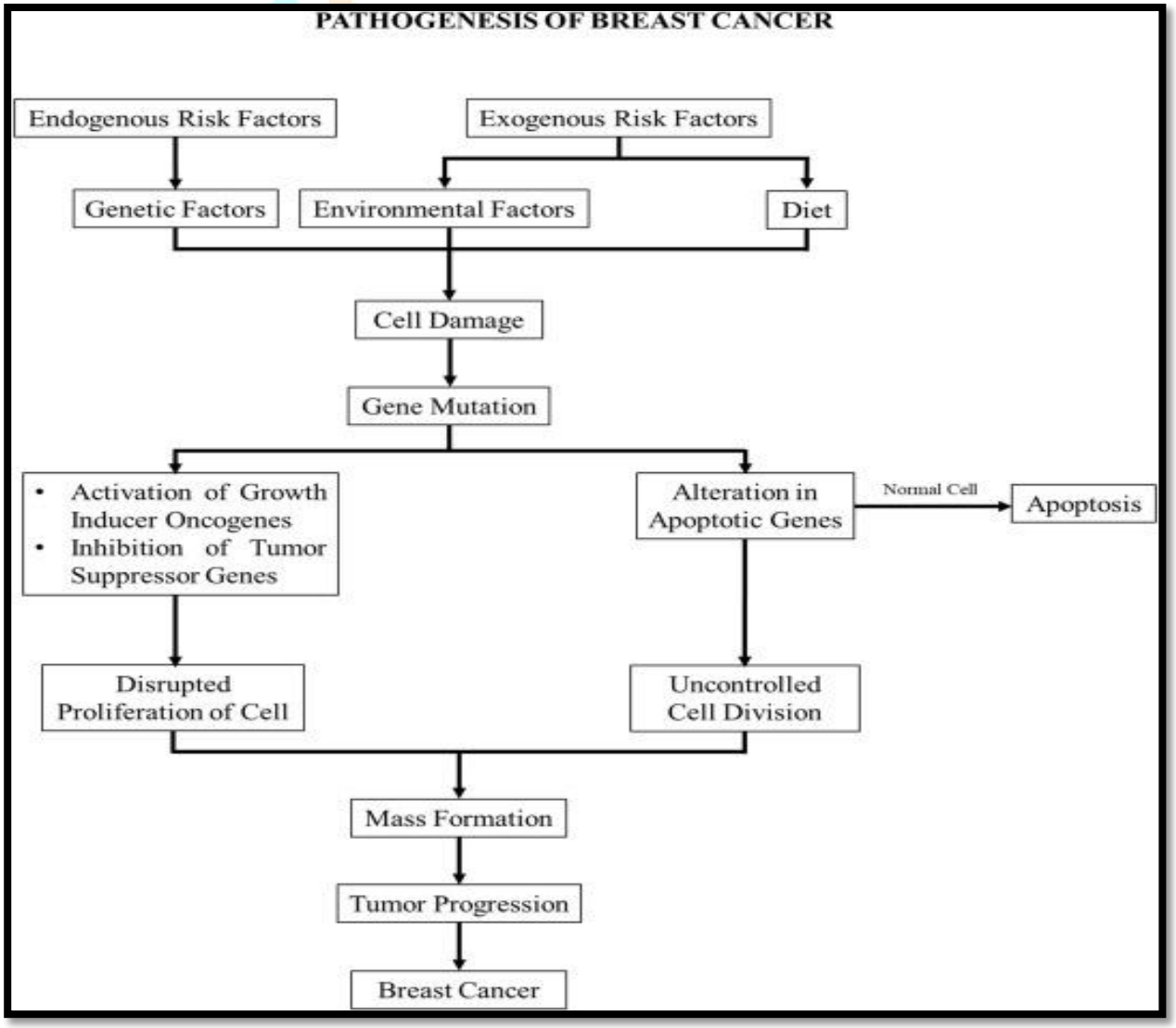

Fig. 1. Pathophysiology of breast cancer.

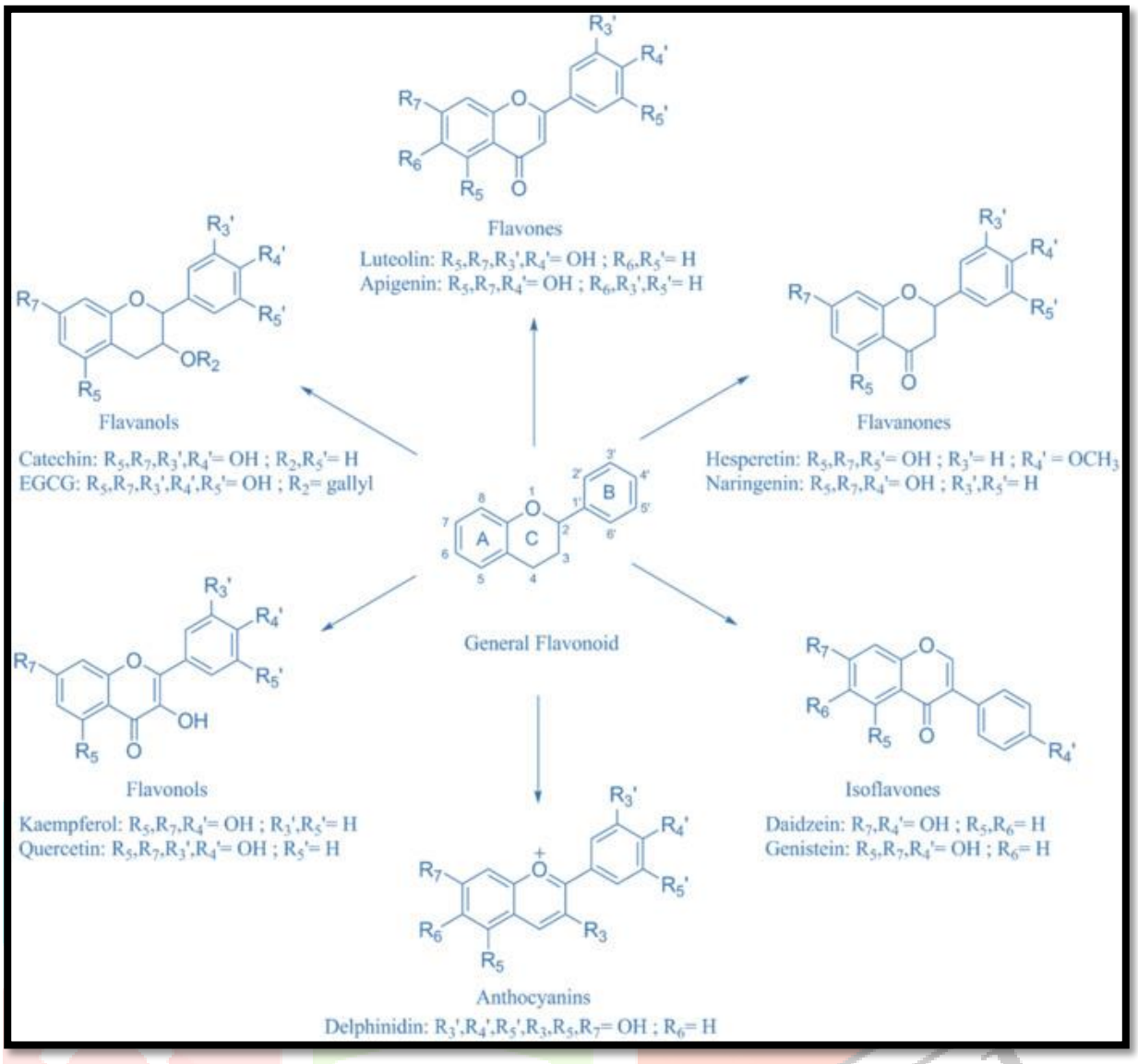

Fig. 2. the overall structure of flavonoids as well as the key flavonoid subfamilies' representative structures.

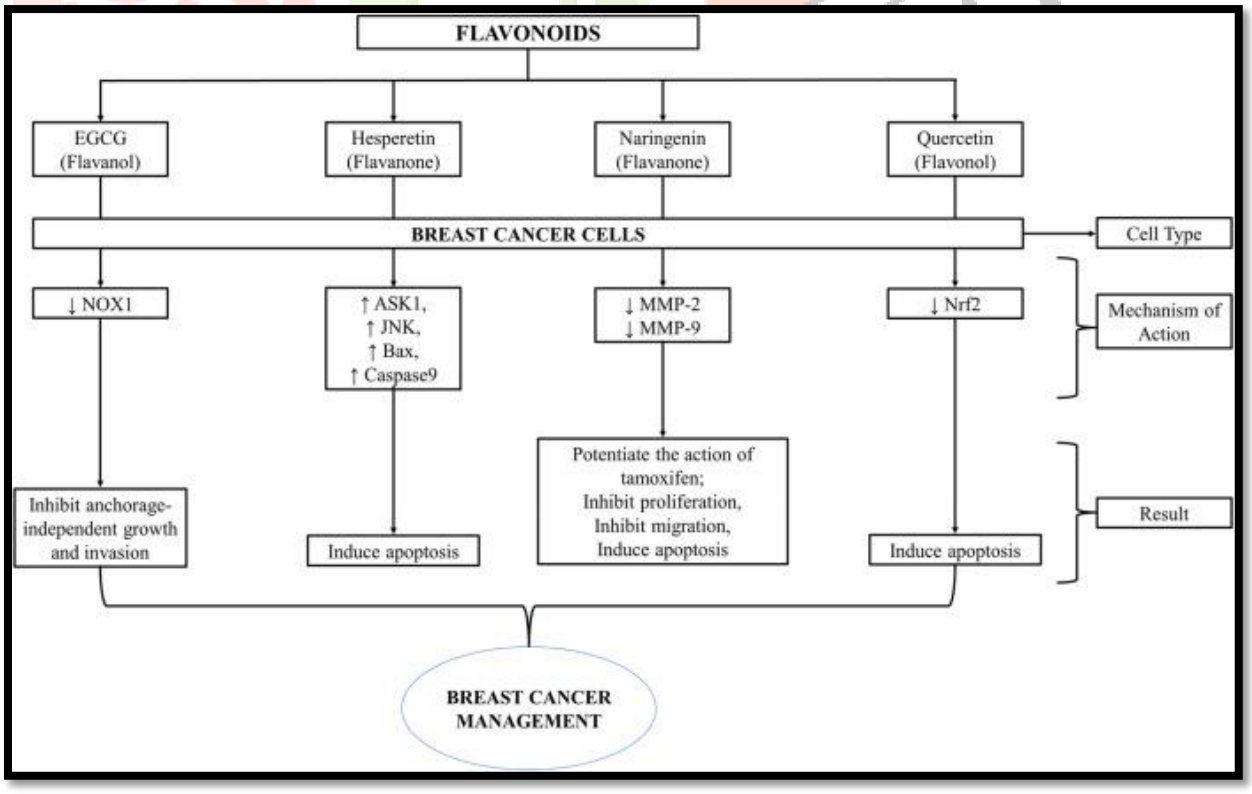

Fig. 3. Flavonoids in the Treatment of Breast Cancer

NADPH oxidase 1 (NOX1), Apoptosis signal-regulating kinase 1 (ASK1), c-Jun N-terminal kinases (JNK), BAX (Bcl-2-associated X protein), MMP-2&-9 (matrix metallopeptidase-2&-9), and Nrf2 (nucleus erythroid 2) are some examples of the proteins that are involved in this process.

- **Flavanols**

1. **Epigallocatechin gallate (EGCG)**

Being the main ingredient in green tea, a plant with many health benefits, EGCG is one of the flavonoids that has been researched extensively [84]. It is true that green tea can help prevent a number of illnesses, such as diabetes, cancer, neurological conditions, obesity, and cardiovascular diseases [85]. What gives EGCG its anti-malignant characteristics is its ability to stop cancer from starting, growing, and spreading [86,87]. EGCG also has anti-promotional and anti-progressional effects in several cancer types. For example, 2-amino-1-methyl-6-phenyl imidazole [4, 5-b] pyridine (PhIP) induces malignant transformation in breast cancer cells, but EGCG inhibits this transformation. Cooked beef also contains the carcinogen PhIP, which is known to initiate multiple cellular processes linked to cancer. These consist of invasion, migration, development without anchoring, and a decreased need for growth factors. The NOX1/ROS axis activation in premalignant and malignant cells is tightly linked to the PhIP-induced activities. Interestingly, EGCG treatment halted the tumorigenic processes in these cells and significantly reduced NOX1/ROS signalling [88].

- **Flavanones**

1. **Hesperidin**

Citrus fruits, especially sweet oranges, mandarins, and clementines, are rich in well-known flavanones called hesperidin and hesperetin [89]. In addition to having dissimilar structures, the two compounds also have dissimilar absorption characteristics. Hesperetin is instantly absorbed by the enterocytes of the digestive system, in contrast to hesperidin, which must first be broken down by the colon microbiota. This suggests that the former absorbs faster than the latter. It's interesting to note that polymeric nanoparticles can enhance hesperetin's dispersion and bioavailability in biological systems. As a result, hesperetin is now a potentially valuable pharmaceutical substance. The reduction of invasiveness brought on by MMP has been associated with hesperdin's ability to scavenge ROS. Additionally, hesperidin exhibits significant cytocidal effects linked to antioxidants in a number of carcinomas, such as those of the breast, cervix, and larynx. Hesperidin activates glutathione transferase as an antioxidant while blocking and inhibiting glutathione peroxidase, catalase, and superoxide dismutase [11]. Additionally, hesperetin promotes the Bax/caspase 9-mediated programmed cell death in breast cancer cells via activating the JNK/ASK1 signalling pathway in response to ROS.

- **Naringenin**

Because it might lessen cellular oxidative stress, a flavanone known as naringenin may have anticancer effects [89]. There's an abundance of garden thyme and citrus fruits, notably grapefruit. However, an abundance of evidence indicates that naringenin may function as an anti-cancer agent due to its pro-oxidative capacity. This is because to the compound's detrimental effects on glutathione reductase, an antioxidant enzyme [11]. Naringenin causes oxidative stress, which kills off several kinds of cancer cells. Naringenin increases ROS levels, which in turn increases tamoxifen's action in breast cancer cells.

- **Flavonols**

1. **Quercetin**

This flavonoid is present in considerable amounts in a few plants, such as kale, onions, and broccoli, as well as in various tea infusions and red wine. In contrast to other flavonoids, not much is known about the relationship between the antioxidant activity and anticancer effects of quercetin. Less is known about quercetin's anticancer properties in breast cancer. Indeed, a study on the MCF-7 breast cancer cell line demonstrated that quercetin plus vitamin C therapy reduces oxidative stress and decreases Nrf2 activity, which in turn promotes apoptosis. Alternatively, quercetin-induced apoptosis in MCF-7 cells has been connected to the accumulation of ROS in these cells. In this regard, it was suggested that the effects of quercetin can be biphasic, contingent on treatment duration and dosage.

2. **Aurones**

Medicinal chemists have been paying close attention to the naturally occurring chemical aurone in the last few years. The majority of these components are secondary plant metabolites that are created when aurone synthases are present during the oxidative cyclization of 2-hydroxy chalcones. Aurones are members of the flavonoid family, which also includes chalcones, anthocyanins, flavones, flavonols, flavanones, and flavanonols, often known as catechins or flavonols. While there are important biological functions associated with all of these flavonoids, aurone has a considerable advantage over chalcones due to its high stability, which makes it easier for it to undergo cyclization and produce flavanones. The attractiveness of aurone is found in its simplicity and

high drug-likeness ratings, which make these little compounds an intriguing source of leads. Despite being a very rare bioactive moiety in nature, aurones exhibit a wide range of biological activities, including as anti-inflammatory, antibacterial, antimalarial, antileishmanial, and anti-Alzheimer effects. Aurones are straightforward, planar compounds that have been shown to play a major part in the creation of anticancer drugs.

Isoflavones' involvement in cancer

Isoflavones are mostly found in members of the Leguminosae family. Soybeans are among the foods that contain the highest quantities of isoflavones, although other foods that include them include lentils, beans, and chickpeas. The isoflavone content of isolated soybean proteins ranges from 466 to 615 mg/kg. Soymilk, bean curds, and bean sprouts can contain up to 2030 mg of isoflavone per kilogramme, depending on the source ingredient and processing method. The main isoflavones present in soybeans are glycitein, daidzein, and genistein. The majority of isoflavone research has focused on genistein because it has significant bioactivity and is good for human health. It is commonly recognised that isoflavones are usually found in plants as glycosides while they are dormant. Bacterial beta-glucosidases hydrolyze isoflavone glycosides, such as genistein and daidzein, in the intestines to provide their corresponding bioactive aglycones [55]. The aglycones are mainly transformed into glucuronides in the hepatic system after being absorbed from the intestine into the blood and subsequently excreted in the urine. Genistein and daidzein are the two primary isoflavones that have been detected in human blood and urine. Given that isoflavone aglycones are digested more quickly and at higher levels in humans than their glycoside counterparts, isoflavone aglycone-rich products may be more effective in cancer chemoprevention than glycoside-rich ones.

Nanomedicine for breast cancer

Nanomedicine is one of these fascinating new avenues for treatment. Nanomedicine is the use of materials with at least one dimension less than 100 nm in biomedicine; however, devices with a diameter of 100–200 nm are commonly called nanomedicine. Examples of nanomedicine include liposomes, nanoparticles, micelles, dendrimers, nanotubes, and other forms. They may consist of lipids, phospholipids, proteins, polymers, inorganic components, or a combination of these. Some of these, such as liposomes like Doxil from Janssen Products in Titusville, New Jersey, and nanoparticles like Abraxan, are already being used successfully in clinical breast cancer treatment. One of these cutting-edge novel therapeutic approaches is nanomedicine. The biomedical application of materials with at least one dimension smaller than 100 nm is referred to as nanomedicine, even if devices between 100 and 200 nm are typically referred to as such. Liposomes, nanoparticles, micelles, dendrimers, nanotubes, and many more structures are examples of nanomedicine. Breast cancer obstacles are displayed in Fig. 4. They can be made of proteins, polymers, lipids, phospholipids, inorganic components, or a combination of these. A few of these are already being utilised successfully in clinical breast cancer treatment, such as liposomes like Doxil and nanoparticles like Abraxane® from Janssen Ingredients in Titusville, New Jersey.

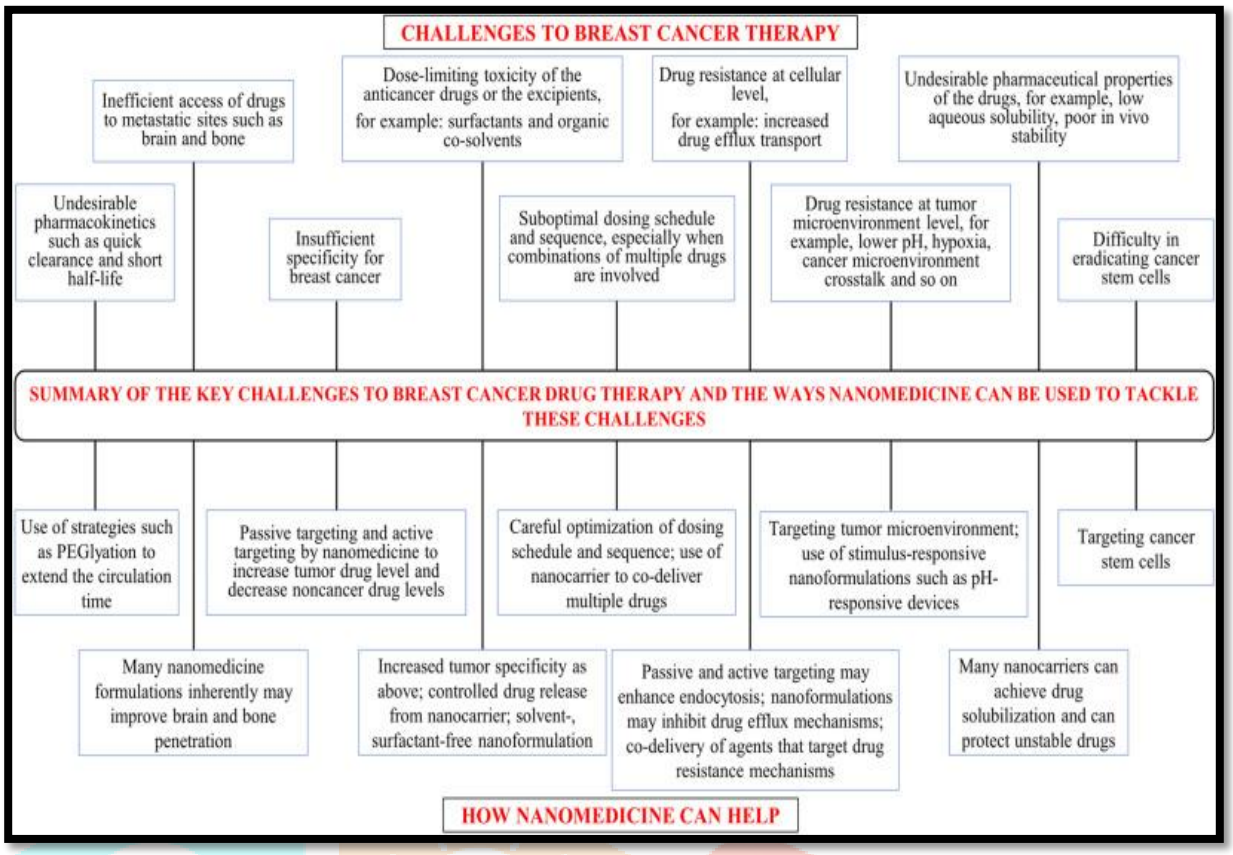

Fig. 4. An overview of the main obstacles to breast cancer medication therapy and how nanomedicine can help to overcome them.

Current approaches to breast cancer treatment and potential applications of nanomedicine

These days, women with breast cancer are often treated with a multimodal strategy that includes certain optional alternative therapies like acupuncture and diet control along with mainstream modalities like surgery, radiation, and drug therapy. The first two treatment options mainly include the removal of the primary breast tumour and any localised malignant tissues. Its value tends to decrease as cancer grows and spreads. We focus on the last strategy, drug therapy, which shrinks the tumour and either stops, decelerates, or treats cancer metastases. Two popular forms of breast cancer drug therapy include hormonal treatment, which uses hormones or hormone-like drugs to restrict cancer cell proliferation, and chemotherapy, which primarily focuses on eradicating malignant cells with cytotoxic substances. Recent advancements in immunotherapy and molecular biology have led to an increase in the use of targeted medicines that are especially suited to the pathophysiology of different subtypes of breast cancer. This approach frequently makes use of a monoclonal antibody or small molecule drug that targets a specific biochemical pathway in order to stop or manage cancer from spreading, growing, or becoming resistant to treatment.

Conclusion :

However, advancements in medical research have made it possible to identify and classify the majority of breast cancer forms, as well as the treatments that go along with them. However, the incidence and prevalence of breast cancer are rising alarmingly in both developed and developing countries due to a number of risk factors. Thanks to advancements in synthetic medication and hormone therapy, there has been a decline in the incidence of breast cancer, an increase in survival rates, and an improvement in the quality of life. When taken over an extended period of time, the toxic effects of synthetic anticancer drugs on normal cells have been related to a number of health risks or side effects. Herbal chemicals are a subject of great attention and are thought to be an accessible, economical, manageable, and agreeable approach to the treatment and control of cancer. Herbal remedies have a major role in the treatment of breast cancer and the ensuing therapeutic toxicity. Breast cancer is the deadliest and most challenging type of cancer to cure when it spreads. Breast cancer often spreads to the brain, liver, bone, and lung, but most anticancer treatments, including nano formulations, have trouble getting to many of these sites. It is imperative to develop nano formulations that can sufficiently penetrate each of these locations without causing appreciable harm. The development of breast cancer nanomedicine is expected to require close cooperation with experts in immunology, bioavailability, toxicity, and oncology in the future.

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