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Nano Thermosensitive Hydrogels Curcumin in Drug Delivery Systems in Breast Cancer Therapy: Systematic Literature Review

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ABSTRACT

The enormous side effects of cancer chemotherapy are driving the development of new medicines derived from plants. Curcumin has pharmacological activity as an anti-cancer. However, its oral bioavailability is low due to poor solubility and rapid degradation, limiting its clinical application. Curcumin has now been widely developed in the form of nanoformulations, including nano-thermosensitive hydrogels, which are increasingly explored as drug carriers. The drug delivery system for breast cancer therapy using nano-thermosensitive hydrogels has shown improved performance due to polymer characteristics responsive to temperature changes. This system enhances drug release control and provides an advantage over conventional intravenous administration. This study aims to assess the effectiveness of nano-thermosensitive hydrogels loaded with curcumin in delivering breast cancer drugs. The methods used were Systematic Literature Review (SLR) and bibliometric analysis. The results showed that curcumin in nano-thermosensitive hydrogel formulations improves bioavailability and therapeutic efficacy in breast cancer treatment. In conclusion, curcumin incorporated in nano-thermosensitive hydrogels offers significant potential as an alternative therapy for breast cancer, although further research is needed to verify its safety and effectiveness in cancer therapy.

Keywords: *curcumin; nano thermosensitive hydrogels; drug delivery; breast cancer*

INTRODUCTION

Breast cancer is a common type of cancer in women worldwide, with more than 2.3 million new cases each year (Arnold et al., 2022). Breast cancer is caused by genetic, hormonal, reproductive, and environmental factors. Common therapy options for cancer include surgery, radiation, and chemotherapy (Trayes and Cokenakes, 2021). These conventional therapies can be used in combination to treat various types of cancer, depending on its severity. Although these therapies have been proven effective in treating cancer, they have significant side effects on normal cells due to drug deposition outside the target cells, as well as toxicity to healthy tissues, caused by limitations in the drug delivery system (Damyanov et al., 2018; Senapati et al., 2018). Therefore, the development of an effective drug delivery system for cancer treatment is urgently needed today.

Targeted drug delivery systems are widely researched and developed to reduce side effects and toxicity at non-target sites (Cao et al., 2019). These systems have a significant impact on the effectiveness of early-stage cancer therapy compared to systemic drugs. The use of natural ingredients in targeted drug delivery systems is crucial to ensure the safety and compatibility of the treatment with the body's natural processes. Natural compounds are better tolerated by the body, reducing the risk of adverse reactions or complications (Sauter, 2020). In addition, the use of natural ingredients can improve the biocompatibility of the drug delivery system, thereby enhancing its overall effectiveness and therapeutic outcomes. One of the promising natural ingredients with anticancer activity for drug delivery systems is curcumin.

Curcumin has activity in inhibiting the spread of breast cancer cells by inducing programmed cell death (apoptosis), activating caspases, and upregulating cancer suppressor genes such as P53 (Yu et al., 2021). Despite its advantages as an anticancer agent, curcumin's low water solubility results in poor bioavailability and low chemical stability (Nagahama et al., 2016). According to research by Kharat, Zhang, and McClements (2017), curcumin tends to be unstable and susceptible to chemical degradation in neutral (pH = 7) and alkaline

environments (pH > 7), while also tending to crystallize in aqueous acidic solutions (pH < 7). Therefore, to enhance its potential as an anticancer agent, curcumin is formulated in nano thermosensitive hydrogels.

Nano thermosensitive hydrogels utilize nanoparticle technology that enables controlled drug release and responsiveness to temperature changes (Chatterjee et al., 2018). The development of a targeted drug delivery system based on curcumin-loaded nano thermosensitive hydrogels requires further research to determine its therapeutic effectiveness in breast cancer therapy. Curcumin and conventional cancer drugs formulated in nano thermosensitive hydrogels are continuously reviewed through the analysis of research articles conducted worldwide using the Systematic Literature Review (SLR) method and bibliometric analysis.

The Systematic Literature Review (SLR) is a structured method used to identify, evaluate, and synthesize relevant studies, offering a more rigorous and structured approach compared to traditional literature review methods (Triandini et al., 2019). Meanwhile, bibliometric statistics is a quantitative method for analyzing scientific literature, playing an important role in academic evaluation, decision-making, and planning future research strategies, particularly in the development of targeted drug delivery systems based on nano thermosensitive hydrogel for breast cancer therapy. The bibliometric analysis was conducted using VOSviewer (Visualization of Similarities) software version 1.6.16. Therefore, this review is of particular interest because the data collection and information gathered can provide estimates of publication trends regarding the development of targeted drug delivery systems based on nano thermosensitive hydrogels, especially curcumin, in the future

METHODS

This review is an original peer-reviewed analysis of international articles sourced from the SCOPUS database using Harzing's Publish or Perish 8 software and following the systematic review methodology outlined by PRISMA (P), as illustrated in Figure 1. The scope of the study was determined based on articles published in reputable international journals, ensuring the quality of the articles through a rigorous peer-review process. Scopus is an international abstract and comprehensive database that serves as a reference for publications in several countries.

Article Criteria

The review was conducted based on the following criteria: (i) articles related to hydrogels and curcumin, and (ii) all articles discussing breast cancer. The exclusion criteria were articles that were not original research, not in English, not open-access, or outside the 2014–2024 time frame. The authors used these inclusion and exclusion criteria to limit the analysis and ensure the quality of the data studied in this article.

Data Source

The data in this review were obtained from an analysis of the Scopus database, accessed on June 1, 2024. The articles used were published within the last ten years (2014–2024) and focused on hydrogels and curcumin as drug delivery methods in breast cancer therapy. The keywords used in the search were: "nano thermosensitive hydrogels" AND "hydrogels" AND "local" OR "in situ" AND "breast cancer" OR "cancer" AND "treatment" OR "delivery." In this analysis, a meta-analysis was not performed due to the heterogeneity of the articles.

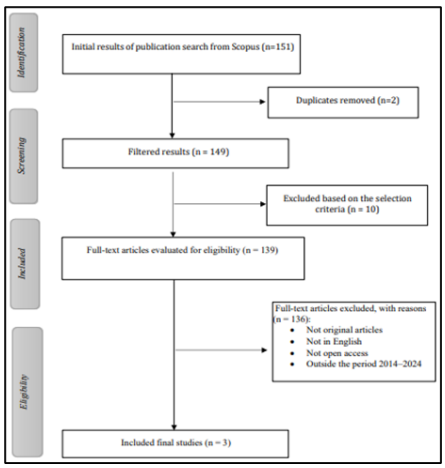

Figure 1. PRISMA Flow Diagram for Systematic Review.

RESULTS AND DISCUSSION

The final study results, based on the inclusion and exclusion criteria shown in Figure 1, included 3 articles, which were then processed using VOS-viewer version 1.6.16. The network visualization in Figure 2 displays the correlation among authors related to nano thermosensitive curcumin hydrogels and breast cancer.

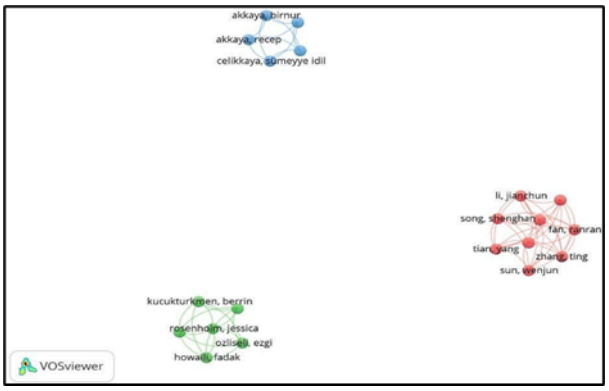

Figure 2. Network Visualization of Co-Authorship

Figure 2 shows a network visualization of co-authorship, marked by nodes (circles) representing authors or researchers and edges (lines) representing relationships between them. A group of nodes connected by edges indicates a correlation or collaboration among the researchers. The bibliometric analysis of the authors above shows that collaborations occur only within each group (indicated by the same color) in research on nano thermosensitive curcumin hydrogels and breast cancer therapy. There is no collaboration or citation between authors from different color groups.

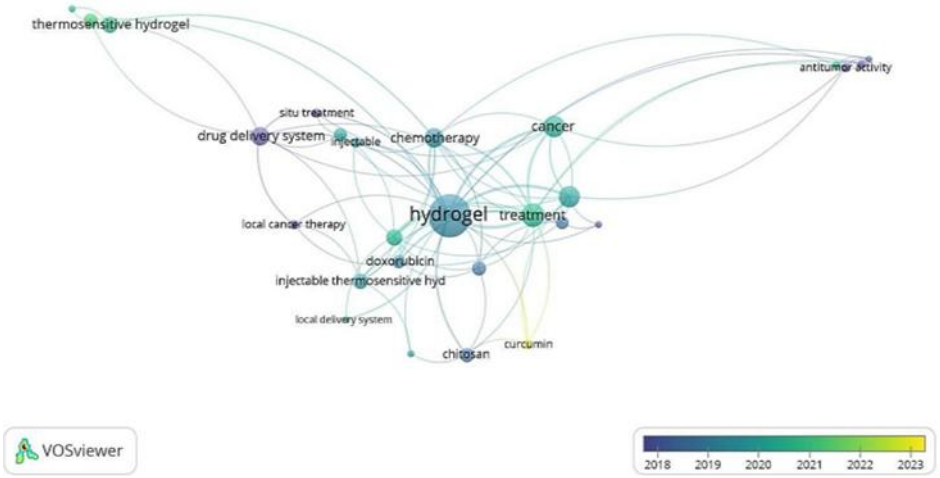

Figure 3. Overlay visualization of co-occurrence

Information obtained from the overlay visualization in Figure 3 can be used as a reference to identify and detect the state of the art (novelty) of research on curcumin thermosensitive hydrogel for breast cancer conducted during the period 2018–2024. The keyword "hydrogel" is positioned at the center with many connections, indicating that this topic has numerous correlations with other research areas. In contrast, "curcumin" has fewer related studies, as evidenced by the smaller size of its node (circle), but it has become a trending topic since 2023. Therefore, further research on curcumin as a nano thermosensitive hydrogel for breast cancer therapy is needed.

Table 1. Literature Review Results on the Effect of Thermosensitive Nanopolymer Hydrogels on Drug Release

Reference	Year	Anticancer Drug Agent	Polymer	Cell Type	Active Concentration of Curcumin as Anticancer	Drug Release Mechanism	Result
(Howaili, 2021)	2021	Curcumin	Chitosan	MDA-MB-231 and MCF 10A cells	0.25 and 0.5 mg/ml or 2.5 and 5 µg/ml	The nanogel shrinks above the LCST, releasing curcumin through free diffusion. Chitosan enhances the LCST of the nanogel and provides a pH-responsive mechanism for drug release.	Curcumin is released for up to 72 hours with dual thermo-pH responsive behavior (37°C).
(Pourmadadi, 2023)	2023	Curcumin	Polyacrylic acid (PAA)	MCF-7	5 µg/mL	Drug release is influenced by the structure and interaction of nanocarrier components, which maintain stability and inhibit degradation, leading to diffusion-dependent release.	61% of curcumin (CUR) was released at pH 7.4 after 96 hours at 37°C; 96% of curcumin was released at pH 5.4 after 96 hours at 37°C.
(Karami, 2023)	2023	Curcumin	Chitosan	MCF-7	5 µg/mL,	Drug release is diffusion-based.	72% and 99% were released within 96 hours in neutral and acidic media, respectively, at an evaluation temperature of 37°C.

Drug Release Mechanism of Thermosensitive Hydrogel

The effectiveness of anticancer drugs applied in a targeted or localized manner depends on the accessibility of the therapeutic agent to cancer cells. Generally, the drug release mechanisms of thermosensitive hydrogels include (1) diffusion control, (2) swelling control, and (3) erosion control (Fan et al., 2022). Controlled drug diffusion is also referred to as reservoir or matrix systems. Drug release from hydrogels depends on the dimensions of the gel matrix and the size of the drug molecules. Several factors influence release, especially the degree of rigidity and cross-linking within the chemical structure of the material. Additionally, the type and intensity of external stimuli, when applicable, are important factors. The size of the hydrogel network significantly affects its physical properties, such as mechanical strength, degradability, and diffusion behavior.

In a swelling-controlled drug delivery system, the drug is dispersed or dissolved in a hydrophilic polymer that is initially in a hard and rigid state, preventing the drug from diffusing (Adepu and Ramakrishna, 2021). When the system comes into contact with a thermodynamically compatible release medium (water), the polymer swells and becomes viscoelastic, allowing the drug to be released. This swelling controls the drug release from the polymer.

Meanwhile, erosion control regulates the rate at which the hydrogel decomposes and releases the drug into the surrounding environment (Correa et al., 2021). The drug is released either from the surface or as the hydrogel completely erodes. Degradation is a fundamental process in hydrogel dissolution, where the polymer's molecular chains are broken down, then the drug is release.

Application of Thermosensitive Nano Hydrogel in Anticancer Drug Delivery System

Controlled and targeted drug release can be tailored not only to specific cell types but also to specific cellular components. Many studies are currently exploring nano thermosensitive hydrogels as an alternative approach for anticancer drug delivery. From several studies reviewed, curcumin is a complex molecule with diverse mechanisms of action that target and affect many molecules involved in cancer initiation, growth, and metastasis (Urošević et al., 2022). By targeting key enzymatic reactions within molecular pathways, it can inhibit the activity of numerous receptors and growth factor cofactors. Additionally, it can modulate the expression of inflammatory cytokines that have the potential to promote cancer spread, suppress protein growth, and inhibit the cell cycle to halt the growth and activation of cancer cells. Apoptotic proteins play a role in destroying cancer cells (Kasi et al., 2016). Furthermore, combining curcumin with conventional drugs tends to show better efficacy

than monotherapy. Multi-drug combination therapy can work on multiple pathways and targets simultaneously, providing stronger antitumor effects (Huang et al., 2023). This delivery system also has the potential to release both hydrophobic (water-insoluble) and hydrophilic (water-soluble) drugs, while reducing cellular toxicity to achieve high efficacy.

CONCLUSION

Thermosensitive hydrogel curcumin nanodelivery system in breast cancer therapy offers great potential as an alternative to improve therapeutic effectiveness. This technology utilizes nanoparticles to increase the bioavailability of curcumin and allows for controlled drug release specifically to cancer cells. However, further studies are needed to verify its safety and effectiveness in anticancer therapy, in order to enhance its future application in breast cancer treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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