Original Article

Teratogenic Effects of Thallium and Protective Role of the Aqueous Extract of *Annona muricata* in the Fetuses of Pregnant Mice

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ABSTRACT

Background: Humans are exposed to thallium sulfate (TO), a toxic heavy metal, through contaminated drinking water, food, or air. Medicinal plants with antioxidant properties such as *Annona muricata* (soursop) can be used as a natural solution to the problems caused by TI exposure.

Objectives: This study aims to determine the preventive effects of *A. muricata* on the toxic effects of TO in pregnant mothers and their fetuses.

Methods: Pregnant females were divided into 3 experimental groups. The first group received distilled water and served as the control group. The second group was given an aqueous solution of custard apple leaves and, after 4 hours, drinking water containing TO. The third group was given drinking water containing only thallium sulfate. Pregnant mice in the second and third groups received experimental materials from the first day of pregnancy to the 15th and 18th days of pregnancy. Blood samples were taken from pregnant mice on the two days (D15, 18). Histological preparations were performed on the placenta to observe the changes in the second and third groups. During the two days of the investigation, the fetuses' phenotypic alterations were also examined.

Results: The results showed the effect of TO + *A. muricata* on placental tissue (cystic of glycogen cells, increment in thickness of trophoblast septa with deposition of fibrin, dilation of maternal sinusoid, and vacuolated degeneration. Also, there were morphologic changes in fetuses, such as hemorrhage with permanence of the severity effects of TO in the brain, hemorrhage and spinal bifida, atrophy of the rhombencephalon, open eyelids, septo-optic dysplasia, abnormalities of the fetal extremities, hump body, hematoma. Finally, the majority of the results for the second group were similar to the rates of the control group.

Conclusion: The graviola apple plant's leaves can be used at the stated amounts to counteract the effects of TO in drinking water.

Keywords: Annona, Embryos, Mice, Pregnancy, Thallium

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Introduction

Thallium sulfate (TO) is a toxic heavy metal that may cause a wide range of public health effects, including neurotoxicity, hair loss, pathological changes in the stomach, kidneys, liver, brain, intestines, cardiovascular system, and mental disorders resulting in death in acute poisoning of high doses (Osorio-Rico et al., 2017). The name thallium is derived from the Greek Thallos, meaning "little green shoot." TO was discovered in 1861 by chemist William Crookes, who observed a bright green line in the spectrum of his selenium sample in sulfuric acid factories (Karbowska, 2016). It is found in natural and aquatic environments in large quantities. It can also be found in iron, lead, cadmium, and zinc ores, but it is more dangerous and toxic than these ores; that is why the COST Action TD1407 included it in the list of critical technological elements due to these threats to human health (Cobelo-Carcia et al., 2016).

Humans are exposed to this toxic metal through contaminated drinking water, food, or air (Shipkowski et al., 2023). It is then distributed throughout the body via the blood and can cross the blood-brain barrier, accumulating in the brain and other organs such as the kidneys and liver (Tyagi et al., 2011). TO was previously used as a rodenticide and insecticide, but was banned due to its toxic effects. It is also used in fluorescence imaging to detect malignant diseases such as breast cancer, lymphomas, and even cardiovascular diseases (Genchi et al., 2021).

Annona muricata, also known as soursop, is a tropical tree widely cultivated in tropical countries such as Southeast Asia and South Florida. Mexico is the largest producer of this plant (Gajalakshi et al., 2012; Ana-Coria et al., 2016). All parts of the plant have been used in traditional folk medicine, including the bark, leaves, and roots (Adewole et al., 2009). The leaves have been used to treat bladder infections, diabetes, headaches, high blood pressure, liver and skin diseases (Sousa et al., 2011). The seeds have been used as an antiparasitic agent and to reduce fever and diarrhea (Kedar et al., 2014). The fruits, which have high nutritional value, are widely used for food because they contain fiber and vitamins (Rahman et al., 2020), according to a study by Gyesi et al. (2019). *A. muricata* fruits contain large amounts of phenolic compounds and have antioxidant activities. Studies have shown that the fruit pulp helps inhibit the spread of breast cancer cells (Prasad et al., 2020). Custard apple is known by many names, including guanabana, sawsak, and cuyabano (Badrie & Schauss, 2010). TO is everywhere around us, and exposure to it is easy for both the general public and pregnant women in particular. Therefore, in this study, we sought a natural solution to the problems caused by TO exposure. The leaves of the soursop plant were the substance targeted in the study.

Materials and Methods

Study animals

The experiments used 35 female mice mated with 18 males, placed in cages designated for them in suitable environmental conditions for temperature, humidity, food, and water. After fertilization, the vaginal plug was observed, and the day it was observed was considered day 0, with the day following it as the first day of pregnancy (Damayanti et al., 2021).

Materials used in preparing *A. muricata*

Dried leaves were purchased from East Java Company and the aqueous solution of the leaves was prepared by grinding (500 g) of the leaves until they became a fine powder, then soaked in (1000 mL) of boiled distilled water, then filtered and extracted and placed the extract under low pressure (60±1 °C) in a rotary evaporator, then the aqueous extract was freeze-dried. Finally, 12.7 g of green color was obtained; the dose given to mice was 100 mg/kg of body weight (Ahmed & Sabra, 2018).

TI

We purchased TO with 99.9% purity from Sigma-Aldrich, and the dose given to pregnant mice was 50 mg/kg body weight (Shipkowski et al., 2023), after dissolving it in drinking water at a concentration of 0.5 mL.

Experimental design

Group$_1$: It contains 5 pregnant mice (as a control sit given distal water).

Group$_2$: Five pregnant mice were given drinking water containing T1.

Group$_3$: Five pregnant mice were given aqueous extract of *A. muricata* leaves plus drinking water containing TO (T+A).

Morphological and histological preparations

After the end of the dosing period, the pregnant mice (day 15, day 18) were dissected. The placentas and fetuses were obtained and washed with physiological solution

(NaCl, 0.9%) and fixed with 10% formalin (48 hours). All operations were performed according to Suvarna et al. (2019), and the operations were completed using a Heebrag Wild dissecting microscope; control embryos were photographed with a Sony DSC-W320 digital camera. Tissue sections were examined under a Reichert-Jung Neofluor light microscope. After examination, the sections were photographed using a compound microscope equipped with an Olympus OM-Japan digital camera.

These sections were collected from pregnant females on days 15 and 18 (the dates for dissection to determine the effects) after anesthetizing them with chloroform. Blood was drawn from the eye cavity using anticoagulant-free capillary tubes, which were left at room temperature for 15 minutes. The samples were subsequently centrifuged at 3000 rpm for 10 minutes at 25 ˚C. After centrifugation, the serum was transferred to new tubes for hormone testing. The concentrations of estrogen and progesterone were determined using the enzyme-linked immunosorbent assay (ELISA) technique (AccuBind Kit, USA).

Statistical analysis

The results were analyzed statistically using SPSS software, version 19, and analysis of variance and the least significant difference test were used to determine significant differences between the experiments.

Results

Effects of TO and Annona leaves on placenta weight

The results showed a significant decrease ($P<0.05$) in placenta weight in the group$_2$ (T) compared to the group$_1$ (C) and the group$_3$ (A + T) (Figure 1).

Effects of TO and Annona on abortion

The current study found that TO increased abortion rates significantly ($P<0.001$) on days 15 and 18. However, the aqueous extract of custard apple leaves, when administered with TI, decreased abortion rates ($P<0.05$) on days 15 and 18 (Figure 2).

Effects of TO and Annona leaves on the estrogen levels on day 15 and day 18

The results showed a significant increase in estrogen levels with TO dosing ($P<0.05$). In contrast, pregnant mice given an aqueous extract of Annona leaves and drinking water containing TO exhibited estrogen levels similar to those of the control group on days 15 and 18 (Figure 3).

Effects of TO and Annona leaves on progesterone levels on days 15 and 18

The study found a significant decrease in progesterone hormone levels ($P<0.001$) in the TI-dosed group on days 15 and 18. In contrast, the group (pregnant mice given aqueous extract of Annona leaves + drinking water containing TI) showed progesterone levels that were high

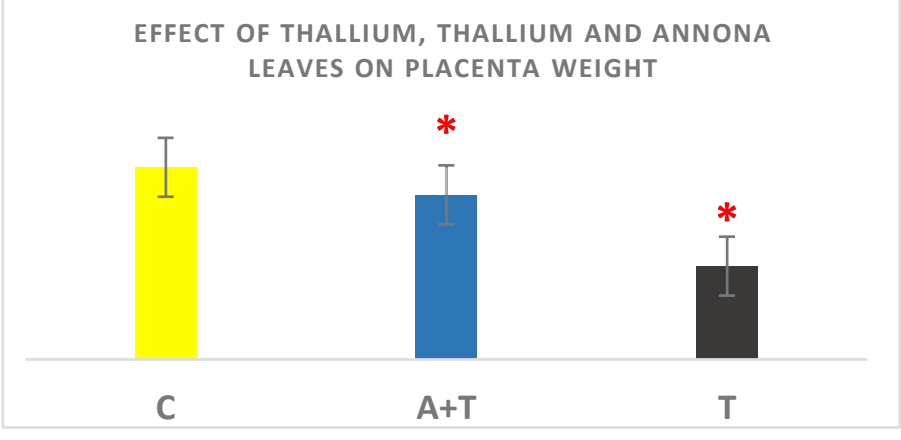

Figure 1. Changes in placenta weight on day 18

Note: There is no significant difference between the control and Annona and TI, while there is a significant difference between the control group and TI. Data are represented as Mean±SD; n=35; *P<0.05.

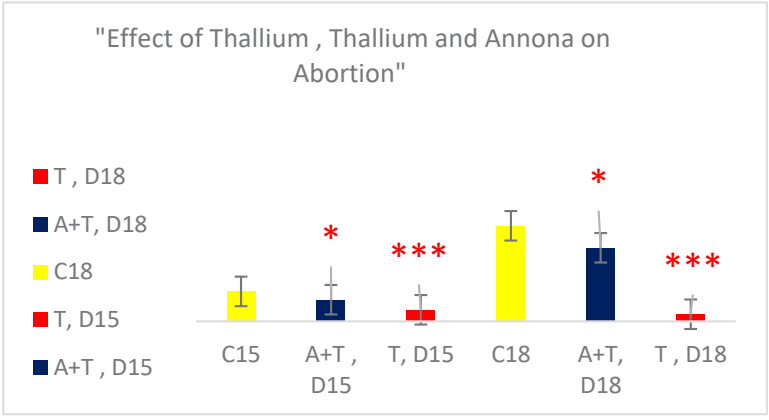

Figure 2. Abortion on day 15 and day 18

Note: Changes in the means of abortion resulted in a significant decrease in two days.*P<0.05 to TO and Annona; ***P<0.001 to TI. Data are represented as Mean±SD, n=35.

and similar to those of the control group on both days 15 and 18 (Figure 4).

Congenital malformations on day 15

The study results revealed several congenital abnormalities in fetuses of the TI-dosed group, including spina bifida, hemorrhage, hematomas in various parts of the body, atrophy of the rhombencephalon, septo-optic dysplasia, body hump, and abnormalities of the fetal extremities, In contrast, the group that received the aqueous extract of *A. muricata* leaves along with TO exhibited fewer severe deformities, including reduced incidences of eye and extremity abnormalities and hemorrhage (Figure 5).

Congenital malformation on day 18

The study found that the TI-only group exhibited greater severity of congenital malformations than pregnant mice given the control sit with distilled water. These abnormalities included hemimegalencephaly, absence of the eye, agenesis of the corpus callosum, cleft lip, hemorrhage in the trunk, HB, and limb contortions. In addition, findings included omphalocele (absence of the anterior abdominal wall), encephalocele, septo-optic dysplasia, and further limb contortions and hemorrhage. In contrast, the mice dosed with an aqueous solution of *A. muricata* leaves with TO showed no noticeable deformities and resembled the control group (Figure 6).

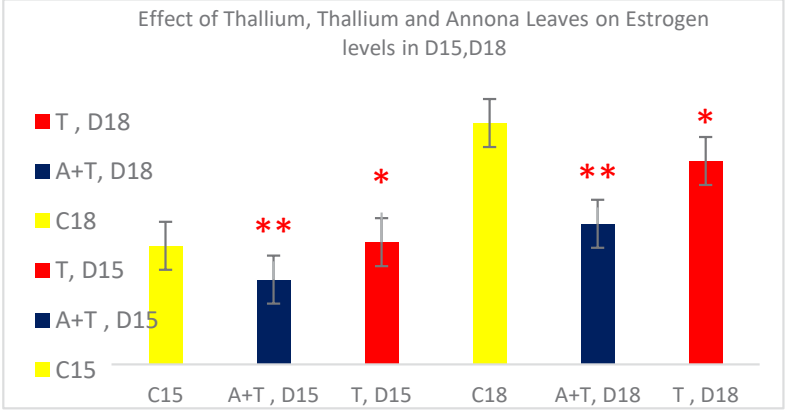

Figure 3. The levels of estrogen hormone (ng/mL) on days 15 and 18

Note: Changes in estrogen levels over 2 days show a significant decrease compared with the control group, Annona, and the TO group, and between the control and TO groups. Data are represented as Mean±SD; n=35; *P<0.05, *P<0.01.

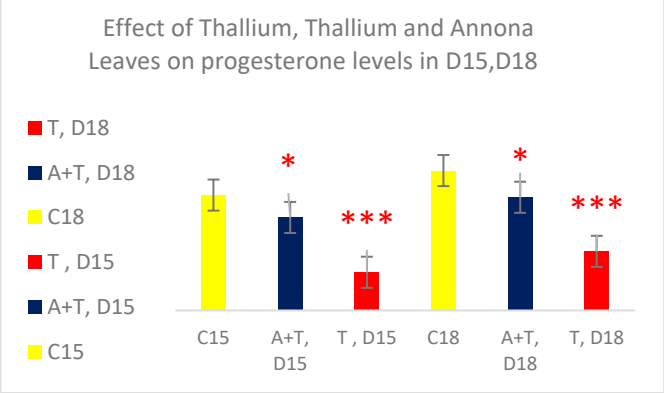

Figure 4. View levels of progesterone hormone (ng/mL) on days 15 and 18

Note: Significant differences in these levels in two days, a decrease (*P<0.05) in day 15, and (***P<0.001) in day 18. Data are presented as Mean±SD, n=35.

Pathological histological changes of the placenta on day 18

The study showed that the aqueous extract of custard apple leaves, when administered with TI, did not alter the placental tissue structure and appeared similar to normal tissue. In contrast, the TI-only group exhibited several tissue changes in the placental structure. These changes included vacuolar degeneration, congestion, fibrin deposition, and increased thickness of the trophoblast barrier. The results also revealed coagulative necrosis, nuclear condensation, and bleeding in various parts of the placental sections, along with trophoblast degeneration (Figure 7).

Discussion

The present study was conducted to determine the protective effects of aqueous extract of *A. muricata* leaves on the pathological changes caused by TO in pregnant mice and their fetuses for several variables, including (placenta weight, miscarriage, estrogen and progesterone levels, morphological abnormalities of fetuses on days 15 and 18, and histopathological changes in the placenta).

The study showed a significant decrease in placental weight in the second and third groups (day 18), and the *A. muricata* leaf dose did not improve the damage to placental weight observed in the TO group. The survival and growth of fetuses depend on the function of the placenta (Redecha et al., 2009). It serves as a vital mediator between the mother and the fetus, facilitating metabolic and gaseous exchanges, and plays an important role in eliminating fetal waste (Lv et al., 2012). These results are consistent with those of Sodani (2012), who reported a decrease in placental weight after injecting lead acetate into the peritoneum of pregnant mice.

As for the abortion axis, the results found a significant increase in its occurrence in the second group, and our results are consistent with several studies that were

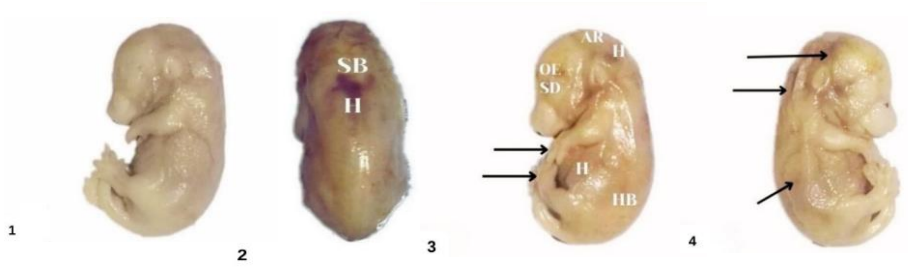

Figure 5. The fetuses of different groups on day 15

Note: Picture (1) shows the fetal control group mice. Picture (2) shows fetuses with a mother dosed with TI, including hemorrhage (H) and spina bifida (SB). Picture (3) shows atrophy in rhombencephalon (AR), open eyelids (OE), septo-optic dysplasia (SD), abnormalities of the fetal extremities (arrow), hump body (HB), and hematoma (H). Picture (4) shows fetal mice whose mother was dosed with aqueous extract of *A. muricata* and TI, which shows reduced severity of deformities in this group, including the appearance of eye, extremities, hemorrhage, with permanence of the severity effects of TO in the brain (arrows).

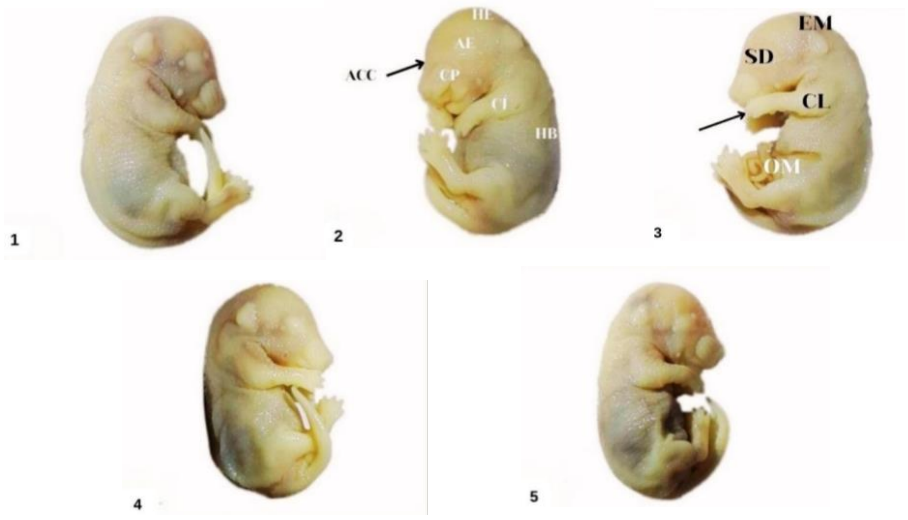

Figure 6. The fetuses of different groups on day 18

Note: Picture 2 shows fetuses in a group of TI. It reveals agenesis of the corpus callosum (ACC), cleft lip (CP), hemorrhage in the trunk (HT), hump body (HB), and limb contortion (CL). Picture 3 shows the absence of anterior abdominal wall (omphalocele) (OM), encephalomemigocele (EM), septo-optic dysplasia (SD), contortion of limbs (CL), and hemorrhage (H). Pictures 4 and 5 show mouse embryos dosed with aqueous extract of Annona leaves without deformities. It looks similar to the control group.

conducted to determine the effect of lead on abortion, as one study found that high doses of lead caused abortion (Aprioku, 2013). Another study found that lead can cause hormonal changes that directly affect pregnancy events, including miscarriage (Kumar et al., 2018). It is a complex event with several causes, the most important

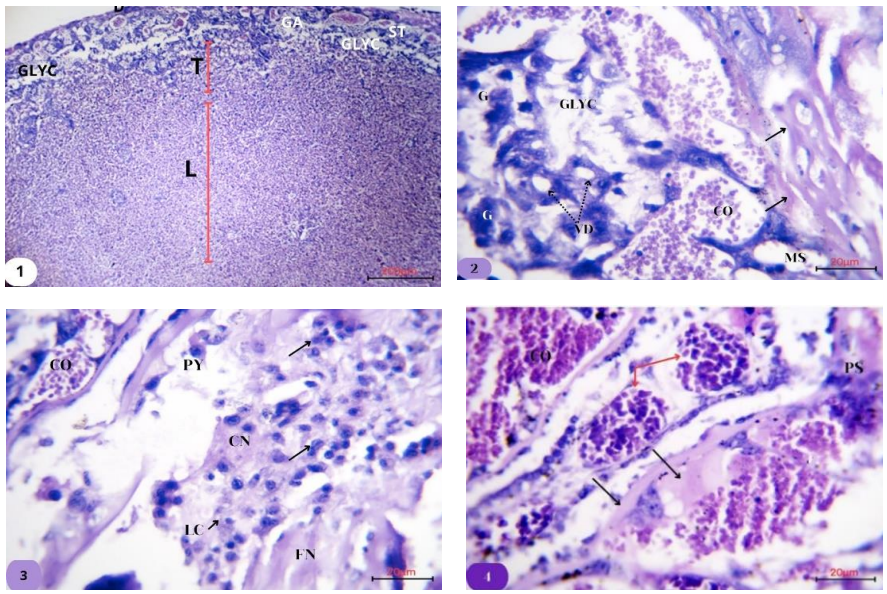

Figure 7. Histological tissues on day 18

Note: Picture 1 shows the labyrinth zone (L), giant cells (G), glycogen cells (Glyc), spongiotrophoblast (ST), decidua basalis (CD), and trophoblast zone (T). In the aqueoes extract of Annana leaves and TI, picture 2 shows the histopathological leshions in placenta in TO group view shows increment in the number of giant cells (G), cystic of glycogen cells (Glyc), increment in thickness of trophoblast septa with deposition of fibrin (black arrows), dilation of maternal sinusoid (MS), vacuolated degeneration (VD), lost architecture of labyrinth zone and congestion (CO), coagulative necrosis (CN), laceration cytoplasm (LC), pyknosis (PY), and hemorrhage (H). Picture (3) shows pyknotic spogiotrophoblast (PS), vascular irregularity (red arrows), fibrinoid necrosis (black arrows), and Hemorrhage (H) P(4).

of which are hormonal changes (Koech, 2023). Hormonal changes and miscarriage were two factors closely related to each other. Bagshawe et al. (2018) indicated that miscarriage can disrupt the natural hormonal balance.

The study found an increase in estrogen levels and a severe decrease in progesterone levels in the second group. This finding is consistent with several studies, including Ma et al. (2018) and Bjorklund et al. (2019), which examined the effects of mercury poisoning on fertility and pregnancy. Massanyi et al. (2020) studied the effect of some heavy metals on the female reproductive system. The results can be explained by the association of estrogen with miscarriage. Receptors for this hormone stimulate uterine cells to respond to it (Patel et al., 2015). Estrogen is expressed in two identical forms, alpha and beta, which help prepare the uterine lining for pregnancy (Gibson et al., 2020). Any disruption in the regulation of these receptors alters their expression (Fazleabas et al., 2010). Decreased expression of these receptors also causes miscarriage (Takaya et al., 2018). This decrease in progesterone levels may be explained by the formation of free radicals induced by TO dosing, which, in turn, affects its production. Hormone receptors are expressed in two isoforms (PR-A and PR-B), and disturbances in their expression are linked to miscarriage, although the mechanism remains unclear.

Thus, the defect in this hormone is due to poor regulation, not to its availability (Agrawal et al., 2013). Regarding the balance in estrogen and progesterone levels in the third group, our results are consistent with studies examining the effect of *A. muricata* leaves on mercury chloride toxicity. The results showed that they enhance sex hormones and the female reproductive system in general (Rosner & Sarao, 2019). The results of our study are consistent with those of Chinwuko and Asomugha (2024), which showed an increase in progesterone levels following soursop leaf dosing. Therefore, there must be a balance between the hormones estrogen and progesterone to ensure embryo implantation; any imbalance in these hormones leads to non-implantation (Patil et al., 2012).

As for the level of the morphological changes that appeared on the fetuses in the (second group) (day 15, day 18). The results found many deformities in the brain, eyes, limbs, and trunk. These results are consistent with studies on pregnant female mice examining the effects of TO on the fetuses. The study found numerous morphological deformities in the fetuses, including defects in the front and hind limbs, delayed bone hardening, and trunk curvature (Álvarez-Barrera et al., 2019; Alnuimy, 2020; Haramipour et al., 2022). Previous scientific research indicates that TO can cross the blood-brain barrier, affecting the nervous system. In a study conducted on PC12 cells, which resemble sympathetic neurons, the results showed that TO led to a decrease in cell vitality, a decrease in glutathione levels, an increase in oxidants, a significant increase in hydrogen peroxide production, and a decrease in membrane potential (Hanzel & Verstraeten, 2006; Rundk et al., 2025). The results of studies indicate that TO may induce apoptosis in these cells, as P38 acts as a mediator of this process (Pino et al., 2017). Other studies have found that TO causes shortening of neuronal dendrites, an increase in cytoplasmic calcium levels, a dose-dependent increase in mitochondrial reactive oxygen species (mtROS), and a decrease in membrane potential (Bramanti et al., 2019).

As for the histopathological changes in the (second group), many were observed, the most important of which were degeneration, necrosis, fibrin deposition, and hemorrhage. The results of our study were consistent with those of Kazemi et al. (2011) and Sodani (2012). Inhibition of the enzyme estrogen sulfotransferase (EST) is associated with platelet aggregation through an increase in the level of active estrogen, which leads to a state of blood clotting and causes bleeding and necrosis of the placenta, which in turn causes miscarriage as a result of the defect that affected the placenta due to the total dependence of the fetus on the placenta (Wang et al., 2015). Necrosis occurs for several reasons, including the failure of mitochondria to generate energy and the depletion of the cellular adenosine triphosphate compound, which leads to the failure of the calcium pump of the plasma membrane and the free entry of calcium into the cytoplasm, then activating the phospholipase process and destroying the cell membrane, this process causes necrosis (Stevens, 2009; Faouzi et al., 2025). As for the histological appearance of the placenta, similar to the control group in the third group, it can be attributed to the pharmacological properties and abundance of phytochemicals such as alkaloids, megastigmane, triglycerides, flavonoids, phenols, cyclopeptides, and essential oils in the leaves of the soursop plant (Atanu et al., 2018).

Finally, heavy metals pose a risk to fetuses (Sabra et al., 2017), as TO can reach the fetus through the maternal placenta (Li et al., 2019), one of the most dangerous causes of TO toxicity and the link between the toxic mechanism of TO ions and potassium ions (Fujihara & Nishimoto, 2024). In the reduced state, the radius of the TO ion is 1.76 angstroms. In comparison, the radius of the potassium ion is 1.60 angstroms (Rinklebe

et al., 2020). TO ions compete with potassium ions for potassium channels, thereby interfering with potassium-dependent biological functions. The toxicity arises from its interaction with the sulfhydryl group in mitochondrial membrane proteins (Peter et al., 2005). It shows a high affinity for disulfide bonds and forms thiol complexes in proteins (Cvjetko et al., 2010). In experiments conducted on mice, results showed that TO reduces the activity of the copper-zinc superoxide dismutase (SOD) enzyme (Galván-Arzate et al., 2005). TO toxicity is similar to that of other heavy metals in that it binds to the thiol group in glutathione (Genchi et al., 2021; Chang et al., 2023). Thus, TI-induced toxicity is comprehensive and broad-spectrum, representing the most common mechanism of inducing oxidative stress (Chang et al., 2023).

Conclusion

The study concluded that TO causes many negative effects, as with other heavy metals, including fetal malformations (day 15, day 18) and pathological tissue changes in the placenta. It also disrupts the levels of the hormones estrogen and progesterone. The results showed an improvement in many of these conditions when using the leaves of the custard apple plant, due to the plant's many medicinal properties.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Scientific Committee of the Department of Biology, College of Education for Pure Sciences, University of Mosul, Mosul, Iraq. The mice were treated and euthanized under its guidance.

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Conflict of interest

The author declared no conflict of interest.

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