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LETROZOLE SUPPRESSES HEPATIC OXIDATIVE STRESS AND AMELIORATES LIPID ACCUMULATION IN FRUCTOSE-EXPOSED WISTER RATS

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An increase in sugar intake, especially fructose or fructose-containing sweeteners, poses a serious public health challenge globally. Unlike glucose, fructose metabolism results in generation of oxidative stress, which promotes hepatic lipid accumulation and consequently increases the risk of non-alcoholic fatty liver disease (NAFLD). Chronic administration of letrozole has been previously reported to decrease lipid peroxidation and increase antioxidants but its effect on fructose-induced lipid accumulation has not been investigated. Thus, the present study sought to investigate the ameliorative effect of letrozole on hepatic oxidative stress and lipid accumulation in high fructose-taking Wister rats. After 3-week of exposure, our results reveal that fructose intake increased hepatic total cholesterol ($p< 0.01$), triglycerides ($p< 0.001$) and free fatty acid ($p< 0.001$). Similarly, fructose increased hepatic malondialdehyde (MDA) ($p< 0.001$ vs. control) and decreased catalase and superoxide dismutase activities ($p< 0.001$ and $p < 0.05$ vs. control, respectively). Furthermore, our data show that high fructose intake elevated levels of uric acid and xanthine oxidase activity in the liver ($p< 0.001$ vs. control). However, letrozole treatment attenuated the hepatic lipid accumulation, reduced MDA level, and suppressed uric acid biosynthesis in high fructose-taking rats. Conclusively, this study has demonstrated that high fructose intake induces hepatic uric acid synthesis, generating oxidative stress and promoting hepatic lipid accumulation in male Wister rats, while administration of letrozole attenuates the fructose effects. Our findings, therefore, suggest the efficacy of letrozole in attenuating hepatic lipid accumulation, hence, lowering the risk of NAFLD associated with excessive fructose intake.

Keywords: *Fructose, Letrozole, hepatic lipid, oxidative stress, NAFLD*

INTRODUCTION

Excessive calories intake is a global public health concern as it increases lipid accumulation and consequently increases the risk of metabolic syndrome[1.] The liver plays a major role in lipid metabolism, serving as a central organ that orchestrates fatty acids (FA) synthesis and coordinates their distribution to other tissues where they serve as energy source[2]. In physiological conditions,, the liver processes a large amount of FA and stores only small amounts in the form of triglycerides (TG), maintaining balance between FA acquisition and disposal[3&4]. However, abnormal protein regulation in pathological state disrupts lipid metabolism, causes excessive hepatic lipid accumulation, and consequently, hepatotoxicity and non-alcoholic fatty liver disease[5].

Non-alcoholic fatty liver disease (NAFLD) is the global commonest liver disease, affecting about 25% of the adult population[6]. Middle-East has the highest prevalence rate of NAFLD (32%), while Africa has the lowest prevalence rate (19%), but with a very high prevalence in severely obese (90%) and patients with type 2

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diabetes (76%)[6]. More so, mortality due to NAFLD is on an increase, especially in other diseased conditions such as cardiovascular disease, hepatocellular carcinoma, and liver-related events[7]. Among several factors that promote the risk of NAFLD, fructose consumption contributes significantly to the incidence and pathogenesis of NAFLD. Over-consumption of fructose exerts different toxic effects that include increased fatty acid synthesis and hepatic TG accumulation, which are both hallmarks of NAFLD[8]. More so, it has been long reported that exposure of rats to fructose-containing diet results in rapid development of fatty liver[9]. Besides, several studies have shown that fructose induces NAFLD in humans[10&11] as well as rodents[12&13].

Oxidative stress likely mediates fructose-induced hepatic lipid accumulation. This is evidenced in the study of Lanaspa *et al.*,[14] where initial rapid phosphorylation of fructose to fructose 1-phosphate by fructokinase generated uric acid, which then directly regulated hepatic lipogenesis through oxidative stress generation. Oxidative stress due to excessive formation of reactive oxygen species (ROS) depletes the endogenous antioxidants, leading to cellular injury. Interestingly, hepatocyte mitochondria and endoplasmic reticulum form the major site for ROS generation, promoting various forms of liver diseases[15].

Decreased lipid peroxidation with a concomitant increase in antioxidants has been previously reported in rats with polycystic ovary syndrome, following 14 and 21 days of letrozole administration[16]. Hence, we hypothesized that letrozole, a selective and highly potent aromatase inhibitor would attenuate hepatic oxidative stress and subsequently lower hepatic lipid accumulation in rats. This study, therefore, investigated the effect of letrozole on hepatic lipid accumulation in high fructose-taking male Wistar rats.

MATERIAL AND METHODS

Experimental animals

Twenty male Wister rats (96 – 110 g) were procured from the animal holdings, Ladoke Akintola University of Technology Ogbomosho, Oyo state, Nigeria and subsequently transferred to the animal house, Department of Zoology, University of Ilorin, Ilorin, Nigeria. They were allowed free access to standard rat chow and tap water. After 2-week acclimatization, the animals were randomly assigned to four groups (*n=5/group*) vis-à-vis: control group (received distilled water only), fructose group [received 10% fructose (w/v) in drinking water], letrozole group (received 1 mg/kg body weight, p.o. daily) and fructose + letrozole group [received a combination of 10% fructose (w/v) in drinking water and 1 mg/kg letrozole, p.o daily]. The rats were maintained under standard conditions of temperature, relative humidity, and 12-hrs day/night cycle, as treatments last for 3 weeks. Animals were handled as humanly as possible, in conformity to the regulation of the University of Ilorin Ethical Committee and in accordance with the National Institutes of Health guidelines on the care and use of laboratory animals.

Sample preparation

Rats from each group were sacrificed via cervical dislocation at the end of the experiment. Thereafter, the liver was excised, cleansed of blood and the attached connective tissues, and then mechanically homogenized in cold sucrose solution. The resulting homogenates were further processed for biochemical analyses, by an independent technologist who was not aware of the animal grouping.

Biochemical Assays

Lipid parameters

Hepatic levels of total cholesterol (TC), triglycerides (TG) and free fatty acid (FFA) were determined by a standardized colorimetric method, using an assay kit obtained from Fortress Diagnostics Limited, Antrim, UK.

Redox biomarkers

Malondialdehyde (MDA), catalase and superoxide dismutase (SOD) were determined in liver homogenates by standard spectrophotometric methods, using reagents obtained from Fortress Diagnostics Limited, Antrim, UK.

Uric acid and xanthine oxidase

The nonenzymatic colorimetric method was employed for estimating the hepatic level

of uric acid, using assay kits obtained from Oxford Biomedical Research Inc., Oxford, USA, while the hepatic activity of xanthine oxidase (XO) was assessed by the standard enzymatic colorimetric method, using reagents obtained from Fortress Diagnostics Limited, Antrim, UK.

Statistical analysis

All data were presented as mean ± SEM and analyzed by GraphPad Prism software version 8.0 (GraphPad Software, USA). One-way analysis of variance (ANOVA), followed by Tukey post-hoc, was used to compare the mean values among the groups. The significant difference was determined at 95% confidence level and $p< 0.05$, $p< 0.01$ and $p< 0.001$ were considered statistically significant.

RESULTS AND DISCUSSION

Results

Letrozole attenuates hepatic cholesterol, triglycerides and free fatty acid levels in high fructose-taking rats

As revealed in Fig. 1, fructose significantly elevated hepatic levels of total cholesterol (TC), triglycerides (TG) and free fatty acid (FFA) as compared with the control group, whereas, letrozole alone did not significantly alter hepatic TC, TG and FFA. In contrast, administration of letrozole in rats taking fructose, significantly reduced hepatic TC ($p< 0.01$), TG and FFA ($p< 0.001$, respectively) when compared with the group that received fructose only.

Effect of letrozole on hepatic malondialdehyde (MDA), catalase and superoxide dismutase (SOD) in high fructose-taking rats

To evaluate the level of lipotoxic effect of high fructose intake, we assessed hepatic MDA and antioxidant enzymes activities. High fructose exposure elevated hepatic MDA level ($p< 0.001$) and decreased the activities of the antioxidant enzymes, catalase ($p< 0.001$) and SOD ($p< 0.05$) when compared with the control group (Fig. 2). In contrast, letrozole alone lowered MDA ($p< 0.05$), increased catalase activity ($p< 0.001$) but suppressed SOD activity. Whereas, administration of letrozole in fructose-taking rats reduced hepatic MDA level to normal and slightly increased the SOD activity. However, letrozole treatment failed to attenuate the fructose-induced decrease in catalase activity.

Letrozole lowers hepatic uric acid level and decreases the activity of xanthine oxidase (XO) in fructose-taking rats

As presented in Fig. 3, there was a significant increase ($p< 0.001$) in the hepatic level of uric acid as well as hepatic XO activity when compared with the control rats, while letrozole alone did not significantly alter uric acid and XO activity levels ($p> 0.05$). In contrast, administration of letrozole in rats taking fructose lowered the hepatic levels of uric acid and XO activity to normal levels.

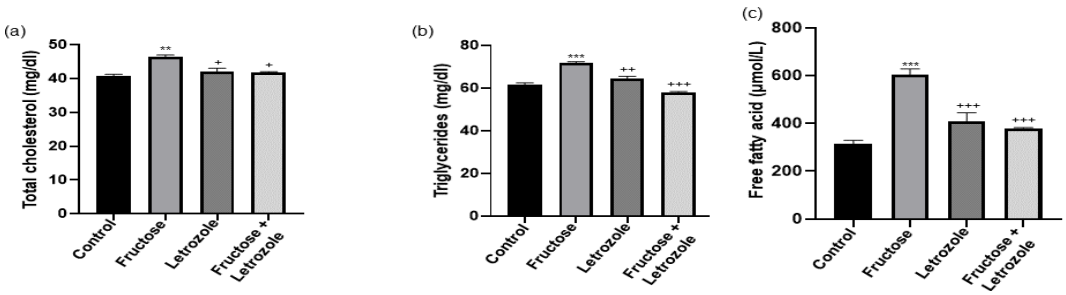

Fig. 1: Effect of Fructose (10%) w/v, Letrozole, (1mg/kg body wt), and Fructose (10%) w/v +letrozole 1mg/kg on hepatic (a) total cholesterol (TC), (b) triglycerides (TG) and (c) free fatty acid (FFA) in male Wistar rats. Fructose treatment elevated hepatic TC, TG and FFA, whereas letrozole administration attenuated fructose-induced elevation of hepatic TC, TG and FFA. Data were expressed as mean ± SEM. n = 3. Data were analyzed by one-way ANOVA followed by the Tukey post hoc test. (**$p< 0.01$ vs control; ***$p< 0.001$ vs control; +$p< 0.05$ vs fructose; ++$p< 0.01$ vs fructose; +++$p<0.001$ vs fructose).

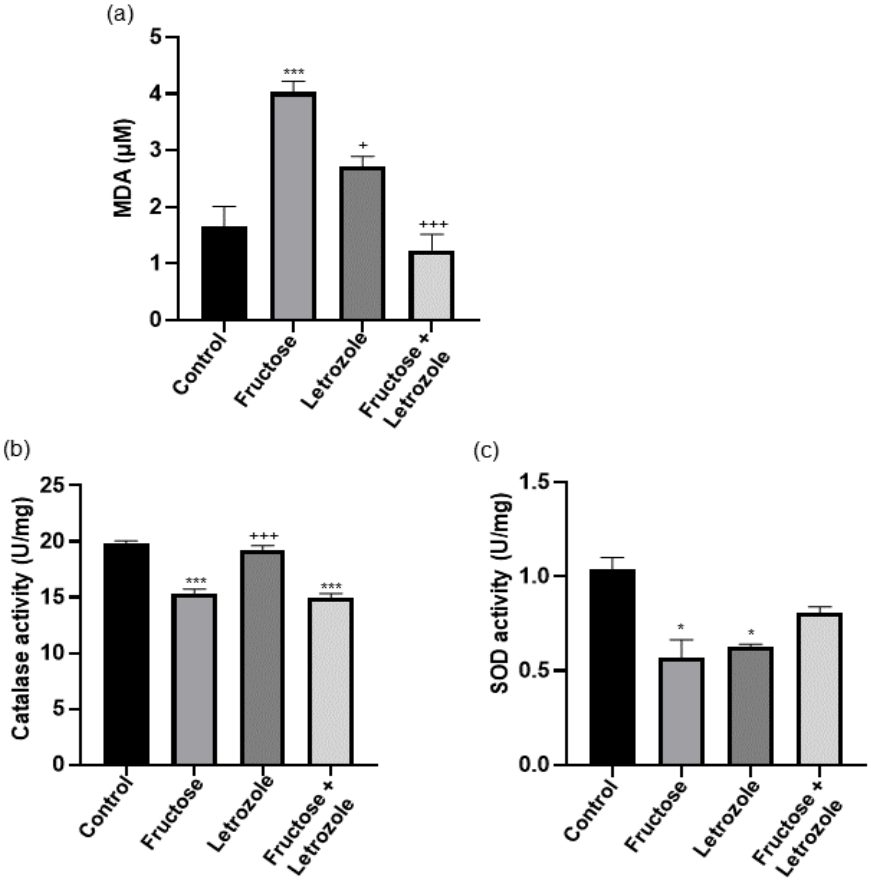

Fig. 2: Effect of Fructose (10%) w/v, Letrozole, (1mg/kg body wt), and Fructose (10%) w/v +letrozole 1mg/kg on hepatic (a) malondialdehyde (MDA), (b) catalase activity and (c) superoxide dismutase activity in male Wistar rats. Fructose but not letrozole elevated hepatic MDA and decreased catalase activity, while both fructose and letrozole individually reduced SOD activity. Letrozole administration attenuated fructose-induced elevation of hepatic MDA and slightly elevated SOD activity but failed to restore catalase activity. Data were expressed as mean ± SEM. n = 3. Data were analyzed by one-way ANOVA followed by the Tukey post hoc test. (*p< 0.05 vs control; ***p< 0.001 vs control; +p< 0.05 vs fructose; +++p<0.001 vs fructose).

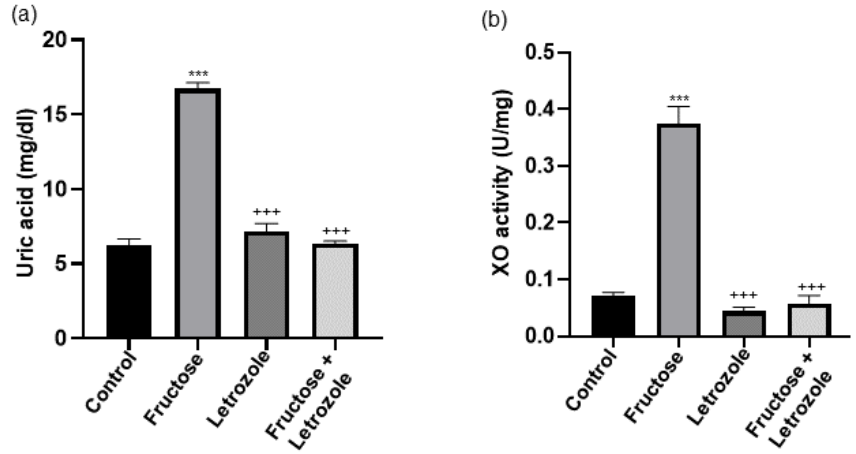

Fig. 3: Effect of Fructose (10%) w/v, Letrozole, (1mg/kg body wt), and Fructose (10%) w/v +letrozole 1mg/kg on hepatic (a) uric acid, and (b) xanthine oxidase (XO) activity in male Wistar rats. Fructose but not letrozole elevated hepatic levels of uric acid and XO activity, while letrozole treatment brought uric acid and XO activity, while letrozole treatment brought uric acid and XO activity to normal. Data were expressed as mean ± SEM. n = 3. Data were analyzed by one-way ANOVA followed by the Tukey post hoc test. (***p< 0.001 vs control; +++p<0.001 vs fructose).

Discussion

The present study demonstrated that high fructose intake elevates hepatic uric acid formation, inducing oxidative stress that consequentially results in hepatic lipid accumulation in male Wister rats. Furthermore, we showed that letrozole attenuates hepatic uric acid synthesis, mitigates oxidative stress, and prevents lipid accumulation in the liver of the fructose-taking rats. Our findings that show increased hepatic levels of TC, TG and FFA are in support of previous studies in human[17] and rodents[18&19] that have reported lipid accumulation in the liver, following high fructose consumption. Increased hepatic level of FFA in rats taking fructose alone may indicate that excessive intake of fructose increases FFA delivery from adipose tissues to the liver and/or enhances *de novo* lipogenesis, which leads to TG formation and accumulation in the liver[20]. When fructose is absorbed by the hepatocytes, trioses-phosphate disposal pathways are activated, increasing de novo synthesis and secretion of TG[21]. Excessive accumulation of TG in hepatocytes is a hallmark of NAFLD[4], thus, our study further implicates high fructose intake as a risk factor for NAFLD. Meanwhile, administration of letrozole attenuated fructose-induced hepatic lipid accumulation, suggesting the efficacy of letrozole in protecting against liver lipotoxicity and the risk of NAFLD.

Malondialdehyde (MDA), produced as an end product of lipid peroxidation of polyunsaturated fatty acids, is a widely accepted biomarker of oxidative stress[22]. It is highly reactive, penetrating tissues easily and generating ROS that subsequently modify tissue structure and function[23]. In this study, we observed that a 3-week intake of fructose in drinking water elevated hepatic MDA and suppressed the activities of first-line defensive antioxidants (catalase and SOD),), indicative of oxidative stress generation. This finding is in consistence with previous studies[24&25] that reported increased markers of oxidative stress in rats after 3 weeks of fructose administration in drinking water. Liver injury of different origins has been linked with the generation of oxidative stress[15]. Therefore, the observed hepatic lipid accumulation in fructose-taking rats may be due to ROS formation, which then promoted oxidative stress. Letrozole treatment reduced hepatic MDA level and relatively increased SOD activity. This may suggest that the lowering effect of letrozole on hepatic lipid accumulation is in part due to its potency to mitigate oxidative stress.

Unlike glucose, fructose metabolism is characterized by uric acid formation[21]. Notably, excess uric acid has been shown to induce oxidative stress and lipid accumulation, hence an association between elevated uric acid level and NAFLD[14&26]. More so, a previous study has reported the efficacy of uric acid inhibition in preventing hepatic lipid accumulation[27]. In this study, we show that high levels of hepatic lipid accumulation and oxidative stress were accompanied by elevated hepatic uric acid in rats exposed to high fructose intake. The observed elevated level of hepatic uric acid may be due to increased *de novo* synthesis, as evidenced by the concomitant increase in hepatic XO activity. XO converts hypoxanthine to xanthine, and then to uric acid, with subsequent formation of ROS such as superoxide anion and hydrogen peroxide. Our study, therefore, suggests that formation of uric acid by XO mediates fructose-induced hepatic lipid accumulation via lipid peroxidation. These findings corroborate the previous study of Nishikawa *et al.,* [27] that had earlier shown the pathophysiological importance of hepatic levels of uric acid and XO activity in the pathogenesis of NAFLD, instead of plasma uric acid levels. Our findings reveal that letrozole lowered hepatic XO activity and uric acid levels in high fructose-taking rats. This suggests that letrozole alleviated fructose-induced hepatic lipid accumulation by directly reducing lipid peroxidation via inhibition of hepatic uric acid synthesis, rather than by improving antioxidants.

Conclusions

The present study has demonstrated that high fructose intake induces hepatic uric acid synthesis, generates oxidative stress, and promotes lipid accumulation in rats, while administration of letrozole attenuates the fructose effects. Our findings, therefore, suggest the potential of letrozole to attenuate hepatic lipid accumulation and lower the risk of NAFLD, associated with excessive fructose intake.

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نشرة العلوم الصيدلية
جامعة أسيوط

BULL. PHARM. SCI. Assiut Univ.

عقار ليتروزول يقلل الإجهاد التأكسدي الكبدي ويخفف من تراكم الدهون في جرذان ويستر المعرضة للفركتوز

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تشكل زيادة تناول السكر ، وخاصة الفركتوز أو المحليات المحتوية على الفركتوز ، تحديًا خطيرًا للصحة العامة على مستوى العالم. على عكس الجلوكوز ، يؤدي استقلاب الفركتوز إلى توليد الإجهاد التأكسدي ، الذي يعزز تراكم الدهون في الكبد وبالتالي يزيد من خطر الإصابة بمرض الكبد الدهني غير الكحولي (NAFLD). سجل سابقًا أن الاستخدام المزمن لليتروزول يقلل من بيروكسيد الدهون ويزيد من مضادات الأكسدة ولكن لم يتم التحقيق في تأثيره على تراكم الدهون الناجم عن الفركتوز. وبالتالي ، سعت الدراسة الحالية إلى التحقيق في التأثير التحسني لليتروزول على الإجهاد التأكسدي الكبدي وتراكم الدهون في فئران الوستر التي تحتوي على نسبة عالية من الفركتوز. بعد ٣ أسابيع من التعرض ، كشفت نتائجنا أن تناول الفركتوز زاد من الكوليسترول الكلي في الكبد ($p < ٠.٠٠١$) ، والدهون الثلاثية ($p < ٠.٠٠٠١$) والأحماض الدهنية الحرة ($p < ٠.٠٠٠١$). وبالمثل ، زاد الفركتوز من مالونديالديهايد الكبد (MDA) ($P < ٠.٠٠٠١$ مقابل مجموعة التحكم) وانخفض أنشطة ديسموتاز الكاتلاز وفائق الأكسيد ($P < ٠.٠٠٠١$ و $P < ٠.٠٥$ ، على التوالي مقابل مجموعة التحكم). علاوة على ذلك ، تظهر نتائجنا أن تناول الفركتوز المرتفع يزيد من مستويات حمض اليوريك ونشاط أوكسيديز الزانثين في الكبد ($P < ٠.٠٠٠١$ مقابل التحكم). ومع ذلك ، خفف علاج ليتروزول من مستوى الدهون في الكبد ، وخفض مستوى MDA وقمع التخليق الحيوي لحمض البوليك في الفئران التي تتناول الفركتوز.

بشكل قاطع ، أثبتت هذه الدراسة أن تناول الفركتوز العالي يؤدي إلى تخليق حمض اليوريك الكبدي ، وتوليد الإجهاد التأكسدي وتعزيز تراكم الدهون الكبدية في ذكور الجرذان الوستر ، في حين أن إعطاء ليتروزول يخفف من تأثيرات الفركتوز. لذلك ، تشير النتائج التي توصلنا إليها إلى فعالية ليتروزول في تخفيف تراكم الدهون في الكبد ، وبالتالي تقليل مخاطر NAFLD بعد تناول الفركتوز العالي.