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REVIEW ARTICLE

# Next-Generation Phytochemical Nanomedicine: Naringin and Skimmin Nanoformulations as Targeting Triple-Negative Breast Cancer and Metastatic Progression

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Triple-negative breast cancer (TNBC) is a type of breast cancer that is aggressive with no specific targets of therapy, which could have a low prognosis and a high potential of metastasis. In painting this picture, phytochemicals like naringin and skimmin have shown good anticancer properties such as anti-proliferative, anti-inflammatory and pro-apoptotic. They are however limited in clinical translation due to poor bioavailability and high rate of metabolism. Nanomedicine proposes a novel way of addressing such shortcomings by means of better drug delivery, increased tumour targeting and regulation of release. The review examines the emerging nanoformulations of naringin and skimmin as a target of TNBC and preventing metastatic disease progression. The focus is put on their ways of action, nano-carrier systems and therapeutic benefits. Phytochemicals and nanotechnology integration is an important paradigm shift in cancer treatment as it can provide safer, more effective and targeted treatment regimens of aggressive cancers of the breast.

**Keywords:** Naringin; Skimmin; Nanomedicine; Triple-Negative Breast Cancer; Metastasis

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## Abbreviations

Akt – Protein kinase B
Bcl-2 – B-cell lymphoma 2
CSCs – Cancer stem cells
EMT – Epithelial–mesenchymal transition
ER – Estrogen receptor
HER2 – Human epidermal growth factor receptor 2
MAPK – Mitogen-activated protein kinase
MMPs – Matrix metalloproteinases
NF-κB – Nuclear factor kappa B
NPs – Nanoparticles
PR – Progesterone receptor
ROS – Reactive oxygen species
TNBC – Triple-negative breast cancer
VEGF – Vascular endothelial growth factor

## 1 Introduction

Triple-negative breast cancer (TNBC) is a highly clinically difficult breast cancer disease type which lacks oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This molecular profile makes TNBC resistant to the traditional hormonal and targeted therapy, which forces the use of chemotherapy, which in most cases has a low response rate and high systemic toxicity (1-5). TNBC is estimated to be between 15-20 percent of all breast cancer and is linked with aggressive tumour behaviour, early recurrence, and high tendency of metastasis especially to lungs and the brain. **Figure 1**

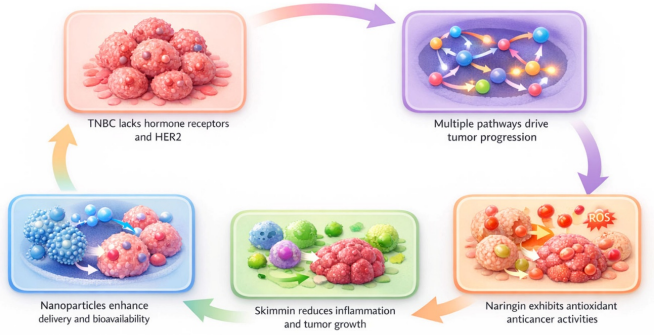


**Fig. 1** This figure illustrates TNBC molecular mechanisms and highlights nanoformulated phytochemicals targeting signaling pathways, improving bioavailability, enhancing targeted delivery, and reducing toxicity for effective and safer breast cancer therapy strategies.

Recent developments in cancer biology have identified the importance of the signalling pathways including NF-kB, PI3K/Akt, and MAPK in the progression, survival, and metastasis of TNBC. Besides, epithelial-mesenchymal transition (EMT), cancerous stem cell (CSCs), and interactions between the tumour background and the microenvironment are also important contributors of therapeutic resistance and disease development (6-10). These intricacies explain why there is an urgent need of new therapeutic approaches capable of efficiently finding low toxicity multi-therapeutic approaches to various oncogenic pathways.

Phytochemicals that are of natural origin have received a lot of interest because they exhibit a wide range of pharmacological activity and have desirable safety profiles. Naringin is a flavonoid, which is mainly available in citrus fruits, and it has been demonstrated to have a strong antioxidant, anti-inflammatory and anti-cancer effects. It is also reported to regulate major molecular processes that are involved in apoptosis, cell cycle arrest as well as inhibition of metastasis. On the same note, Skimming, which is a coumarin glycoside produced in medicinal plants, has demonstrated the potential in alleviating oxidative stress, inhibiting inflammatory mediators, and suppression of tumour growth. In spite of these desirable properties, the two compounds also have low solubility, bioavailability, and clearance in the body, which restricts their use in therapy.

Drug delivery systems through nanotechnology have become one of the revolutionary technologies that have created an improved clinical use of phytochemicals. Nanoparticles (NPs) allow delivering drugs specifically to the location, enhancing pharmacokinetics, and controlled drug release, which enhances therapeutic effects and reduces adverse effects. Liposomes, polymeric nanoparticles and solid lipid nanoparticles are some of the nanocarriers that have been used to deliver bioactive compounds to the tumour tissues through passive and active targeting.

Phytochemicals such as naringin and skimmin should be incorporated in nanoformulations, which act as a complementary approach to the treatment of TNBC (11-15). These nanoformulations do not only enhance stability of drugs and bioavailability, but also allow selective tumour targeting and increased intracellular uptake. Moreover, they have the potential to regulate various signalling pathways, and therefore, are promising alternatives to deal with drug resistance and inhibit metastatic progression.

The purpose of the review is to give a broad overview of the next-generation phytochemical nanomedicine with specific emphasis on naringin and skimmin nanoformulations in the treatment of TNBC. It brings into focus their mechanisms of action, development of nano-delivery systems and their possible use in meeting the unmet clinical requirements in treating the aggressive breast cancer management. **Table 1**

**Table 1** This table summarizes TNBC characteristics, molecular pathways, phytochemicals, associated limitations, and nanoformulation strategies, highlighting the role of nanotechnology in enhancing therapeutic efficacy and overcoming pharmacokinetic challenges in cancer treatment.

| Aspect | TNBC Characteristics | Signaling Pathways | Phytochemicals | Limitations | Nanoformulation Approach |
|---|---|---|---|---|---|
| Disease Profile | Aggressive, metastatic | NF-kB activation | Naringin | Poor solubility | Liposomes (1-5) |
| Receptor Status | ER/PR/HER2 negative | PI3K/Akt pathway | Skimmin | Low bioavailability | Polymeric nanoparticles (6-10) |
| Progression | Early recurrence | MAPK signaling | Flavonoids | Rapid clearance | Solid lipid nanoparticles (11-15) |
| Cellular Factors | EMT, CSCs | Survival pathways | Natural compounds | Stability issues | Targeted delivery |
| Microenvironment | Tumor interaction | Inflammatory mediators | Citrus-derived agents | Systemic toxicity | Controlled release |
| Therapeutic Need | Limited treatment options | Multi-pathway targeting | Plant bioactives | Poor pharmacokinetics | Enhanced uptake |

## 2 Naringin and Skimmin in TNBC Molecular Targets

### 2.1 *Modulation of Apoptotic Pathways*

Naringin and skimmin have a strong anticancer application in TNBC that controls intrinsic and extrinsic apoptotic signalling pathways, which in many cases are disrupted in aggressive tumours. Naringin induces mitochondrial-mediated apoptosis through increased expression of pro-apoptotic proteins including Bax and Bad coupled with decreased expression of the anti-apoptotic proteins including Bcl-2 and Bcl-xL (16-20). This change in the Bax/Bcl-2 ratio results in the release of cytochrome c and activation of downstream caspases including caspase-3 and caspase-9, which eventually causes the programmed cell death. Besides, naringin has the potential to induce death receptor mediated apoptosis by activating caspase-8. Topping these effects, Skimmin reduces oxidative stress and inhibits the well-known survival pathways of NF-kB and PI3K/Akt that are generally overexpressed in TNBC. The two compounds have similar effects of arresting cell cycle at G0/G1 or G2/M stages, thus, suppressing tumour growth. Their multi-targeted apoptotic control is a potential avenue of getting over the apoptosis resistance in TNBC treatment. **Figure 2**

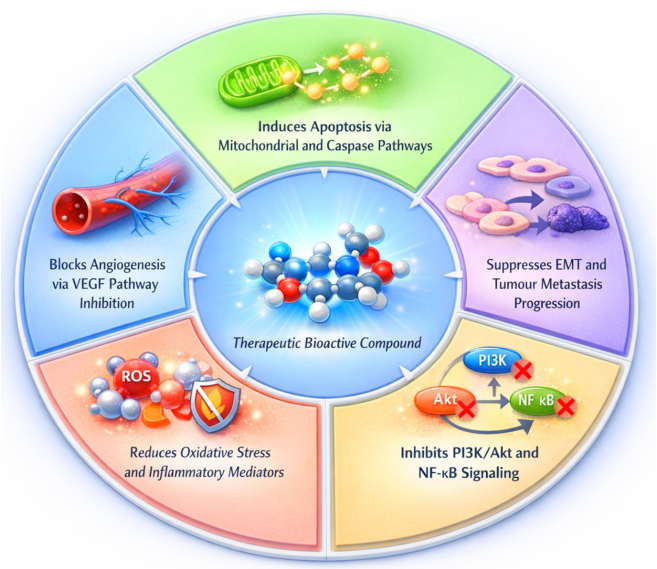


**Fig. 2** This figure illustrates mechanisms of naringin and skimmin in TNBC, including apoptosis induction, EMT suppression, anti-inflammatory effects, oxidative stress reduction, and inhibition of angiogenesis via multiple interconnected molecular pathways.

### 2.2 *Inhibition of Metastasis and EMT*

Epithelial-mesenchymal transition (EMT), which increases the invasiveness of tumour cells and their migratory ability, has been associated with the propensity of metastasis in TNBC. Naringin has also proven capable of reversing EMT by inhibiting transcriptional factors to include Snail, Slug and Twist in addition to re-expressing epithelial markers like E-cadherin. The result is a lower motility of cells and a lower ability to metastasize cells. Skimmin also adds to anti-metastatic effects by suppressing the matrix metalloproteins (MMP-2 and MMP-9) which are fundamental in degrading the extracellular matrix and invasion of tumour (21-25). Both phytochemicals also control important signalling pathways, such as PI3K/Akt, MAPK, and TGF-b that control the progression of EMT and metastasis. They also suppress angiogenesis by suppressing VEGF expression, thus reducing tumour vascularization. By means of these concerted efforts, naringin and skimmin are highly promising treatments against the spread and metastatic colonisation of tumours, thus making them an effective intervention tool in the treatment of advanced TNBC.

### 2.3 *Anti-inflammatory and Anti-oxidant processes*

Oxidative stress and chronic inflammation are crucial factors in the development of TNBC, tumor microenvironment remodeling and anti-therapy. Naringin has a high level of antioxidant properties through their ability to scavenge the reactive oxygen species (ROS) and increase the endogenous antioxidants (superoxide dismutase, catalase, and glutathione peroxidase). It also prevents lipid peroxidation as well as cellular components against oxidative damage (26-30). In addition, naringin can inhibit the inflammatory signalling pathways especially the NF-kB, which results in downregulation of pro-inflammatory cytokines such as TNF-a, IL-6 and COX- 2. Skimmin complements these protective effects by decreasing the effects of oxidative stress and the generation of inflammatory products. It also balances the redox homeostasis in the cell and averts the damages of DNA caused by ROS. These phytochemicals can be used as a supplementary approach to managing TNBC since they can be used to normalise the tumour microenvironment, prevent cancer cell survival, and sensitise tumour cells to therapeutic interventions by modulating both oxidative and inflammatory pathways. **Table 2**

**Table 2** This table summarizes molecular mechanisms of naringin and skimmin in TNBC, highlighting apoptosis induction, metastasis inhibition, anti-inflammatory actions, oxidative stress modulation, and key signaling pathways contributing to tumour suppression.

| Mechanism | Naringin Action | Skimmin Action | Key Targets | Pathway Affected | Outcome |
|---|---|---|---|---|---|
| Apoptosis | ↑ Bax, ↓ Bcl-2 | Reduces survival signaling | Caspases | Intrinsic/Extrinsic | Cell death (16-20) |
| Death Receptor | Activates caspase-8 | Supports apoptosis | Caspase-8 | Extrinsic pathway | Apoptosis induction (21-25) |
| Cell Cycle Arrest | G0/G1, G2/M arrest | Similar arrest effect | Cyclins | Cell cycle control | Growth inhibition (26-30) |
| EMT Inhibition | ↑ E-cadherin, ↓ Snail | Suppresses MMP-2/9 | EMT markers | PI3K/Akt, TGF-β | Reduced metastasis |
| Anti-angiogenesis | ↓ VEGF | ↓ VEGF | VEGF | Angiogenesis | Reduced vascularization |
| Anti-inflammatory | ↓ TNF-α, IL-6 | Reduces inflammation | NF-κB | Inflammatory pathways | Tumour suppression |

## 3 Nanoformulation Strategy of Phytochemicals

### 3.1 *Polymeric Nanoparticles and Liposomes*

Polymeric nanoparticle and liposomes are the most flexible and a popular nanocarrier system with uses in drug delivery of phytochemicals like naringin and skimmin. Biodegradable polymers such as PLGA or chitosan are commonly used as polymeric nanoparticles to deliver drugs in a controlled and sustained manner and minimise the chances of enzymatic degradation of the released compound. Polymeric nanoparticles loaded with naringin have been found to exhibit high cellular uptake, stability and have longer circulation times leading to high anticancer activity (31-35). Liposomes, which consist of phospholipid bi layers, have the benefit of being biocompatible and entrap hydrophilic and lipophilic molecules. This is enabled by these systems where the targeted delivery is aided by the heightened permeability and retention (EPR) effect which enables preferential accretion in tumour tissues. Its solubility and bioavailability are increased by incorporating skimming into liposomal systems. The targeting of these carriers on the surface with targeting ligands can also enhance specificity to the TNBC cells, reducing toxicity in the system and enhancing therapeutic efficacy. **Figure 3**

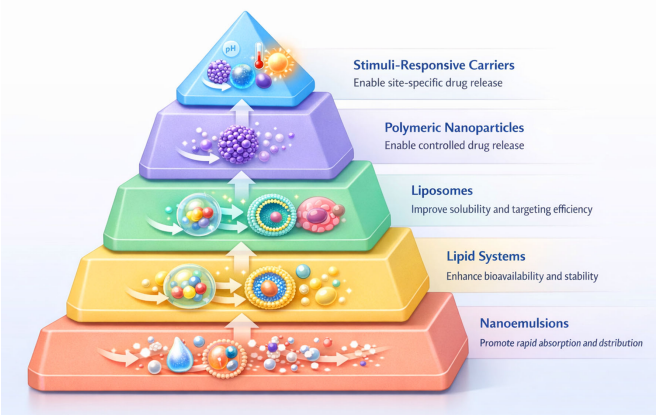


**Fig. 3** Illustration showing diverse nanoformulation strategies including polymeric nanoparticles, liposomes, lipid-based systems, and stimuli-responsive carriers designed to enhance phytochemical delivery, improve bioavailability, and achieve targeted anticancer therapeutic effects.

### 3.2 *Nanoparticles and Nanoemulsions of Solid lipid*

Nanoemulsions and solid lipid nanoparticles (SLNs) are now known as promising lipid-based vehicles of enhancing the therapeutic efficacy of hydrophobic phytochemicals. The SLNs consist of solid lipid cores that are stabilised by surfactants thereby offering a higher stability to the drugs, release control in addition to protection against chemical degradation. Naringin loaded SLNs have shown to have better bioavailability and higher intracellular uptake and have shown better anticancer activity in experimental models (36-40). Nanoemulsions have a high surface area as well as the existence of small droplets, which makes them benefit, including enhanced solubilization, high absorption rate, and large-scale manufacturing capability. Introduction of skimmin into nanoemulsions improves the pharmacokinetic characteristics and treatment activity of this drug. Such lipid systems are especially adequate to be used in oral and parenteral routes of administration and allow efficient delivery of phytochemicals across biological barriers. They are useful in enhancing phytochemical-derived cancer therapy development as their properties of enhancing drug solubility and stability.

### 3.3 *Stimuli-Responsive and Targeted Nanocarriers*

Specific and stimulus sensitive nanocarriers are major development of the targeted cancer therapy, which makes it possible to target drugs and release them selectively in tumour tissues. Such systems may be designed to have surface ligands like antibodies, peptides or folate groups that specifically interact with receptors that are overexpressed on TNBC cells to increase cellular uptake and therapeutic selectivity (41-45). Nanocarriers can be stimulus responsive to release their cargo to internal cues like acidic pH, redox gradients or enzyme activity in the tumor microenvironment. As an example, naringin and skimmin can be delivered by pH-sensitive nanoparticles to the acidic tumour environment without causing harmful effects to normal tissues. Also, controlled drug release can be applied to external stimuli, which are temperature or light. These are advanced delivery systems that enhance drug concentration at the tumor site, minimize the systemic toxicity and increase the therapeutic effect. This kind of innovation is essential in eliminating existing constraints in the treatment of TNBC. **Table 3**

**Table 3** Summary of nanoformulation strategies highlighting carrier systems, materials, advantages, and applications for improving phytochemical delivery, stability, targeting efficiency, and therapeutic outcomes in cancer treatment, particularly triple-negative breast cancer.

| S. No | Strategy Type | Carrier System | Key Materials | Advantages | Applications |
|---|---|---|---|---|---|
| 1 | Polymeric Nanoparticles | PLGA/Chitosan | Biodegradable polymers | Controlled release | Anticancer delivery (31-35) |
| 2 | Liposomes | Phospholipid bilayer | Natural lipids | Biocompatibility | Targeted therapy (36-40) |
| 3 | Solid Lipid Nanoparticles | Lipid core | Surfactants | Stability enhancement | Oral delivery (41-45) |
| 4 | Nanoemulsions | Oil-in-water | Emulsifiers | Improved solubility | Drug absorption |
| 5 | Targeted Nanocarriers | Ligand-conjugated | Antibodies/ Peptides | High specificity | TNBC targeting |
| 6 | Stimuli-responsive Systems | Smart nanoparticles | pH/Temperature sensitive | Controlled release | Tumor micro environment |

## 4 Therapeutic Potential and Future Perspectives

### 4.1 *Enhanced Bioavailability and Pharmacokinetics*

The low solubility and oral bioavailability of naringin and skimmin as well as rapid systemic excretion are major disadvantages that impair the clinical utility of these agents. The nanoformulation approaches are effective to overcome these shortcomings by increasing the solubility of drugs, inhibiting their degradation by the metabolic system, and extending their circulation in the body (46-50). The role of encapsulation in nanoparticles is that it enhances better pharmacokinetic characteristics, such as the half-life and tissue distribution. These nano-carriers allow the effective concentration of phytochemicals at the tumour locations by passive targeting systems like enhanced permeability and retention (EPR) effect. Also, nanoformulations enhance cellular absorption through endocytosis resulting in the enhancement of intracellular drug concentrations. This has a positive outcome leading to an increase in therapeutic effectiveness and decreased dosage frequency. Better pharmacokinetics also help in the reduction of systemic toxicity and adverse effects. Altogether, nanoformulated naringin and skimmin provides a promising approach to the optimization of drug delivery and better clinical results in the treatment of TNBC. **Figure 4**

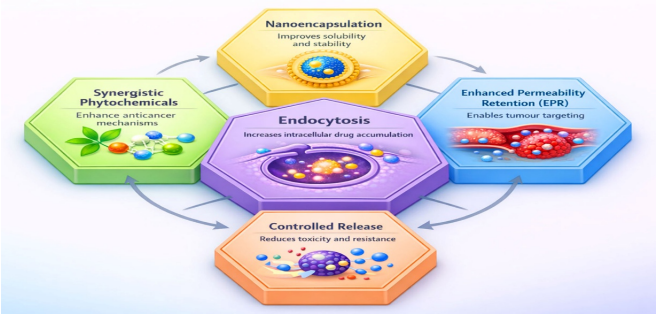


**Fig. 4** Illustration depicts nanoformulated delivery of naringin and skimmin showing improved bioavailability, tumour targeting via EPR effect, enhanced cellular uptake, synergistic anticancer actions, and controlled drug release mechanisms in TNBC therapy.

### 4.2 *Synergistic Anticancer Effects*

Combination of phytochemicals and nanotechnology offers prospects of synergistic effects of anti-cancer therapies by multi-targeted therapy. Naringin and skimmin may be co-delivered with a single nanocarrier, which would allow the combination of many signalling pathways that contribute to the progression of TNBC to be coordinated. Naringin and skimmin have complementary activity, such as induction of apoptosis, metastasis inhibition, and inflammatory inhibition, which combine to produce an overall effect on anticancer action. Also nanoformulations help in orchestrated release of drugs, which allows optimum concentrations of drugs to the tumour site. This will help to suppress drug resistance which is usually a problem in the treatment of TNBC by attacking many pathways at the same time (51-55). Moreover, it is possible that combination therapy can can be used to reduce the dosage of the classical chemotherapeutics, which will reduce the toxicity and increase the patient tolerance. These synergistic efforts will be the way forward in coming up with more effective and safe treatment regimens of aggressive breast cancers.

### 4.3 *Clinical Translation and Problems*

Although there have been tremendous improvements in the field of phytochemical nanomedicine, a number of issues need to be overcome in order to translate them successfully to clinical use. One of the major challenges is large-scale production of nanoformulations with the ability to produce consistent quality and replicated quality (56-60). Also, the problems of the stability, storage, and scalability should be streamlined. The processes of regulatory approval of nanomedicines are complicated as there are no standardised principles, and safety testing has to be conducted on a large scale. The toxicity, distribution of nanoparticles in the long run, and its immunogenicity should be researched. Also, the individual variability of patient response and heterogeneity of tumours could affect the results of therapy. Limited clinical trials of the effectiveness and safety of naringin and skimmin nanoformulations serve as a basis to emphasise the necessity of conducting additional studies. To overcome these difficulties, it is necessary to conduct interdisciplinary research, collaboration between researchers and clinicians, and regulation. It will be necessary to continue innovating and high-level validation to convert these promising nanoformulations into clinical treatments of TNBC. **Table 4**

**Table 4** This table summarizes key challenges, nanoformulation strategies, pharmacokinetic improvements, and therapeutic outcomes of naringin and skimmin, highlighting their potential and limitations in triple-negative breast cancer treatment development.

| Aspect | Challenge | Nanoformulation Strategy | Pharmacokinetic Impact | Therapeutic Outcome | Limitation |
|---|---|---|---|---|---|
| Solubility | Poor aqueous solubility | Nano-encapsulation | Improved dissolution | Enhanced bioavailability | Scale-up issues (46-50) |
| Stability | Rapid degradation | Polymer/lipid carriers | Increased stability | Prolonged drug action | Storage concerns (51-55) |
| Bioavailability | Low oral absorption | Nanocarriers | Enhanced absorption | Higher plasma levels | Cost constraints (56-60) |
| Targeting | Non-specific delivery | EPR-based targeting | Improved distribution | Tumour accumulation | Variable EPR effect |
| Synergy | Limited single-agent effect | Co-delivery systems | Controlled release | Enhanced anticancer activity | Complex formulation |
| Translation | Regulatory challenges | Standardization | Consistent kinetics | Clinical potential | Limited clinical data |

## 5 Future Directions

Future studies on naringin and skimmin nanoformulations must entail the development of precision-targeted treatments of TNBC by combining with the emerging technology, including artificial intelligence and personalised medicine. Technology Multifunctional nanocarriers with the potential of co-delivering phytochemicals and chemotherapeutic agents, gene therapies, or immunomodulators has great potential in enhancing treatment outcomes. The selectivity and off-target effects can be further increased by exploring the use of ligand-binding targeting methods, such as antibodies or aptamers against TNBC biomarkers. Moreover, tumour-sensitive stimuli-responsive systems like pH or hypoxia or enzyme activity are also of interest and should be examined further. The efficacy, safety and the pharmacokinetics of the new drug need to be validated through comprehensive in vivo studies and properly designed clinical trials. It will be important to deal with the issues of large-scale production, regulatory issues, and chronic toxicity. On the whole, a combination of nanotechnology and phytochemicals presents a new avenue of approach to more efficient, safer, and individualised methods of treating cancer.

## 6 Discussion

Incorporation of nanotechnology as well as phytochemicals like naringin and skimmin in curing TNBC is a promising method of treatment of this cancer subtype as it is a very aggressive and resistance-to-treatment form of cancer. These agents have multi-targeted effects, such as the induction of apoptosis and the inhibition of metastasis as well as in the regulation of inflammatory and oxidative pathways. Their clinical use has however, been restricted by low bioavailability and rapid metabolism and this can be easily solved using nanoformulation methods. Other types of nanocarriers such as polymeric nanoparticles, liposomes and lipid-based systems have showed better delivery of drugs, better targeting of tumours and lower toxicity of the system. Although there are promising results in preclinical studies, the issues of heterogeneity of tumours and variability of patient reactions, and absence of standard clinical procedures, are still important obstacles. Moreover, in the long term, safety and the possible immunogenicity of nanocarriers should be considered. Further interdisciplinary investigation and clinical validation would be required to achieve maximum potential of the phytochemical nanomedicine in the treatment of TNBC.

## 7 Conclusion

To sum up, the next-generation phytochemical nanomedicine presents a decent and novel strategy to treat triple-negative breast cancer. It is shown that naringin and skimmin have a strong anticancer potential due to their capacity to regulate important molecular pathways that mediate tumour growth, apoptosis, inflammation, and metastasis. Introduction of these bioactive substances into nano formulations is an effective way to overcome the obstacles of low bioavailability, low solubility and clearance of the system. Nanocarrier systems with advanced technologies are more specific in delivering drugs, enhance their pharmacokinetics, and decrease adverse effects, thus improving their therapeutic effects. Also, they are multi-targeted, which means they can be used as a part of the combination therapy, which will solve the issue of drug resistance and tumour heterogeneity. Although it is a promising technology, it needs more studies to be safe, scalable, and approved by regulators to be used in clinical practise. Comprehensively, the intersection of phytochemistry and nanotechnology will be a revolutionary approach to creating safer and more efficient remedies to these aggressive types of cancers such as TNBC.

### 7.1 CRediT Author Statement

Dhanalakshmi N, Shanmugasundaram Palani, Mangirish Deshpande conceptualization of the study, drafted the manuscript, designed the figures, manuscript review and editing. All authors reviewed the manuscript.

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### 7.2 Declaration Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

## Conflicts of Interest

All authors declare that there are no conflicts of interest associated with the publication of this manuscript.

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