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Original article

White guava (*Psidium guajava L.*) fruit juice ameliorated the number of spermatogenic cells in rats (*Rattus Novergicus*) exposed to lead acetate

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ABSTRACT

This study aims to determine the effect of oral administration of white guava fruit juice (*Psidium guajava* L.) on the spermatogenic cells of rats (*Rattus norvegicus*) exposed orally to lead acetate. Twenty-five male rats (*Rattus norvegicus*) of the Wistar strain were randomly divided into five groups. Placebo group rats (P0) were given 0.5 mL distilled water twice every day orally at four-hour intervals. Groups T0, T1, T2, and T3 were given lead acetate 50 mg/kg bw orally, then respectively given distilled water, 100, 50 and 25% (v/v) white guava (*Psidium guajava* L.) fruit juice orally four hours later for 14 days. On day-15, the rats were sacrificed and their testicles were taken for histological preparations. Data were analyzed using Analysis of Variance followed by Duncan's Multiple Range Test. The results showed that the number of spermatogonia, spermatocytes and spermatids cells of rats in T0 group was lower ($p < 0.05$) than in P0 group. Higher spermatogonia, spermatocytes and spermatids cells ($p < 0.05$) were found in the T1 group compared to the T0 group. However, the number of spermatogonia and spermatocytes in the T1 group was still lower than in the P0 group. The number of spermatids in the T3 group was almost the same ($p > 0.05$) as in the P0 group. This study found that white guava pure juice without dilution was the best for maintaining the number of spermatids, but was unable to restore the number of spermatogonia and spermatocyte cells in rats exposed to lead acetate.

Keywords: quercetin, spermatids, spermatocytes, spermatogonia, vitamin C

INTRODUCTION

Lead was a heavy metal that is naturally found in the earth. Mining and its massive use on an industrial scale to meet human daily needs had resulted in widespread environmental pollution in the world (Halmo and Nappe, 2023; WHO, 2023). The widespread use of products containing lead such as materials on agricultural land, oil, paint, mining materials, etc. could cause lead contamination in the environment which could expose animals and humans along

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the food chain (Kumar *et al*., 2020). Lead toxicity could cause toxic effects on plants, animals and humans (Collin *et al*., 2022). Humans who occupied the top chain of the food chain could experience lead accumulation which subsequently caused health problems (Kumar *et al*., 2020).

Lead that entered the body could not simply be eliminated because it was stored in various organs. Lead poisoning could cause problems with the reproductive system (Collin *et al*., 2022). Case studies showed that severe lead poisoning could occur in both children and adults. In children, lead poisoning could come from tin pots, tin foil, and lead-based paint on children's toys. In adults, this incident came from containers of packaged food, drinking water, or vegetables grown in soil contaminated with industrial waste (Nicolli *et al*., 2020). Lead toxicity increased oxidative stress and affected sodium ion concentration (Debnath *et al*., 2019). Lead disrupted ionic processes and caused oxidative stress, causing enzyme and protein damage (Collin *et al*., 2022).

Antioxidants were needed to overcome oxidative stress in cells by scavenging ROS (Collin *et al*., 2022). External antioxidants should be given to complement internal antioxidant defense mechanisms. Herbal plants were the main source of natural antioxidant compounds which contained non-enzymatic phytochemical compounds such as flavonoids, polyphenols, and glutathione, as well as several vitamins (Chaudhary *et al*., 2023). *Psidium guajava* fruit contained lots of vitamin A, vitamin C, iron, phosphorus, and calcium as well as minerals, and also organic compounds as secondary metabolites for example polyphenol antioxidants. Quercetin was considered the most active antioxidant in guava (Hartati *et al*., 2020). Guava fruit ethanolic extract could improve sperm quality and quantity and could be used to treat infertile men (Naseer *et al*., 2018). Antioxidants, especially vitamin C, were used for the treatment and improvement of lead poisoning caused by oxidative stress (Debnath *et al*., 2019).

Guava (*Psidium guajava L.*) could be divided into two types, white or red depending on the color of the flesh. Guava (*Psidium guajava L.*) contained vitamins (A, B, C, β-carotene), antioxidants (flavonoids, flavonols, viscous tannins) (Angulo-López *et al*., 2021). Study on the use of white guava fruit juice had proven to improve integrity of sperm plasma membrane, percentage of sperm morphologic abnormality, viability, and motile sperm of rats exposed to lead acetate orally (Alifia *et al*., 2023). Hence, this study aims to determine the influence of administration of white guava (*Psidium guajava L.*) fruit juice on the number of spermatogonia, spermatocyte, and spermatids of rats (*Rattus norvegicus*) exposed to lead acetate.

MATERIALS AND METHODS

This study used 25 male rats (*Rattus Novergicus*) aged 12 weeks, weighing approximately 200 grams. This research procedure had been approved by the Universitas Airlangga Study Ethics Commission number 555/HRECCFODM/XII/2020.

Lead acetate dose

The lead used in this study was Lead (II) acetate trihydrate (Millipore Merck), at a dose of 50 mg/kg bw (Massanyi *et al*., 2007). Lead acetate was dissolved in distilled water for oral application (Septiani *et al*., 2022).

Preparation of white guava fruit juice

White guava fruits were washed clean, then cut into cubes and ground in a food processor. Guava juice was filtered and used as 100% concentration. The concentration was adjusted to 50 and 25% (v/v) by adding distilled water (Alifia *et al*., 2023).

Treatment of rats

Rats were divided randomly into five groups and then adapted for one week in individual cages. Rat food pellets (RatBio) and drinking water were given twice a day in the morning and evening. After seven days of adaptation, the rats

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were given treatment. Placebo group (P0) rats were given 0.5 mL distilled water twice a day at four-hour intervals. Groups T0, T1, T2, and T3 were given lead acetate at a dose of 50 mg/kg bw, followed by successive administration of distilled water, 100, 50, and 25% (v/v) white guava fruit juice four hours later. More specifically, lead acetate solution was given at 08.00, while distilled water and white guava fruit juice were given at 12.00. All solutions were administered orally using a probe in a volume of 0.5 mL for 14 days. On day-15, the rats were anesthetized with ketamine and then sacrificed by cervical dislocations, after which the rats were dissected and both testicles were taken to make microanatomical preparations.

Examination of spermatogonia, spermatocytes, and spermatids

Microanatomical preparations of rat testicles were stained with Hematoxylin-eosin and observed using a microscope (Nikon Eclipse Ci) with 400x magnification. Three seminiferous tubules of round cross-section were randomly observed and averaged. The parameters observed were the number of spermatogonia, primary spermatocytes and spermatids. Spermatogonia are characterized by oval or spherically shaped nuclei located closest to the basal lamina. Spermatocytes are located in the seminiferous tubules, characterized by a cell shape that contained fine chromatin granules and the largest nucleus is located apically.

Spermatids were located in the seminiferous tubules. They can be recognized by their small cell size with dense chromatin areas and their location close to the tubule lumen (Machmudia *et al*., 2021).

Data analysis

Data were analyzed using the Analysis of Variance followed by the Duncan's test to determine which treatments were different. Statistical analysis was carried out using the Statistical Program and Service Solution for Windows version 23.

RESULTS

Histologically, the testicles of rats (*Rattus norvegicus*) exposed to lead acetate without or with guava fruit juice showed changes in the number of spermatogonia, spermatocytes, and spermatids (Figure 1).

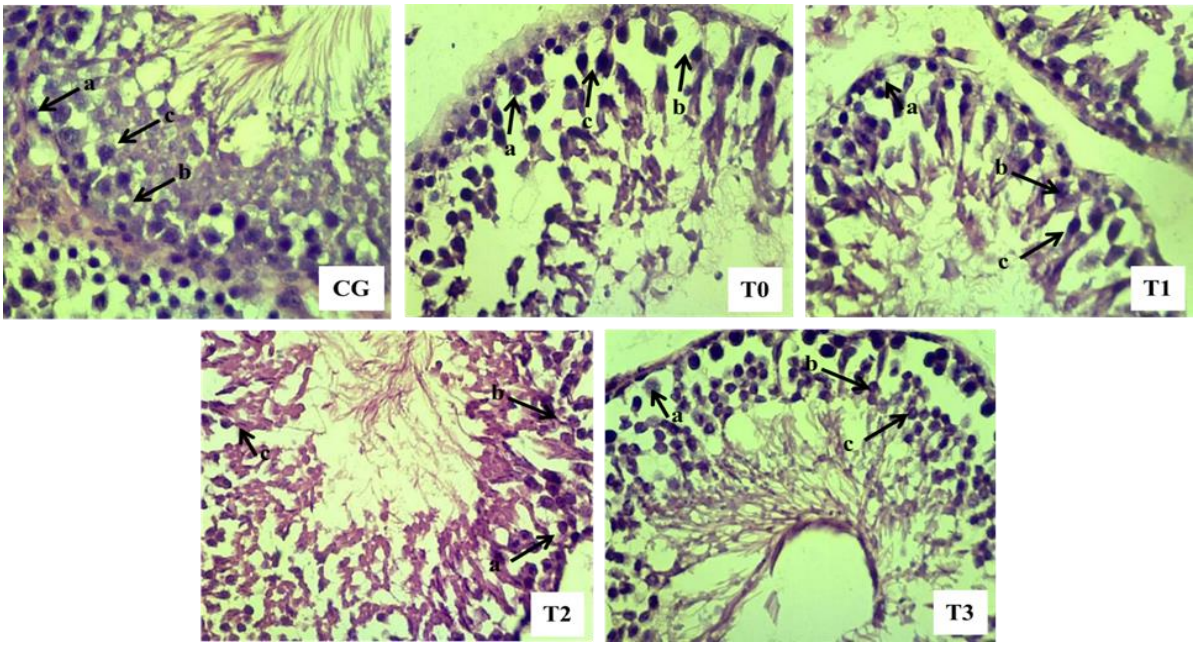

Figure 1 Testicular histopathology shows spermatogonia, spermatocytes, and spermatids of rats

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(*Rattus norvegicus*) exposed to lead acetate after being treated with white guava fruit juice; P0: rats were given 0.5 mL distilled water twice a day at four-hour intervals; T0, T1, T2, and T3: rats were given 50 mg/kg bw of lead acetate every day at 08.00 followed by the administration of respectively distilled water, 100, 50 and 25% (v/v) white guava (*Psidium guajava* L.) fruit juice four hours later; all solution were given orally using a probe in a volume of 0.5 mL for 14 days; preparations were Hematoxylin-eosin stained, examined with a light microscope (Nikon Eclipse Ci) at 400 x magnification; a: spermatogonia; b: spermatocytes; c: spermatids.

The mean number of spermatogonia, spermatocytes, and spermatids in rats (*Rattus norvegicus*) exposed to lead acetate without the administration of guava fruit juice (T0 group) was lower ($p < 0.05$) than in placebo group(P0) rat. Administration of white guava fruit juice to rats exposed to lead acetate resulted in a repair response to spermatogonia, spermatocytes, and spermatids that varied between treatment groups (Table 1).

The number of spermatogonia in groups T2 and T3 (given 50 and 25% (v/v) white guava fruit juice) was not significantly different ($p > 0.05$) from group T0 (without white guava fruit juice). The pure (100% undiluted) guava fruit juice given in the T1 group resulted in a higher number of spermatogonia ($p < 0.05$) than in the T0 group (without guava fruit juice administration). However, it was lower ($p < 0.05$) than group P0 (only given placebo).

The number of spermatocytes in the T3 group (given 25% white guava fruit juice) was not significantly different ($p > 0.05$) from the T0 group (without white guava fruit juice). Guava fruit juice given in groups T1 and T2 (100% and 50%) resulted in a higher number of spermatogonia cells ($p < 0.05$) than in group T0 (without guava fruit juice), but lower ($p < 0.05$) than group P0 (only given placebo). There was no significant difference ($p > 0.05$) in the number of spermatocytes in the T1 and T2 groups.

Table1 Number of spermatogonia, spermatocytes, and spermatids (means ± SD) of rats (*Rattus norvegicus*) exposed to lead acetate after being treated with white guava fruit juice with different concentrations

	spermatogonia	spermatocyte	spermatid
P0	35.60 ± 1.94 ^{d}	34.00 ± 1.58 ^{c}	48.40 ± 11.17 ^{c}
T0	24.20 ± 1.48 ^{a}	25.00 ± 1.22 ^{a}	32.40 ± 2.07 ^{a}
T1	32.00 ± 1.87 ^{c}	31.20 ± 4.20 ^{b}	44.60 ± 5.17 ^{c}
T2	28.80 ± 3.49 ^{b}	30.20 ± 1.78 ^{b}	41.80 ± 1.09 ^{c}
T3	26.00 ± 1.41 ^{ab}	26.40 ± 2.40 ^{a}	34.80 ± 1.30 ^{b}

Different superscripts in a column indicate significant differences ($p < 0.05$); P0: rats were given 0.5 mL distilled water twice a day at four-hour intervals; T0, T1, T2, and T3: rats were given 50 mg/kg bw of lead acetate every day at 08.00 followed by the administration of respectively distilled water, 100, 50 and 25% (v/v) white guava (*Psidium guajava* L.) fruit juice four hours later; all solution were given orally using a probe in a volume of 0.5 mL for 14 days.

The number of spermatids in group T3 (given 25% white guava fruit juice) was higher ($p < 0.05$) than in group T0, but lower ($p < 0.05$) than in group P0 (placebo). Giving guava fruit juice to groups T1 and T2 (100% and 50%) resulted in a higher number of spermatogonia ($p < 0.05$) compared to group T0 and not significantly different ($p > 0.05$) compared to group P0 (placebo). There was no significant difference ($p > 0.05$) in the number of spermatids in the T1 and T2 groups.

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DISCUSSION

Exposure to lead acetate without administration of white guava fruit juice to rats (*Rattus norvegicus*) was followed by a decrease in the number of spermatogonia, spermatocytes, and spermatids compared to healthy rats. These results were in accordance with the report by Haouas *et al*. (2015) and Offor *et al*. (2019) that the number of spermatogonia, spermatocytes I, and spermatids decreased sharply in rat exposed to lead acetate.

Damage to testicular tissue due to exposure to lead acetate could originate from impaired function of extra-testicular cells (endocrine cells of the hypothalamus and pituitary) and the testicles. As was known, spermatocytogenesis involved complex molecular processes, requiring appropriate interactions between Sertoli cells, germ cells, tubular epithelial cells, and the integrity of the blood-testis barrier. Endocrinologically, spermatogenesis was influenced by hormones from the hypothalamus-pituitary-testis axis. The hypothalamus produced gonadotropin-releasing hormone (GnRH) which induced the anterior pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Santi *et al*., 2021). FSH stimulated Sertoli cells to produce androgen-binding protein, while LH functioned to control testosterone production by Leydig cells. Androgen-binding protein captured testosterone, maing testosterone less lipophilic, and functioned as a transcriptional factor in the synthesis of glial cell line-derived neurotrophic factor (Oduwole *et al*., 2021). FSH bound to receptors on Sertoli cells, then Sertoli cells released glial cell-derived neurotropic growth factor to stimulate mitosis of spermatogonia to become primary spermatocytes and entered the lumen of the seminiferous tubules. Primary spermatocytes underwent meiosis I division to become secondary spermatocytes which then quickly underwent meiosis II to produce spermatids (Cannarella *et al*., 2020).

ROS could be triggered by various exogenous chemicals. The highly reactive nature of ROS could react and modify any molecule through oxidation resulting in structural and functional changes. Excessive ROS levels could disrupt the antioxidant defense system, causing oxidative stress. Oxidative stress was the main cause of damage to the sperm plasma membrane. Plasma membranes were rich in polyunsaturated fatty acids which were susceptible to oxidative damage (Qamar *et al*., 2023). Oxidative stress was characterized by a decrease in the activity of the antioxidant enzymes superoxide dismutase, glutathione peroxidase, and catalase, as well as an increase in malondialdehyde levels in the testicles. Molecularly, lead downregulated aromatase P450 (Cyp19) and ERα mRNA, which in turn reduced testosterone production from Leydig cells (El-Magd *et al*., 2017).

As was known, lead exposure caused oxidative stress. All cell membranes and cell organelles membranes were composed of a lipid bilayer containing many polyunsaturated fatty acids which were susceptible to oxidative stress due to exposure to ROS (Su *et al*., 2019), including endocrine cells of the hypothalamus and pituitary. Disruption of the hypothalamic and pituitary cell membranes disrupted the production and release of FSH and LH. FSH bound to its receptor on Sertoli cells to then regulate survival, supply nutrients to germ cells, limited their apoptosis, and initiated spermatogenesis (Wang *et al*., 2022). FSH deficiency caused a significant decrease in sperm count (Oduwole *et al*., 2018).

Administration of lead acetate to male rats caused an increase in intracellular ROS which induced oxidative stress in testicular tissue. Functional cells in testicular tissue included Leydig cells as testosterone producers, Sertoli cells as nurse cells, and spermatogonia which in the process of spermatogenesis would become spermatocytes, spermatids, and spermatozoa (Dolati *et al*., 2021). Testosterone regulated spermatogenesis in a paracrine manner, diffusing from Leydig cells into the seminiferous tubules (Smith and Walker, 2015). Disturbances in testosterone levels or its receptors caused spermatogenesis not to progress beyond the

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meiosis stage (Grande *et al*., 2022). Oxidative stress in Sertoli cells as nurse cells, and spermatogonia which in the process of spermatogenesis would become spermatocytes, spermatids, and spermatozoa caused male infertility (Dutta *et al*., 2021). Under normal conditions, the endogenous antioxidant system was mainly involved in redox control regulation. However, certain pathological conditions were associated with excessive ROS production thereby overcoming redox control. Under such circumstances, antioxidants from exogenous sources could play an important role in ameliorating the adverse effects of oxidative stress (Qamar *et al*., 2023).

In general, administration of white guava fruit juice increased spermatogonia, spermatocytes, and spermatids of rats (*Rattus norvegicus*) exposed to lead acetate. Giving pure white guava fruit juice (undiluted) resulted in higher numbers of spermatogonia, spermatocytes, and spermatids compared to rats exposed to lead acetate alone. The number of spermatogonia and spermatocytes in this group of rats was still lower than in normal rats. Meanwhile, the number of spermatids in this group had restored to that of normal rats. This increase in spermatogenic cells follows previous study which stated that administration of white guava could increase spermatogenesis in white rats exposed to free radicals from cigarette smoke (Anggraini, *et al*., 2021). The results of this study also follow the report by Alifia *et al*. (2023) that white guava fruit juice was effective in restoring spermatozoa plasma membrane integrity, morphological abnormalities, viability, and motility of rats exposed to lead acetate. White guava was known to contain a lot of antioxidants quercetin and vitamin C (Hartati *et al*., 2020). Giving quercetin had been proven to be able to improve the negative effects of lead in male rats (Dolati *et al*., 2021).

Antioxidants could inhibit and reduce cellular oxidative stress due to excessive ROS (Sharifi-Rad *et al*., 2020). Antioxidants worked by sharing one or more electrons, then the oxidant turned into a more stable compound (Santos-Sánchez *et al*., 2019). Vitamin C could effectively protect sperm DNA from ROS due to its high antioxidant competence. Quercetin was a flavonoid that had strong antioxidant properties due to the presence of three OH^* groups which were able to clean ROS (Qamar *et al*., 2023). Quercetin maintained oxidative balance through the mechanism of increasing glutathione antioxidant capacity, enzymatic antioxidant activity, signal transduction pathways, and reducing ROS production (Xu *et al*., 2019; Qi *et al*, 2022).

CONCLUSION

Pure white guava (*Psidium guajava* L.) fruit juice (100%, undiluted) was optimal for maintaining the number of spermatids but was unable to restore the number of spermatogonia and spermatocytes of rats exposed to lead acetate. Administration of diluted guava fruit juice (50% and 25%) was not sufficient to restore the number of spermatogonia, spermatocytes, and spermatids of rats (*Rattus norvegicus*) exposed to lead acetate.

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AUTHOR'S CONTRIBUTIONS

Muhammad Faizal Adiutomo (MFA), Herry Agoes Hermadi (HAH), Hardany Primarizky (HP), Wurlina Wurlina (WW), Rochmah Kurnijasant (RK), Suzanita Utama (SU).

SU, MFA: Contributed to the design of the study. MFA: sample and data collection, drafted the manuscript. HAH and HP: analysis and interpretation of data. WW, RK and SU: Supervised the study. All authors have read, reviewed, and approved the final manuscript.

CONFLICTS OF INTEREST

The authors have no competing financial

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interests or personal relationships that could have appeared to influence the work reported in this paper.

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