

Evaluation of targeted therapy on the activity of curcumin and doxorubicin anticancer agents in breast cancer: A systematic literature review

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Abstract. Breast cancer is one type of cancer that causes the most deaths in women. Currently, doxorubicin chemotherapy treatment is widely used, but due to untargeted side effects, a hydrogel-thermosensitive preparation has been developed by comparing the activity of the active substance curcumin with doxorubicin. This systematic review aims to determine the development of research on the anticancer activity of modified hydrogel-thermosensitive breast cancer and to examine its activity by looking at the IC₅₀ value. The method used in searching for articles was using the Scopus database with the type of literature analyzed, namely research on the cytotoxic activity of curcumin and doxorubicin with key keywords ("Doxorubicin" OR "Curcumin" AND "Breast" AND "Cancer" AND "Therapy" AND "Cytotoxicity"). The inclusion criteria used were journals containing cytotoxic or anti-breast cancer tests from curcumin and doxorubicin with publication years 2020-2024, and full-text journals. The exclusion criteria used were journals that did not test cytotoxicity on MCF-7 cells, no IC₅₀ value, journals regarding review articles, and paid journals. The analysis results show that curcumin has an IC₅₀ value comparable to doxorubicin with the mechanism of inducing apoptosis in cancer cells by activating caspase 3 and caspase 9. So the development of a thermosensitive hydrogel provides an opportunity for the anticancer activity provided to be more targeted.

1 Introduction

Breast cancer is a malignant tumor formed from breast cells that grow and develop uncontrollably so that it can spread to tissues or organs that are close to the breast or other parts of the body [1]. It can occur in both men and women, although it is more common in women with an incidence rate of 15% of all cancer cases [2]. Early detection and treatment are critical in improving the prognosis and survival rates of those diagnosed with breast cancer [3].

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Breast cancer occurs when abnormal cells within the breast tissue develop uncontrollably, forming malignant tumors. Currently, breast cancer treatment mostly uses conventional therapies that include treatments such as surgery, chemotherapy, radiation therapy, and hormone therapy [4]. Based on statistics from the Global Cancer Observatory [5] new cases of cancer in Indonesia were recorded at 396,914 and the number of deaths reached 234,511 people. The high mortality rate due to breast cancer requires the development of types of therapy to prevent death. Current cancer therapy options include surgery, radiation therapy, and chemotherapy [6].

Chemotherapy is still the main option in breast cancer therapy. However, problems in breast cancer therapy still often occur due to its toxicity and effectiveness. Conventional chemotherapy has major side effects on normal cells because the drug is deposited outside the target cells due to pressure on the drug delivery system of cancer cells [7], [8]. So, innovative targeted drug delivery system technology needs to be developed to attack cancer cells specifically without damaging the surrounding healthy cells [9].

Hydrogel-thermosensitive in Sustained Local Drug Delivery (SLDD) systems offer the potential to deliver targeted drug doses with better release control to optimize therapeutic effectiveness [10]. Hydrogel-thermosensitive is a polymeric material that can change responsively to changes in temperature [11]. Hydrogel-thermosensitive can change from liquid to gel when exposed to certain temperatures to form a stable network. In addition, its ability to regulate the speed and pattern of drug release can increase drug concentration at the target site thereby reducing drug toxicity to surrounding healthy tissues [12].

Doxorubicin is one of the commonly used chemotherapeutic agents in the treatment of breast cancer [13]. The main mechanism of doxorubicin is through the induction of apoptosis, which is a genetically regulated programmed cell death process [14]. Besides doxorubicin, the anticancer agent curcumin is also able to inhibit cancer cell proliferation and tumor cell growth [15]. Curcumin is also able to regulate the expression of apoptotic genes so that it can induce breast cancer apoptosis inhibit angiogenesis and regulate the expression of anti-apoptotic proteins [16], [17]. Beberapa penelitian menunjukkan bahwa kandungan polifenol tersebut memiliki aktivitas antikanker, salah satunya yaitu kanker payudara [18]–[20].

The Hydrogel-thermosensitive in the treatment of breast cancer is expected to increase the effectiveness of anticancer activity with the IC_{50} value. The purpose of the systematic literature review is to find out the development of research on breast anticancer activity with hydrogel-thermosensitive modification, understand trends in research topics, collaboration patterns, and characteristics of scientific publications, and to compare the potential effectiveness of curcumin compared to doxorubicin by looking at the IC_{50} value.

2 Methods

The method of this literature review is a non-experimental design of the PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), namely the search for original research literature using Scopus as a database source on Harzthing's Publish or Perish 8 software. The choice of Scopus is based on the fact that the published articles come from accredited and highly reputable journals, so their authenticity is maintained.

2.1 Article Criteria

The review was based on the following criteria: (1) publications in English language journals; (2) papers related to anticancer activity with IC_{50} values; (3) all articles about breast cancer; and iv) only original peer-reviewed papers, so editorials, proceedings, communications, letters, and reviews were excluded.

In this study, the inclusion criteria used were journals containing cytotoxic or breast anticancer tests of the active substances curcumin and doxorubicin published in 2020-2024,

and full-text journals. The exclusion criteria used are journals that do not test cytotoxicity on MCF-7 cells, there is no IC₅₀ value, journals regarding article reviews, and paid journals.

2.2 Data Source

The writing of this systematic literature review (SLR) is based on the author's review of several published research articles using the PRISMA guideline systematic review. This review includes original peer-reviewed studies based on the criteria listed in the schematic diagram of Figure 1. The search engine used in identifying articles is SCOPUS using the following keywords: ("Doxorubicin" OR "Curcumin" AND "Breast" AND "Cancer" AND "Therapy" AND "Cytotoxicity"). The article search was conducted on May 31, 2024, with a range of years 2020-2024.

2.3 Data Analysis

In this study, several journal articles obtained were analyzed by bibliography on bibliometrics. This analysis was used to examine and visualize data on bibliometric networks using Vosviewer (Visualization of Similarities) software version 1.6.16. Vosviewer is used at the level of its ability to analyze data effectively and efficiently and can produce publishing networks, researcher schemes, and an overview of articles in shared fragments through the keyword map generation cycle so that it can be used to see trends in research topics related to breast anticancer activity (Nur et al., 2020).

Data analysis techniques include: (1) mapping the distribution of journal publications based on the year of publication; (2) mapping the results of bibliometric network visualization and journal publication trends using Vosviewer (Visualization of Similarities) based on the number of clusters and items; and (3) mapping research topics around anticancer activity using a systematic literature review study (Budianto, 2022). Furthermore, using VosViewer's systematic literature review, this research can describe the distribution of research topics, and the number of studies within them and identify the opportunities in research that need to be developed about breast anticancer activity.

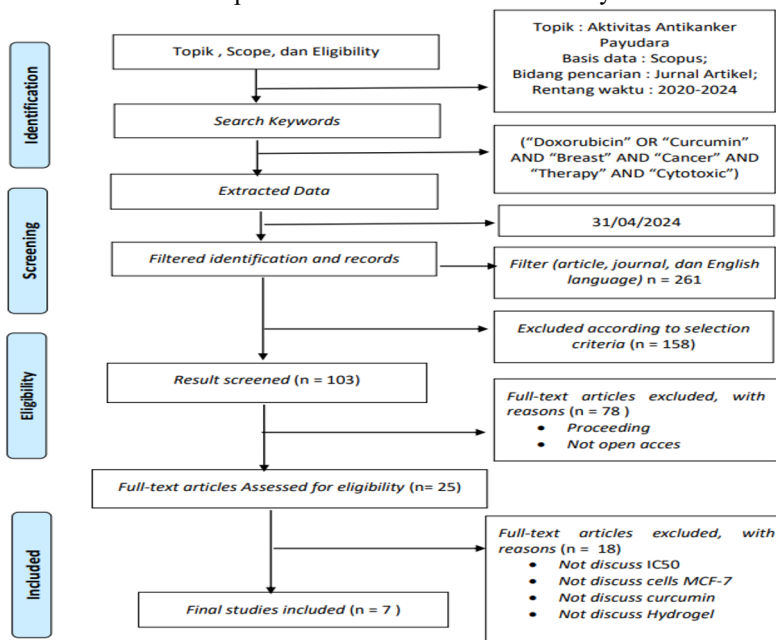


Fig. 1. PRISMA systematic guideline diagram

3 Results and Discussion

In this study, Bibliometrics and VOSviewer software were used separately. Bibliometrics is used for performance analysis of publications on the selectivity of anti-breast cancer activity, VOSviewer for analysis of co-occurrence network maps, and analysis of article publications by year can be seen in Figure 2.

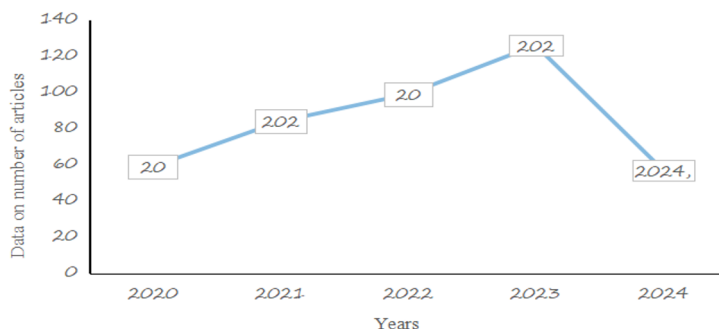


Fig. 2. Data of articles publication on breast anticancer activity by years

The results of the search for scientific publications related to breast anticancer activity in the period 2020-2024 show an increase in publications each year, especially in the last 4 years. Publications related to breast anticancer activity have increased rapidly every year until in 2023 they reached 126 articles per year. In May 2024, 57 articles have been successfully published and there is still a possibility to experience a continuous increase. The article publication data shows that the average scientific publication related to breast anticancer activity is more than 90 articles every year.

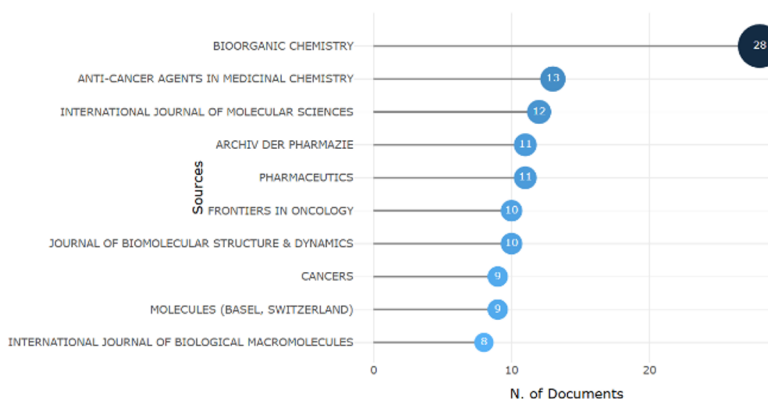


Fig. 3. Data on affiliation names of publishers of articles on breast anticancer activity

Figure 3 shows the publisher affiliations of research articles on breast anticancer activity. The item diagram shows the level of relevance of research articles that have been published in each journal. BIOORGANIC CHEMISTRY occupies the top position with the highest number of published documents, namely 28 articles. This is because the journal is relevant to the topic discussed. Whereas in the results shown from the 10 affiliate lists of publishers of articles on the topic of breast anticancer activity, the International Journal Of Biological Macromolecules occupies the lowest position with the number of publications of 8 articles. This means that in terms of quantity and relevance, the theme of anticancer activity selectivity is still lacking in the most relevant data sources.

- 1) Cluster 1 purple color consists of 2 topics namely breast cancer cell and MCF.
- 2) Cluster 2 dark green color consists of 5 topics namely effect, study, efficacy, vitro and cancer.
- 3) Cluster 3 light green color consists of 3 topics namely cell, treatment, drug.
- 4) Cluster 4 yellow color consists of 4 topics namely dox, combination, triple negative breast cancer, and tumor.

This map representation can be used in hierarchical clustering of research topics, where this visualization map illustrates the distribution of relationships between elements in the group as a result of the analysis. The results of this map analysis show the relations between one topic and another, whether purple, dark green, light green, or yellow clusters. In the visualization map, several topics are part of one cluster, showing the relationship between them in research articles on the topic of breast anticancer activity in the period 2020-2024. After seeing the trend of research topics with VOSviewer bibliometrics and screening journal articles related to breast anticancer activity, the development of curcumin as an anticancer agent has not been widely developed. Based on the results of the search, 206 journals were obtained that discussed breast anticancer activity and only 4 journals met the inclusion and exclusion criteria, then the results of the study were analyzed and listed in Table 2.

Table 2. Results of review articles on breast anticancer activity

Ref	Method and Cell Test	Mechanism	Parameters IC50			Result
			Cur	Dox	Cur + Dox	
[21]	MTT assay, MCF-7 cells	Curcumin induces apoptosis by increasing the expression of caspase 9.	CUR 49,57 µg/mL CUR NP (7:3) 14,83 µg/mL CUR NP (6:4) 19,32 µg/mL	-	-	PGMD/curcumin nanoparticles exhibit potent anticancer activity on breast cancer cells
[22]	MTT assay, MCF-7 cells	MDR mechanisms include drug transport proteins, anti-apoptotic defenses, and topoisomerase activity	15,56 µg/mL	12,13 µg/mL	10,65 µg/mL)	(DOX+CUR)-FA-NPs exhibit tumor targeting and reduced drug accumulation
[23]	MTT assay, MCF-7 cells	[1] Doxorubicin will exert its effects by binding to the DNA double helix and inhibiting the formation of the DNA-Topoisomerase II Complex during the process of cell division [CUR by increasing the expression of apoptosis-related proteins including cleavage at caspase-3, caspase-9, Bcl-2, and Bax	12,93 µg/mL	13,87 µg/mL	5,02 µg/mL	[Successful encapsulation of DOX and CUR in pH-sensitive niosome particles. Co-loading enhances cytotoxicity in cancer cells, suggesting synergistic interactions

[24]	MTT assay, MCF-7 cells	[1] GuC-HMNSAP induces apoptosis in MCF-7 cells through specific pathways. [2] GuC-HMNSAP is an efficient nanocarrier for cancer cell death	14,73 µg/mL)	-	-	[1] Developed GuC-HMNSAP nanocarriers for targeted breast cancer therapy. [2] Demonstrated effective induction of apoptosis through molecular research
[25]	MTT assay, MCF-7 cells	RCP (Resveratrol, Curcumin and Piperine) induces cytotoxicity in MCF-7 cells by reducing GLO1 activity.	30,5 µg/mL	-	-	The exposure of resveratrol, curcumin and piperine in the enzyme expression of the glyoxalase system as well as the mRNA expression of glyoxalase 1 and 2 should be further investigated as chemotherapeutic targets.
[26]	MTT assay, MCF-7 cells	Anticancer effects through apoptosis where changes in genes and proteins in apoptosis, namely inducing apoptosis in p53, caspase-3, Bax, Bcl-2.	98,8 µg/mL	101,3 µg/mL	23,7 µg/mL	The dual delivery (combination) nanoformulation efficiently inhibited cancer cells compared to DOX and free CUR (single delivery) as indicated by the lowest IC50.
[27]	MTT assay, MCF-7 cells	Synthesis of zinc(II) - berberine/jatrorrhizine complex - curcumin can accumulate in mitochondria, and trigger mitophagy and apoptosis.	21 µg/mL	-	-	Anticancer evaluation showed that Zn(CurBer) inhibited MCF-7 xenograft tumor growth more effectively than doxorubicin and Zn(CurJat). So it has the potential to be a molecular and anti-neoplastic drug that targets mitochondria.

Cytotoxic Activity Of Anticancer Agents

One method of measuring cytotoxic activity is using the MTT test method with the aim of evaluating the cytotoxicity of various concentrations of active substances on MCF7 cells [23]. A compound can be said to have a cytotoxic effect if the compound is able to damage normal cells and cancer cells, and can inhibit the growth of malignant tumor cells [28]. Based

on Table 1, it can be seen that curcumin and doxorubicin research as anticancer shows inhibition of cancer cell growth in vitro and using the MTT Assay test method.

Research conducted by Kumari [21] tested the anticancer activity of CUR NPs synthesized using both polymers (PGMD 7:3 and PGMD 6:4) tested on MCF-7 cell line. The cells were exposed to both CUR-NPs at varying concentrations (20 μM , 40 μM , 60 μM and 80 μM) for 24 hours and 48 hours. Results showed curcumin nanoparticles were more potent than curcumin alone. In addition, the nanoparticles showed a time- and dose-dependent decrease in cell viability.

The anticancer activity of both CUR-NP formulations was almost the same in MCF-7 cell line and the IC_{50} of both formulations (CUR-NP 7:3 and CUR NP 6:4) was found to be in the range of 14.83 and 19.32 $\mu\text{g}/\text{mL}$ for 48 hours, respectively. CUR and nano-CUR exhibited dose-dependent anti-proliferative effects where higher efficacy was seen in nano-CUR [21], [22]. In a reported study with curcumin nanoparticles containing folate-modified-chitosan-nanoparticles, the survival of MCF-7 cells was observed to decrease with increasing incubation time [29].

Research conducted Kumari [21] reported that anticancer testing with target cells used, namely MCF-7 cells (breast cancer) involving curcumin and doxorubicin compounds showed that treatment with active substances curcumin and doxorubicin was able to inhibit cell proliferation by inducing cell apoptosis. Where the IC_{50} Cur value is 15.56 $\mu\text{g}/\text{mL}$; Dox: 12.13 $\mu\text{g}/\text{mL}$; Cur + Dox: 10.65 $\mu\text{g}/\text{mL}$ [23], the results showed IC_{50} values for free DOX and CUR of about 12.93 $\mu\text{g}/\text{mL}$ and 13.87 $\mu\text{g}/\text{mL}$ respectively. After encapsulation in niosomes, these values increased to 23.12 $\mu\text{g}/\text{mL}$ and 24.93 $\mu\text{g}/\text{mL}$. This shows that despite the modification of the drug delivery system with nanoparticles, the active substance still exerts anticancer activity by providing a certain IC_{50} . Specifically, using 250 $\mu\text{g}/\text{mL}$ particles containing CUR and DOX resulted in 20% and 17% higher cell death rates compared to 0.25 $\mu\text{g}/\text{mL}$ respectively. Notably, co-administration of DOX- and CUR-containing particles showed a synergistic effect, substantially reducing MCF-7 cell viability from 61% to 30% after 72 hours of incubation.

The identification of IC_{50} values performed by Viswanathan [24] showed that modification of free guanidine with HMSNAP to Gu-HMSNAP, and GuC-HMSNAP resulted in lower toxicity in MCF-7 cells. In cytotoxicity assays, 30 μM curcumin induced 50% cell death in MCF-7 [30], [31] and the IC_{50} values of free guanidine, Gu-HMSNAP, and GuC-HMSNAP were 40, 35, and 25 μM , respectively, at 24 hours. Therefore, cell death caused by guanidine alone and by the guanidine-curcumin complex is directly correlated in a dose- and time-dependent manner. After 48 h incubation with MCF-7 cells, 35 μM free guanidine, 30 μM Gu-HMSNAP, and 20 μM GuC-HMSNAP induced 50% cell death. At 72 hours incubation, 25 μM guanidine, 20 μM Gu HMSNAP, and 15 μM GuC-HMNSAP induced 50% cell death.

Therefore, the IC_{50} value of guanidine-curcumin complex payload with nanocarrier decreased the amount of guanidine by 50% compared to the concentration of free guanidine. Thus, the combination of guanidine-curcumin complex cargo with silica nanospheres (HMSNAP) efficiently induces apoptosis at minimal guanidine concentration.

In this result, cells treated with GuC-HMNSAP showed that 3 to 10% cell death occurred within 24 to 72 hours after incubation. Necrosis gradually increased depending on time, and significant necrosis was found with Gu-HMSNAP (16.50%) and GuC-HMSNAP (19.20%) at 48 hours and with guanidine (18.42%), Gu-HMSNAP (27.84%), and GuC-HMSNAP (36.34%) at 72 hours [24].

SYNERGISM EFFECT

Concurrent administration of anticancer drugs with different antitumor mechanisms is a promising strategy to combat MDR [32]. Data research of Mohajeri & Sahebkar [33] showed

that CUR has a protective effect against DOX toxicity. Therefore, concurrent administration of CUR and DOX may be an effective combination oncology therapy. The results of research Guo [22] proved that the combination drug therapy ((CURth DOX), (SURthDOX)-FA-NPs, and (CURthDOX)-NPs) showed stronger anti-cell proliferation compared to single drugs (CUR or DOX). This suggests that the combination of CUR and DOX is an effective strategy for the treatment of breast cancer (CURthDOX) showed the best anticancer activity, as the cells were in direct contact with the drugs, and both lipophilic drugs easily penetrated the cell membrane. On the other hand, when CUR and DOX were incorporated into nanocarriers, cell cytotoxicity was significantly reduced [22], [34].

The molecular mechanisms underlying the synergistic effects of DOX and CUR in cancer therapy are known to be the incorporation of DOX with natural compounds, the combination of DOX with genistein, quercetin, or berberine, respectively a natural isoflavone, flavonoid, and alkaloid, showed synergistic cytotoxic effects on prostate and breast cancer cells via modulation of PI3K/Akt/mTOR axis and oxidative stress-related signaling pathways [34], [35].

MECHANISM ACTION OF ANTICANCER AGENTS

The results of other studies, Chang & Chen [36] showed the results of turmeric rhizome extracts containing CUR are thought to have high potential anticancer activity by acting on protein expression related to the cell cycle and cell apoptosis. According to [21]. The expression levels of apoptosis-related proteins include cleavage in caspase-3, caspase-9, Bcl-2, and Bax. The level of apoptosis increased after treatment. Meanwhile, the expression of anti-apoptotic Bcl-2 decreased. The caspase-3 inhibitor was used to confirm that CUR induces apoptosis. In addition, Benko [36] also showed that CUR is an excellent Pgp inhibitor that effectively maintains high DOX concentrations in drug-resistant MCF-7/ADR human breast cancer cells.

Doxorubicin is one of the most effective drugs for the treatment of breast cancer and will exert its effects by binding to the DNA double helix and inhibiting the formation of DNA-Topoisomerase II Complex to achieve apoptosis and inhibition of cell growth [13], [37]. This shows similar results to the study by Van Ravenstein [38], Individually, DOX is known to intercalate into DNA, causing DNA damage, inhibition of topoisomerase II, and ultimately cell death eventually the cell will die.

THERMOGEL AS A TARGETED THERAPY

The main focus of anticancer drug development is to effectively induce cancer cell death. While hydrogels and nanogels have received much attention as promising drug delivery systems, few studies have investigated nanogel delivery of curcumin in cancer therapy. As a drug delivery system, thermogel as a natural polymer has advantages over synthetic polymers, namely biodegradability and biocompatibility [39], [40]. In addition, thermogels have unique features, including large surface area for drug uptake and porous structure for drug loading and release [39], [41]. Chitin nanogels containing curcumin have been used as a transdermal system for the treatment of skin cancer [40] and have shown more specific toxicity against human skin melanoma [39]. This delivery system shows very high uptake efficiency [41]. The results of the study [24] showed that by synthesizing using the sol-gel emulsion method can develop GuC-HMNSAP nanocarriers for targeted breast cancer therapy. By showing effective induction of apoptosis.

CONCLUSION

Based on VOSViewer bibliometric analysis, it is known that curcumin thermogels have not been widely studied, but based on the IC50 value curcumin has the potential as an anticancer agent comparable to doxorubicin with the mechanism of inducing apoptosis in cancer cells by

activating caspase 3, and caspase 9, so it needs to be studied further related to the cytotoxic effects and anticancer effects of curcumin thermogels.

REFERENCE

- 1 Y. Feng *et al.*, Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes Dis.* **5**, 77 (2018)
- 2 G. Menon, F. M. Alkabban, and T. Ferguson, Breast Cancer in *NCBI Bookshelf*, (Treasure Island (FL), 2024)
- 3 C. Taylor *et al.*, Breast cancer mortality in 500 000 women with early invasive breast cancer diagnosed in England, 1993-2015: population based observational cohort study. *BMJ* **381**, e074684 (2023)
- 4 Sardi, Respon kemoterapi neoadjuvant dengan gambaran ER dan atau PR positif serta HER-2 negatif pada penderita kanker payudara. (2022)
- 5 F. Bray *et al.*, Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA. Cancer J. Clin.* **74**, 229 (2024)
- 6 S. D. Setiawan, The effect of chemotherapy in cancer patient to anxiety. (2015)
- 7 S. Senapati, A.K. Mahanta, S. Kumar, and P. Maiti, Controlled drug delivery vehicles for cancer treatment and their performance. *Signal Transduct. Target. Ther.* **3**, 7 (2018)
- 8 C.A. Damyanov, I.K. Maslev, V.S. Pavlov, and L. Avramov, Conventional treatment of cancer realities and problems. *Ann. Complement. Altern. Med.* **1**, 1 (2018)
- 9 V.F.C. Dartora, J.S. Passos, L.V Costa-Lotufo, L.B. Lopes, and A. Panitch, Thermosensitive polymeric nanoparticles for drug Co-Encapsulation and breast cancer treatment. *Pharm.* **16**, (2024)
- 10 M. Lee *et al.*, A paintable and adhesive hydrogel cardiac patch with sustained release of ANGPTL4 for infarcted heart repair. *Bioact. Mater.* **31**, 395 (2024)
- 11 S. Chatterjee and T.F. Burns, Targeting heat shock proteins in cancer: A promising therapeutic approach. *Int. J. Mol. Sci.* **18**, (2017)
- 12 S. Mansha *et al.*, Development of pH-Responsive, thermosensitive, antibacterial, and anticancer CS/PVA/Graphene blended hydrogels for controlled drug delivery. *Gels* **10**, (2024)
- 13 M. Kciuk *et al.*, Doxorubicin—an agent with multiple mechanisms of anticancer activity. *Cells* **12**, 26 (2023)
- 14 O. Tacar, P. Sriamornsak, and C.R. Dass, Doxorubicin: An update on anticancer molecular action, toxicity and novel drug delivery systems. *J. Pharm. Pharmacol.* **65**, 157 (2013)
- 15 R. Farghadani and R. Naidu, Curcumin as an enhancer of therapeutic efficiency of chemotherapy drugs in breast cancer. *Int. J. Mol. Sci.* (2022)
- 16 N.A. Cacciola, R. Cuciniello, G.D. Petillo, M. Piccioni, S. Filosa, and S. Crispi, An overview of the enhanced effects of curcumin and chemotherapeutic agents in combined cancer treatments. *Int. J. Mol. Sci.* **24**, (2023)
- 17 M. Wang *et al.*, Potential mechanisms of action of curcumin for cancer prevention: focus on cellular signaling pathways and miRNAs. *Int. J. Biol. Sci.* **15**, 1200 (2019)
- 18 A.A. Dayem, H.Y. Choi, G.M. Yang, K. Kim, S.K. Saha, and S.G. Cho, The anti-cancer effect of polyphenols against breast cancer and cancer stem cells: Molecular mechanisms. *Nutrients* **8**, (2016)
- 19 R. Farghadani and R. Naidu, The anticancer mechanism of action of selected polyphenols in triple-negative breast cancer (TNBC). *Biomed. Pharmacother.* **165**, 115170 (2023)

- 20 M. Ali *et al.*, Anti-arthritis and anti-cancer activities of polyphenols: a review of the most recent in vitro assays. *Life* **13**, 1 (2023)
- 21 M. Kumari *et al.*, PGMD/curcumin nanoparticles for the treatment of breast cancer. *Scientific reports* **11**, 3824 (2021)
- 22 F. Guo *et al.*, Star polyester-based folate acid-targeting nanoparticles for doxorubicin and curcumin co-delivery to combat multidrug-resistant breast cancer. *Drug Deliv.* **28**, 1709 (2021)
- 23 S. Saharkhiz, A. Zarepour, N. Nasri, M. Cordani, and A. Zarrabi, A comparison study between doxorubicin and curcumin co-administration and co-loading in a smart niosomal formulation for MCF-7 breast cancer therapy. *Eur. J. Pharm. Sci.* **191**, (2023)
- 24 T.M. Viswanathan *et al.*, Guanidine–curcumin complex-loaded amine-functionalised hollow mesoporous silica nanoparticles for breast cancer therapy. *Cancers (Basel)*. **14**, (2022)
- 25 B. Schmidt, C. Ferreira, C.L.A. Passos, J.L. Silva, and E. Fialho, Resveratrol, curcumin and piperine alter human glyoxalase 1 in mcf-7 breast cancer cells. *Int. J. Mol. Sci.* **21**, 1 (2020)
- 26 K. AbouAitah *et al.*, Co-delivery system of curcumin and colchicine using functionalized mesoporous silica nanoparticles promotes anticancer and apoptosis effects. *Pharm.* **14**, (2022)
- 27 S.-H. Zhang, Z.-F. Wang, and H. Tan, Novel zinc(II)–curcumin molecular probes bearing berberine and jatrorrhizine derivatives as potential mitochondria-targeting anti-neoplastic drugs. *Eur. J. Med. Chem.* **243**, 114736 (2022)
- 28 N. Purwanto, E. Rismawati, and E.R. Sadiyah, Uji sitotoksik ekstrak biji salak (*Salacca zalacca* (Gaert) Voss dengan menggunakan metode Brine Shrimp lethality test (BsLt). *Pros. Penelit. Spes. Unisiba* 616 (2015)
- 29 S. Esfandiarpour-Boroujeni, S. Bagheri-Khoulenjani, H. Mirzadeh, and S. Amanpour, Fabrication and study of curcumin loaded nanoparticles based on folate-chitosan for breast cancer therapy application. *Carbohydr. Polym.* **168**, (2017)
- 30 L. Harini, S. Srivastava, G. P. Gnanakumar, An ingenious non-spherical mesoporous silica nanoparticle cargo with curcumin induces mitochondria-mediated apoptosis in breast cancer (MCF-7) cells. *Oncotarget*. (2019)
- 31 H. Narasimhan *et al.*, *Mesoporous Silica Nanoparticle Loaded with Curcumin Reduces the Cell Survival of MCF-7 Cells*. 2015.
- 32 S. Lin *et al.*, Efficiency against multidrug resistance by co-delivery of doxorubicin and curcumin with a legumain-sensitive nanocarrier. *Nano Res.* **11**, 3619 (2018)
- 33 M. Mohajeri and A. Sahebkar, Protective effects of curcumin against doxorubicin-induced toxicity and resistance: A review. *Crit. Rev. Oncol. Hematol.* **122**, (2017)
- 34 G. Ling *et al.*, Mechanisms and drug intervention for Doxorubicin-induced cardiotoxicity based on mitochondrial bioenergetics. *Oxid. Med. Cell. Longev.* **2022**, 7176282 (2022)
- 35 W. Wiese *et al.*, PI3K/Akt/mTOR signaling pathway in blood malignancies—new therapeutic possibilities. *Cancers (Basel)*. **15**, (2023)
- 36 C.-Y. Chen, J.-C. Lien, C.-Y. Chen, C.-C. Hung, and H.-C. Lin, Design, Synthesis and Evaluation of Novel Derivatives of Curcuminoids with Cytotoxicity. *Int. J. of Molec. Sci.* **22**, (2021)
- 37 N. K. Sharma *et al.*, *Understanding Cancer's Defense against Topoisomerase-Active Drugs: A Comprehensive Review*. **16**, (2024)
- 38 S.X. Van Ravenstein *et al.*, Topoisomerase II poisons inhibit vertebrate DNA replication through distinct mechanisms. *EMBO J.* **41**, 1 (2022)
- 39 N. Lomis, S. Westfall, L. Farahdel, M. Malhotra, D. Shum-Tim, and S. Prakash, Human serum albumin nanoparticles for use in cancer drug delivery: Process optimization and

- in vitro characterization. *Nanomaterials* **6**, (2016)
- 40 F. A. Siddiqui *et al.*, Curcumin decreases Warburg effect in cancer cells by down-regulating pyruvate kinase M2 via mTOR-HIF1 α inhibition. *Sci. Rep.* **8**, 2 (2018)
- 41 W. Song, M. Muthana, J. Mukherjee, R. J. Falconer, C. A. Biggs, and X. Zhao, Magnetic-Silk Core-Shell nanoparticles as potential carriers for targeted delivery of curcumin into human breast cancer cells. *ACS Biomater. Sci. Eng.* **3**, 1027 (2017)