Review

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A Comprehensive Review on Current Knowledge and Future Potential of Topical Therapies in Breast Cancer Treatment

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ABSTRACT

Breast cancer remains one of the most prevalent malignancies among women globally. Despite advances in therapeutic options, the prognosis often remains challenging. Breast cancer typically originates in the epithelial lining of glandular tissue ducts (85%) or lobules (15%). Initially confined to these areas (*in situ*), it generally remains asymptomatic and poses little risk of metastasis. The primary treatments for breast cancer include surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy. Although these interventions have advanced significantly and have improved patient survival rates, they are connected with numerous im mediate and long-term side effects. Effective breast cancer treatment aims to maximize efficacy while minimizing adverse effects. Given that many breast cancers are specific to the breast, developing safe and targeted therapeutic strategies will be of benefit. This review examined the current literature on the effectiveness of topical therapies for breast cancer. Studies and clinical trials were evaluated that have investigated these treatments, focusing on their safety, ease of application, and patient acceptance. Recently, topical drug delivery is transforming breast cancer therapy, offering precision and reduced systemic toxicity. Emu oil-enhanced tamoxifen showed superior transdermal effectiveness, while raloxifene gel achieved 2.77 times greater bioavailability than oral forms. Tamoxifen nanoemulgels and microneedle arrays with resveratrol further enhanced localized delivery, These therapies have gained patient acceptance due to their non-invasive nature, lack of gastrointestinal side effects, ease of application, and favourable safety and therapeutic profiles and setting a new benchmark for innovative and patient-friendly treatments. This review summarizes the findings from various studies, highlighting the benefits and limitations of topical therapies. Topical therapies offer a promising noninvasive option for breast cancer treatment with fewer side effects. These treatments have shown favorable therapeutic and safety profiles, making them an attractive option for patients.

Keywords: Breast cancer; topical treatment; breast skin; local transdermal therapy; nanoformulation

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Key Points

- Topical therapies are localized treatments that target the breast tumour location specifically.
- By limiting the drug's exposure to the rest of the body, this strategy lowers the possibility of systemic adverse effects.
- The efficacy of the therapy may be increased by direct application to the tumour location.
- These therapies function by directly targeting cancer cells through skin penetration, which can help minimise tumour size and relieve symptoms.
- To increase the overall effectiveness of treatment, topical treatments are frequently used in conjunction with other therapies including radiation, surgery, or systemic chemotherapy.

Introduction

In 2022, Globally 670,000 individuals died of breast cancer. Around fifty percent of all breast cancers occur in women who have no recognised risk factors beyond their gender and age. In 2022, breast cancer was the most common cancer among women in 157 of 185 countries (1). It can affect women post-puberty, with incidence increasing notably later in life, equating to one new case every 14 seconds. Survival is more difficult in advanced stages of cancer development. More than fifty percent of Indian women have breast cancer at stages three and four at diagnosis.The post-cancer survival rate for women with breast cancer is reported at 60% in India, while in the United States, it stands at 80% (2). Breast cancer chemoprevention may be necessary for women who are at an increased risk of developing the disease. This entails using pharmacological medications to delay the early stages of carcinogenesis and development.

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Premalignant cells lead to invasive illness. Current standards imply that tamoxifen and raloxifene were administered orally for a period of five years. However, systemic exposure to these medicines is linked to a higher risk of endometrial cancer and thromboembolism (3). Advances in therapeutic interventions have been facilitated by the increasing incidence of breast cancer. As a result, the administration of local and systemic antitumor medications has improved patient survival rates, including survival without illness and overall survival (4). In clinical and survivorship studies for breast cancer, however, standard of living has surpassed survival as the most important outcome metric due to technological advances in disease detection and treatment over time (5).

Individuals who have received a breast cancer diagnosis undergo a variety of management strategies, such as hormonal therapy, radiation therapy, targeted therapy, chemotherapy, and conserving surgery (lumpectomy) (6). Less invasive alternatives to surgery include cryotherapy, microwave irradiation, radiofrequency ablation, laser irradiation, and high-intensity focused ultrasound ablation. The most suitable candidates for these interventions are patients who have small (2-3 cm) tumors that are at least 1 cm away from the chest wall or skin and have minimal to no *in situ* component (7). Despite this, the majority of these approaches have significant limitations; therefore, it is imperative to explore innovative therapeutic methods (8). The primary objectives of treatment for individuals with distant metastases are typically to increase survival rates and life expectancy. For the treatment of breast cancer, a number of modern medications are suggested (9). In individuals at increased risk of developing breast cancer, the administration of anti-estrogens (e.g., raloxifene or tamoxifen) as part of medical therapy may prevent the disease. In certain circumstances where a woman has an elevated risk of developing cancer, an additional preventive measure involves the surgical removal of both breasts (10).

The emphasis on early-stage breast cancer has grown, due to the awareness of the treatment's long-term impact on health, patient involvement in treatment selection, and the availability of less invasive alternatives offering comparable medical benefits (11). Consistently, over the course of several years, clinical research has demonstrated that the majority of therapeutic approaches reduce relative recurrence rates across the risk spectrum as determined by anatomical stage (12).

Recent research findings from countries that have robust early-stage breast cancer screening programs suggest that the prognosis for the majority of women diagnosed with this malignancy continues to improve (13). Advances in treatment and early detection for breast cancer have led to better outcomes for women diagnosed with small, early-stage tumours. These patients often receive a combination of treatments known as "multidisciplinary treatment". This approach has greatly improved their chances of recovery, lowering the risk of cancer recurrence and increasing survival rates (14). However, the treatments are not without their drawbacks, both immediate and prolonged, including cardiovascular complications, an increased risk of secondary cancers, peripheral neuropathy, anemia, myelosuppression, thrombosis, and psychological distress (15). Furthermore, it is possible that the decreased survival rate is attributable to the rapidity of cancer development and metastasis (16). For breast cancer treatment to guarantee patients a high quality of life, it must be as effective as feasible while causing the fewest adverse effects possible. A carefully selected combination of therapeutic interventions affords patients the opportunity to optimize their treatment outcomes while simultaneously mitigating or eradicating unfavourable consequences, recurrence and resistance (17).

Despite the efficacy of these medications being established through successful breast cancer preventive studies, they have been poorly received by women at high risk for developing the disease (18). Reductions in quality of life, the likelihood of more severe side effects, as well as healthy women's unwillingness to use oral medicine for prevention, are among the factors. However, in order to manage breast cancer, the medication should only be applied to the breast; systemic exposure is unnecessary and potentially harmful (19).

Most breast malignancies are non-metastatic and breast-specific, including ductal carcinoma (over 75% of cases) and lobular carcinoma, both treatable with targeted therapy. Developing safe therapeutic strategies for breast cancer is important, therefore (20). Transdermal drug delivery (TDD) is an effective means of delivering drugs via the skin, reducing the risks and limits associated with oral medication administration. TDD is an effective alternative to oral treatment, avoiding gastrointestinal absorption, hepatic first-pass metabolism, and minimizing deleterious effects from peak plasma drug concentrations (21).

The investigation of topical administration of anticancer medications to the epidermis of the breast has also been undertaken as a targeted therapy strategy (22). The unique anatomical structure of the mammary papilla (nipple) presents a possible avenue for administering drugs directly to the underlying breast tissue. The nipple's surface duct apertures are directly connected to the numerous terminal duct lobular units of the breast (23). Moreover, the epidermis of the nipple-areola complex are thinner compared to the skin. The nipple-areola complex comprises various appendages, including sebaceous, apocrine, and eccrine perspiration glands, all of which have the potential to serve as transport routes to the underlying breast tissue (24, 25). This review offers a concise synopsis of the research conducted on topical treatments for breast cancer, encompassing *in vitro*, preclinical, and clinical investigations.

A Critical Analysis of Recent Research on Topical Breast Cancer Treatment

Endoxifen *In Vitro* Evaluation in Human Epidermis

To enhance endoxifen (ENX) uptake to match that of transdermal estradiol (EST), Lee et al. (26), studied the skin permeation of tamoxifen's metabolites, N-desmethyl-4-hydroxytamoxifen (ENX) and 4-hydroxytamoxifen (4-OHT) through human skin. Oral tamoxifen, despite its efficacy in breast cancer prevention, has low acceptance due to adverse effects. The study found that ENX's skin penetration was initially inferior to 4-OHT. However, adding 1% oleic acid (OA) significantly enhanced ENX absorption and tissue penetration over 24 hours. For effective transdermal delivery using a 60% ethanolic vehicle, the optimal OA concentration was 0.25–0.5%. Combining ENX with OA improved skin deposition and absorption to levels comparable to EST. While 4-OHT also showed increased penetration, ENX's improvement was more pronounced, indicating its promise for transdermal delivery (26).

Treatment of Breast Cancer via Iontophoretic Administration

Komuro et al. (27), applied iontophoresis to the nipple as an innovative drug delivery system (DDS) to enhance miproxifen phosphate (TAT-59) efficacy against ductal tumors compared to systemic delivery (IP

administration). Using rat epidermis, they found that iontophoresis facilitated TAT-59 transfer. Autoradiography confirmed direct delivery of TAT-59 to lactation ducts via IP administration. The plasma concentrations of TAT-59 and its active metabolite DP-TAT-59 were lower following IP treatment compared to DDS. In mammary tissue, DDS delivery provided drug availability approximately three times greater than IP treatment at a six-fold lower dosage. This approach minimizes systemic exposure and potential adverse effects because of low plasma concentrations. The study concluded that DDS effectively delivers DP-TAT-59 to ductal lesions, highlighting its suitability for targeted therapy (27).

Drug Delivery via Transpapillary Means to the Papilla and Breast

The objective of the research conducted by Dave et al. (24) investigated the topical administration of the hydrophobic compound EST and the hydrophilic substance 5-fluorouracil (5-FU) to the breast via the mammary papilla (nipple).

***In Vitro* Diffusion Study**

In vitro diffusion experiments using Franz diffusion cells showed that the penetration of 5-FU through human nipples was significantly reduced by keratin inserts compared to porcine nipples and breast skin. Removing the keratin plug from the human nipple significantly reduced latency time and increased flux and total 5-FU penetration compared to human breast epidermis. Similarly, for hydrophobic compound like EST, the keratin plug significantly impacted penetration through the human nipple, with EST concentration three times higher in the nipple than in the breast epidermis. Removing the keratin plug made EST absorption through pig nipples similar to human nipples, resembling 5-FU behaviour.

***In Vivo* Studies**

In addition to *in vitro* methods, the study includes *in vivo* tests where 5-FU was topically applied to rat nipples. The efficacy of localised administration was assessed by measuring the drug's concentration in the breast tissue following application and comparing it to systemic levels in plasma and other organs.

High Drug Concentration in Breast Tissue

The findings showed that, following six hours of topical application, the concentration of 5-FU in the breast tissue was two to three times more than that obtained by transdermal and intravenous (IV) administration. This implies that localized medication administration to the breast can be accomplished effectively through the nipple.

Minimal Drug Amounts in Plasma

Crucially, the study discovered that topical treatment of 5-FU resulted in substantially lower amounts of the drug in plasma compared to transdermal and IV delivery. This reduced systemic exposure indicated that the localized administration technique could decrease potential side effects often associated with higher plasma drug levels.

The *in vivo* results demonstrated the feasibility of localized topical delivery through the nipple, supporting the idea that this method can achieve targeted therapeutic effects in the breast while limiting drug distribution to other organs. These investigations highlight the potential of using the nipple as a direct route for drug delivery, particularly for treatments aimed at breast cancer and other breast-related conditions, by achieving high local concentrations with reduced systemic impact. These methods collectively provided a comprehensive understanding of drug penetration levels and the potential for localized drug delivery through the nipple (24).

Administration of Cytotoxic Therapies to Breast Tumors via Local Iontophoretic Administration

The iontophoretic delivery of cisplatin was evaluated using SUM149 human xenograft and T11 syngeneic orthotopic breast cancer models. The study compared device-administered cisplatin, IV cisplatin, and a combination of both. Both IV cisplatin and device effectively inhibited tumor growth compared to controls, with device cisplatin demonstrating superior efficacy compared to combined treatment.

Moreover, the study investigated enhancing cislatin's efficacy with radiation therapy. Mice with T11 tumors received treatments: device + radiation, IV + radiation, device + cisplatin, or device + cisplatin + IV + radiation over five days post-tumor inoculation. Three main groups emerged: Those receiving radiation alone, device cisplatin, or IV cisplatin showed similar survival and tumor growth rates (17 days), all better than untreated controls. Combination therapies (device cisplatin plus radiation, IV cisplatin plus radiation, or device + IV cisplatin) resulted in similar outcomes (23 days). The most favorable results were observed in the device + IV cisplatin + radiation group, with the highest tumor inhibition and survival (26 days) (p<0.0002, log-rank test). The study concluded that integrating systemic treatment, device therapy, and radiation significantly enhances survival and inhibits tumor growth in breast cancer models (28).

Studies on the *In Vitro* Permeation of α-Santalol Across the Epidermis of the Breast and Nipple

Dave et al. (29), investigated the *in vitro* viability of administering an α-santalol formulation transdermally to rodents. They assessed the permeability of porcine, rat, and human breast tissues (nipple and breast skin), combining data from pig/human tissues. Rat breast tissue showed a reduced lag time compared to pig and human tissues, with significantly diminished tissue retention. However, the cumulative amount of α-santalol infiltrating the breast tissue over 24 hours (122-236 g/mL) was seven to fifteen times more than the IC50 value for human breast cancer cells.

The chemopreventive efficacy of the α-santalol formulation was tested using an experimental 7,12-dimethylbenz anthracene (DMBA) model of breast cancer. After a 12-week treatment period, the vehicle and control groups each had three tumors, while the α-santalol treatment group had only one tumor. This indicates that α-santalol significantly reduced tumor incidence and multiplicity. The study concludes that developing an effective and safe transdermal chemoprevention approach for breast cancer using α-santalol was feasible (29).

Emu Oil Transfersomes Delivered Locally via Transdermal Route

Oral tamoxifen for estrogen-positive ductal carcinoma *in situ* (DCIS) is poorly accepted due to adverse effects, though its effectiveness comes from its metabolite, 4-OHT. Sundralingam et al. (30), used a mouse breast cancer model to compare 4-OHT transfersomal formulations (without and with emu oil) to oral tamoxifen. They found that both transfersomal formulations were as effective as oral tamoxifen in reducing tumor volume and necrosis. However, these formulations had significantly lower plasma concentrations of 4-OHT compared to the oral tamoxifen group (10.24±0.07 and 32.45±0.48 ng/mL, respectively). The study suggests that emu oil-enhanced transdermal formulations could treat breast cancer effectively while minimizing the adverse effects of oral tamoxifen (30).

Liposome Nanoparticles of Raloxifene

In an effort to improve the binding and antitumor efficacy of raloxifene (RXF) as a prospective therapy for breast cancer, Salem et al. (31), developed a stable deformable liposome formulation. In order to investigate deformable liposomal penetration, RLDL formulation was incorporated into a carbopol gel in order to assess penetration and antitumor efficacy.

The anticancer activity was assessed by weekly measuring of the quantity and diameter of papillomas greater than 1 mm in female rodents injected with a single dose of the tumor initiator DMBA. The ideal gel formulation demonstrated 2.77 times greater bioavailability than oral RXF and, as a result, exerted a substantial antitumor effect. In light of the author's conclusion, the optimal RLDL gel may represent an effective breast cancer treatment (31).

Nanogel Topically Applyable Tamoxifen Citrate

The objective of the research conducted by Alyami et al. (20), was to develop a water-insoluble nanoemulgel (NEG) formulation of the potent anticancer drug tamoxifen citrate (TAM) in order to improve topical delivery, induce substantial accumulation at the tumor site, and preserve healthy tissues. The nanoemusion system was designed and developed with the objective of optimizing the therapeutic efficacy of topical breast cancer treatment through enhancements in the anticancer TAM lipophilic agent's solubility, skin deposition, and permeation. The assessment of the formulations' *ex vivo* skin penetrability properties was conducted on albino rats. Consequently, the researchers reached the conclusion that the recently developed TAM-NEGs functioned as a potentially effective vehicle for enhancing the transdermal effectiveness of poorly diffusable TAM medications, particularly in the context of long-term breast cancer management, primarily by eliminating systemic adverse effects induced by oral TAM administration (20).

Modification of Microneedles and Microemulsions for Augmenting the Topical Delivery of Celecoxib

In addition to optimizing microemulsions for transdermal delivery of celecoxib to the breast surface, Mojeiko et al. (32) evaluated the efficacy of their formulation in conjunction with microneedles. The assessment of encapsulation's impact on the cytotoxicity of celecoxib towards MCF-7 breast cancer cells was conducted via cytotoxicity assays. By reducing the IC50 of celecoxib in MCF-7 cells by 3.3-fold, microemulsion incorporation suggests that the drug's cytotoxicity may be enhanced by the presence of formulation components in the breast tissue. In breast tissue, the presence of formulation components may mitigate the cytotoxicity of the drug. The potential for microneedle application to increase the delivery of microemulsion components to mammary tissue and facilitate the cytotoxic effects of drugs in cancer cells was attributed to its ability to penetrate the epidermis (32).

Targeted Delivery of Resveratrol-Loaded Nanostructured Lipid Carriers via Microneedle Assistance

Gadag et al. (33) devised nanostructured lipid carriers (NLCs) containing resveratrol (RVT) in order to enhance the efficacy of localized drug delivery to breast tissues via microneedle arrays. When compared to unadulterated RVT, the RVT-NLCs administered via microneedle array 1200 exhibited enhanced transdermal RVT penetration while minimizing skin retention. Based on cell viability studies, RVT-NLCs exhibited greater cytotoxicity compared to purified RVT. Preclinical studies conducted on rodents demonstrated that the bioavailability and localized effect of RVT were enhanced when combined with the benefit of microneedle arrays, in contrast to pure RVT administered orally. This finding established the superior treatment efficacy of RVT-NLCs in the context of breast cancer (33).

Clinical Efficacy of 4-OHT Percutaneous Gel in a Study of Breast Cancer

Rouanet et al. (34) conducted a randomized trial with 55 postmenopausal women diagnosed with invasive estrogen receptor-positive breast cancer to compare the efficacy of oral tamoxifen (20 mg/day) and 4-OHT gel (0.5, 1, or 2 mg/day) applied percutaneously. The study lasted two to three weeks. The oral tamoxifen group had higher plasma levels of 4-OHT compared to the gel groups. There was no dose-dependent effect on progesterone or estrogen receptor levels, and the topical gel was well tolerated. Both the higher gel concentrations and tamoxifen induced hot flashes at similar rates. The study concluded that percutaneous 4-OHT gel effectively regulates local tumor proliferation (34).

Transdermal 4-Hydroxytamoxifen Gel Compared to Oral Tamoxifen

Lee et al. (35) conducted a phase II randomized, double-blind, placebo-controlled trial comparing oral tamoxifen (20 mg/day) with topical 4-OHT gel (4 mg/day) in 27 pre- and post-menopausal women with DCIS. Treatment lasted six to ten weeks before surgery, with tamoxifen and metabolite levels measured in plasma, nipple aspirate fluid, and breast adipose tissue using liquid chromatography. The primary outcome, Ki-67 staining in DCIS lesions, showed post-therapy decreases of 3.4% in the 4-OHT group and 5.1% in the oral tamoxifen group (p = 0.03, between-group p = 0.99). Mean 4-OHT concentrations in mammary adipose tissue were comparable (5.4 ng/g for oral *vs.* 5.8 ng/g for 4-OHT, p = 0.88), while plasma levels differed significantly (0.2 ng/mL oral *vs.* 1.1 ng/mL 4-OHT). Oral tamoxifen increased plasma sex hormone binding globulin, factor VIII, and von Willebrand factor, and decreased plasma insulin-like growth factor-1 levels. The study suggests exploring local transdermal therapies for breast cancer prevention and DCIS treatment (35).

A Phase II Placebo-Controlled Trial of Telapristone Acetate Local Transdermal Delivery

In a phase II trial, Lee et al. (36) randomized women considering mastectomy to receive a progesterone receptor antagonist, telapristone acetate (TPA), either orally (12 mg/day) or transdermally (12 mg/breast) for 4±1 weeks. Tissue and plasma concentrations were measured using liquid chromatography at five locations within the mastectomy specimen. The breast-to-plasma concentration ratio was higher in the transdermal group (2.73 *vs.* 1.44, p = 0.02). Oral TPA significantly decreased serum EST and progesterone, while transdermal TPA did not affect these hormones because of low systemic levels. Despite limited dermal penetration, drug distribution in the breast was consistent across both groups, unaffected by tissue adiposity. The study demonstrated that transdermally applied drugs can effectively traverse the entire breast with distribution similar to the oral route (36).

Increased scientific attention has been devoted to the development of novel therapeutic agents via the application of nanotechnology. Various drug delivery systems, including transfersomes, microemulsions, nanogels, microneedles, and iontophoresis (Figure 1) can efficiently transport drugs to breast cancer cells. These systems are capable of traversing biological barriers, such as the stratum corneum in the skin.

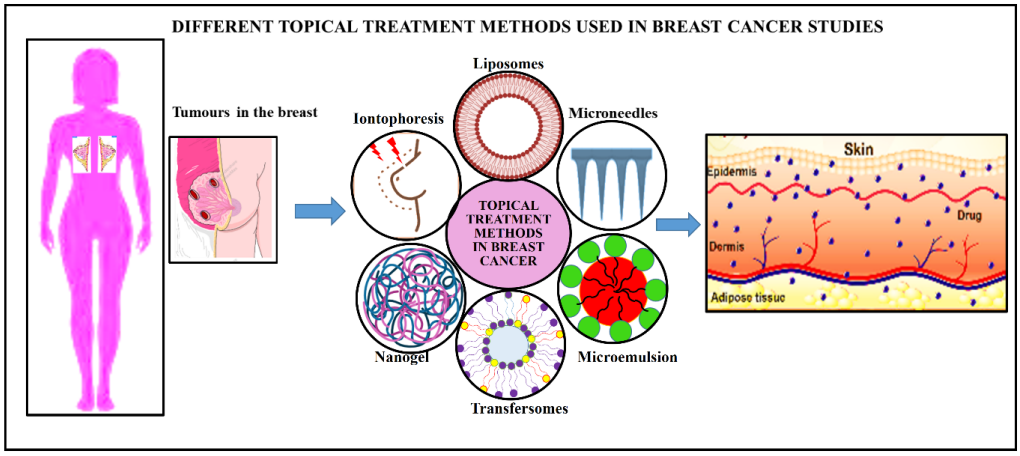

Figure 1. Different topical drug delivery system used in breast cancer studies

Furthermore, their capability to deliver components to the intended site is especially beneficial when co-delivering substances or combining treatments.

Future Prospective Aspects of Topical Treatment for Breast Cancer

Elevated local drug concentrations may be achieved through the direct administration of medication to the breasts, thereby potentially improving efficacy, safety, and acceptability. Local transdermal treatment administered via the breast skin has been hypothesized to increase drug concentrations in the breast tissue as a consequence of both deep and percutaneous absorption and local penetration (29).

Advances in topical and TDD techniques have facilitated the precise administration of remedies to the intended site of action, resulting in enhanced penetration of the stratum corneum and increased bioavailability. The significance and potential of natural drug discovery are expanding at a rapid rate. Phytoconstituents are experiencing a surge in prominence due to their reduced toxicity in comparison to synthetic compounds. Through modulation of signaling pathways and gene expression, these phytochemicals have the capability to impede cancer cell proliferation and surmount resistance (37).

A multitude of studies have reported that the concurrent administration of phytochemicals and chemotherapy resulted in reduced toxicity, a synergistic effect, and an enhanced response against multidrug-resistant breast cancer (38). The constraints of traditional treatment act as an ongoing impetus for the advancement of optimized and refined transdermal and TDD systems. Compared to conventional therapy, these may provide numerous advantages, including enhanced solubility for highly hydrophobic pharmaceuticals and improved drug stability. By employing a constant formulation, multiple agents can be delivered concurrently to a single site, ensuring synergy and facilitating the more accurate determination of the optimal medication ratio and dose for maximum therapeutic effect (39).

When contrasting topical therapy with systemic agents, the former potentially facilitates increased drug concentrations at the tumor site while minimizing overall toxicity. Furthermore, the co-administration of numerous drugs possessing diverse physicochemical properties may potentially exert a synergistic influence on cancerous cells, potentially overcoming the therapeutic barrier to the treatment (40). As a result, numerous novel prospects exist regarding the identification, development, and application of novel pharmaceuticals intended for topical treatment of breast cancer.

Discussion and Conclusion

Previous research studies have demonstrated that local transdermal formulations for the treatment of breast cancer are just as effective as oral approaches, with no or minimal adverse effects. In addition, topical gel applied to the breast surface has been shown in clinical trials to have an antiproliferative effect comparable to that of oral medications. A multitude of novel compounds and inventive amalgamations are undergoing clinical evaluation; should any prove efficacious, they could potentially be implemented in real-world environments, providing a ray of optimism for the efficient management of breast cancer. This review has summarized the substantial body of research that has been conducted thus far and anticipates the advancement of novel pharmaceuticals delivered transdermally via topical means. These have the potential to mitigate adverse effects, improve user safety, and elevate overall quality of life.

Footnotes

Authorship Contributions: Concept: N.B.S.T.,V.P.K., R.G., C.S.; Design: N.B.S.T.,V.P.K., R.G., C.S.; Data Collection or Processing: N.B.S.T.; Analysis or Interpretation: N.B.S.T.,V.P.K., R.G., C.S.; Literature Search: N.B.S.T.; Writing: N.B.S.T.

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