

Effect of Artemisia vulgaris Extract on P53 Expression and Caspase-8 Expression (Study on Adenocarcinoma Mammariae C3H Mice Given Adriamycin- Cyclophosphamide Chemotherapy Regimen)

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ABSTRACT

Background : The incidence of breast cancer worldwide is still high. Surgery remains the top choice with other modalities of chemotherapy, radiation, and immunotherapy such as *Artemisia vulgaris* (AV). **Purpose :** The study was aimed to demonstrate that administration of AV extract increased the levels of *p53* and *Caspase-8* in adenocarcinoma mammae. **Methods :** This study used "Post test only control group design" on 24 females C3H mice that were randomly selected and divided into four groups : group K (control), P1 (chemotherapy), P2 (extract), and P3 (combination). Adenocarcinoma mammae comes from the inoculation of donor mice. Chemotherapy of Adriamycin 0.18 mg and Cyclophosphamide 1.8 mg were given in 2 cycles. AV 13 mg (0.2 ml) was given once daily orally. *P53* and *Caspase-8* levels were evaluated by immunohistochemical staining. **Results :** Mean of *p53* and *Caspase-8* levels were found in groups K, P1, P2, P3 were 22.06 ± 1.73 , 37.16 ± 1.20 , 24.60 ± 1.08 , 39.78 ± 1.19 dan 17.16 ± 1.28 , 26.20 ± 1.11 , 24.60 ± 1.08 , 39.78 ± 1.19 . The statistical analysis showed that there were significant differences in the levels of *p53* between groups of K vs P1, P3 ($p=0.001$), K vs P2 ($p=0.048$), P1 vs P2 ($p=0.001$), P1 vs P3 ($p=0.039$), P2 vs P3 ($p=0.001$), and in *Caspase-8* between groups of K vs P1, P3 ($p=0.001$), K vs P2 ($p=0.048$), P1 vs P2 ($p=0.001$), P1 vs P3 ($p=0.039$), P2 vs P3 ($p=0.001$). Correlation analysis between *p53* and *Caspase-8* showed significant correlation ($p=0.047$ dan $r=0.883$). **Conclusion :** *Artemisia vulgaris* can improve the effectivity of Adriamycin-Cyclophosphamide chemotherapy on C3H mice with adenocarcinoma mammae in terms of elevated levels of *P53* and *Caspase-8*.

1. Introduction

Breast cancer is one of main health concerns for women around the globe. In 2009 there are around 192,370 new cases of invasive breast cancer and 62,280 new cases of in situ breast cancer diagnosed in United States. In Indonesia, breast cancer has become the second most common malignancy after cervical cancer. Breast cancer incidence rate is 100 for each 100,000 women.¹ Estimated number of cases in Indonesia is 12/100,000 women, meanwhile mortality is as high as 27/100,000 or 18% out of total woman death toll. Breast cancer can also attack men with frequency of around 1%. More than 80% of cases in

Indonesia are found at advanced stage which hinder therapeutic efforts.²

Main defenses against cancerous growth in human body are mediated by two main pathways involving Retinoblastoma (RB) and P53 protein. These two pathways are often found on cancer cells in inactivated state. P53 is a protein with molecular mass of 53 kilodalton coded by TP53 / P53 genes.⁸ This gene contains 11 exons and a total sequence of 20 kb. P53 regulates both repression and transcription activation of some downstream genes with vital role on cellular response upon environmental stress, genotoxic effects

(such as DNA alteration triggered by UV radiation, carcinogens, cytotoxic chemotherapy treatment), and also non-genotoxic effects (hypoxia, oncogen activation, nucleotide repression, microtubule damage, and loss of intercellular contact).⁸ Some of its functions includes inducing apoptosis, controlling and shutting down cell cycle (cell cycle arrest), helping DNA repair, and inhibiting angiogenesis.⁸ The specific qualitative and quantitative activities of P53 depend on its integrity (mutation status), number, post translation specific modification in response to environmental stress and interactions with a number of its cofactors.⁹

The function of P53 in regulating cellular response to environmental stress contributes greatly in preventing tumors, which makes P53 known as one of Tumor Suppressor Genes. The evidence of P53 gene functioning as tumor suppressor can be seen from mice which phenotype modified to mutate or lose one or two of P53 allelgen developed tumor and die earlier than mice with normal two alleles of P53 gene.^{8,10} Another study in human subjects showed that more than half of tumor types contain P53 gene mutation.¹¹

P53 mutation can also negates its tumor suppressing function by altering P53 functions as apoptosis inducing factor and transcription factor. Germline mutation in P53 can be found in hereditary cancers such as Li-Fraumeni Syndrome, which cause different types of cancer to manifest early in life. P53 somatic mutation can also be found in 25-30% sporadic breast cancer cases. Most of P53 mutations occur in DNA binding area and \pm 90% occurs in form of missense point mutation. A number of study showed that point mutation mostly happens on exon 5 to 8.¹⁰

This study aimed to prove the effectivity of *Artemisia vulgaris* extract as adjuvant the rapy to mammary adenocarcinoma chemotherapy in orde r to incre ase expre ssion of P53 and de crease re tinoblastoma prote in in C3H mice tre ated with Adriamycin-Cyclophosphamide. We hope the re sults of this study can support the use of *Artemisia vulgaris* as adjuvant to che motherapy for bre ast cancer.

Treatment for breast cancer includes surgery, radiotherapy, chemotherapy, and hormonal therapy.^{5,8}

Chemotherapy is a process of treatment using drugs to destroy cancer cells of slow down their growth. Chemotherapy side effects are caused by the drugs attacking not only cancer cells, but also healthy cells especially cells which divide rapidly. Chemotherapy for breast cancer is administered in regiments. Most common drug combination for chemotherapy are Fluorouracil, Doxorubicin, and Cyclophosphamide (FAC); Fluorouracil, Epirubicin, and Cyclophosphamide (FEC); Doxorubicin and Cyclophosphamide (AC); Cyclophosphamide, Methotrexate and Fluorouracil (CMF). These regiments are administered on an intermittent basis each three or four weeks. FAC, FEC and CMF are administered in 6 cycles (18 to 24 weeks) while AC is administered in 4 cycles (12 to 16 weeks).³

Chemotherapy success rate is determined by objective response rate after treatment (Partial Response dan Complete Response – CR/PR). Breast cancer chemotherapy has CR/PR rate of only 20-40%, meanwhile it develops immunosuppresion and produces side effects to liver, kidney, heart, and various other organs.⁴

Various studies have been focused on developing safer chemotherapy by exploring anti-cancer properties of new substances, including herbal medicines. There are a lot of herbal medicine derivates known to have wide antibiotic and antimalignancy properties to fight effectively against numerous diseases.⁵

There have been many studies of herbal medicines as chemotherapy adjuvant, such as : God's crown (*Phaleria macrocarpa*), fennel (*Nigella sativa*), green tea (*Camellia sinensis*), and mugwort (*Artemisia vulgaris*). *Artemisia vulgaris* is one of commonly used herbs. *Artemisia vulgaris* is known to have selective cytotoxic effect against cancer cells and have been used as adjuvant to treat colorectal cancer, renal cancer, prostat cancer, hepatic cancer, pancreatic cancer, skin cancer, and gastric cancer. The application of *Artemisia vulgaris* as chemotherapy adjuvant for breast cancer still needs a deeper study. A pilot study showed that *Artemisia vulgaris* contains terpenoid (artemisinin, artesunate), flavonoid, tannin and coumarin (scopoletin) analog. Artemisinin and artesunate have

been widely used as antimalaria. but they also showed cytotoxic activity against cancer cells by inducing apoptosis and inhibiting angiogenesis. disrupting cancer cell cycle. and toxicity against free radicals. Artemisinin has the advantage of having selective toxicity while still being cytotoxic. This falls into consideration in terms of safety for its users. This selective cytotoxicity is a supporting factor for preliminary pre-clinic studies.⁶

Earlier study on mice with hepatic carcinoma given artemisinin with dose of 100mg/kg per day showed anticancer activity.⁷

2. Methods

Research design

This research is an experimental laboratory study with post-test only control group design. The research group was divided into 4. namely the control group (K). treatment 1 (P1). treatment 2 (P2). and treatment 3 (P3). The division of treatment groups is as follows: K : Control group. tumor inoculated mice. P1 : Treatment group 1. tumor inoculated mice. after developing tumors received chemotherapy Adriamycin - Cyclophosphamide. P2 : Treatment group 2. tumor inoculated mice. after developing tumors received *Artemisia vulgaris* extract 13 mg/times per day. P3 : Treatment group 3. tumor inoculated mice. after developing tumors received AC chemotherapy and *Artemisia vulgaris* 13 mg/times per day.

Research samples

Animals used are C3H strain mice (*Mus musculus*) purchased from Bogor mice breeder. Inclusion criteria: 8 weeks old female mice. C3H strain. body mass of 20-30 grams after acclimatization. no visible anatomical abnormalities. Exclusion criteria: no tumor growth after inoculation. mice looked ill (inactive movement) during inoculation and treatment.

Sample size according to WHO. each group needed minimal 5 samples with 10% reserves. This study used 6 mice per group.⁴²

Time and location

Research and data collection was carried out for five months. *Artemisia vulgaris* extract was made at LPPT I. Faculty of Medicine. Gajah Mada University. Mice treatment and tissue extraction was carried out at LPPT IV. Faculty of Medicine. Gajah Mada University. Paraffin blocks processing. HE staining. and immunohistochemistry staining were carried out at the Anatomical Pathology Laboratory. Faculty of Medicine. Gajah Mada University / Dr. Sardjito Central General Hospital Yogyakarta.

Research variable

The independent variables in this study were administration of *Artemisia vulgaris* extract. administration of chemotherapy Adriamycin and Cyclophosphamide. and administration of *Artemisia vulgaris* extract with a combination of chemotherapy Adriamycin and Cyclophosphamide.

The dependent variables in this study were expression of P53 and Caspase-8.

Operational definition

Administration of *Artemisia vulgaris*: *Artemisia vulgaris* extract is an extract derived from the leaves extracted with ethanol solvent. with a dose of *Artemisia vulgaris* 100mg / kg body weight / day orally (13 mg/dose).

Adriamycin administration: Adriamycin administered intravenously at dose of 60 mg/m² body surface area (mice BSA 0.003 m² = 0.18 mg/dose). Treatment given in 2 cycles (1 cycle = 1 dose each 21 days). Variabel scale : nominal

Cyclophosphamide administration : Cyclophosphamide administered intravenously at dose of 600 mg/m² body surface area (mice BSA 0.003 m² = 1.8 mg/dose). Treatment given in 2 cycles (1 cycle = 1 dose each 21 days). Variabel scale : nominal

P53 expression was calculated by examining the amount of cells expressing antigen after exposed to P53 marked by brown-coloured nucleus. 10 field of view was examined from each slide under 400X

magnification. Allred scoring system was used to evaluate number/percentage of positive expressing cells and their color intensity. Variable scale: ratio.

Expression of Caspase-8 was analyzed by immunohistochemistry. 4pM parts of pretreatment TMA automatically applied to pretreatment module (PT - Link. Dako. Glostrup. Denmark) and then stained (Autostainer Plus; Dako) with anti Caspase-8 monoclonal antibody DSC - 6 (Dako). diluted into 1:50. Caspase-8 expression intensity (negative. low. medium. or high). and positive cancer cell proportion (0 = 0 - 1%. 1 = 2-25%. 2 = 26-50%. 3 = 51-75% dan 4 = >75%). For further statistical analysis. Caspase -8 expression divided into negative (no expression) and positive (all expression. no matter fraction and intensity). Staining examined by two independent evaluator blinded from clinical data and results. with Clinical Agreement of 95 %. Variable scale : ratio

Materials and tools

Sample animals are 8 weeks old C3H strain female mice. with body mass 20-30 grams. Mice were obtained from breeders in Bogor. During experiment. mice were place in cages and given food and water ad libitum. Mice underwent 1 week adaptation period before treatment.

Simplicia of *Artemisia vulgaris* was obtained from Biopharmaca Cultivation Conservation Unit. Center for Biopharmaca Studies. Bogor Agricultural Institute. The material used is *Artemisia vulgaris* extract. which was obtained by One kg of dried leaves of *Artemisia vulgaris* is finely ground. The powder is put into a socket device (capacity of 50 mg). and the extraction is carried out by soaking using ethanol solvent for 8-10 cycles. The extract was put into a rotary evaporator flask. and vacuum distilled until it became highly concentrated (temperature 40°C). The extract was dried in an oven at 40°C for 1 hour to evaporate the ethanol. The results obtained were 5.5 mg of extract for every 1 kg of material (0.55%). and the products were diluted with aquabidest until a concentration of 0.2 mg/ml was reached.

Adenocarcinoma cells were obtained from donor

mice. Tumor containing adenocarcinoma cells was transplanted from donor mice to recipient mice. Some tumor from donor mice were biopsied and underwent histopathology examination to confirm tumor type.

Data analysis

Collected data were cleaned. coded and tabulated. Data analysis comprised of descriptive analysis and hypothesis testing. In descriptive analysis. P53 and Caspase-8 data are presented in form of mean tables. standard deviation. median and box plot graphs. To determine normality of data. a normality test was performed using Saphiro-Wilk test.

Hypothesis testing for P53 data was performed using One Way Anova test with non parametric alternative Kruskal Wallis. followed by Post-Hos test to evaluate disparity between groups.

Hypothesis testing for Caspase-8 data was performed using One Way Anova test with non parametric alternative Kruskal Wallis. followed by Post-Hos test to evaluate difference between groups.

Correlation testing between variables of P53 and Caspase-8 was performed with Pearson correlation test if the data were distributed normally and Spearman's rho correlation test if the data were not distributed normally.

Level of significance limit was $P \leq 0.05$ with 90% confidence interval. Data analysis was performed using SPSS Ver. 21.0 software for Windows.

Data collection

Six micron wide specimen was made from each group. stained with HE and examined for lymphocyte spread and histology degree. Another specimen was also made from each group to evaluate perforin expression using anti-P53 monoclonal antibody staining and Caspase-8 and examined for number of lymphocytes near the cancer cell that produce perforin.

Ethical requirements

This study applies animal ethics in managing sample animals. This study has been approved by

Ethics Commission for Health Research. Faculty of Medicine. Diponegoro University. All sample animals were treated and cared for according to standard animal caring procedure.

3. Results

P53 expression

Bonferroni Post-Hoc test (Table.3) showed significant difference between groups: K vs P1 ($p = 0.001$); K vs P2 ($p = 0.048$); K vs P3 ($p = 0.001$); P1 vs P2 ($p = 0.001$); P1 vs P3 ($p = 0.039$); and P2 vs P3 ($p = 0.001$). Box plot as shown in figure 12 below shows median P53 level in group K is lower than group P2 and P53 level in group P1 is lower than group P3. Average P53 level was found higher in group P3 than group P1. Difference of P53 level analysis using One Way ANOVA test, followed with Post Hoc test showed a significant difference and thus the first hypothesis may be accepted.

Caspase-8 expression

Bonferroni Post-Hoc test (Table.5) showed significant difference between groups: K vs P1 ($p = 0.001$); K vs P2 ($p = 0.069$); K vs P3 ($p = 0.001$); P1 vs P2 ($p = 0.001$); P1 vs P3 ($p = 0.059$); and P2 vs P3 ($p = 0.001$). Box plot as shown in figure 13 below shows median Caspase-8 level in group K is lower than group P2 and P53 level in group P1 is lower than group P3.

Average Caspase-8 level was found higher in group with chemotherapy and *Artemisia vulgaris* extract combination than group with only chemotherapy. Apoptosis index difference analysis using One Way ANOVA test, followed with Post Hoc test showed a significant difference and thus the second hypothesis may be accepted.

Correlation between P53 and caspase-8

Correlation test between P53 level and Caspase-8 level was performed on group P3 (combination therapy). Normality test for data from both variables was performed with Shapiro-Wilk test. Shapiro-Wilk test resulted in normal distribution ($p > 0.05$) and thus correlation analysis was performed using Pearsons test

Pearsons correlation test as shown in table 6 resulted in $p = 0.047$ and $r = 0.883$. Because p value is < 0.05 thus can be concluded a significant correlation between P53 level and Caspase-8 level. This means if P53 level is increased, Caspase-8 level will also increase accordingly.

Pearsons correlation analysis between P53 level and Caspase-8 level in group that received combination of Adriamycin-Cyclophosphamide chemotherapy and *Artemisia vulgaris* extract showed a significant positive correlation between two variables, thus the third hypothesis may be accepted.

Research plan schematic is as follows :

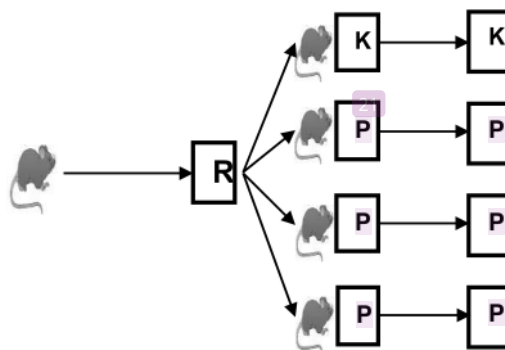


Table 1. P53 data characteristics

Group	N	Mean \pm SD	Median	Min	Max
K	5	22.06 \pm 1.73	22.00	20.10	24.30
P1	5	37.16 \pm 1.20	37.00	35.90	38.80
P2	5	24.60 \pm 1.08	24.70	23.20	25.90
P3	5	39.78 \pm 1.19	39.60	38.60	41.60

P53 expression data characteristics presented in percentage.

One way anova test showed $p < 0.001$

Table 2. P53 level between groups Post Hoc analysis

Group	P1	P2	P3
K	0.001	0.048	0.001
P1	-	0.001	0.039
P2	-	-	0.001

* Tested with *Bonferroni* (significant if $p < 0.05$)

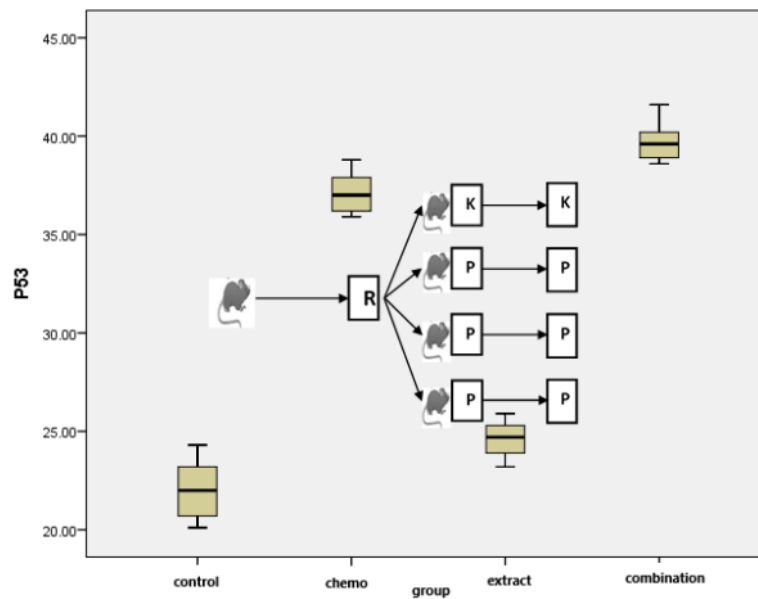


Figure 1. P53 data box plot graph

Table 3. Caspase-8 data characteristics

Group	N	Mean \pm SD	Median	Min	Max
K	5	17.16 \pm 1.28	17.00	15.50	18.90
P1	5	26.20 \pm 1.11	26.00	24.90	27.70

P2	5	24.60 ± 1.08	24.70	23.20	25.90
P3	5	39.78 ± 1.19	39.60	38.60	41.60

Caspase-8 expression data characteristics presented in percentage.

One way anova test showed $p < 0.001$

Table 4. Caspase-8 between groups Post Hoc analysis

Group	P1	P2	P3
K	0.001	0.069	0.001
P1	-	0.001	0.059
P2	-	-	0.001

* Tested with *Bonferroni* (significant if $p < 0.05$)

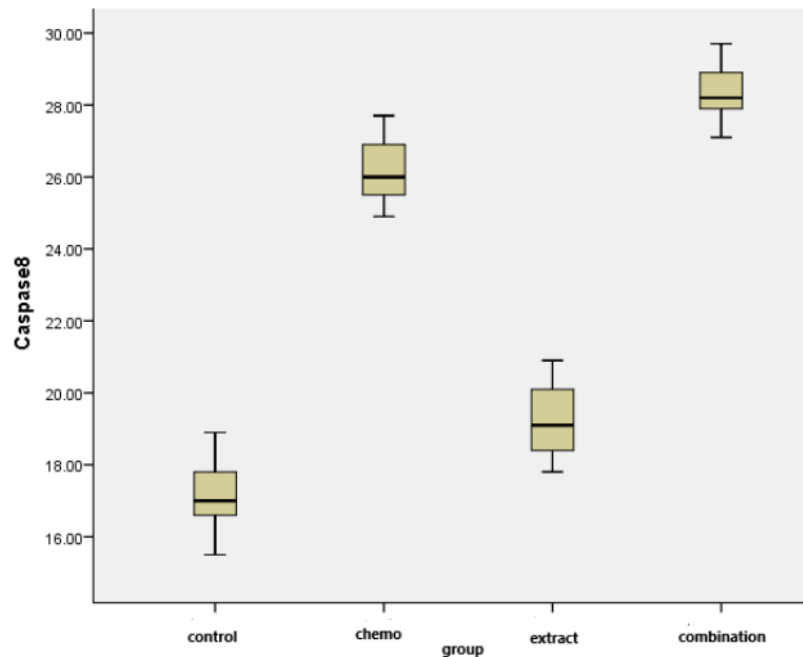


Figure 2. Caspase-8 data box plot graph

Tabel 5. Pearsons correlation test results

Variable	P	R
P53 level		
Caspase-8 level	0.047	0.883

4. Discussion

This study aimed to prove the influence of *Artemisia vulgaris* extract administration to C3H mice with mammary adenocarcinoma that received Adriamycin-Cyclophosphamide chemotherapy in terms of P53 and Caspase-8 levels. Result discussion will be explained orderly starting from P53 level. Caspase-8 level. followed with witnessing the correlation between said two variables.

Average P53 level was found higher in the group that received combination of chemotherapy and *Artemisia vulgaris* extract than the group that received only chemotherapy. This corresponds to the study by Eunjeong C et.al in which mentioned that artemisinin. one component of *Artemisia vulgaris* can perform anticancer effects by regulating apoptosis process through estrogen receptor-related pathway.²⁴ Another study by Langroudi et.al also mentioned that artemisinin has a role in increasing immune function by suppressing T-reg cells.²⁵

In this study. chemotherapy was only administered in 2 cycles instead of recommended 4 cycles for human.²⁶ Significant increase of P53 and Caspase-8 levels in the group that received combination therapy in opposed to the group that only received chemotherapy proved that *Artemisia vulgaris* extract can improve the effects of apoptosis and cell proliferation suppression from chemotherapy.

Average Caspase-8 level was found higher in the group that received combination of chemotherapy and *Artemisia vulgaris* extract in opposed to the group that received only chemotherapy. This corresponds with a study by Jia et.al. in which mentioned that artemisinin can inhibit G1 phase of cell cycle. increase production of Reactive Oxygen Species (ROS) causing the collapse of mitochondria potential membrane and triggering the release of cytochrome-c from mitochondria into cytoplasm. which in turn activating Caspase-3 mediated apoptosis.²⁷ according to Li et.al. 2016. artemisinin and its derivatives perform pro-apoptosis role not only by cytochrome-3 release and Bax over-expression. but also by increasing Bax/Bcl-2 ratio. activating Caspase-8 which activates Bid protein which

in turn will trigger the release of cytochrome -c from mitochondria. Released cytochrome-c will be captured by procaspase-9. which in turn activates Caspase-9 and Caspase-3.^{22, 28} Blazquez et.al mentioned that artemisinin might be having a direct interaction in DNA replication during the process of inducing apoptosis.²⁹ According to Mu et.al. 2007. artemisinin and its derivatives trigger apoptosis in cancer cells by increasing intracellular calcium level and activating p38.³⁰ All said studies showed various mechanisms of artemisinin as an active component of *Artemisia vulgaris* in inducing apoptosis.

This study was able to prove correlation between P53 level and Caspase-8 level. but there are various other pathways that can cause the apoptosis process.

^{27 - 30}

Artemisia vulgaris extract has the potential to be used as immunomodulator that supplements a primary therapy. as an alternative use of traditional medicine. We realized this study contained numerous flaws that needed to be countered in order to complete and perfect the study. To emphasize the concept of this study. there is a need for a follow-up research to determine other factors contributing to the increase of P53 and Caspase-8 levels. A new clinical trial on human subjects may be considered to be carried out.

5. Conclusion

Artemisia vulgaris suppresses cell proliferation in mammary adenocarcinoma inoculated C3H mice treated with Adriamycin-Cyclophosphamide by increasing P53 level. *Artemisia vulgaris* also promotes apoptosis effect by increasing Caspase-8 level. There was a significant correlation between P53 level and Caspase-8 level in mammary adenocarcinoma inoculated C3H mice treated with a combination of Adriamycin-Cyclophosphamide and *Artemisia vulgaris* extract.

6. Conflict of interest and funding

Authors did not received funding or profits from the industry or elsewhere for conducting this research.

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