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Evaluation of female rats' genital system alterations caused by cadmium with consumption of total methanolic garlic extract

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ABSTRACT

Cadmium (Cd) is an environmental contaminant linked to various health issues, particularly in reproductive health. Garlic, *Allium sativum* is noted for its numerous health benefits, including its potential positive effects on female's reproductive health. Despite its recognized therapeutic properties, research specifically addressing garlic's impact on the female reproductive system remains limited, prompting the need for further investigation into its protective effects against cadmium-induced toxicity. This study investigates the protective effects of methanolic garlic extract (GE) against cadmium (Cd) toxicity in female rat, focusing on its impact on hematological and biochemical parameters, as well as histopathological changes in the uterus. A total of twenty-one healthy female mice were divided into three groups: one receiving Cd treatment, another receiving GE, and a control group. The experiment lasted eight weeks, during which various parameters were assessed. Results indicated that Cd exposure led to significant increases in liver enzymes (SGPT, SGOT, ALP) and caused moderate edema in the endometrium, characterized by the separation of endometrial stromal cells and hyperplasia of the uterine mucosa and glandular epithelium.

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Conversely, treatment with GE at a dosage of 300 mg kg^{-1} resulted in a statistically significant reduction in these liver enzyme levels and ameliorated the histopathological changes in the uterus, including decreased edema and hyperplasia. Additionally, hematological assessments revealed that GE treatment normalized the counts of red blood cells, white blood cells, and lymphocytes, which were adversely affected by Cd exposure. The findings suggest that garlic extract possesses detoxifying properties that can mitigate the adverse effects of cadmium on the female reproductive system. This research highlights the potential of incorporating garlic into dietary practices or using it as an adjunct in chelation therapy for Cd toxicity treatment, emphasizing its beneficial role in maintaining reproductive health and liver function in the context of heavy metal exposure.

Keywords: Rat, Cd, Uterus, Liver, Garlic.

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INTRODUCTION

Cadmium is introduced into the environment due to anthropogenic activities and is commonly detected as a contaminant in biological tissues obtained from human populations globally (Amanpour *et al*. 2024). Reproductive health and gynaecological disorders represent significant challenges within the medical domain, as these issues impact individual well-being in diverse manners and impose substantial economic strain on communities. Currently, there exists a pronounced interest in integrating complementary and alternative medicine to address health-related concerns (Gheibi *et al*. 2023). Complementary and alternative medicine, encompassing traditional medicine (TM), offers a plethora of therapeutic approaches, including the utilization of phytotherapy. The application of herbal remedies constitutes a crucial aspect of complementary medicine for the prevention and management of various diseases globally. In TM, multiple plant components, such as roots, stems, leaves, and flowers, are employed as herbal remedies. These herbal preparations can be administered as extracts, decoctions, or in formulations such as tablets and ointments. TM is predominantly rooted in traditional medical practices, although certain aspects are substantiated by empirical research and clinical investigations (Hosseini *et al*. 2021). TM is frequently utilized for an extensive array of ailments, including gastrointestinal disturbances, respiratory issues, dermatological conditions, hormonal imbalances, and compromised immune function. Some prevalent herbs in traditional medicine include ginger, turmeric, ginseng, chamomile, and garlic (Pearson *et al*. 2007; Parham *et al*. 2020).

Garlic, *Allium sativum* has been recognized in traditional medicine for centuries owing to its numerous health advantages. It is an edible species belonging to the Liliaceae family (Jasim *et al*. 2023). Historically, garlic has served as a culinary spice to enhance flavour. For an extended period, garlic has been investigated for its therapeutic properties in managing various human ailments. Research indicates that garlic possesses a multitude of beneficial characteristics, including antibacterial, antifungal, and antiviral properties. Recently, the potential influence of garlic on women's reproductive health has garnered attention (Eftekhari *et al*. 2012; Eftekhari 2020). Additionally, garlic exhibits antimicrobial properties and has the potential to bolster immune defences. Traditionally, this herb has been employed to avert and treat respiratory infections such as colds and influenza. Moreover, garlic contains compounds that exhibit anti-inflammatory properties, thereby mitigating bodily inflammation. Several investigations have suggested that garlic may possess anticancer capabilities. This herb appears to inhibit the proliferation of cancerous cells to some extent and may exert a protective effect against various forms of stomach, intestinal, and bladder cancers. Furthermore, garlic can enhance digestive health by promoting the secretion of digestive enzymes and fostering the proliferation of beneficial gut flora (Pearson *et al*. 2007). The female reproductive system comprises a complex arrangement of organs crucial for reproduction. It encompasses structures such as the ovaries, fallopian tubes, uterus, and vagina, all of which collaborate to facilitate menstruation, ovulation, and gestation (Gheibi *et al*. 2020).

The preservation of a robust reproductive system is crucial for both psychological well-being and fertility in females. Research has indicated that garlic may confer advantageous effects on the female reproductive system. For instance, it has been documented that this botanical possesses antimicrobial characteristics, which can inhibit and manage infections associated with external reproductive organs. Historically, garlic has been utilized to remedy vaginal yeast infections. Its antifungal attributes can be efficacious in averting and alleviating such infections. Owing to its anti-

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inflammatory qualities, garlic may also mitigate inflammation within the reproductive system and alleviate symptoms linked to conditions such as endometriosis and pelvic inflammatory disease (Jiao *et al*. 2022). Several studies have examined the impact of garlic on hormonal regulation in women. Hormones are pivotal in modulating the menstrual cycle and the standard reproductive process. Research has indicated that garlic might influence certain hormones, including estrogen and progesterone; however, further investigations are necessary to elucidate these effects more comprehensively. Additionally, some animal studies have suggested that garlic could enhance fertility by increasing the quantity of viable ova in female subjects. Nevertheless, to attain more conclusive outcomes, human clinical trials are imperative (Suleria *et al*. 2015; Kimura *et al*. 2017).

Garlic is rich in numerous compounds, including various vitamins such as B_2, B_6, B_1, A, and C, as well as a substantial array of antioxidants, flavonoids, and phenolic and sulfur compounds. Allicin and ajoene are two biologically active compounds derived from garlic sulfur content. Allicin (dialkyl thiosulfinate) is integral to the therapeutic properties of garlic and is synthesized through the enzymatic action of allinase on alliin (S-alkyl-l-cysteine sulfoxide; (Dorrigiv *et al.* 2020). Allicin and ajoene have been recognized for their potential therapeutic benefits. Reports suggest that these compounds possess antimicrobial, anti-inflammatory, and antioxidant properties (Eftekhari 2020). However, research on their effects specifically concerning the female reproductive system remains limited. The influence of garlic on hormonal equilibrium, fertility, and sexual health has been investigated. In one study, Jiao *et al.* (2022) explored the application of herbal remedies for menstrual treatment in women and the incidence of menstrual disorders across various regions.

Numerous studies have previously been undertaken to explore the potential of certain substances to mitigate heavy metal toxicity, demonstrating their ability to reduce concentrations of lead, cadmium, and mercury in various organs such as the liver, kidneys, and bones. Consequently, this research focuses on the methanol extract of *A. sativum* to assess its protective effects against cadmium toxicity in rat, as there has been no prior investigation into the effects of this extract on Cd-induced toxicity in the female genital system.

MATERIALS AND METHODS

Collection and extraction of garlic

Fresh garlic was collected from a local market. The bulbs were separated and washed thoroughly with clean water so that any dirt or dust could be removed. Thereafter, the washed blubs were dried and grounded in a high-capacity grinding machine separately to turn them into a coarse powder. For extraction powder was soaked into methanol for 14 days at room temperature (22-25 °C) with regular stirring. Afterward, cotton filtration was employed to get the filtrate, and the filtrate was transferred to the rotary evaporator to concentrate the filtrate and remove methanol. Then the dried extract was kept in an air-tight container and preserved in the refrigerator at −20 °C before the experiments were conducted since this temperature supports the long-term storage of garlic extract until further research was conducted (Kopeć *et al*. 2020).

Animal grouping and treatment

The animal model experiments were conducted based on the ARRIVE guideline. To prevent the possibility of pregnancy, only female Wistar rats were utilized in the study. These rats were housed individually in polypropylene cages within a temperature-controlled environment (22 ± 3 °C) and maintained at a humidity level of 55%. The lighting was regulated to provide a 12-hour dark/light cycle, and the rat had unrestricted access to standard laboratory feed and water. They were acclimatized for a minimum of one week before the commencement of the experiments. A total of twenty-one healthy female rats were allocated into three distinct groups: Group I, II, and III. Group I received treatment with Cd at a concentration of 2 mg kg^{-1}, while Group II was administered garlic extract at a dosage of 300 mg kg^{-1} body weight. Group III served as the control group, receiving only distilled water once daily. The duration of the experiment spanned eight weeks, with all treatments administered at a volume of 1 mL per day via gavage (Akter *et al.* 2022).

Determination of total phenolic content

The quantitative assessment of total phenolic compounds was conducted using a colorimetric approach based on the Folin–Ciocalteu (FC) method, with slight modifications as described previously. Gallic acid served as the standard reference, and the absorbance of the sample solutions was recorded at a wavelength of 765 nm utilizing a U-2910

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UV–Vis spectrophotometer (Hitachi High Technologies, USA). The total phenolic content was quantified and expressed in terms of milligrams of gallic acid equivalents (GAE) per gram of dried extract, employing a calibration curve derived from gallic acid. All experimental procedures were carried out in triplicate (Kumaran & Karunakaran 2007).

Estimation of total flavonoid content

The total flavonoid content in the methanol extract of garlic was determined using a spectrophotometric method as outlined by Kumaran & Karunakaran (2007), with quercetin serving as the standard reference. The absorbance of the sample solution was recorded at a wavelength of 415 nm using a U-2910 UV–Vis spectrophotometer, and the flavonoid concentration was reported in milligrams of quercetin equivalents (QE) per gram of dried extract. Each measurement was conducted in triplicate to ensure accuracy (Wolfe *et al.* 2003).

Collection of blood samples and Female genital organs

After eight weeks, the animals were anesthetized with ketamine at a dosage of 500 mg kg^{-1} via intraperitoneal injection. Blood samples were then collected from the post vena cava and subjected to centrifugation at 4000 rpm for 10 minutes at 4 °C to prepare serum. This serum was subsequently utilized for hematological assessments, including counts of white blood cells (WBC), red blood cells (RBC), neutrophils (NEU), lymphocytes (LYM), monocytes (MON), and eosinophils (EOS). Additionally, plasma and serum samples were obtained for the analysis of biochemical parameters, specifically serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase (ALP), and aspartate aminotransferase (SGOT) levels. The measurements of SGPT, SGOT, and ALP were conducted using commercial kits designed for these tests, adhering to the manufacturer's instructions. At the experiment conclusion, the animals were euthanized through the administration of an overdose of xylazine and ketamine, and the organs were isolated (Vahabi Barzi *et al.* 2022). The obtained uterus samples from rats were fixed in a 10% formalin solution for tissue processing. The fixed samples were embedded in paraffin, and serial paraffin sections (with a thickness of 4-6 µm) were prepared for haematoxylin and eosin staining (Amanpour *et al*. 2024).

Statistical analysis

Data are expressed as mean ± standard error of the mean (SEM). Data comparisons were carried out using one-way analysis of variance (ANOVA) followed by independent samples t-test to compare means between groups and to observe the significance level. *p*-value < 0.05 has been considered as the level of significance.

RESULTS

Total phenolic and flavonoid contents

The total phenolic content was calculated using the calibration curve of the gallic acid which yielded an equation of $y = 0.0089 x - 0.1607$ ($R^2 = 0.9987$). The results obtained from the evaluation of total phenolic content were 11.2 ± 1.1, 25.12 ± 1.2, and 62.44 ± 0.56 mg of GAE g^{-1} for the concentrations of 200, 400, and 800 µg mL^{-1} of the extract, respectively.

The total flavonoid content was determined through the application of a calibration curve for quercetin, which produced the equation $y = 0.0013 x - 0.0125$ ($R^2 = 0.9985$). The analysis revealed total flavonoid concentrations of 2.8 ± 0.16, 6.26 ± 0.34, and 8.96 ± 0.24 mg of QE g^{-1} corresponding to extract concentrations of 200, 400, and 800 µg mL^{-1}, respectively.

Table 1. Total phenolic and flavonoid contents in garlic extract.

Conc. of garlic extract (µg mL^{-1})	Total phenolic content (mg of GAE g^{-1})	Total flavonoid content (mg of QE g^{-1})
200	11.2 ± 1.1	2.8 ± 0.16
400	25.12 ± 1.2	6.26 ± 0.34
800	62.44 ± 0.56	8.96 ± 0.24

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Effect of GE on hematological and biochemical parameters

The influences of GE on hematological and biochemical parameters were assessed. When comparing group III (the control group) to group I (the model group), there was a notable increase in the counts of neutrophils (NEU) and eosinophils (EOS) in the Cd-treated group. Conversely, the levels of red blood cells (RBC), white blood cells (WBC), lymphocytes (LYM), and monocytes (MON) were found to be lower in the model group. Additionally, a significant elevation ($p < 0.05$) in the biochemical parameters, including SGPT, SGOT, and ALP was observed in the control group when compared to the model group. The results of this investigation indicated a reduction in the counts of neutrophils (NEU) and eosinophils (EOS) across all dosage levels of garlic extract (GE). In contrast, the counts of red blood cells (RBC; $p < 0.05$), white blood cells (WBC; $p < 0.01$), neutrophil (N; $p < 0.05$) and lymphocytes (LYM; $p < 0.01$), exhibited an increase in the GE received group in comparison to the model group. Additionally, the biochemical parameters, including serum SGPT, ALP, and SGOT, showed a decrease across all dosage levels in Cd-received rats when treated with varying doses of GE. Furthermore, significant alterations were recorded for WBC ($p < 0.001$), LYM, ALP, ALP, SGPT, and SGOT ($p < 0.05$) in Cd-received rats receiving 300 mg kg^{-1} GE.

Table 2. Effects arsenic and different doses of garlic extract on hematological and biochemical parameters.

Parameters	**Control**	**Model**	**Model + GE 300 mg kg^{-1}**
White blood cell (× 10^9 cells L^{-1})	9.80 ± 0.42	6.32 ± 0.26	8.36 ± 0.27
Red blood cells (cells μL^{-1})	5.29 ± 0.18	4.16 ± 0.16	5.11 ± 0.16
Neutrophil (cells μL^{-1})	57 ± 3.08	60.23 ± 0.45	56.23 ± 2.85
Lymphocyte (× 10^9 cells L^{-1})	39.20 ± 3.53	33.16 ± 1.13	45.33 ± 2.40
Eosinophil (cells L^{-1})	2.66 ± 0.23	3.16 ± 0.30	2.70 ± 0.12

Histopathological evaluation of the uterus

Fig. 1 presents representative H & E-stained sections of uterine tissue from the Control, Model, and Model+Garlic Extract (GE) groups.

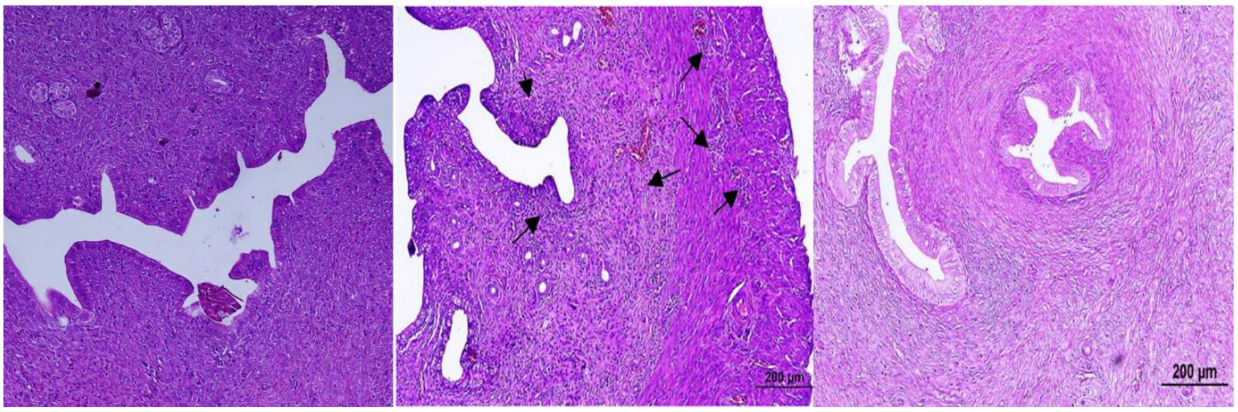

Fig. 1. Histopathological analysis of uterine tissue in different experimental groups. Representative H&E-stained sections of uterus from the Control, Model, and Model+Garlic Extract (GE) groups. In the Control group, normal uterine architecture is observed with intact endometrial and myometrial layers. The Model group shows severe pathological changes including stromal fibrosis, disrupted glandular structure, and dense inflammatory cell infiltration (black arrows), confirming successful induction of uterine injury. Treatment with garlic extract in the Model+GE group attenuated these alterations, showing reduced inflammation and partial restoration of normal tissue morphology.

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Control group shows normal uterine histoarchitecture with well-preserved endometrial and myometrial layers. The epithelial lining is intact, and no signs of inflammation, fibrosis, or structural disruption are observed. Model group demonstrates marked pathological alterations in the uterine tissue. These include disorganized endometrial glands, stromal fibrosis, and prominent infiltration of inflammatory cells (indicated by black arrows). The overall architecture is severely distorted, confirming successful induction of uterine injury or pathology in the model group. Model+GE group shows significant histological improvement following treatment with garlic extract. The uterine tissue exhibits reduced inflammation and fibrosis, along with partial restoration of normal glandular and stromal structure. These observations suggest a protective and restorative effect of garlic extract on uterine histopathology.

DISCUSSION

Numerous controlled investigations have been carried out to assess the biochemical impacts of cadmium across various animal models. This research aims to evaluate the toxicological effects of cadmium and garlic extract therapeutic effects, focusing on its individual and synergistic impacts on female reproductive organs when GE orally. The observed increase in liver enzyme levels in the rats exposed to Cd indicates the metal capacity to induce kidney insufficiency. Additionally, Cd caused uterus toxicity with moderate edema of the endometrium, which was characterized by the separation of endometrial stromal cells, a moderate increase in thickness of both the uterine mucosa and the endometrial glandular epithelium, as well as hypertrophy of the smooth muscle cell layers. However following the garlic extraction prescription, the infiltration of eosinophils decreased and the thickness of both the uterine mucosa and the endometrial glandular epithelium declined.

Raji *et al.* investigated the effects of aqueous garlic extract on various reproductive parameters in female albino rats of the Wistar strain. Their results suggested that the extract does not negatively impact the reproductive performance of these female rats (Raji *et al.* 2012). In a separate study, Wassem *et al.* performed a hormonal assessment to evaluate the efficacy of garlic extract in mitigating lead acetate toxicity within the fallopian tubes (Waseem 2015). Similarly, Bashir *et al.* examined the effects of aqueous garlic extract on androgen-induced changes in the ovaries of prepubescent female rats. Their findings revealed that the extract significantly reduced both the number and size of cystic follicles in the ovaries of androgen-treated immature rats (Bashir *et al.* 2017).

The precise toxicological mechanisms by which cadmium exerts its effects remain inadequately elucidated; however, it is recognized that cadmium operates at the intracellular level, primarily through the induction of free radical-mediated damage. This damage predominantly affects vital organs, including the lungs, kidneys, heart, bones, central nervous system, and reproductive systems. Furthermore, research indicates that cadmium may provoke oxidative damage across various tissues, exacerbating the peroxidation of membrane lipids due to the suppression of antioxidant enzymes. Additionally, some studies have suggested that exposure to cadmium could result in lipid peroxidation, which in turn may lead to an elevation in the activities of antioxidant enzymes. The modulation of antioxidant enzyme activities is likely influenced by multiple factors, including the dosage of cadmium, duration of exposure, method of administration, and the presence of other metallic elements.

Allium sativum serves as a natural therapeutic agent, primarily characterized by the presence of alliin, its principal amino acid. Alliin, which contains sulfur analogues, undergoes conversion to allicin in the presence of the enzyme alliinase. This transformation leads to the formation of various compounds, such as vinyldithiines, ajoenes, and polysulfides. These compounds exhibit chelating properties that enable them to form complexes with arsenic, facilitating its rapid excretion from the organism. Additionally, these compounds are recognized for their potent antioxidant capabilities (Eftekhari 2020). Preliminary phytochemical analyses have also indicated the presence of flavonoids in garlic extract (GE). Flavonoids are particularly noted for their significant biological activity, especially their antioxidant effects, which are attributed to their ability to inhibit reactive oxygen species (ROS) generation by either obstructing the activity of relevant enzymes or chelating trace elements that contribute to ROS production. Furthermore, flavonoids possess the capacity to scavenge ROS, thereby enhancing their antioxidant efficacy (Suleria *et al*. 2015).

This investigation revealed a notable alteration in biochemical parameters, including SPOT, SGPT, and ALT levels, in the group exposed to Cd when compared to the control group. The group treated with Cd exhibited the highest liver enzymes level which subsequently decreased in the group receiving treatment with GE. Increased ALP levels are associated with liver injury and inflammation. Cd metabolism in the liver involves binding to thiol groups of liver

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proteins or enzymes, which compromises the integrity of the hepatocyte plasma membrane and facilitates leakage. Serum SGPT serves as a significant biomarker for assessing liver function, with deviations from normal SGPT levels indicating potential hepatic damage and dysfunction. The liver is essential for the detoxification of various xenobiotics and plays a crucial role in metabolic processes. When the liver is exposed to arsenic, it experiences changes in the levels of certain enzymes due to the accumulation of arsenic and resultant hepatocyte injury, leading to an increase in serum SGPT levels. Notably, the treatment group, which received a dosage of 300 mg GE, demonstrated a statistically significant reduction in ALT, SGPT, and SGOT levels (Eftekhari 2020).

While the findings are promising, more studies are necessary to fully understand the mechanisms by which garlic affects reproductive health and its potential as a therapeutic agent against heavy metal toxicity.

CONCLUSION

The research we conducted revealed the considerable efficacy of methanolic garlic extract (GE) in mitigating Cd-induced toxicity in rat models. The detoxifying properties of GE were indicated by the normalization of altered hematological and biochemical parameters in rats subjected to Cd exposure besides ameliorative effect on the uterus tissue. Therefore, incorporating a specific amount of garlic into one's diet or using it as an adjunct to chelation therapy could be advantageous for health in the context of Cd toxicity treatment.

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