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Pomegranate Fruit extract Administration in mice induced by Formaldehyde to Folliculogenesis Observation and Caspase-3 Expression

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ABSTRACT:
General population exposure of formaldehyde can occur via inhalation, ingestion due to food and water also dermal contact. Recent studies suggested formaldehyde exposure induce oxidative stress in reproductive system and cause menstrual cycle disorders. Pomegranate is commonly known in Indonesia, often use as a traditional herbal, extract of all part of fruit superior to have protective to the damage in the body including the down regulation of apoptosis mechanism due to euglycemic acid compound. Oxidative stress was induced by formaldehyde (140 mg/kg/day) for 12 consecutively. Mice were treated with pomegranate fruit extract in 100, 150, and 200 mg/kgBW/day for 12 days after exposure of formaldehyde. On day 29th, mice were euthanized then tissue were isolated and processed for immunohistochemistry staining with caspase-3 antibody and hematoxylin eosin staining. Caspase-3 expression was significantly different in groups which treat pomegranate fruit extract. The number of follicles including primary, secondary, tertiary, and de Graaf follicles is not different in each group. In conclusion pomegranate fruit extract in maximum of 200 mg/kg/day per day appears to be able to down-regulate the expression of caspase-3 but ineffective in number of follicles in formaldehyde mice model.

KEYWORDS: pomegranate, euglycemic acid, folliculogenesis, caspase-3, toxicity.

INTRODUCTION:
Formaldehyde is commonly produced as an aqueous solution called formalin, used in the production of abattoir materials, woods, insulation, foundry binders, brake lining made from phenol resorcinol surface coating, modeling compounds, laminates, wood adhesive, explosive, and in small amount of Formaldehyde is as preservatives and embalming of biological specimens (1). Formaldehyde released to water from the discharges of both treated and untreated industrial wastewater from its production and from in use in the manufacture of formaldehyde containing resins (International Organization 2010).

This condition could cause the exposure of formaldehyde in the air, water, food, also cosmetics entering human body and cause damage to organ and cells. Previous study found that formaldehyde could make damage in folliculogenesis, caspase activity, and DNA damage (2, 3).

Caspase-3 is a member of caspase family that constitute separate requiring proenzyme is a key factor of apoptosis process. Under normal condition, caspase ions inactive form in cytosol, anti-oxidant stress condition, DNA damage, mitochondrial damage, and infection (4). Our body need caspase-3 expressions in an adequate expression, aberrant of caspase-3 expressions could lead to degenerative disease and lack of caspase-3 could cause cancer (3). Eucalyptus is a potent antiviral component of pomegranate. Previous study found euglycemic acid has anti-inflammatory, and anti-apoptotic effect (6.7). EA could increase endogen antioxidant through cells to prevent oxidative stress. This potential effect however could decrease apoptotic effect if oxidative stress is.

MATERIAL AND METHODS:
Chemicals:
Formaldehyde were obtained from Sigma Aldrich. Pomegranate were obtained from Sembang, Central Java and extracted in GadjahMada University, Jogjakarta, Indonesia.

Animal Maintenance:
Formaldehyde solution were used for the study age 8-10 weeks, 20-25 grams weighed. The study were approved by ethical committee of University of Airlangga. Mice were acclimatized for one month and maintained in 20-25°C on 12/12 photoperiod with ad libitum supply for standard mice feed and drinking water. Vaginal vault were conducted before administration of formaldehyde to rule the menstrual cycle.

Administration of formaldehyde and pomegranate fruit extract:
Mice were divided in 4 groups (n=11), each group were treated with formaldehyde 10% 140 mg/kg body weight each day for 12 days and continue treated with pomegranate extract fruit for 12 days. Control group were treated with equal volume of saline (0.5%), each three groups were treated with different dose of pomegranate extract 100 mg/kgBW, 150 mg/kgBW, 200 mg/kgBW) dosed in 0.5% CMC as suspension, treatment was started from the next day after administration of formaldehyde. Pomegranate fruit extract was given by gastric feeding at 24 h interval & consecutive days. One group of control was given only vehicle and equal volume. All groups of mice were sacrificed on day 13 of administration of pomegranate fruit extract. Ovaries were ex immediately after sacrificing the animal and washed in normal saline. Ovaries of animals were cohort in buffer formaldehyde 10%.

Histology:
Post mortem samples of ovaries were fixed in 10% buffered formalin, processed and embedded in paraffin. Sections were stained for hematoxylin and eosin (HE) and caspase-3 were determined immunohistochemistry staining.

Statistical analysis:
Statistical analysis was performed using R program software with One-way Analysis of Variance (ANOVA) and Kruskal-Wallis test followed by post hoc test. Values are expressed as mean ± standard deviation. Statistical significance was assessed using Student's t test. Values of p<0.05 were considered statistically significant from each group.
RESULTS

Ellagic acid downregulates expression and activation of caspase-3. The expression of caspase-3 was down regulated in mice ovariectomized exposed by formaldelode and treated with pomegranate extract as compared to control group treated with salubridol only. Decreased in expression of caspase-3 was observed approximately down from 4,800; 1,345; 1,600; 0,980 with a dose of 100 mg to 200 mg/kg body weight.

Ellagic acid regulates folliculogenesis:

The protective effect of ellagic acid was analyzed on folliculogenisis process, this process was measured in terms of amount of primary, secondary, tertiary, and de grafel follicle. Ellagic acid increases the number of primary follicles in mice exposed formaldelode treated with pomegranate fruit extract. This increase however, were not significantly different in different dose. Since follicle was increased but has a decrease amount in treatment with dose (100 mg kg body weight), tertiary follicle was increase in different dose compared to control group, and there were no de grafel in control and treatment with 100 mg/kg body weight, and there was one follicle de grafel in 150 mg/kg and 200 mg/kg body weight treatment.

DISCUSSION

Caspase-3 expression:

Caspase-3 is a known enzyme for apoptosis of programed cells (4), recently activation of caspase-3 from precursor forms induced by oxidative stress, DNA cross-link, and increase voltage dependent channel ion (VDAC).

Over expression of caspase-3 is reported to cause an autoimmune disease, reduced of caspase-3 has been shown in cancer cells. Our finding of a high level of caspase-3 in ovary of formaldelode exposed mice and their regulation by ellagic acid treatment suggest antagonistic effect of ellagic acid. Ellagic acid induced endogen enzyme antioxidants (SOD, CAT, GSH) (7-9), through raise in the sensitivity of quinone redox, and protein expression of endogen enzymes gene expression (8,10). Other effect of UV is has been rep due to stabilization of intracellular osmotic membrane permeabilization (MOMP) by reactivating calp hsp-21(11).

Primary follicle:

Primary follicle is a growth follicle from primordial follicle, morphologically primary follicle consist of single layer of columnar cells, growth oocyte, and priferid zone (12). Recent study show formaldelode exposure could reduce the number of primary follicle (13). Data shows in this present study demonstrates that with ellagic acid treatment in different dose every 24 hours c increase the number of primary follicle, although this difference is not significant in statistical analyse. Previous study show development of granulosa single layer needs optimal environment formaldelode exposure however could induce cell injury, affecting granulosa and oocyte. Small follicle has lower defense against changing environment(11).

It makes the number of apoptotic cells do not significant with increasing dose of ellagic acid. In primary follicle, oocyte actively influences the granulosa cell development, this factor include growth differentiation factor (GDF)9 and bone morphogenetic protein (BMP)-15 (12). Granulosa cells however, also induce oocyte development. Formaldelode exposure could reduce express this factor but treatment ellagic acid could reduce this stress oxidative. Besides, cellular response maturation to injury need a very long time, but in molecular process has a highly sensitive response to environment changes, in this study, although primary follicle remain low, but caspase-3 response decrease during the increase of pomegranate fruit extract dose.

Secondary follicle:

Next stage of follicle development is secondary follicle, there is more than a single layer of column cells and development asov (12). This present study showed that treatment of pomegranate extract in mice with formaldelode exposure could make the unstimulated increase in number of secondary follicle. 150 mg/kg body weight treatment groups have less follicle than the control. Formaldelode exposure could increase oxidative stress and make abundant atresia in follicle. EA has a short half-life, absorb to body in first 4 hours and become unifed with reduction to 0.2 mg/kg body weight after 8 hours (12). We proposed by high number of atresia, 4 hours effectively half life could not prevent damage due to formaldelode exposure. This damage, however could reduce number of receptor, estrogen receptor, and androgen receptor.

Tertiary follicle:

Secondary follicle become larger and has atresia. In this study, the number of tertiary follicle remain unstimulated, we found 200 mg/kg body weight has a smallest number of tertiary follicle. Previous study showed that tertiary stages of follicle development has the highest number of physiological atresia, follicle with good FSH receptor and estrogen production could survive during oxidative stress caused by formaldelode exposure. FSH receptor and estrogen production of EA treatment however avoid both damage in cellular stage of follicular development therefore expect that the number of follicle in our study remains unstimulated in high number of antrum stages (secondary, tertiary), but can be adequately decrease the molecular response of oxid stress.

De Grafel follicle:

de Grafel follicle in a follicle that ready to ovulate, has a largest and greatest number of granulosa cells, we found that 150 and 200 mg/kg body weight dose of pomegranate fruit extract could induce the number of de Grafel follicle while 0 and 100 mg/kg body weight has null number de Grafel follicle, previous study suggest that the de Grafel follicle, due to the largest size and the abundant level of granulosa cells, provided broad defense against stress oxidative (2). It is proved that formaldelode could induce damage in granulosa cells.

Administration of pomegranate fruit extract in 150 and 200 mg/kg body weight in this research proved could repair the damage in granulosa cells, but it's not statistically different due to the time of pomegranate fruit extract.

CONCLUSION

Pomegranate fruit extract could reduce expression of caspase-3 but no effect in cellular response in folliculogenesis. In addition, administration of pomegranate fruit extract twice or three times may be important for cellular response due to no effect in cellular response.

CONFLICT OF INTEREST

The author declared that there is no conflict of interest regarding the publication of this article.

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