

The Effect of Alcoholic Extract of the Celery Seeds *Apium graveolenes* on the Histological Characteristics of the Swiss Rat Testis Treated with the Depakine Drug

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Abstract

The current study has been conducted in the animal house / Department of Biology at the College of Education for Women / University of Kufa between 1-2-2022 and 1-1-4-2022 comprising the use of 24 males of white rats of (the Sprague Dawley Breed) at an age of more than 12 weeks and with an average weight ranging between (200 and 300g) that have been divided randomly into four equal groups: The first group is considered as a control group which has been injected with the physiological saline at a concentration of 0.9%. The second group has been injected with the Depakine at a concentration of 500 mg/kg inside the peritoneum. The third group has been injected with the alcoholic extract of celery seeds at a concentration of 75 mg/kg. As for the fourth group, it has been injected with the Depakine 500 mg/kg & alcoholic extract of celery seeds at a concentration of 75 mg/kg. All experimental animals have been treated once daily for 30 days. After the end of the experiment, the animals were sacrificed, and the genitals (testes) were taken for the purpose of the histological study. The histological examination of the testicles of males treated with Depakine showed several histopathological changes, including a marked decrease in the number of sperm cells in different stages of development, sloughing of spermatogenic cells from the germinal epithelium of the seminal tubule, infiltration of inflammatory cells into the lumen of the seminal tubule, atrophy of the diameters of the seminiferous tubules, necrosis of cells for hands, and a decrease Its preparation within the interstitial tissues and the disintegration of the interstitial tissue that separates the seminiferous tubules, the dilation of the diameter of the blood vessel, and the collection of blood cells inside it. About the group treated with alcoholic extract of celery seeds, the histological sections showed slight decrease in histological parameters compared to the control group, and there were several changes, including irregularity in the diameters of the seminiferous tubules, a decrease in the number of sperms in the lumen of some seminiferous tubules, a disintegration of the interstitial tissue, a decrease in the number of leydig cells , and the separation of The germinal epithelium layer and the disintegration of the germinal cells of the epithelium, the increase in the number of Sertoli cells, and a little agglutination between the cells that form sperm. As for the group treated with Depakine & alcoholic extract of celery seed, the results of the histological examination have confirmed a significant improvement in all the histological parameters compared to the group treated with Depakine, such as the regularity of the diameters of the seminiferous tubules and decrease in the cavities of them, an increase in the number of Leydig cells and their regularity within the interstitial tissue, an increase in the number of sperm-producing cells, and a decrease in their agglutination, the histological examination also showed an increase in the number of mature sperm within the lumen of the seminal tubule, in addition to a regularity in the germinal epithelial tissue . It has shown that the group that is treated with Depakine & alcoholic extract also showed a slight decrease in some histological feature as compared to the Control Group, the germinal epithelium of some seminiferous tubules were separated and the diameters of some

of these seminiferous tubules were irregular, as well as the presence of a slight agglutination between the sperm cells and decrease in their numbers within the germinal epithelium of some tubules. This result indicates that the protective efficiency of the alcoholic extract of celery seeds increases with the use of higher concentrations for the purpose of removing all the toxic effects, which are induced by the Depakine drug.

Keywords

Celery Seeds, Depakine, Alcoholic Extract, Histological Characteristics

The utilization of most drugs leads to the emergence of several effects, the therapeutic effect is the only effect that is required, whereas the other effects are mostly undesirable, whether they are harmful in essence or not, the Depakine or the so-called sodium valproate (VAP)), drug is no exception to this rule. This is widely used to control the epileptic seizures (Mattson et al., 1985) and muscle spasms (Oka et al., 2004) Verity et al. (1995). Medical reports have shown the negative effects of this drug on the various organs of the body, including the testicles. A study that has been conducted by researchers Sveberg Roste et al. (2001) has stressed that the treatment with the Depakine led to the appearance of phenotypic changes in the testes of rats, in addition to a decrease in the sperm motility. Nishimura et al.(2000) have assured that most of the bodies of living organisms do not have an effective mechanism to remove the damage caused by taking these drugs, so recent studies have tended to use some medicinal plants and adopt them as sources of the antioxidants that can contribute effectively to reducing the oxidative stress and thus protecting the various organs of the body from damage (Bors et al. 1996). Among these medicinal plants is the celery plant (*Celery*) *Apium graveolenes*. This plant contains many substances and active antioxidant elements, the most important of which are flavonoids and phenols (Phenoles Pietta & Simonetti, 1998). These compounds play a vital role in removing free radicals and promoting the vital functions of the various organs of the body, including the sex glands, and this was confirmed by several research studies that revealed the positive effect of the celery plant in preventing damage to the testicular tissues in the rats that are treated with the Valproate (Hamza & Amin, 2007) as well as the Atrazine (Abarikwn et al., 2011).

In relation to the role of the celery seeds in enhancing fertility, about 16 studies have recently been conducted. 13 of which have found that the alcoholic and aqueous extracts

of the celery leaves have a role in enhancing the fertility and increasing sperm production in addition to increasing the concentration of sex hormones, and this effect is due to the plant's containing of chemical compounds called Phytoestrogens that have properties and effect similar to that of the sex hormones that contribute to an increase in the activity of the sex glands. As for the three other studies, it was reported that the aqueous and alcoholic extracts of the celery has an anti-fertility effect through its effect on the feedback mechanism and inhibition of the secretion of the sex hormones, thus reducing the activity of the testes(Kooti et al., 2017).

The current study aims to assess the negative effects of Depakine concentration of 500 mg/kg on the testicular tissues of male white rats and the protective effect of the alcoholic extracts of the celery seeds in removing the pathological effect with the Depakine.

Materials and Methods**Preparing the Animals**

The current study has comprised 24 white rats that have been brought from the Research Center / University of Karbala and were free from diseases and then evacuated to the animal house of the Department of Biology / College of Education for Women / University of Kufa for their care. All animals were subjected to similar laboratory conditions in terms of lighting (12 hours of Light - 12 hours of dimness) and a temperature of (22-25) Celsius degrees. Animals were given food and drinking water regularly throughout the study span, and the rats were left to acclimatize for at least two weeks prior to commencing the experiment.

Determining the dosage:

The drug dose has been determined according to the pharmacopoeia and based on the weight of each of the rats.

Preparing the Alcoholic Extract of Celery Seed

The method of Harbone, (1973) has been employed as follows:

20g of the celery seed powder have been weighed and mixed with 200ml of absolute ethanol alcohol at a concentration of 99.9% and placed in a Soxhlet extractor that has been operated for 72 hours. Then, the gelatinous extract has been obtained, the gelatinous extract has been weighed, then 100ml of distilled water has been added to it to get a dilute concentration of the prepared extract. A dilute solution was prepared from the readymade extract at a concentration of 75mg/kg according to the following equation: $N14V1=N24V2$

Animal Treatment

The animals have been divided into four groups, with six rats per group

The First group is approved as a Control group that is injected with the physiological saline solution. The Second group is injected with a concentration of the Depakine 500 mg/kg. The Third group is injected with the alcoholic extract of the celery seeds with a concentration of 75mg/kg. Finally, the Fourth group is injected with the Depakine 500 mg/kg and alcoholic extract of the celery seeds at a concentration of 75 mg/kg. All animals were injected in the peritoneum tissue as a single dose daily for 30 days.

The Histological study

The animals were terminated using diethyl ether, 24 hours after the last dose, and the abdominal cavity was opened with a scalpel and sharp scissors. The testis were removed and placed in the physiological solution. The surrounding fatty parts were removed and then fixed using a solution of formalin stabilizer (10%) and left for (24) hours and then transferred to ethyl alcohol (70%) for the purpose of making tissue sections .

The Histological study

The histological sections of the male reproductive organs represented by the testes have been studied to determine the effect of the extract on them. The method of Bancroft & Gamble(2008) has been adopted.

The fixed organs were washed several times with ethyl alcohol, and then the Dehydration process was carried out by passing them several times through a series of rising concentrations of ethyl alcohol of (100%-95%-90% 80%-70%) for two hours with each concentration, followed by the process of Clearing with xylene for two hours. Next, comes the process of Infiltration with paraffin wax at a melting point that ranges between (58-56) Celsius degrees for two hours, and finally the process of Embedding is commenced when the tissues are placed in special molds of paraffin wax and left to dry where sequential cross sections are made with Rotary Microtomes. The sections are fixed on clean glass slides using the Mayer's albumin adhesive after being placed in a water bath at a temperature of 50-45°C for two minutes and then left to dry on a hot plate at a temperature of 37°C. Two minutes later it is sent through a series of low concentrations of ethyl alcohol of (70%-95%-100%) for two minutes in each concentration, then it is allowed to sink in the hematoxylin dye, then in the eosin dye for two minutes in each dye, then it was passed a series of increasing concentrations of ethyl alcohol (10-95%-70%) and finally it is let to go into the xylene for two minutes, then the mounting process is performed as the Tissue slides are covered with glass cover, using the Canada balsam material.

The Histological Slides Examination

The slides were examined by a light microscope to find out the histological changes of the testes such as the regularity of the diameters of the seminiferous tubules and the numbers of cells forming sperm in the different stages of growth and development, in addition to examining the concentration of sperm inside the lumen of each seminiferous tubule

The Histological Study

The Histological changes of the testes treated with the Depakine:

The histological examination of the testicular sections in the group treated with the Depakine has indicated that many pathological-histochemical changes occurred,

including the separation of the spermatogenic cells from the epithelial layer of the seminiferous tubules, in addition to a significant decrease in the number of sperm cells in the different stages of growth and division, a decrease in the number of Sertoli cells, agglutination and infiltration of inflammatory cells within the lumen of the seminiferous tubules and decrease in the number of sperms within the lumen of the seminiferous tubules, as illustrated in Figures (1,2), and (3). Moreover, the tissue sections have affirmed a clear degeneration and necrosis in the cells of Leydig and decrease in their numbers within the interstitial tissue, in addition to the presence of disintegration in some of these tissues. This degeneration or necrosis has been also observed in the cells of the germ epithelium of the seminiferous tubules, and these cells assemble in the cavities of some seminiferous tubules, in addition to the appearance of an expansion and congestion in the blood vessels as demonstrated in Figures (2), and (3).

The Histological changes of the testes treated with alcoholic extract of the celery seeds:

The cross-sections of testes of the rats that are treated with the alcoholic extract of the celery seeds at a concentration of 75 mg/kg has revealed slight changes in some histological parameters, including irregular seminiferous tubule diameters and a decrease in the number of sperm inside the cavities of these tubes, as well as the disintegration of the interstitial tissue and a decrease in the number of Leydig cells within. The basement membrane of the seminiferous tubules is separated from the germinal epithelium in addition to the disintegration of parts of this epithelium and therefore a reduction in the height of the lining epithelium as a result of the reduction in the number of sperm-forming cells as shown in Figures (4), and (5) With regard to the numbers of Sertoli cells, the histological results of this group have verified an increase in the number of Sertoli cells, in addition to a slight agglutination in the spermatogenic cells and a decrease in their numbers in the epithelial epithelium of some seminiferous tubules, as shown in Figures (5)

The Histological changes of testes in the group treated with Depakine & alcoholic extract of celery seed:

The histological examination of the testicles in this group has confirmed a positive effect on all the histological indicators in comparison to the group treated with the Depakine, such as the regularity of the seminiferous tubule diameters and the decrease in the lumen diameter of some of them, add to that the increase in the number of sperms inside the cavities of some seminiferous tubules, as shown in Figures (6,) and (7). As for the numbers of the sperm cells for this group, the results have aided a noticeable increase in the sperm-producing cells and a noticeable decrease in the agglutination of these cells with each other, adding to that the presence of a regular number of the Sertoli cell Figures (7). No disintegration was observed in the interstitial tissue separating the seminiferous tubules with the regularity of the numbers of cells within the interstitial tissue as in Figures (6), Finally, with regard to comparing the histological changes of this group with the control group, the results of the study recorded a decrease in some histological indicators, including the detachment of the germinal epithelium of some seminiferous tubules, a decrease in the number of sperm-forming cells and agglutination with each other, in addition to the irregularity of the diameters of some seminiferous tubules, as shown in Figures (8), and (9).

The Control Group

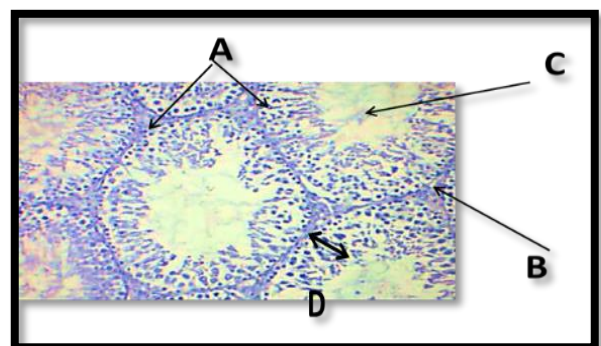


Figure (1) A Cross-section of the tests in Control Group demonstrating A- The Arrangement of seminiferous tubules. B- The Regular interstitial tissue with cells of Leydig C- lumen of the seminiferous tubule D- epithelial tissue layers (Hematoxylin & Eosin 100X).

The Depakine Group

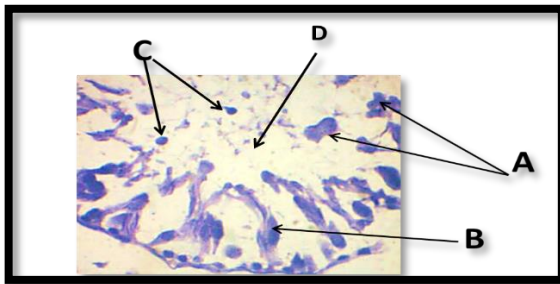


Figure (2) A cross section of the testes of the rats treated with the Depakine (500mg/kg) illustrating A- the Sperm cells agglutination with each other and noticeable decline in the number of sperm cells at the various stages of the growth B- the declining numbers of Sertoli cells and agglutination with the spermatogenetic cells C- the Infiltration of the inflammatory cells D- The Declining numbers of sperms inside the lumen (Hematoxylin & Eosin 400X).

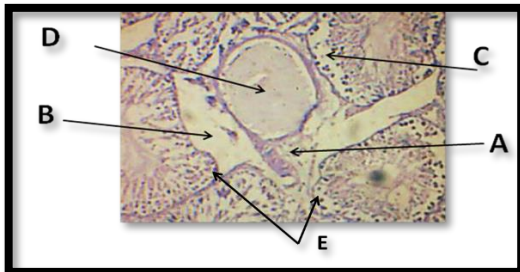


Figure (3) A cross section in the testes of the rats treated with the Depakine at a concentration of 500 mg/kg) depicting A- degeneration and declining numbers of Leydig cells B- The disintegration of the interstitial tissue C- The dissociation and necrosis of the epithelial tissue layers D- The widening of the diameter of the blood vessel and the aggregation of the blood cells inside (E- The irregular seminal tubule diameter.(Hematoxylin & Eosin 100X).

The Extract Group

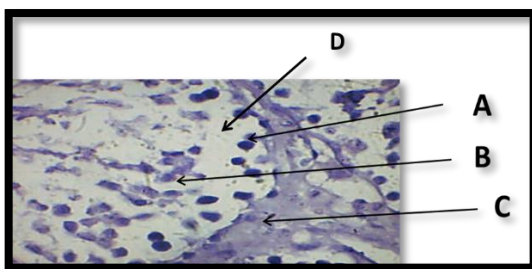


Figure (4) A cross-section of the testes in the group that is treated with the alcoholic extract of the celery seeds at a concentration of (75mg/kg) shows A- slight decrease in the number of the sperm-forming cells B- A slight agglutination between the sperm-producing cells C- A decrease in the number of leydig cells D- Slight disintegration in the germinal epithelial cells tissues (Hematoxylin & Eosin 400x)

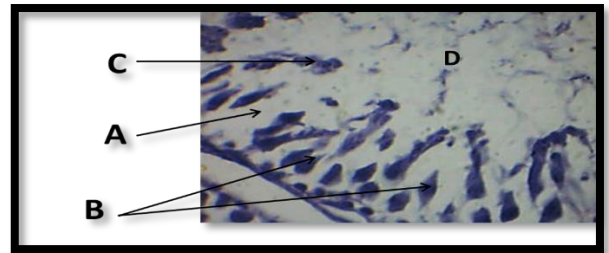


Figure (5) A cross-section of the testes in the group that is treated with the alcoholic extract of the celery seeds at a concentration of (75mg/kg) shows A- The disintegration in the germinal epithelial cells tissues B- Increase in number of sertoli cells C- slight agglutination between the sperm-producing cells. D- The lowered numbers of the sperms in seminiferous tubules (Hematoxylin & Eosin 400x)

Depakine and Celery seeds group

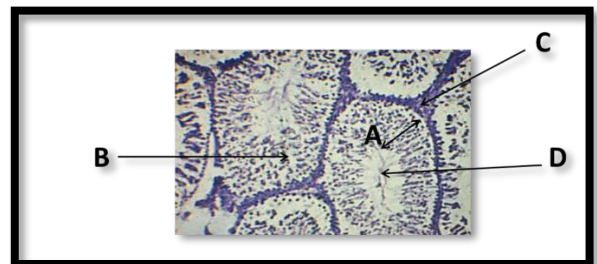


Figure (6) A cross sectional image in the testes of the group treated with the Depakine at a concentration of 500mg/kg) and the alcoholic extract of the celery seeds at a concentration of 75mg/kg) elucidating a noticeable improvement in the histological parameters of this group comparison to the group of the Depakine, confirming A- The regularity in all germinal epithelial tissue layer with normal Arrangement of seminiferous tubules. . B- Normal numbers of the sperm-forming cells C- Normal interstitial tissue D- The marked decrease in the diameters of the seminiferous tubule cavities (Hematoxylin + Eosin (100X).

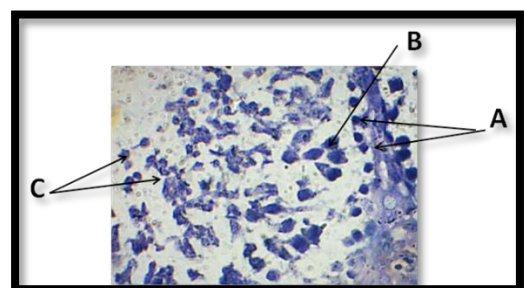


Figure (7) A cross sectional of the group treated with the Depakine (500mg/kg) and alcoholic extract of the celery seeds (75mg/kg)) showing a remarkable improvement in the histological parameters of this group as compared to that of the Depakine group, approving the following: A - Increasing the numbers of spermatoctyts cells B – the Regular numbers of Sertoli cells C- A Decreased agglutination between sperm-forming cells (Hematoxylin + Eosin 400X).

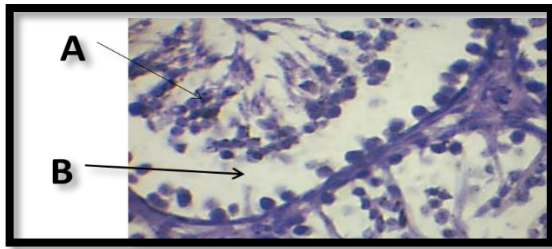


Figure (8) A cross-sectional of the testicles of the group treated with the Depakine & the celery extract at a concentration of 75 mg/kg, showing a slight decrease in some of the histological parameters of this group as compared to the Control Group asserting A- the presence of a slight agglutination between the cells B- the detachment of the germinal epithelium in some seminal tubule (Hematoxylin &Eosin 400X).

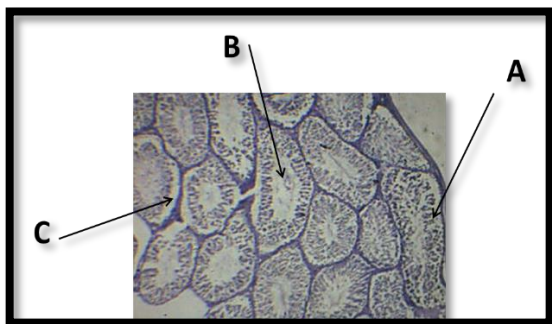


Figure (9) A cross section of the testes of the group treated with the Depakine & the celery extract of 75mg/kg indicates a slight decrease in some of the histological parameters of this group as compared to the Control Group asserting the A- irregular diameters of some seminiferous tubules B - widening of the lumen diameter of some seminiferous tubules C - separation of the germinal epithelium layer in some seminiferous tubules (hematoxylin & Eosin 40X).

Discussion

The Histological changes that happen in the sex glands, like the decline in the number of the sperms in the cavities of the seminiferous tubules and decrease in the number of spermatogenetic cells, are the most important indicators of low fertility (Meistrich et al., 1982). The results and findings of the present study have confirmed the fact that the Depakine (VAP) drug is responsible for the appearance of pathological effects in the testicular tissues. The results reached in this study are in agreement with another study that is conducted by Bairy et al. (2010), which has assured that the pathological effects of the Depakine rely on the amount of dose and the

time during which the treatment has been carried out, as the effects were much more greater when treated with a high dose in the tenth week in comparison to the first weeks of treatment . The stages of growth and division in the generative cells are sensitive to any chemical effects that can interfere with the growth and division in the generative cells as compared with the stage of differentiation that occurs in the spermatids (Sharpe:1994), as Bairy et al (2010) have indicated that the pathological effects of the Depakine in the testicular tissues can be reversed, referring to the ability of the generative cells to restore their function after stopping the treatment with this drug. Another study by Yang & Wang (2016)& Roste et al (2003) have reported that the persons who have been on the Depakine drug for more than six months have shown a decrease in the sexual drive and have had issues with erection and ejaculation as compared to the persons who have been on other medications of the epilepsy drugs. The results that have been arrived at in the present work also have tallied with the other studies that have been conducted by the researchers Nishimura et al. (2000). It has concluded that the treatment with the Depakine has resulted in some pathological toxic changes in the testicular tissues, which caused a noticeable decrease in the parameters of the sperms. Moreover, the morphological abnormalities that have been observed in the sperms were caused by genetic mutations that can occur at any stage of the sperm growth and differentiation as a result of the sperm exposure to chemicals and overlap of these Chemicals with the growth and division processes happening in testicular tissues. This study has classified the Depakine among the genotoxicity drugs Russell & Russell (1991) and Sharma et al. (1979). In terms of the effect of treatment with the alcoholic extract of the celery seeds has led to slight changes in the histological parameters. The results of the present paper have come in total concord with another study by AL- Sana bra et al. (2013) that has indicated that the treatment with high concentrations of 300 mg/kg of the alcoholic extract of the celery seeds has resulted in a sharp decline in the histological indicators of the testes. The alcoholic ethanol

extract of the celery seeds incorporates some active substances that are called flavonoids and terpenes that have estrogenous properties that can rival with the natural estrogens in the body and therefore affect the activity of the sex glands and the concentration of secreted hormones (Zhou,2009). The results of the current study disagree with another study performed by the researchers Hardani et al. (2015) who have reported that oral administration of the aqueous extract of the celery leaves that have had a positive effect on the sperm parameters and on improving the level of sex hormones in the male rats. The difference in the results of the two studies is due to several reasons, including that the celery seeds contain higher concentrations of active substances compared to the leaves, and there are active substances that may have toxic effects on the tissues that are completely dissolved in the alcoholic extract, while their solubility and concentration is lower in the water extract, and the method of dosing It plays a role in the metabolic mechanism, as oral administration reduces the absorption of substances into the body compared to injections, and this is what was agreed upon by another study conducted by researchers Modaresi et al. (2012).

As for the results of the protective effect of the alcoholic extract of the celery seeds in reducing the toxic effects of the Depakine drug, the results of the tissue sections have demonstrated astonishing improvement in the tissue structure of the testes of rats as compared to the group treated with the Depakine. The results of the current study are consistent with other studies that have indicated that the celery seeds contain flavonoids, the most important of which is Apigenin that is a powerful antioxidant. (VAP) and thus reduce the damage to the testicular tissues and protect them from the toxic effects of this drug Hamza & Amin (2007). Also, the results of the current study agreed with the results of other studies on the role of alcoholic extract of celery seeds in protecting testicular tissues from the damage of some drugs, including Atrazine Abarikwn (2012) and quinine sulfate Farombi (2012). Additionally, the tissue sections of the group treated with the Depakine and the alcoholic extract of the celery seeds have asserted a decrease in some of the histological parameters as compared to the Control Group,

which assures that the amount of damage caused by this drug, which requires the use of higher concentrations of antioxidants and for longer periods for the purpose of removing all pathological effects on tissues.

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