

Long Term Toxicity of Aspartame on Ovaries and Blood Components of Adult Female Albino Rats

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Abstract

Introduction: Aspartame (ASP) is a synthetic sweetener low-caloric consumed worldwide by 200 million subjects. Recently, drawbacks of aspartame have been detected on several body tissues including the reproductive system and blood parameters. **Aim:** The present work aimed to detect effects of long-term intake of aspartame at two doses over blood picture and ovaries in adult female albino rats. **Material and Methods:** In the present work, 40 adult female albino rats divided into 4 groups, two control groups (without any treatment) and another two groups receiving aspartame (50, and 100mg/kg/b.wt) using oral gavage for 91 days. First, rats were euthanized, then, blood samples and ovarian tissues, collected for histomorphological studies. ANOVA and post-hoc test employed to compare group means under study. **Results:** ASP (50 & 100 mg/kg/b.wt) had resulted in a considerable decrease in serum estrogen and significant changes in blood picture parameters: decrease in RBC count, MCV, MCH and a significant decrease in WBC count than in control groups. Histopathological results were indicative of significant ovarian tissue affection in form of decreased ovarian follicles, less mature graafian follicles, most cells showed vacuolations, some showed atrophic changes. Ovarian stroma revealed a large number of noticeably dilated and congested blood vessels. There were hemorrhagic and necrotic foci with chronic inflammatory infiltrate and fibrosis. An increase in surrounding adipose tissue was detected. A notable drop in serum estrogen detected in aspartame groups in contrast to control groups. **Conclusion:** Aspartame has a negative effect (50 & 100mg/kg/b.wt/day doses) on blood components and a considerable histopathological deterioration of ovarian structures. **Recommendations:** Further studies needed to detect whether aspartame effects were reversible or not.

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Aspartame, Ovary, Estrogen, CBC.

Introduction

Aspartame (ASP) is a low-caloric, artificial sweetener. It is a white powder nearly two hundred times sweeter than sugar. It is used as a food additive in foodstuffs such as desserts, chewing gums, sweets, weight control products and also as a table-top sweetener (Alleva et al., 2011).

L-Aspartyl-L-phenylalanine methyl ester (ASP) formed of union of phenylalanine and aspartic acid, its sweetening power 180 to 200 times more than sucrose (Portela, 2007). After ingestion ASP, is efficiently hydrolyzed to 10% methanol, 40% aspartic acid and 50% phenylalanine (Bailey and Ayling, 2009).

Under strong alkaline or acidic conditions, aspartame hydrolyzed generating methanol. With severe conditions, peptide bonds resulted in free amino acids by hydrolysis (Ager et al., 1998).

Acceptable daily intake (ADI) level of aspartame, and many studied food additives, defined as "amount of a food additive ingested daily over a lifetime with no detected health risk, expressed on a body weight basis". The Joint FAO/WHO Expert Committee on Food Additives (JECFA) and European

Commission's Scientific Committee on Food have announced that the value 40 mg/kg.b.wt as ADI for aspartame, while ADI of aspartame is 50 mg/kg according to Food and Drug Association (FDA) (Renwick, 2006).

Recently, many studies had confirmed that aspartame increases the incidence of leukemia, lymphoma, genital, reproductive system and urinary tract damage, central nervous system damage and apoptosis process when high doses were used (Okasha, 2016 and Anbara et al., 2021).

Recently, many experimental studies have confirmed that aspartame is a multipotential carcinogenic agent and increases the risk of lymphoma, leukemia, urinary tract tumors, and neurological tumors, even at a daily dose (20 mg/kg) that is much less than the acceptable daily dose (40 mg/kg). In addition, several studies have suggested an association between aspartame consumption and the risk of type 2 diabetes, preterm delivery, nephrotoxicity, hepatotoxicity, and induction of histopathological changes in the parotid salivary glands. With regard to neurotoxicity of

aspartame, most of the previous studies were concerned about central nervous system toxicity. Aspartame affects the cerebral cortex and cerebellar cortex, affecting memory, learning, and behavior (Okasha, 2016).

Objective of the current research was evaluation of long-term administration effects of two doses of aspartame on the ovaries with blood components in adult female albino rats.

Material and Methods

Animals:

The current work was performed on 40 sexually mature female albino rats (aging 7 weeks) weighting 230-260 grams. Dividing rats into 4 separate groups, each group 10 rats. Animals were housed for 1 week prior to experimentation for accommodation. Animals were housed in a room which is temperature-controlled (22 ± 2 °C) at a humidity of $50 \pm 10\%$, with 12–12 h dark–light cycles. Animals received standard pellet feed and water. The Scientific Ethical Committee of Sohag Faculty of Medicine, Sohag University approved the protocol (510/2022-1).

Material:

1. Pure ASP powder was purchased from Pharco Company.

Chemicals:

1. ASP: 50 mg/kg/b.wt/day (1/100 LD50) (Kotsonis and Hjelle, 1996), were administered orally for 91 days.
2. ASP: 100 mg/kg/b.wt/day (1/50 LD50) were administered orally for 91 days.
3. Kits to measure serum estrogen level (estradiol).
4. Kits to measure complete blood count.

Methods:

Rats divided into 4 groups, 10 rats each;

Group I: Negative control group: in which animals didn't receive any treatment.

Group II: Positive control group: Animals received distilled water by orogastric tube.

Group III: Rats received 50 mg/kg b.wt/day of aspartame dissolved in distilled water and given orally through orogastric tube / 91 days.

Group IV: Animals given 100 mg/kg b.wt./day of aspartame, dissolved in distilled water and given orally using orogastric tube daily / 91 days.

Analytical examination:

Sacrification of rats were done under ether inhalational anesthesia at the end of research, 5 ml blood were collected from jugular vein for chemical analysis of:

- Serum estrogen level using commercial kits. Estrogen was performed on an ARCHITECT i2000SR system using ARCHITECT estrogen kits supplied by Abbott (Panel et al., 2007).
- Complete blood count analysis using commercial kits, blood sample 2 milliliters were dispensed gently into a tube containing EDTA as anticoagulant (1 mg/ml) and was used immediately for complete blood count using (automatic cell counter (CELL DYN 3700, 28 parameter) (Enver et al., 2003)

Histopathological examination:

After scarification of animals using inhalational anesthesia, histopathological examination of ovaries was carried out to detect any associated changes that were compared in animal groups.

The ovaries were immediately dissected out, the specimens had been fixed in Bouin's solution overnight at ambient temperature, and routine histological processing was carried out. Tissue sections had been dehydrated through increasing alcohol concentrations after that embedded in paraffin. Tissues are sectioned in blocks (5 μ m thickness) mounted on slides. Sections were deparaffinized using xylene and then hydrated with decreasing concentrations of alcohol. Finally, staining of sections with hematoxylin and eosin (H&E) stain was done, examined by a light microscope to determine any histopathological changes (Bancroft and Layton, 2013).

Statistical analysis:

Using one-way analysis of variance (ANOVA) to assess the significance of the variations between average values, also we use Tukey's post-hoc test for multiple comparisons.

For each group, data were expressed as means \pm standard deviation of mean (version 19; SPSS Inc., Chicago, Illinois, USA).

Results

First of all, comparing all groups of the study in between each other's, there was a statistical significance of serum estrogen level, red blood cells (RBCs) and white blood cells (WBCs) counts were very highly significant, hemoglobin (Hb) level, mean corpuscular volume (MCV) and hematocrit value (HCT) were statistically significant while both mean corpuscular hemoglobin (MCH) and platelets (PLTs) count were insignificant table (1).

Effects of prolonged intake of ASP with dose 50 mg/kg.b.wt/91 days on female albino rats serum estrogen, blood picture parameters.

Table (1) indicated that ASP 50 mg/kg.b.wt/day caused a considerable decrease of serum estrogen and as regard blood picture parameters, there were a significant decrease in RBC count, MCV, MCH and WBC count.

Effect of chronic ASP consumption with a dose of 100 mg/kg.b.wt/day mg for 91 days on female albino rat's serum estrogen, blood picture parameters

Table (1) showed that ASP 100 mg/kg.b.wt/day caused a considerable decrease of serum estrogen and significant changes in blood picture parameters like decrease in RBC count, MCV, MCH and WBC count.

Table (2) showed comparison of each group with other study groups, comparing negative control group (group I) (received ordinary feeding only) with the positive control group (group II) (received only distilled water using gavage plus ordinary feeding) to assure if there is any hazard of the stress response of just manipulating the rats or giving water using gastric tube or not, there wasn't any statistical significant difference between all parameters.

There weren't any significant differences between both control groups concerning either serum estrogen or haematological parameters table (2).

Effects of ASP consumption for 91 days using the two studied doses, 50 mg/kg.b.wt/day & 100 mg/kg.b.wt/day respectively, we found that there were no significant differences regarding estrogen levels or complete blood count parameters, which indicates that these doses have a similar deleterious effect on the ovarian function and hematological parameters too table (2).

Histopathological Results:

At the end of the study, weight of rats was detected showing no significant difference between groups.

After dissection, ovaries of rats were examined grossly, showing increased fat tissues around ovaries in aspartame treated groups in comparison with control groups and no other noticed gross changes.

In control groups I & II, ovarian tissues appeared normal with usual structural components; they revealed two different anatomical areas (outer cortex and inner medulla). Developing ovarian follicles at different

developmental stages found in outer layer. Large blood vessels, lymphatics, and nerves surrounded by a connective tissue stroma are found in the inner central layer. Developing follicle contains a large cavity called the antrum that contains liquor folliculi, lined from inside by the granulosa cell layer and from outside by theca lutein cell layer (Figure1).

In aspartame-treated groups (III&IV): Ovarian tissues showed less ovarian follicles, less mature graffian follicles, most cells showed vacuolation and some showed atrophic changes. The ovarian stroma showed multiple markedly congested and dilated blood vessels. In addition, there were hemorrhagic and necrotic foci with chronic inflammatory infiltrate and fibrosis. Also, an increase in surrounding adipose tissue was observed. The fallopian tubes revealed thickened fibrosed wall and narrowed lumen (Figure2).

Table (1): ANOVA test comparison between the 4 groups of the study:

	-ve control group (N=10)	+ve control group (N=10)	50 mg group (N=10)	100 mg group (N=10)	P value*
Estrogen	34.3±6.4	39±6.8	14.3±18.9	18.75±12.3	0.000
RBC (millions)	8.76±0.46	8.5±0.4	7.2±0.3	7.1±0.38	0.000
Hb(g/L)	14.1±0.24	14.26±0.39	15.1±0.5	15.0±0.4	0.000
HCT (%)	40.8±1.5	42.2±1.7	43.8±1.0	42.6±1.2	0.000
MCV	81.66±14.6	76.3±11.6	57.4±3.3	56.7±1.8	0.000
MCH	26.4±4.6	25.8±4.7	21.2±1.0	20.5±0.4	0.000
Platelets	740±36.1	737±48.7	738±24.8	719±53.4	0.67
WBC count	13.6±0.7	12.9±0.7	6.4±0.48	6.49±1.12	0.000

*using ANOVA test, P -value > 0.05: Non significant, P -value < 0.05 :Significant, P -value < 0.01: Highly Significant

Table (2): Post hoc Tukey test comparison between the 4 groups of the study:

	P1 between group 1 & 2	P2 between group1& 3	P3 between group 1 &4	P4 between group 2 & 3	P5 between group 2 & 4	P6 between group 3 & 4
Estrogen	0.83	0.005	0.03	0.00	0.004	0.85
RBC (millions)	0.4	0.000	0.000	0.000	0.000	0.92
Hb(g/L)	0.97	0.000	0.001	0.000	0.003	0.8
HCT (%)	0.14	0.000	0.03	0.059	0.9	0.24
MCV	0.6	0.000	0.000	0.000	0.000	0.9
MCH	0.98	0.008	0.002	0.02	0.006	0.9
Platelets	0.99	1.0	0.7	1.0	0.7	0.7
WBC count	0.25	0.000	0.000	0.000	0.000	1.0

P1: P6 performed by Tukey's post-hoc test for multiple comparisons.

N=P-value < 0.05: Non-significant *P-value < 0.05: Significant

**P-value < 0.01: Highly Significant

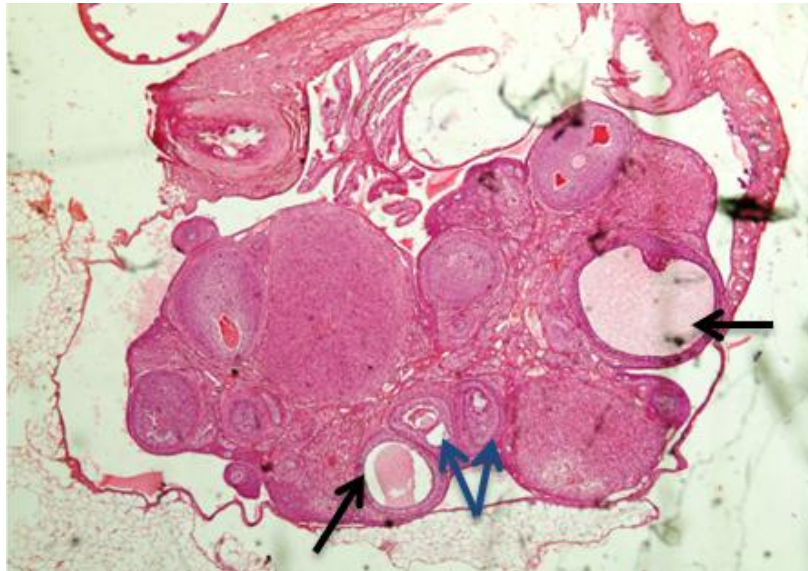


Figure (1): A photomicrograph showing section of ovary of adult female albino rat (control groups I & II), ovaries showed normal histological picture and different developmental stages of ovarian follicles; completely formed mature secondary follicles (black arrows) in alternation with small primary follicles (blue arrows), low power H&E X40.

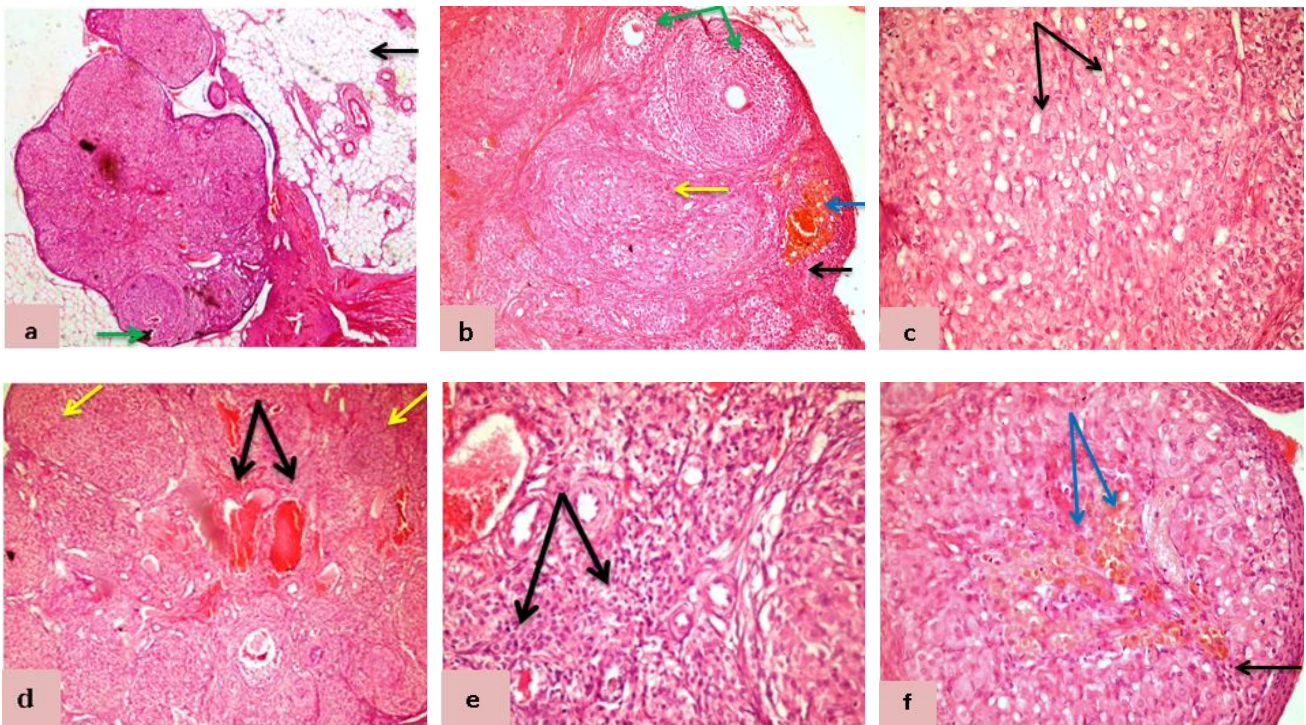


Figure (2): Group III & IV (Aspartame-treated) showed histopathological changes including:

- Decreased number and failure in development of ovarian follicles with less mature secondary follicles (green arrow), increased surrounding adipose tissue (black arrow), low power H&E X40.
- Decreased number of follicles in ovaries with less mature secondary follicles (green arrows), degenerated necrotic cells (yellow arrow), chronic inflammatory cell infiltrate (black arrow), foci of hemorrhage (blue arrow), H&E X100.
- Vacuolated cells (black arrows), H&E X200.
- Numerous markedly congested and dilated blood vessels (black arrows), degenerated necrotic foci (yellow arrows), H&E X100.
- Chronic inflammatory cell infiltrate (black arrows), H&E X200.
- Diffused hemorrhagic areas (blue arrows) and chronic inflammatory cell infiltrate (black arrow), H&E X200.

Discussion

Aspartame was restrictively used in 1981 in dry foods, also used in carbonated beverages in 1983, then accepted for wide use in 1996, it is now used as a sweetener and flavor enhancer in several products as carbonated soft drinks, candies, desserts, yogurt, table top sweetener, chewing gum and many pharmaceutical products like vitamins and drops for cough (Butchko and Stargel, 2001).

Aspartame considered as the most controversial artificial sweetener due to its probable toxicity problems. Many studies found that aspartame may be toxic and causing different side effects due to its toxic metabolites like aspartic acid, phenylalanine and methanol which are broken down to formaldehyde and formate which affect various body structures like liver, kidney, brain and reproductive system (Butchko and Stargel, 2001; Stokes et al., 1991; Roberts, 2007 and Soffritti et al., 2007).

Several European agencies, including European Food and Safety Agency (EFSA), European Food Safety Authority Panel on Food Additives and Processing Aids and Materials, concluded that "no need to revise the previously documented ADI of aspartame (40 mg/kg b.wt) EFSA (2009).

Few researches investigated the probable hazardous effects of aspartame on blood components and the ovaries.

Concerning the potential hazards of aspartame on blood components, a full blood count was done to all groups (control and aspartame both doses). The results of the present work indicated that administration of ASP to adult female albino rats by both (50 mg/kg.b.wt/day and 100 mg/kg.b.wt/day) had led to a considerable decrease in RBC count, MCV, MCH and WBC count in comparison with control group, mainly due to direct effect of aspartame toxic metabolites on the bone marrow as also suggested by other studies (Soffritti et al., 2006 and Eva et al., 2013).

On the other hand, Marko et al., (2015) conducted a study on ASP administration with a dose 40 mg/kg.b.wt/day/six weeks (two groups, 5 rats/group), they observed no significant changes in RBCs count, PLT count, HGB and HCT values among ASP groups and control groups. However, the study results demonstrated a significant decrease in WBCs after administration of ASP ($P < 0.05$) as observed in the present study.

This difference between the present study and the previously mentioned study may be due to difference in aspartame dose, duration of administration and number of studied animals.

On comparing the adverse effects of administering two different doses of aspartame 50 & 100 mg/kg.b.wt/day, it was found that both doses caused considerable changes in blood picture parameters as, decrease in RBC count, MCV, MCH and a significant decrease in WBC count comparing to control group, but both at a non-significant way to each others.

Concerning the potential hazardous effects of ASP administration upon reproductive system in adult female albino rats especially ovaries,

It was postulated that ASP affect the hypothalamus, it produces gonadotropin-releasing hormone (GNRH) that reaches the pituitary stalk causing stimulation of pituitary gland to form gonadotropins, then stimulates testicles to form testosterone (USEPA, 1996; James, 2000 and Puica et al., 2009). Aspartame is completely metabolized in gut and hydrolysed to methanol, phenylalanine, aspartic acid and diketopiperazine. Over 86 ° F (30° c), methanol formed from aspartame liberates formic acid and formaldehyde. Ingestion of aspartame, methanol harmfully affects eyes, GI tract, CNS and can damage testes, kidneys, and the liver (Choudhary and Raithinamy, 2016).

Few researches had investigated the effects of chronic ASP administration on biochemical and histopathological structure of the ovaries.

In the present study, it's found that long term administration of ASP for 91 days to adult female albino rats by two doses 50 & 100 mg/kg.b.wt/day caused a marked decrease in serum estrogen compared to control groups.

Decreased estrogen level in ASP treated groups in comparison to control group could be explained to be due to either neurodegenerative changes, especially in hypothalamus and major functional and structural changes in hypothalamo-pituitary axis, which in turn leads to reduction GNRH, FSH, LH beside testosterone suppression, synthesis and secretion of estradiol (James, 2000). The second way is supposed to be due to methanol poisoning (the main ASP metabolite) which is postulated to cause direct injury to the testes and ovaries by producing damage structurally and functionally to heat shock proteins (HSPs) which plays role in regulating spermatogenesis, oogenesis, cytoprotective actions, and increasing cell resistance to environmental stress which can be also expressed by the significant histopathological changes.

Omar (2021) revealed that ASP administration (40 mg/kg.b.wt./day for 90 days) caused marked drop in estrogen levels compared to control group.

Histopathological examination of ovaries of ASP-treated groups (III & IV) revealed some structural changes, including decreased number of ovarian follicles, less mature graffian follicles. Some follicles showed atrophic and destructive changes. Numerous congested dilated blood vessels and diffused hemorrhagic and necrotic areas were found. The ovarian stroma showed chronic inflammatory cell infiltrate and fibrosis. Also, there is increase in surrounding adipose tissue. The fallopian tubes revealed thickened fibrosed walls and narrowed lumens. The findings were near to those reported by Hosseini and his colleagues, who reported that long-term exposure to aspartame causes histopathological changes to ovarian tissue in form of a reduced number of developmental ovarian follicles (Hosseini et al., 2021).

On the other hand, a previous study revealed that ASP-treated groups didn't show any detectable histopathological changes in the ovarian tissue and had normal histological architecture, while groups treated with both aspartame and monosodium glutamate showed similar findings to the present work results (Mostafa et al., 2021).

As noticed in the present work, Mohsen et al., (2021) reported that ASP administration (160mg/kg.b.wt/day/91days) caused multiple side effects on histomorphology of rat ovaries such as decreased number of growing follicles and significantly increased follicular atresia.

On comparing the adverse effects of administering two different doses of aspartame 50 & 100 mg/kg.b.wt/day, It was found that both doses caused decrease in serum estrogen and histopathological changes in rat ovaries in the present study.

Conclusion

Aspartame has an effect (both 50 and 100mg/kg.b.wt/day doses for rats) on analysis of blood components and a considerable histopathological and analytical deterioration of ovarian structures and function.

Recommendations

1. Further studies to measure other biochemical parameters such as GRH, FSH and LH and gene study related to the ovarian functions in human.
2. Further studies needed to detect whether aspartame effects were reversible or not.
3. Further studies needed to detect carcinogenic effect of aspartame and its apoptotic effect in human cells.
4. The need of conferences, seminars, social media to increase awareness of the general population on aspartame chronic toxicity on fertility and its carcinogenic effects.

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سمية الأسبارتام على المدى الطويل على المبايض ومكونات الدم في إناث الجرذان البيضاء البالغة

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الملخص العربي

مقدمة: يعد الأسبارتام أحد المواد التي تضاف إلى الأطعمة فهو مُحلي صناعي منخفض السعرات الحرارية، يستهلكه حوالي 200 مليون شخص حول العالم. وبالرغم من انتشاره عالمياً، إلا أنه في السنوات الأخيرة ظهرت له العديد من الآثار السلبية على أنسجة الجسم المختلفة بما في ذلك الجهاز التناسلي ومكونات الدم.

الهدف: من هذه الدراسة هو بحث تناول الأسبارتام على المدى الطويل بجرعتين مختلفتين على معايير صورة الدم والمبايض في إناث الجرذان البيضاء. الطريقة: في هذه الدراسة، تم تقسيم 40 أنثى بالغة من الجرذان البيضاء إلى أربع مجموعات، مجموعتين بدون علاج (مجموعات ضابطة سلبية وإيجابية) ومجموعتين تلقت الأسبارتام بجرعتين مختلفتين (بجرعات 50، و 100 مجم / كجم/يوم) تم إعطاء جميع الجرعات عن طريق الفم لمدة 91 يوماً. تم جمع عينات الدم وأنسجة المبيض وفحصها وتم تحليل النتائج احصائياً.

النتائج: بينت الدراسة أن كلا الجرعتين من الأسبارتام تؤديان إلى آثار سلبية على مكونات الدم وأنسجة المبيض. أدى أسبارتام (50، و 100 مجم / كجم / يوم) إلى انخفاض كبير في هرمون الاستروجين في الدم وتغيرات كبيرة في معايير صورة الدم مثل انخفاض عدد كرات الدم الحمراء وانخفاض كبير في عدد كرات الدم البيضاء مقارنة بالمجموعات الضابطة. كان هناك تغيرات سلبية هستوباثولوجية كبيرة وتأثيراً واضحاً على أنسجة المبيض مقارنة بالمجموعات الضابطة.

الخلاصة: للأسبارتام (جرعات 50 و 100 مجم / كجم/ اليوم) تأثيراً سلبياً على مكونات الدم وتأثيراً على نسيج المبيض.

التوصيات: المزيد من الدراسات لاكتشاف ما إذا كانت تأثيرات الأسبارتام قابلة للتحسن بعد إيقاف استخدامه أو استخدام مضادات الأكسدة.

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