

# Efficiency of Transdermal Drug Delivery Systems for the Treatment of Breast Cancer: A Systematic Literature Review

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## Abstract

**Background:** To date, various methods have been developed for cancer treatment, among which transdermal drug delivery has attracted increasing attention due to its reduced side effects and higher patient acceptance. The current study aimed to systematically review available documents on the efficiency of transdermal drug delivery in treating breast cancer. Furthermore, the efficacy and success rate of this method were compared with other conventional drug administration methods.

**Methods:** A systematic literature search was performed using PubMed, Scopus, Ovid, ScienceDirect, EMBASE, and Google Scholar databases. Due to limited data in this field, all available human and animal studies were included for data extraction. Three authors independently assessed the selected documents and extracted the relevant data.

**Results:** Only two human trials involving 87 women, in addition to 16 animal studies, were included. The results of the included studies showed that transdermal drug delivery may be superior to oral and injectable routes of drug administration due to higher efficacy, lower side effects, and higher patient acceptability.

**Conclusion:** Transdermal drug delivery can be considered a preferred method for site-specific drug administration, which can produce a high local drug concentration while maintaining low circulating drug levels, reducing the risk of adverse side effects and decreasing the frequency of drug administration.

**Keywords:** Transdermal drug delivery, Breast cancer, Systemic effect, Site-specific drug delivery

## Introduction

Breast cancer is the most common cancer among women and the second most frequent malignancy with about two million new cases each year worldwide.<sup>1</sup> Although breast cancer is the most common cancer among women, it can also be found in men.<sup>2</sup> Treatment approaches for breast cancer depend on several factors, including the stage of the cancer, the presence of metastasis, and the size and growth rate of the tumor. Each of these factors plays an important role in the success of treatment. Conventional treatment methods, including surgery and chemotherapy, have several side effects such as severe inflammation and pain.<sup>3</sup> Pharmacotherapeutic approaches offer potential benefits for the treatment of various types of cancer. To date, a wide range of anticancer agents have been introduced, many of which exhibit strong and selective antitumor properties.<sup>4,5</sup> Drugs used to treat breast cancer are typically systemic treatments administered either orally or through intravenous injection. However, these therapies are often associated with adverse side effects, poor bioavailability, and low efficacy.<sup>6</sup> These problems mainly result from limited drug uptake, low penetration

and permeation, and drug metabolism.<sup>7</sup> Therefore, targeted drug delivery routes have been suggested as promising alternatives, particularly for drugs with poor bioavailability.<sup>8</sup>

Dermal drug delivery is a non-invasive method for the administration of therapeutic agents and offers various advantages such as high efficiency, low cost, and improved patient satisfaction.<sup>9</sup> Additional benefits include the ability to apply high concentrations of the drug to the skin, reducing systemic drug exposure and associated side effects, avoiding the first-pass metabolism, enabling sustained drug release, and minimizing the frequency of use, especially for drugs with a short half-life. Furthermore, the ease and painlessness of application are other advantages of this method over other conventional methods. Novel transdermal delivery techniques have been recently introduced that overcome the skin's barrier and enhance drug penetration into tumors.<sup>10</sup> This type of topical delivery of antitumor agents represents a promising method for targeted drug delivery, which can reduce systemic side effects and improve treatment success rates.

In the current study, we aimed to systematically review the available literature on the efficiency of transdermal drug delivery systems for the treatment of breast cancer. Additionally, the effectiveness of this method was compared to other types of systemic medications.

## Methods

### Study Search and Inclusion Criteria

In the current review, we performed a systematic literature search in January 2021 using Web of Science, Scopus, ScienceDirect, Embase, Medline via PubMed, and Google Scholar. The search terms used for this purpose included “transdermal drug delivery” and “breast cancer”, along with their equivalents and similar terms. To exclude unqualified articles, the search was first limited to English-language articles. Review articles, case reports, short communications, editorials, and conference abstracts were excluded from further evaluation. Subsequently, irrelevant documents were also removed. All procedures, including design, database searching, article selection, and data extraction were independently performed by three authors. Any disagreements among the authors were discussed and resolved at each step before processing further. The PRISMA 2009 checklist, a standard protocol for reporting systematic reviews, was followed during the study design and article selection process<sup>11</sup>. According to the inclusion criteria, all relevant *in vivo* and human studies were included for data extraction.

### Data Synthesis and Variables

All available information, including the author’s names, publication dates, and types of medication were first extracted. Moreover, additional information such as the dosage of administered drugs and measured variables were extracted and described.

## Results

Database and manual searches yielded a total of 1220 articles, of which only 1101 were qualified for further evaluation. After a step-by-step screening and selection process, 18 relevant articles were identified, including two human studies and 16 animal studies. The detailed selection process is demonstrated in Figure 1. The most commonly measured outcomes in the included studies were tumor volume reduction, toxicity, skin penetration, efficacy, cellular uptake, dermal drug distribution, skin absorption, drug effects, bioavailability, drug flux, and safety.

The results of two clinical trials using telapristone acetate and 4-hydroxytamoxifen administered via transdermal delivery demonstrated that the efficiency of the method is similar to that of the oral route of administration.<sup>7,12</sup> However, all animal studies confirmed that transdermal delivery of anticancer drugs can lead to higher skin penetration rates, enhanced cellular uptake, improved dermal drug distribution, and increased bioavailability. These advantages may lead to higher

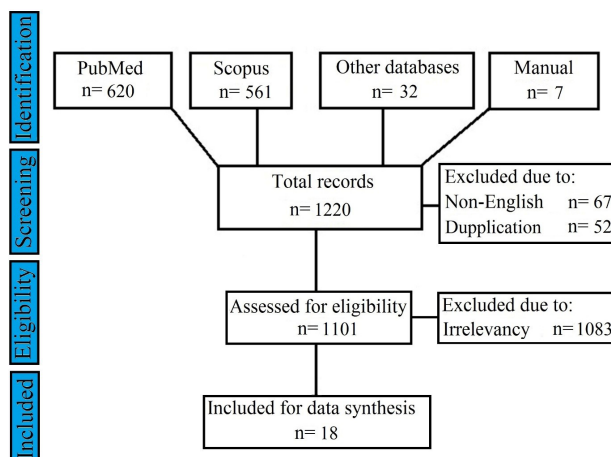


Figure 1. Flowchart of Article Selection Process

efficacy and subsequently greater reduction in tumor volume. Letrozole identified as the most efficient drug using transdermal delivery demonstrated a 95-fold higher effectiveness than oral and intravenous administration.<sup>13</sup> Findings from animal studies showed that the transdermal route can result in about 86% inhibition of tumor growth. Moreover, this type of local therapy was reported to be a safe and non-invasive method, causing no skin injuries, which may contribute to greater patient acceptance. Animal studies also demonstrated that the plasma concentration-time profile and bioavailability of drugs were significantly more favorable with transdermal delivery when compared with the oral formulation.<sup>14</sup> Toxicological evaluations demonstrated that levels of toxicity biomarkers, including blood urea nitrogen, creatinine, aspartate transaminase, and alanine transaminase, decreased remarkably following the transdermal delivery system, indicating an improved safety profile for this therapeutic approach.<sup>13</sup> Findings also suggested the critical role of drug formulation in penetration efficiency and treatment outcomes. Among various enhancers, oleic acid was identified as the most effective, which can improve the delivery by up to 27-fold.<sup>15</sup> The delivery of large molecules has been suggested to be more feasible through the mammary papilla.<sup>16</sup> Additionally, microscopy findings demonstrated that the appendageal route may be the main route for drug penetration into the deeper layers of the skin.<sup>17</sup> A summary of the included studies with relevant data is presented in Table 1.

## Discussion

Breast cancer is one of the most common malignancies in women, affecting an estimated two million people globally each year. Various medications and therapeutic strategies have been used to treat the disease; however, most of these approaches are associated with concentration-dependent side effects that may negatively influence patients’ quality of life. In contrast, site-specific and targeted drug delivery systems are promising choices for enhancing treatment efficiency while minimizing adverse effects. Transdermal drug delivery is the topical application of drugs that

**Table 1.** Summary Findings of Included Documents

| Reference                        | Study Subjects                     | Primary Outcomes                                                                                   | Drug                                                         | Dose                       | Success Rate                      |
|----------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------|----------------------------|-----------------------------------|
| Lee et al <sup>18</sup>          | 60 Women                           | Drug distribution, dermal permeation, efficacy                                                     | Telapristone acetate                                         | 12 mg/breast               | Similar effect to oral medication |
| Sundralingam et al <sup>12</sup> | Women                              | Drug penetration, accumulation                                                                     | 4-OHT                                                        | 4 mg/day                   | Similar effect to oral medication |
| Bathara et al <sup>13</sup>      | Mice, pig                          | Tumor volume reduction, toxicity, penetration, efficacy, cellular uptake, dermal drug distribution | Docetaxel                                                    | 10 mg/kg                   | 4-fold                            |
| Regenthal et al <sup>19</sup>    | Franz diffusion cells, beagle dogs | Skin absorption, drug effects                                                                      | Anastrozole                                                  | 20–30 mg (2.5%)            | 91.5%                             |
| Gupta et al <sup>20</sup>        | Human skin                         | Bioavailability, efficacy, permeation                                                              | Raloxifene                                                   | -                          | 2.33-fold                         |
| Tilawat and Bonde <sup>8</sup>   | Goat ear pinna skin                | Efficacy, drug flux, skin penetration                                                              | Curcumin                                                     | 2.5 mg/mL                  | -                                 |
| Jha et al <sup>15</sup>          | Human skin                         | PPI, distribution, skin irritation, IL-6 levels                                                    | Hyaluronic acid-oleylamine and chitosan-oleic acid conjugate | 200 µL of 10 mg/mL         | 4-fold                            |
| Gao et al <sup>21</sup>          | Pig                                | Histopathology, bioavailability and efficacy                                                       | Exemestane                                                   | 144 mg/kg bw/d             | -                                 |
| Spreafico <sup>22</sup>          | Swiss albino mice                  | Transdermal fluxes, cytotoxicity, tumor volume, inhibition percentages, necrotic effect            | MDHJ                                                         | 0.07 µL/cm <sup>2</sup> /h | 2-fold                            |
| Dave et al <sup>23</sup>         | Rats                               | Permeability, biodistribution and efficacy                                                         | α-Santalol                                                   | 500 µL 10% v/v             | 2.5-fold                          |
| Khan et al <sup>14</sup>         | Breast skin                        | Cytotoxicity, skin penetration, tumor growth inhibition, organ damage                              | Tamoxifen                                                    | 2 mg/d                     | 80%                               |
| Sundralingam et al <sup>12</sup> | Human skin, athymic nude rats      | Drug concentrations                                                                                | 4-OHT                                                        | 1 mg/kg/day                | 7-fold                            |
|                                  |                                    |                                                                                                    | Telapristone                                                 | 1.5 mg/kg/day              | 3-fold                            |
|                                  |                                    |                                                                                                    | Diclofenac                                                   | 129.7 mg                   | 6-fold                            |
| Chaturvedi et al <sup>24</sup>   | Rat skin                           | Bioavailability, distribution                                                                      | Raloxifene                                                   | 60 mg/d                    | 2-fold                            |
| Mane et al <sup>25</sup>         | Rat                                | Skin permeation, transition behavior, drug release                                                 | Exemestane                                                   | 5 mg/kg                    | 6.58-fold                         |
| Mekkawy et al <sup>26</sup>      | Mice                               | combination therapy                                                                                | Letrozole                                                    | 0.75 mg                    | 95-fold                           |
| El-Bakry et al <sup>27</sup>     | Human Skin                         | Skin permeation, tissue disposition, drug accumulation                                             | Anastrozole                                                  | 2 mg                       |                                   |
| Di Cosimo et al <sup>28</sup>    | Male Wistar rats                   | Percutaneous penetration, permeation rate                                                          | Letrozole                                                    | 6 mg/10 cm <sup>2</sup>    | 2-fold                            |
| Wang et al <sup>29</sup>         | Horse, nude mice, baboon           | Tissue distribution, side effects                                                                  | Toremifene                                                   | 2.5 mg/day                 | 50-fold                           |

Note. PPI: Pore permeability index; 4-OHT: 4-hydroxytamoxifen; IL-6: Interleukin-6; bw/d: Body weight per day; MDHJ: Methyl dihydrojasmonate.

has been recently proposed as a safe and non-invasive method with efficient drug loading, controlled release, easy handling, and high effectiveness compared to oral medications.<sup>30</sup> Due to its sustained release kinetics and high skin penetration rate, transdermal drug delivery is theoretically more efficient than intravenous injection or oral administration.<sup>14</sup> In the current study, a systematic literature review was performed to evaluate the efficiency and safety of the transdermal route compared to other administration methods.

The findings of this study demonstrated that localized application of drugs to breast tissue is an effective method of administration, which can increase treatment efficiency through direct drug delivery, improved skin penetration, drug accumulation in the target tissue, and reduced circulating drug concentrations.<sup>14,15,27</sup> Human studies have shown that although the antiproliferative effects of the administered drug were similar between both oral and transdermal therapy, the effects on endocrine and coagulation parameters were lower in local transdermal therapy. This suggests the need for further evaluation of transdermal drug delivery in breast cancer

therapy.<sup>12</sup> Evaluation of pharmacokinetic parameters such as the mean residence time demonstrated a reduced dosing frequency following transdermal administration of the drugs, suggesting that the interval between doses may also be extended compared to oral administration. Furthermore, the success rate of therapy was reported to be two times higher with the transdermal method.<sup>31</sup>

Despite the advantages of topical delivery, dermal drug delivery has limitations, as the skin acts as a barrier against the entry of foreign substances and only lipophilic and small molecules less than 500 Da can penetrate the deeper skin layers. Human studies have also indicated that despite poor dermal permeation, drug distribution through breast skin is similar in transdermal and orally delivered drugs. Moreover, drug concentration strongly correlates with tissue adiposity and drug lipophilicity, suggesting that modifying drugs to enhance skin permeation may enhance therapeutic efficiency.<sup>18</sup>

The success rate of the transdermal delivery system depends on the drug's ability to penetrate and accumulate in the target tissue. This can be achieved by optimizing formulations and delivery methods such as using

physical penetration enhancement methods, chemical penetration enhancers, nanocarriers, dendrimers, and gels.<sup>10</sup> Various technologies, including nanoformulations and microemulsion systems, have been employed to enhance the delivery of drugs and macromolecules through the skin.<sup>32,33</sup> Surfactants within formulations may play a determinant role in optimizing drug absorption through the skin. Additionally, optimizing transdermal flux via drug modification or using ethosome formulation can enhance drug penetration efficiency by more than 21-fold compared to conventional methods such as oral formulation or liposome drug delivery.<sup>20</sup>

Drug-loaded nanovesicles are considered a successful delivery system in transdermal delivery for breast cancer therapy.<sup>34</sup> Hydrochloride-loaded transfersomes demonstrated significantly higher efficiency in drug permeation and deposition through the skin, indicating that enhanced transdermal delivery is a superior alternative to oral drug delivery.<sup>24</sup> Conjugation of drugs with cell-penetrating peptides is also regarded as another effective method to improve drug delivery efficiency.<sup>35</sup>

The major limitation of this study was the limited number of available human trials. However, the results of this review provide a foundation for considering the transdermal drug delivery method with improved formulation as a novel therapeutic approach for breast cancer treatment, potentially reducing the unwanted side effects of conventional cancer therapies. Future research should focus on further improving the efficacy and reducing the toxicity of drugs administered through the transdermal route compared to oral medications.<sup>36</sup> Therefore, large-scale clinical trials are recommended to be performed to confirm the effectiveness of this method.

## Conclusion

Cancer therapy via the transdermal route has demonstrated superior drug delivery properties compared to oral formulation and intravenous methods. The major benefits of the transdermal drug delivery approach include sustained drug release, direct delivery of the drugs to local tissues, high drug concentration at the tissue without producing high serum concentrations, and consequently fewer side effects. These findings indicate that the transdermal approach is an appropriate drug delivery system for the treatment of breast tumors without producing systemic side effects. According to the evidence presented, transdermal drug delivery to breast tissue could be a superior alternative to oral delivery or intravenous drug injection for breast cancer treatment.

## Author's Contribution

**Conceptualization:** Faezeh Talaee.

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**Formal analysis:** Seyedeh Halimeh Najafi.

**Funding acquisition:** Seyedeh Halimeh Najafi, Morteza Marashi.

**Investigation:** Seyedeh Halimeh Najafi.

**Methodology:** Morteza Marashi.

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## Competing Interests

None to declare.

## Ethical Approval

Not applicable.

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