ARTICLE

Alpha Lipoic Acid Ameliorates the Artificial Sugar Induced Injury to the Female Reproductive Organs of Mice

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Competing interests
The authors have declared that no competing interests exist.

Abstract

Background: *High Fructose Corn syrup (HFCS) is one of the most common artificial sweeteners widely used in many foodstuffs. Alpha lipoic acid (ALA) is a natural antioxidant that reduces the level of Reactive Oxygen Species (ROS). This study was aimed to find out, whether alpha lipoic acid can mitigate the toxic effect of High Fructose Corn syrup (HFCS) on the female reproductive organ.*

Materials and Methods: *30 female mice were equally divided into three groups. First group (C) referred as Control was orally administered distilled water using an insulin syringe. Dose group* HFCSI *was administrated with 25% HFCS, while dose group* HFCSII *was administrated with 25% HFCS and 35mg/ kg of BW ALA for 30 days. After the stipulated time, mice were sacrificed to remove ovaries for further study.*

Results*: Histological studies showed different defects in the ovaries of the dose group HFCS I. It included granulosa cells having less intact oocytes, injured primordial follicles, cysts development, degraded oocyte, a reduced count of follicles, and disarrangements of Tunica albuginea and ovarian surface epithelium. While treatment with ALA reduced the ovarian damage by improving the histopathological changes caused by HFCS.*

Conclusion: *The consumption of HFCS may lead to increased oxidative stress (OS) which may leads to distortion of the ovarian morphology as seen in histological sections. ALA is found to have meliorative effects and improved the reproductive pathology, normal count of follicles, and histopathological score by reducing the oxidative stress.*

Key Words: *ALA, Artificial sweetener, Follicle Cells, Oxidative stress*

Introduction

Artificial sweeteners like High Fructose-Corn Syrup (HFCS) are in extensive use in food industry to synthesize canned food, jam, jelly, beverages and bakery products due to its low price and easy handling (Ma et al., 2013; Sinir et al., 2017). HFCS is derived from cornstarch, which is a polymer glucose molecule. Starch molecules are converted into glucose in the presence of alpha-amylase and glucoamylase enzymes, and vice versa glucose isomerase enzyme isomerizes the glucose to fructose (Parker et al., 2010). HFCS has three types i.e., HFCS-90, HFCS-42-and HFCS-55 (Koseler et al., 2018). This artificial sweetener is thought to raise biomarkers, cause oxidative stress, fatness and hypertension. This oxidative stress may cause reproductive pathologies like endometriosis, polycystic ovarian syndrome and reduced fertility, which may lead towards miscarriages in case of pregnancy (Sohrabi & Torabian, 2019; Ahmed et al., 2016). HFCS is usually related with fatness and reduced fertility. It effects the progesterone and luteinizing hormone (LH) secretions before ovulation and leads to changes in the serum hormone levels including LH, FSH and testosterone, ovary, germ cells morphology, follicle (Volk et al., 2017; Tkachenko et al., 2020).

Alpha lipoic acid (ALA) is an antioxidant, which is used to eliminate the free radicals and metal ions chelation as well as reduce vitamin C and cytosolic glutathione (Polat et al., 2020). ALA is

released by the enzymatic activity of lipoic-acid synthase in plant and animal cells. ALA plays very important role in oxidative metabolism and exhibit anti-inflammatory, antioxidant and hypoglycemic properties (Salehi et al., 2019; Votano et al., 2021).

ALA has ability to reduce to dihydrolipoic acid (DHLA), which can neutralize the active oxygen, chelation of metal ions Fe2+, Cu2+ and Cd2+, and regeneration of the body's own antioxidants like glutathione (GSH), vitamin E and vitamin C. The antioxidant potential of ALA increases the antioxidant status of the ovaries and maturation speed of oocytes in mice (Nair et al., 2020). ALA reduces the level of ROS and prevents the rupturing of premature follicle membrane as well as can treat endometriosis.

This histopathological study shows the effective antioxidant ability of ALA as it minimized the ovarian damage which is in agreement with previously reported findings (Ozel et al., 2020).

Materials and Methods

A group of 4-5 weeks old female mice were further divided to three sub-groups were kept under controlled conditions of temperature and humidity with 12-hour light and dark cycle and ± 24℃. First group (C) referred as Control was orally administered distilled water using an insulin syringe, second group (HFCS I) was administrated with 0.1 ml of 25% HFCS, and third group (HFCS II) was administrated with 0.1 ml of 25% HFCS & ALA (35 mg/kg) daily for 30 days period. After 30 days of dose administration, the mice were anesthetized, and dissected to harvest ovaries and in petri dishes containing 0.9% saline solution. After extraction, one ovary from each dose group was placed in Bouin's fixative. Ovaries were chemically treated for histological examination and dehydrated in different concentration of alcohols. Afterwards the wax embedded tissues were cut in thin sections using microtome. The wax ribbons containing tissue sections were mounted to the clean slides coated with Mayer glue. For staining purpose Harris-hematoxylin and Eosin stains were used. Selected histological slides were macro-photographed for observation and study.

Results

In control group, cortex of ovary showed normal ovarian follicles by having granulosa cells, primary oocytes and zona pellucida. Most of the follicles were round shaped. Ovarian surface epithelium and theca follicular were arranged properly. (Figure 1 A, B).

While in dose group HFCS I, histological deformities were clearly observed. It showed jumbled shape follicles, oocytes had no contact with the granulosa cells, and primordial follicles were denatured. Cysts were observed on the surface of ovaries. This group also showed low number of follicles in certain sections of treated ovaries. Fatty tissues were also apparent around the ovary (Figure 1C, D). On the contrary, in recovery dose group HFCSII the section seemed to be normal. An increase in number of Follicles was observed, with oocytes acquiring normal shape as compared to the HFCSI group. Granulosa cells, primordial follicle and zona pellucida also showed the signs of regeneration. There was no cyst development in this group which might be due to the meliorative role of ALA (Figure 1E).

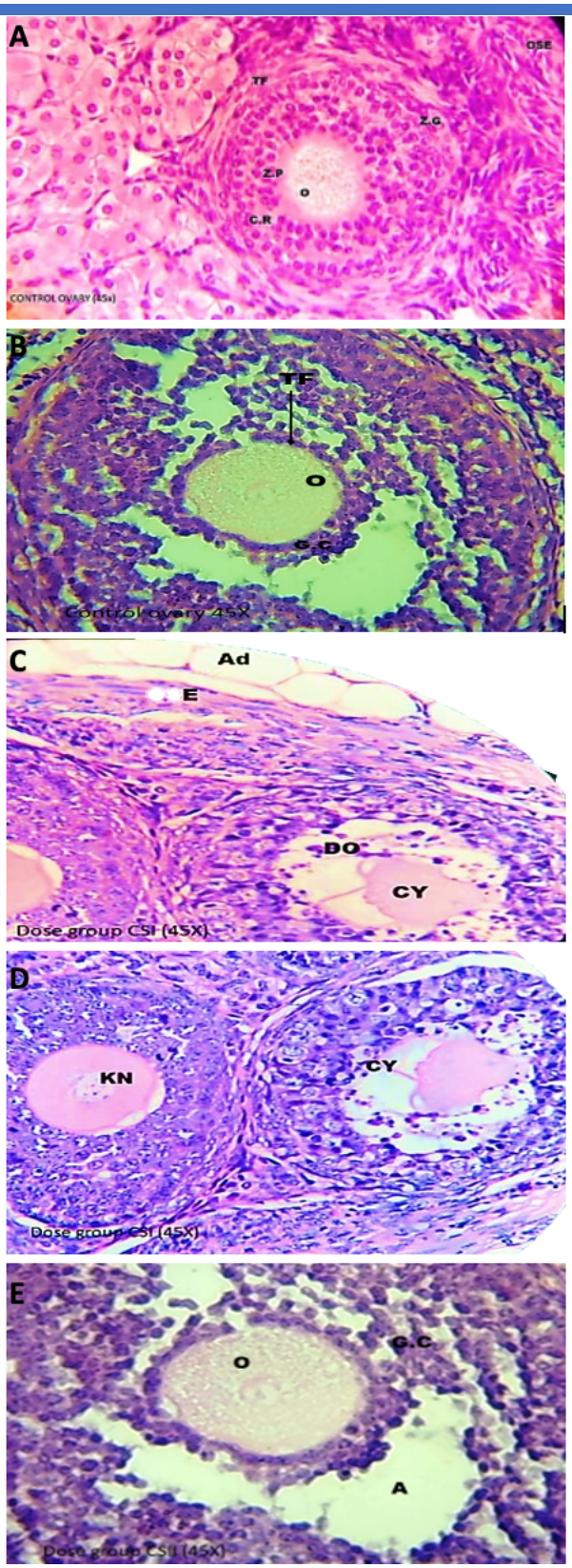

Figure 1: Macro-photographs showing Histology of Ovary of Eight-Week-Old Albino Mice. Control-Group (45×) (A, B), O= Oocyte Z.P= Zona Pellucida C.R= Corona Radiata TF= Theca Folliculi Z.G= Zona Granullosa OSE=Ovarian Surface Epithelium G.C: Granulosa Cells C&D Dose- Group HFCSI (25% HFCS); OSE= Ovarian surface epithelium was not in proper arrangement. CY= Follicular cyst Ad= Adipose tissue DO= Degenerated oocytes due to cyst formation KN= Karyorrhexis of the nucleus of follicle cells (C, D); Dose- group HFCSII (25%HFCS +35mg/kg BW ALA).O= Oocyte G.C= Granulosa cells A= Antrum (E).

Discussion

Artificial sweeteners like HFCS have been widely used in baking and beverage industry. It has been reported a leading cause of reproductive dysfunction as it contributes to the onset of obesity (Meyers et al., 2017). While ALA is an antioxidant rich in sulfur, being very beneficial micronutrient showed different organic and pharmacological properties. It reacts rapidly with reactive-nitrogen (RN) and reactive-oxygen (RO) species, thereby indulged in lessening the oxidative damage (Castro et al., 2019).

During histological analysis, various pathological changes in the ovaries of the HFCS treated mice was observed that included jumbled shape follicles, detached oocytes from granulosa cells, attenuated primordial follicles, abscess formation, and less count of follicles cells with presence of fatty tissues around the ovary. The protective envelope; Tunica albuginea, ovarian surface epithelium as well as primordial follicles were not properly arranged. Whereas the histological study of the mitigated group showed normal development as was observed in the control group. Another research report highlighted that carbohydrate-rich diet was the leading factor in increasing the regressed follicle numbers in the ovaries of treated rats (Nino et al., 2020).

Similarly, research revealed that a diet with high sugar caused ovarian malfunction in female rats like some serious syndromes such as polycystic ovary syndrome (PCOS). Animals fed with this diet also showed ovaries having a higher number of atretic antral follicles (degenerated follicles) as well as follicular cysts. ALA has been reported to preserve the normality of follicle cells and also promoted the development of primordial follicles (Naupas et al., 20201). This study reports that ALA improved the tissues of ovaries due to its ability to control oxidative stress.

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