ORIGINAL ARTICLE

Intisari Sains Medis 2024, Volume 15, Number 1: 402-407
P-ISSN: 2503-3638, E-ISSN: 2089-9084

Published by Intisari Sains Medis

The effect of turmeric extract (*Curcuma longa*) on IL-6 expression

Yohannes Sugiarto[1], Selamat Budijitno[2*]

[1]General Surgery Resident, Dr Kariadi General Hospital, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia;
[2]Oncology Surgery Department, Dr Kariadi General Hospital, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia.

*Corresponding author:
Selamat Budijitno;
Oncology Surgery Department, Dr Kariadi General Hospital, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia;
selamatbdr_undipleturer@hotmail.com

Received: 2024-01-22
Accepted: 2024-03-13
Published: 2024-04-08

ABSTRACT

Background: Breast cancer in Indonesia is reported to have reached 68,858 out of 396,914 new cases of cancer, with an incidence rate of 16.6% based on Globocan 2020 data. Complementary therapies are much sought after for psychological and economic reasons and have minimal side effects. Curcumin has anti-carcinogenic properties. IL-6 plays an important role in the growth and metastasis of breast cancer cells, renewal of breast cancer stem cells, and drug resistance in breast cancer stem cells.

Methods: A randomized controlled trial with post-test only group design using artificial female Balb/c strain rats (Mus Musculus) with DMBA-induced mammary adenocarcinoma nodules were reported, rats were divided into four groups randomly, namely, Control (K), Treatment 1: turmeric extract dose 100mg/KgBW (P1), Treatment 2: turmeric extract dose 150mg/KgBW (P2), Treatment 3: turmeric extract dose 200mg/KgBW (P3). Variables under study were IL-6 expression. One Way Anova test, followed by the Post-hoc Test, was used to test the difference among and between groups.

Results: The mean value of IL-6 expression in groups K (53,59 ± 8,37), P1 (50,66 ± 9,59), P2 (66,93 ± 9,64), P3 (64,58 ± 5,97). The Post-Hoc test showed significant differences in IL-6 expression from group K against P2 (p=0.038), group P1 against P2 (p=0.015), and P3 (p=0.040).

Conclusion: Turmeric extract (Curcuma longa) had an effect on IL-6 expression in the control group and the treatment group.

Keywords: Curcuma Longa, Adenocarcinoma Mammae, IL-6, Adriamycin Cyclophosphamide.
Cite This Article: Sugiarto, Y., Budijitno, S. 2024. The effect of turmeric extract (*Curcuma longa*) on IL-6 expression. *Intisari Sains Medis* 15(1): 402-407. DOI: 10.15562/ism.v15i1.1967

BACKGROUND

Breast cancer is a malignancy in breast tissue that can originate from the epithelium, ducts, or lobules. Breast cancer is a malignant neoplasm caused by abnormal cell growth in breast tissue. Cancer cells divide rapidly and uncontrollably, then infiltrate the surrounding tissue and metastasize. This gene mutation is triggered by a foreign substance entering the body, such as radioactivity, free radicals, or carcinogenic substances originating from external and internal sources of the body. The threat of cancer is increasing frequently with unhealthy lifestyle changes such as smoking, consumption of fast food, environmental pollution, and depletion of the ozone layer.[1]

Breast cancer is currently one of the most common types of cancer suffered by women, with the highest prevalence in all countries in the world. Globally, breast cancer has an incidence rate of 11.6% of all new cancer cases and is the cause of 6.6% of all cancer deaths.[2] WHO recorded that as many as 2.3 million women were diagnosed with breast cancer in 2020, so in 5 years Recently, 7.8 million living women were diagnosed with breast cancer, making it cancer with the most significant prevalence.[3] Breast cancer in Indonesia was reported to have reached 68,858 out of 396,914 new cases of cancer, with an incidence rate of 16.6% based on Globocan 2020 data.[4] Early detection results reached 1,925,943 or 5.2% using the Acetic Acid Visual Inspection (IVA) method to detect cervical cancer and clinical mammary examination (SADANIS) to detect mammary cancer until 2017. Based on statistics from the Social Security Administration (BPJS), cancer has spent 2.1 trillion rupiah as of September 2017.[5]

Management of breast cancer depends on the type and stage experienced by the patient. Breast cancer treatment modalities include surgery, radiotherapy, cytostatics, immunotherapy, and hormonal therapy. Chemotherapy for breast cancer is carried out by administering a systemic regimen, such as Fluorouracil, Adriamycin, and Cyclophosphamide (FAC); Fluorouracil, Epirubicin, and Cyclophosphamide (FEC); Adriamycin and Cyclophosphamide (AC); and Cyclophosphamide, Methotrexate, and Fluorouracil (CMF) are the most frequently used combination regimens. This chemotherapy is given at three to four-week intervals intermittently. FAC, FEC, and CMF are divided into six categories (shown over 18-24 months), while AC is divided into 2 categories (given over 6 weeks).[6]

The results of a meta-analysis study with 2,732 patients who used standard agents for end-stage solid cancer showed that the Complete Response rate for chemotherapy treatment was generally low, namely 7.4%.[7] On the other hand, chemotherapy has side effects that damage the liver, kidneys, heart, and other organs of the body, as well as immunosuppressive effects. Apart from that, the high cost of cancer

treatment means that people are starting to abandon conventional cancer treatment modalities. People try to find other methods of treatment or complementary therapies for psychological and economic reasons, with minimal side effects in dealing with cancer. Complementary or Complementary Alternative Medicine (CAM) is a therapy used as a "complement" or as additional therapy to conventional therapy. Researchers are also looking for ways to increase the efficacy of chemotherapy, namely by diet and improving the immune system. Several studies show that diet in cancer patients receiving chemotherapy provides good results. However, which diet strategy is best cannot be determined, considering that this will vary greatly depending on the patient, type of cancer, and treatment regimen.[8] Complementary therapy can be combined or integrated with conventional therapy, so complementary therapy is also called integrative therapy. One type of complementary therapy is herbal therapy. Many efforts have been made to explore new natural ingredients that improve the immune system against tumors, including Mahkota Dewa, Phylantus niruri, honey, Artemisia, and turmeric.[6]

Turmeric (Curcuma Longa) has many benefits, including anti-cancer effects, such as inhibiting carcinogenesis, angiogenesis, and tumor growth.[9] Turmeric is a plant that is easy to find in everyday life at an affordable price. Minimal side effects are also found in turmeric.[10] Curcumin is one of the phytochemical components of turmeric, and it has the effect of being a chemopreventive agent. This compound is a natural compound extracted from turmeric, which is capable of suppressing, retarding, or inverting carcinogenesis.[9] Curcumin has anti-carcinogenic, anti-migration, anti-oxidant, anti-inflammatory, anti-metastatic, anti-angiogenic, apoptotic, radioprotective, and chemo-sensitizing properties.[11]

IL-6 is a cytokine produced by various types of cells, such as immune cells, fibroblasts, and tumor cells, which plays a role in systemic inflammation and regulates inflammatory responses and tissue metabolism. IL-6 is involved in the pathogenesis of inflammation and cancer through trans-signaling. Il-6 can cause T cells to become unresponsive through activation of transcription (STAT)3 in dendritic cells, disrupting antigen presentation and making it difficult for the immune system to kill breast cancer cells. Approximately 50% of breast cancers express the cytokine IL-6, and high levels of IL-6 in serum are associated with poor prognosis, advanced disease, and metastasis in patients with breast cancer. IL-6 plays an important role in the growth and metastasis of breast cancer cells, renewal of breast cancer stem cells, and drug resistance in breast cancer stem cells, making anti-IL-6/IL-6R/gp130 therapy a promising option for treating and preventing breast cancer.[12]

IL-6 plays a role in cancer cell proliferation through IL-6/JAK/STAT3 signaling. IL-6 binds to the IL-6 receptor (IL 6Ra), then binds to the glycoprotein 130 (gp130) receptor, forming a signal transducer hexameric receptor complex. Janus kinase (JAK) is recruited and activated. Activated JAK phosphorylates signal transducer and activator of transcription 3 (STAT3) for activation, leading to gene regulation. Constitutively active IL-6/JAK/STAT3 signaling stimulates cancer cell proliferation and invasion and suppresses apoptosis. STAT3 enhances IL-6 signaling in inflammation. Aberrant expression of IL-6 occurs in various types of cancer and is associated with poor clinical prognosis and metastasis. In breast cancer, the IL-6 pathway is frequently activated, which can promote breast cancer metastasis while suppressing anti-tumor immune responses. Curcumin suppressed STAT3 phosphorylation on MDA-MB-231 and SKBR-3, confirmed through the inhibitory effect of curcumin on the DNA binding ability of STAT3 and its transcriptional activity. Curcumin targets STAT3 signaling by blocking STAT3 activation in vitro. Inhibition of STAT3 phosphorylation inhibits translocation into the nucleus, resulting in reduced NFκB-STAT3 protein interactions and downregulation of CD44 as a cancer stem cell phenotype marker. Therefore, curcumin blocks STAT3-mediated signaling, which contributes to suppressing the cancer stem cell phenotype. Studies showed IL-6 production was significantly reduced in 4T1 TNBC in vivo after curcumin treatment. Curcumin plays a role in downregulating STAT, JAK, and IL-6 expression and inhibits STAT translocation to the nucleus, thereby suppressing cell proliferation, invasion, and metastasis.[12,13] Curcumin also has a major role in suppressing the production of other major pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-2, IL-8, IL-12, IL-13, IL-15 and some chemokines that contribute to cancer cell proliferation. This research will be focused on IL-6 expression as one of the cytokines that play a role in cancer cell proliferation.[14]

Based on the theoretical description above, further research regarding the effect of administering turmeric extract (Curcuma Longa) on IL-6 expression in mouse mammary adenocarcinoma models receiving Adriamycin-Cyclophosphamide chemotherapy needs to be carried out. It is hoped that the results of this research will support the use of turmeric as a chemotherapy adjuvant for breast cancer.

METHODS

This research is an in vivo experimental laboratory with a Randomized Controlled Trial and a post-test-only group design that uses experimental animals as research objects. This research has received ethical clearance from the Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Diponegoro University, with No.140/EC-H/KEPK/FK- UNDIP/XII/2023. The subjects in this study were female rats (Mus Musculus) of the Balb/c strain with DMBA-induced mammary adenocarcinoma nodules. Inclusion criteria included female rats (Mus musculus) with mammary adenocarcinoma nodules, 5 weeks old, and body weight 150-200 grams. Exclusion criteria in this study included anatomical defects, illness, and inactivity, while the dropout criterion was death during the study. There were 24 subjects in this study, who were divided into 4 research groups, namely the control group, the group with a combination of adriamycin cyclophosphamide and turmeric extract at a dose of 100 mg/kgBW orally, the group with a combination of adriamycin cyclophosphamide and turmeric extract at a dose of 150 mg/kgBW orally, and group with a combination of adriamycin cyclophosphamide and turmeric extract at

a dose of 200mg/kgBW orally. The variables in this study include independent variables, namely the administration of graded doses of turmeric extract, and the dependent variable, namely IL-6 expression. The data was processed and analyzed using SPSS for Windows software. Data analysis was done using descriptive analysis and hypothesis testing. A descriptive analysis was done using a normality test with the Saphiro-Wilk test. Data with normal distribution was tested with parametric statistical analysis, and abnormal distribution was transformed or statistically tested using a non-parametric test. Normal distributed data tested by one-way ANOVA continued with Post Hoc LSD to evaluate the significant differences between groups. Data with abnormal distribution being tested by Kruskal-Wallis continued the Post Hoc Mann-Whitney test to assess the significance.

RESULTS

The research was conducted on 24 female rats (Mus musculus), which were divided equally into 4 groups randomly, namely, Control group (K), Treatment 1 (P1), Treatment 2 (P2), and Treatment 3 (P3), respectively. Each group consisted of 6 rats, and until the end of the study, they were healthy and did not meet the dropout criteria.

Based on the test results, it can be seen that the highest mean IL-6 expression could be found in the group given Adriamycin cyclophosphamide plus 150 mg/kgBW turmeric extract (66.93 ± 9.64), and the lowest was found in the P1 group (50.66 ± 9.59). Based on the results of the normality test using the Shapiro-Wilk test, the data was found to be normally distributed, and the results of the homogeneity test using the Levene test were homogeneous data variants, so the analysis was continued using the parametric one-way ANOVA test followed by the post-hoc test to see the significance of differences between groups.

Based on the results of the normality test using the Shapiro-Wilk test, the data was found to be normally distributed, and the results of the homogeneity test using the Levene test showed homogeneous data variance, so the analysis was continued using the parametric one-way ANOVA test followed by the post-hoc test to see the significance of differences between groups.

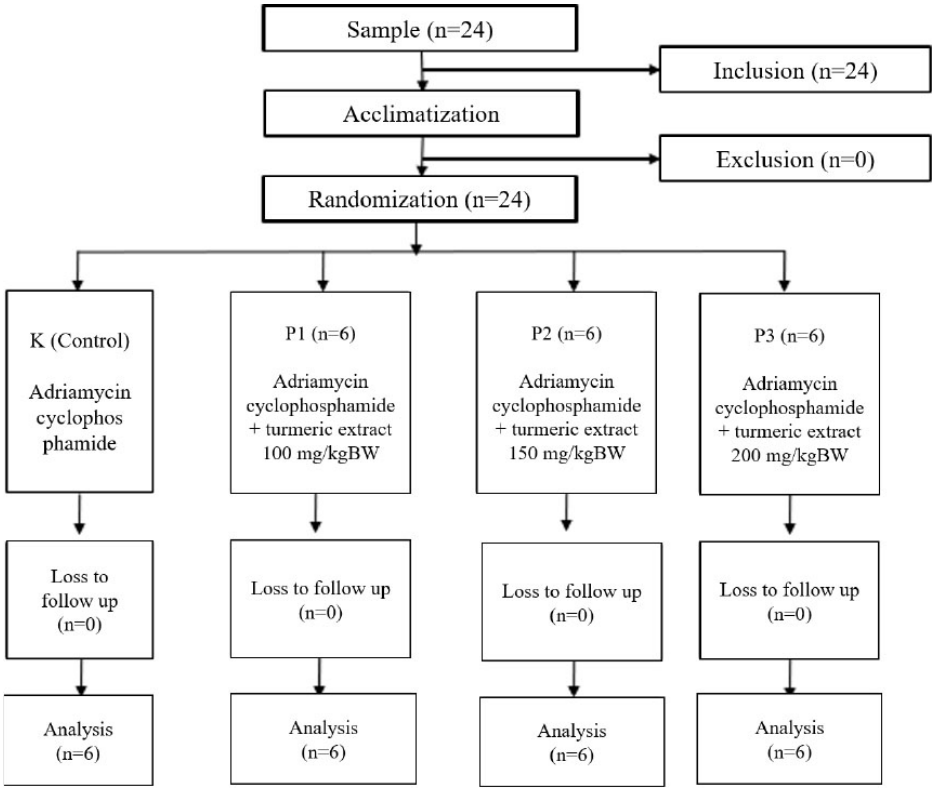

Figure 1. Consort Diagram.

Table 1. Results of descriptive statistics, normality, and homogeneity of IL-6 expression data in each group

Group	IL-6 Expression (%)		p$	Levene
	Mean ± SD	Median (min-max)		
K	53.59 ± 8.37	53.70 (44.99 – 61.98)	0.332*	0.742**
P1	50.66 ± 9.59	49.38 (40.39 – 63.47)	0.780*	
P2	66.93 ± 9.64	67.86 (53.34 – 76.74)	0.681*	
P3	64.58 ± 5.97	64.72 (57.36 – 71.53)	0.998*	

Notes: * Normal (p > 0,05); # Homogen (p > 0,05); $ *Shapiro-wilk*

Based on the results of the One-Way ANOVA test, the value of p = 0.039 (p<0.05) was obtained, so it can be concluded that there is a significant difference in IL-6 expression.

Based on the results of the Post Hoc LSD test, IL-6 expression showed significant differences (p < 0.05) between group K and group P2 (p: 0.038), group P1 and group P2 (0.015), and group P1 and P3 (0.040).

The boxplot graph shows that there are differences in IL-6 expression. The highest mean IL-6 expression could be found in the group given adriamycin cyclophosphamide plus 150 mg/kgBW turmeric extract, namely 66.93 ± 9.64, while the lowest was found in the P1 group, namely 50.66 ± 9.59.

DISCUSSION

This study aimed to see the effect of administering turmeric extract (Curcuma Longa) on IL-6 expression in mammary adenocarcinoma rats with gradual doses, namely 100 mg/kgBW, 150 mg/kgBW, and 200 mg/kgBW over 5 weeks. This effect was assessed by comparing the expression of IL-6 in each group, which was observed using immunohistochemical staining and calculating the cytoplasm or those attached to the brown tumor cells per 100 tumor cells.

This study showed that the highest mean IL-6 expression results could be found in the group given adriamycin cyclophosphamide plus 150 mg/kg of turmeric extract (66.93 ± 9.64), and the lowest was found in the P1 group

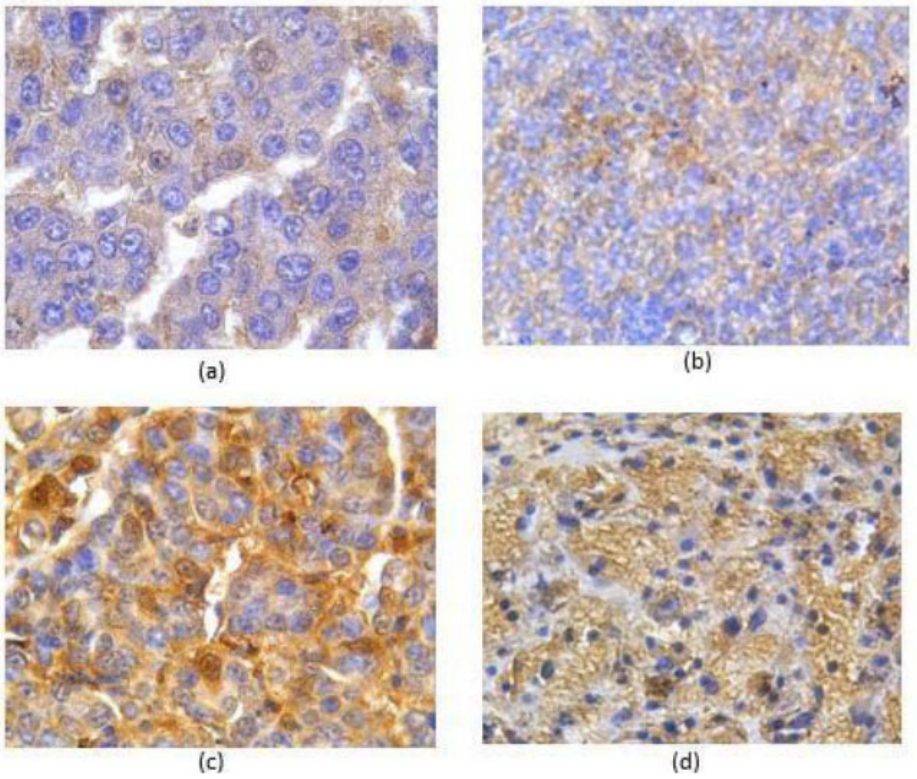

Figure 2. Histopathological picture of IL-6 expression. a) Adriamycin cyclophosphamide; b) Adriamycin cyclophosphamide + Turmeric extract 100mg/kgBW; c) Adriamycin cyclophosphamide + Turmeric extract 150mg/kgBW; d) Adriamycin cyclophosphamide + Turmeric extract 200mg/kgBW

Table 2. Results of One-Way ANOVA Test for IL-6 Expression

Group	Mean ± SD	p
K	53.59 ± 8.37	0.039*
P1	50.66 ± 9.59	
P2	66.93 ± 9.64	
P3	64.58 ± 5.97	

Note : * Significant (p < 0,05)

Table 3. Post Hoc LSD test results for IL-6 expression

Group		p
I	II	
K	P1	0.638
	P2	0.038*
	P3	0.095
P1	P2	0.015*
	P3	0.040*
P2	P3	0.690

Note : * Significant (p < 0,05)

(50.66 ± 9, 59). Statistically, there were significant differences (p < 0.05) between group K and group P2 (p: 0.038), group P1 and group P2 (0.015), and group P1 and P3 (0.040). These findings differ from those conducted by Ghandadi and Sahebkar, which showed a relationship between the downregulation of IL-6 and/or inhibition of IL-6 signaling and the therapeutic effect of curcumin.[15] Research conducted by Mills PJ et al., which examined predictors of inflammation as a response to chemotherapy, showed that chemotherapy can be associated with an increase in specific inflammatory markers, especially endothelial and platelet activation markers.[16] Girard BM et al. also conveyed the same thing, who showed an increase in IL-6 expression in the bladder with cyclophosphamide treatment.[14] Based on a study by Gorabi, AM et al. regarding similar research that the efficacy of chemotherapy treatment integrated with conventional therapy by administering turmeric extract to rats with a cancer-induced reduction in IL-6 expression was ineffective due to several factors, such as hyperlipidemia and other chronic diseases through which chronic inflammatory processes occurred.[17]

Based on the boxplot graph, there are differences in IL-6 expression in the research group, with the highest mean IL-6 expression being found in the group given Adriamycin- cyclophosphamide plus turmeric extract 150 mg/kgBW (66.93 ± 9.64), while the mean IL expression. The lowest IL-6 was found in the P1 group (50.66 ± 9.59). This does not follow several research studies and theories that explain it. A study by Singh M et al. showed that curcumin reduces the production of immunosuppressor cytokines, including IL-6, through the NFκB pathway. A study by Heo, TH, et al. demonstrated that curcumin inhibits tumorgenesis by inhibiting IL-6 expression via the HER2/IL-6/STAT3 signaling pathway. A meta-analysis study also showed that curcumin supplementation caused a significant reduction in circulating IL-6. Still, there was no significant relationship between the dose and duration of curcumin treatment on circulating IL-6 levels. However, this study follows a meta-analysis of 32 studies by Gorabi et al., where there was no significant reduction in IL-6 concentrations after curcumin supplementation.[13,18,19] This can occur due to an increase in pro-inflammatory cytokines, one of which is IL-6, during chemotherapy treatment accompanied by a decrease in microglial immunoreactivity and an increase in the expression of circulating chemokines (CXCL1), so with the administration of Adriamycin cyclophosphamide chemotherapy there is an increase in IL-6. When chemotherapy is administered, cytokine-producing cells are activated, thereby inducing inflammation. This inflammatory response is stimulated by oxidative stress due to chemotherapy

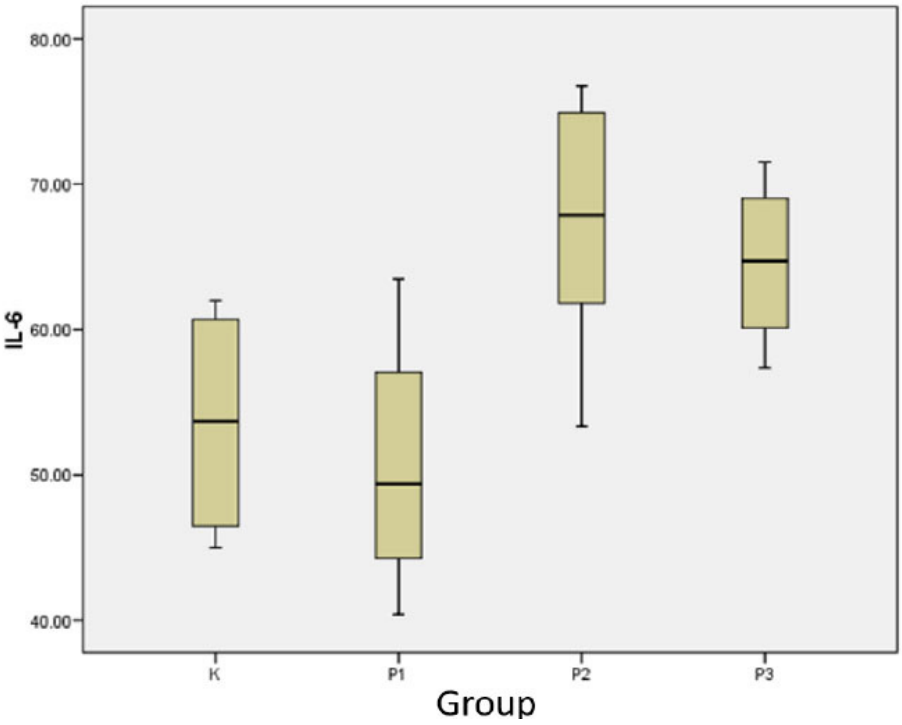

Figure 3. Boxplot graph of IL-6 expression for each group.

rather than damage-associated molecular patterns (DAMPs) from local cell death. This is following the study by Loman, BR, et al., where rats with cancer that were given paclitaxel chemotherapy experienced increased expression of the pro-inflammatory cytokines IL- 6, IL-8, and IL-10 mRNA circulating in the brain (hypothalamus and hippocampus). Systemic inflammation transduced to the central nervous system causes activation of microglia and astrocytes, thereby increasing the expression of pro-inflammatory cytokines in the brain.[15] This explains that the highest mean IL-6 expression was in P2 who were given Adiamycin- cyclophosphamide chemotherapy and 150 mg/kgBW turmeric extract supplementation. IL-6 plays an essential role in the growth and metastasis of breast cancer cells, renewal of breast cancer stem cells, and drug resistance in breast cancer stem cells, so anti-IL-6 therapy is an option for the treatment and prevention of breast cancer.[12,13]

IL-6 is a cytokine produced by cancer cells that is a potent regulator of dendritic cell differentiation in vivo and can activate the expression of signal transducer and activator of transcription (STAT)3 in dendritic cells. With high levels of STAT3, the maturation of dendritic cells can continue and disrupt subsequent antigen presentation, causing T cell non-responsiveness leading to T cell cytotoxicity. A decrease in cytotoxic capacity causes a reduction in granzyme b expression. Turmeric not only increases tumor antigen-specific T cells through tumor-induced reverse immunosuppression but also increases cytotoxic T cells by acting directly on immune cell dysfunction, which is one of the main mechanisms of tumor escape from immune surveillance through signal transducer and transcription activator pathways 3 and nuclear factor kappa B (NF-kB) signaling pathway.[19]

CONCLUSION

The results of the study showed that there was an effect of turmeric extract (Curcuma longa) on IL-6 expression between the control group and the treatment group at doses of 100 mg/KgBW, 150 mg/KgBW and 200 mg/KgBW.

CONFLICT OF INTEREST

The authors declare that there is no conflict interest.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, and not-for-profit sectors.

AUTHOR'S CONTRIBUTION

YS: Planned the study, collected the data, performed the analysis, and wrote the manuscript; SB: critically revised the draft for important intellectual content and finally approved the manuscript. All authors read and approved the final manuscript.

ETHICAL STATEMENT

This research has received ethical clearance from the Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Diponegoro University, with No.140/EC-H/KEPK/FK- UNDIP/ XII/2023.

REFERENCES

1. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Cancer: Targets and Therapy. 2019 Apr;Volume 11:151–64.
2. Bhattacharyya GS, Doval DC, Desai CJ, Chaturvedi H, Sharma S, Somashekhar SP. Overview of Breast Cancer and Implications of Overtreatment of Early-Stage Breast Cancer: An Indian Perspective. JCO Glob Oncol. 2020 Nov;(6):789–98.
3. World Health Organization. Breast Cancer. WHO. 2021.
4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May 4;71(3):209–49.
5. Komisi Penanggulangan Kanker Nasional. Panduan Nasional Penanganan Kanker Payudara. Indonesia; 2015.
6. Jermini M, Dubois J, Rodondi PY, Zaman K, Buclin T, Csajka C, et al. Complementary medicine use during cancer treatment and potential herb-drug interactions from a cross-sectional study in an academic centre. Sci Rep. 2019 Mar 25;9(1):5078.
7. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, et al. Breast cancer. Nat Rev Dis Primers. 2019 Sep 23;5(1):66.
8. Bevers TB, Helvie M, Bonaccio E, Calhoun KE, Daly MB, Farrar WB, et al. Breast Cancer Screening and Diagnosis, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. 2018 Nov 15;16(11):1362–89.

9. Priyadarsini KI. The Chemistry of Curcumin: From Extraction to Therapeutic Agent. Molecules [Internet]. 2014 Dec 1 [cited 2024 Mar 17];19(12):20091. Available from: /pmc/articles/PMC6270789/
10. Mansouri K, Rasoulpoor S, Daneshkhah A, Abolfathi S, Salari N, Mohammadi M, et al. Clinical effects of curcumin in enhancing cancer therapy: A systematic review. BMC Cancer [Internet]. 2020 Aug 24 [cited 2024 Mar 17];20(1). Available from: https://pubmed.ncbi.nlm.nih.gov/32838749/
11. Hardanto GR, Budijitno S, Hardian H. Effect of Artemisia vulgaris Extract on Granzyme Expression and Tumor Mass Diameter (Study of Adriamycin Cyclophosphamide Chemotherapy in Adenocarcinoma Mammae C3H Mice Model). Jurnal Kedokteran Brawijaya. 2021 Aug 31;31(4):205–10.
12. Farghadani R, Naidu R. Curcumin: Modulator of Key Molecular Signaling Pathways in Hormone-Independent Breast Cancer. Cancers (Basel). 2021 Jul 8;13(14):3427.
13. Jalilian E, Abolhasani-Zadeh F, Afgar A, Samoudi A, Zeinalynezhad H, Langroudi L. Neutralizing tumor-related inflammation and reprogramming of cancer-associated fibroblasts by Curcumin in breast cancer therapy. Sci Rep. 2023 Nov 26;13(1):20770.
14. Yadav R, Jee B, Awasthi SK. Curcumin Suppresses the Production of Pro-inflammatory Cytokine Interleukin-18 in Lipopolysaccharide Stimulated Murine Macrophage-Like Cells. Indian Journal of Clinical Biochemistry. 2015 Jan 15;30(1):109–12.
15. Ghandadi M, Sahebkar A. Curcumin: An Effective Inhibitor of Interleukin-6. Curr Pharm Des. 2017 Mar 27;23(6):921–31.
16. Mills PJ, Ancoli-Israel S, Parker B, Natarajan L, Hong S, Jain S, et al. Predictors of inflammation in response to anthracycline-based chemotherapy for breast cancer. Brain Behav Immun. 2008 Jan 1;22(1):98–104.
17. Girard BM, Cheppudira BP, Malley SE, Schutz KC, May V, Vizzard MA. Increased expression of interleukin-6 family members and receptors in urinary bladder with cyclophosphamide-induced bladder inflammation in female rats. Front Neurosci. 2011 Feb 22;5(FEB):8728.
18. Gorabi AM, Razi B, Aslani S, Abbasifard M, Imani D, Sathyapalan T, et al. Effect of curcumin on proinflammatory cytokines: A meta-analysis of randomized controlled trials. Cytokine. 2021 Jul;143:155541.
19. Manore SG, Doheny DL, Wong GL, Lo HW. IL-6/JAK/STAT3 Signaling in Breast Cancer Metastasis: Biology and Treatment. Front Oncol. 2022 Mar 15;12:866014.