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ORIGINAL ARTICLE

Alagebrium and Spironolactone Ameliorate Dietary Induced Metabolic Syndrome in Male Wister Rats

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Abstract

Background: Metabolic syndrome (MS) is associated with chronic hyperglycemia, which leads to formation of advanced glycation end products (AGEs) that involved in the disease pathogenesis. MS is also accompanied by mineralocorticoid receptor (MR) activation, which has deleterious metabolic effects. The present study was designed to compare the effect of alagebrium (ALA), standard AGEs cross link breaker, and spironolactone (SPL), MR antagonist, on MS induced by high carbohydrate and high fat diet (HCFD).

Methods: 32 rats divided into: normal control group (8 rats) fed standard diet, and MS group (24 rats) received HCFD for 10 weeks, after which they were divided into 3 equal subgroups and continued on HCFD for further 6 weeks and served as: MS control, ALA treated (10 mg/kg/day), and SPL treated (50 mg/kg/day). Studied parameters were mean arterial blood pressure (MABP), body weight (BW), fasting blood glucose (FBG), serum insulin, HbA1c, plasma lipids, liver enzymes, oxidative stress & inflammatory markers, and liver histopathology.

Results: HCFD produced MS as evidenced by significant deleterious effect on all parameters, and treatment with either ALA or SPL produced significant favorable effect on these parameters. In comparison, ALA was superior in decreasing FBG, HbA1c, serum TGs, ALT, GGT and hepatic inflammatory markers. SPL was superior in decreasing MABP, BW, serum insulin, LDL, and antioxidant status.

Conclusion: ALA and SPL showed protective effect on dietary induced MS, both could be promising in management of the disease.

Keywords: Alagebrium, Spironolactone, metabolic syndrome, HCFD.

INTRODUCTION

Metabolic syndrome (MS) is a rapidly growing clinical threat, characterized by abdominal obesity, hyperglycemia, hypertension, hypertriglyceridemia, low HDL and insulin resistance [1]. MS enhances the risk of atherosclerotic cardiovascular disease, type-2 DM, and nonalcoholic fatty liver disease (NAFLD) [2]. Prolonged hyperglycemia leads to advanced glycation end products (AGEs) formation by connection of a sugar non-enzymatically with an amino group of proteins [3]. AGEs damage cells by different mechanisms: intracellular glycation of proteins, binding of circulating AGEs to cellular receptors with signal transduction

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cascade activation, extracellular accumulation of AGEs leading to cross-linking and diminished vessels compliance [4].

Alagebrium (ALA) is a standard breaker of AGEs cross-linkage, leads to improvement of the arterial compliance in patients with vascular stiffening [5]. In addition, it has renoprotective effect in diabetes due its action on AGEs [6].

Renin-angiotensin-aldosterone system activation serves as important pathway in MS development [7]. Insulin resistance is associated with increased angiotensin-II and aldosterone production as well as mineralocorticoid receptor (MR) activation [8]. Spironolactone (SPL), a non-selective MR antagonist was reported to improve glucose and lipid metabolism [9].

Up till now there's no specific treatment for MS and, new alternatives are required [7]. The aim of the present study is to investigate and compare the possible effects of alagebrium and spironolactone on hazardous sequels of MS in Wistar rats.

MATERIALS AND METHODS

Drugs:

Alagebrium Chloride (CHEMOS GmbH & Co., Werner-von-Siemens-Str.3, D-93128-Regenstauf, Germany**),** *Spironolactone* powder (Kahira Pharm. & CHEM. IND. CO. Egypt).

Animals:

32 male Wister rats weighing 180-200 gm/each were used in the present study; they were purchased from animal unit of Faculty of Veterinary Medicine, Zagazig University, Egypt. The study protocol was approved by the ethical committee at Zagazig University (ZU-IRB No.3521), which is consistent with the National Institutes of Health guides for care and use of laboratory animals (NIH publications) "No.8023, revised 1996". Rats were housed in standard conditions on standard diet and water was allowed *ad labitum* in Zagazig Faculty of Medicine Animal House, and left for a week before starting the study for acclimatization.

Experimental design and drug treatment:

The rats were randomized into initial two groups: **Normal control group (NCG)** [n=8] received standard chow diet and distilled water for 16 weeks. **Metabolic syndrome groups [**n=24**]** rats were maintained on high carbohydrate and high fat diet (HCFD) composed of condensed milk (39.5%), beef tallow (20%), and fructose (17.5%), together with 25% fructose in drinking water for 16 weeks [10]**.** After ten weeks of HCFD feeding, the blood glucose level was measured by Rightest GS300 Test Strip (BIONIME-Corporation, Taiwan), the blood pressure was measured by 8-Channel Non-Invasive Blood Pressure Monitor [NIBP-8] (Columbus Instruments, USA) and body weights were measured by digital weight scale to confirm the induction of MS as described by **Wong et al** [11]. Rats with established MS were continued on HCFD for further six weeks, and further divided into 3 subgroups (8 rats each): **MS control group (MSCG):** received distilled water (0.3ml/100g/day), alagebrium chloride (**ALA) group:** received 10 mg/kg dissolved in distilled water[5], spironolactone **(SPL) group**: received 50 mg/kg dissolved in 1% ethanol [12]. Drugs were given once daily by oral gavage in a volume not exceed 0.3 ml/100 gm for 6 weeks. At the end of the study rats' body weights were measured, MABP was measured by (Power Lab (4/35) data acquisition system, Australia), blood samples were obtained from the aortic cannula then rat's euthanization was done by decapitation.

Blood and tissue sampling

Blood samples were separated by centrifugation at 3000 rpm for 10 minutes to get clear sera. Livers were excised and rinsed thoroughly with saline, then each organ was divided into two equal parts, one part was preserved in formalin 10% for histopathological examination and the second part was frozed at -80°c by liquid nitrogen and stored till homogenization.

Glucose Metabolism Determinations

FBG was done by glucose-oxidase enzymatic commercial kit (Spinreact SAU, Sant Esteve de Bas, Spain), serum insulin was done by an ultrasensitive insulin enzyme immunoassay commercial kit (Mercodia AB, Uppsala, Sweden), and glycated hemoglobin (HbA1c) by Colorimetric Spectrophotometry method (Crystal Chem, USA).

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Assay of serum LDL, HDL and triglycerides

Quantitative Colorimetric Determination method was used to estimate serum LDL, HDL and triglycerides levels (Elabscience, 14780 Memorial Drive, Suite 216, Houston, Texas 77079, USA).

Assay of serum ALT and γ-GGT activities:

Serum ALT and γ-GGT activities were measured using colorimetric, endpoint method (TECO Diagnostics, USA)

Assay of hepatic Malondialdehyde (MDA) and tumor necrosis factor alpha (TNF-α):

MDA in liver tissue extract was measured by using Quantitative Sandwich ELISA Kit (Life span Bioscience, USA), and TNF-α activity was evaluated by quantitative enzyme immunoassay technique (CUSABIO, USA)

Liver histological studies:

Liver specimens were fixed in 10% formalin; then embedded in paraffin wax, sections were cut at 4μm thickness and stained using Hematoxlin and Eosin and then examined under the light microscopy as described by **Rahn, (2001)** method [13].

Statistical analysis:

Data were expressed as means±S.E, statistical difference between groups was made using one way analysis of variances (one-way ANOVA, and separation of means by LSD test), using the SPSS Software (version-14), SPSS Inc., Chicago, USA. The differences were considered significant when $p< 0.05$.

RESULTS

Effect of ALA and SPL on body weight (BW) and mean arterial blood pressure (MABP):

The BW in MSCG was 403.4±5.116 gm, which was significantly (P>0.05%) higher than that of NCG (343.3±4.361gm). In ALA group BW was 390.3±4.043gm, that wasn't significantly different from MSCG. In SPL group BW was 372.6±6.204gm, which was significantly ($p<0.05$) lower than that of both MSCG and ALA group **(table 1)**.

The MABP in MSCG was 114.5±1.558mm/Hg, which was significantly ($p<0.05$) higher than that of NCG (88.2±1.772mm/Hg). In ALA group MABP was 104.2±0.934mm/Hg, which was significantly ($p<0.05$) lower than that in MSCG. In SPL group MABP was 91.9±1.976mm/Hg, which was significantly ($p<0.05$) lower in comparison to either MSCG or ALA groups **(table 1).**

Effect of ALA and SPL on the FBG, HbA1c, and serum insulin:

The FBG in MSCG was 162.6±2.061mg/dl, that was significantly ($p<0.05$) higher than NCG (94.6±2.162mg/dl). In ALA group FBG was 130±1.006mg/dl, which was significantly ($p<0.05$) lower compared to MSCG. In SPL group FBG was 142.5±1.803mg/dl, which was significantly ($p<0.05$) lower than that of MSCG, in contrast, it was significantly ($p<0.05$) higher than that of ALA group **(figure 1A)**.

The HbA_1c in MSCG was 7.6±0.174%, which was significantly ($p<0.05$) higher than that of NCG (3.8±0.224%). In ALA group, HbA_1c was 4.2±0.283%, which was significantly ($p<0.05$) lower compared to MSCG. In SPL group HbA_1c level was 7.1±0.227%, which wasn't significantly different in comparison to MSCG **(figure 1B)**.

Serum insulin levels in MSCG was 13.2±0.409μIU/ml which was significantly ($p<0.05$) higher than that of NCG (2.4±0.073μIU/ml). In ALA group serum insulin was 7.4±0.178μIU/ml which was significantly ($p<0.05$) lower than that of MSCG. In SPL group serum insulin was 5.9±0.343μIU/ml which was significantly ($p<0.05$) lower than that in either MSCG, or ALA groups **(figure 1C)**.

Effect of ALA and SPL on lipid profile (LDL, HDL and TGs):

Serum LDL and TGs in MSCG were 61.5±0.731 and 83.7±1.176mg/dl respectively which were significantly ($p<0.05$) higher compared to NCG (19.2±0.441 and 34.6±0.545 mg/dl). In ALA group LDL and TGs were 49.2±0.875 and 64.5±1.510mg/dl respectively which were significantly ($p<0.05$) lower compared to MSCG. In SPL group LDL and TGs were 43.4±1.132 and 77.4±2.026mg/dl respectively. Although, LDL was significantly ($p<0.05$) lower in SPL group compared to both MSCG, and ALA groups; serum TGs was only significantly ($p<0.05$) higher in SPL group compared to

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ALA group, with no significant difference between SPL group and MSCG **(table 2)**.

Serum HDL in MSCG was 22.8±0.412mg/dl, that was significantly (p<0.05) lower than NCG (33.5±0.801mg/dl). In ALA group HDL was 25.1±0.566mg/dl which was not significantly different from that in MSCG. In SPL group HDL was 28.2±1.264mg/dl which was significantly (p<0.05) higher than that in both MSCG, and ALA treated group **(table 2)**.

Effect of ALA and SPL on serum liver enzymes:

Serum ALT and γ-GGT in MSCG were 84.6±1.832 U/L and 65.8±1.677 MU/L respectively, which were significantly (p<0.05) higher compared to NCG (31±0.802U/L and 12.3±0.619MU/L respectively). In ALA group serum ALT and γ-GGT were 54.8±1.684U/L and 41.7±0.818 MU/L respectively, which were significantly (p<0.05) lower than those in MSCG. In SPL group serum ALT and γ-GGT levels were 69.3±1.68U/L and 39.2±1.125MU/L respectively. These values were significantly (p<0.05) lower compared to MSCG. Although, ALT was significantly (p<0.05) higher in SPL group compared to ALA group; serum γ-GGT was not significantly different between each other's **(table 2)**.

Effect of ALA and SPL on hepatic MDA and TNF-α:

Hepatic MDA in MSCG was 10.8±0.441ng/gm tissue which was significantly (p<0.05) higher compared to NCG (2.1±0.069ng/gm tissue). In ALA group MDA was 7.2±0.236 ng/gm, which was significantly (p<0.05) lower compared to that in MSCG. In SPL group MDA was 5.8±0.256 ng/gm tissue, which was significantly (p<0.05) lower compared to those in MSCG and ALA groups **(table 3)**.

Hepatic TNF-α in MSCG was 27.3±0.818pg/gm tissue, which was significantly (p<0.05) higher compared to NCG (3.8±0.238 pg/gm tissue). In ALA group TNF-α was 17.4±0.555pg/gm which was significantly (p<0.05) lower than MSCG. In SPL group TNF-α was 20.7±1.208 pg/gm tissue, which was significantly (p<0.05) lower than MSCG, in contrast, it was significantly (p<0.05) higher than that of ALA treated group **(table 3)**.

Histopathology:

Liver sections of MSCG showed marked steatotic changes and ballooning with marked interlobular inflammation compared to NCG liver sections. In ALA group liver sections showed moderate improvement in the fatty liver changes regarding steatosis, hepatocyte ballooning without interlobular inflammation. In SPL group there was mild improvement of the hepatocytes fatty changes regarding steatosis and ballooning with moderate inflammatory cells aggregations compared to liver sections of MSCG **(figure 2)**.

Table (1): Effect of administration of single daily oral dose of 10 mg/kg alagebrium and 50 mg/kg spironolactone for 6 weeks on body weight and mean arterial blood in male wistar rats with metabolic syndrome

Parameter / Groups(n=8)	BW (gm)	MABP (mm/Hg)
NC group	**343.3±4.361** ^{A}	**88.2± 1.772** ^{A}
MS control group	**403.4±5.116** ^{B}	**114.5±1.558** ^{B}
ALA group	**390.3±4.043** ^{B}	**104.2±0.934** ^{C}
SPL group	**372.6±6.204** ^{C}	**91.9± 1.976** ^{D}

- Values represent mean ± SE, values in the same column with different superscript capital letters are significantly (p<0.05) different.
- **NC**: normal control group, **MS**: metabolic syndrome control group, **ALA:** alagebrium treated group, **SPL**: spironolactone treated group, **BW**: body weight, **MABP:** mean arterial blood pressure, **gm**: gram, **n**: number of rats in each group.

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Table (2): Effect of administration of single daily oral dose of 10 mg/kg alagebrium and 50 mg/kg spironolactone for 6 weeks on serum lipid profile and serum liver enzymes in male Wistar rats with metabolic syndrome

parameter / Group (n=8)	serum lipid profile			serum liver enzymes	
	LDL (mg/dl)	**HDL** (mg/dl)	**TGs** (mg/dl)	**ALT** (U/L)	**GGT**(MU/L)
NC group	**19.2±0.441^{A}**	**33.5±0.801^{A}**	**34.6±0.545^{A}**	**31±0.802^{A}**	**12.3±0.619^{A}**
MS control group	**61.5±0.731^{B}**	**22.8±0.412^{B}**	**83.7±1.176^{B}**	**84.6±1.832^{B}**	**65.8±1.677^{B}**
ALA group	**49.2±0.875^{C}**	**25.1±0.566^{B}**	**64.5±1.510^{C}**	**54.8±1.684^{C}**	**41.7±0.818^{C}**
SPL group	**43.4±1.132^{D}**	**28.2±1.264^{C}**	**77.4±2.026^{B}**	**69.3±1.68^{D}**	**39.2±1.125^{C}**

- Values represent mean ± SE, values in the same column with different superscript capital letters are significantly ($p<0.05$) different.
- **NC**: normal control group, **MS**: metabolic syndrome control group, **ALA:** alagebrium treated group, **SPL**: spironolactone treated group, **LDL**: Low density lipoprotein, **HDL:** high density lipoprotein, **TGs**: triglycerides, **ALT:** alanine aminotransferase, **GGT:** gamma glutayl transferase**, n**: number of rats in each group).

Table (3): Effect of administration of single daily oral dose of 10 mg/kg alagebrium and 50 mg/kg spironolactone for 6 weeks on liver tissue extracts oxidative stress parameter MDA and inflammatory marker TNF-α in male Wistar rats with metabolic syndrome

parameter / Group (n=8)	MDA (ng /gm tissue)	TNF-α (Pg/ gm tissue)
NC group	2.1±0.069^{A}	3.8±0.238^{A}
MS control group	10.8±0.441^{B}	27.2±0.818^{B}
ALA group	7.2±0.236^{C}	17.4±0.555^{C}
SPL group	5.8±0.256^{D}	20.7±1.208^{D}

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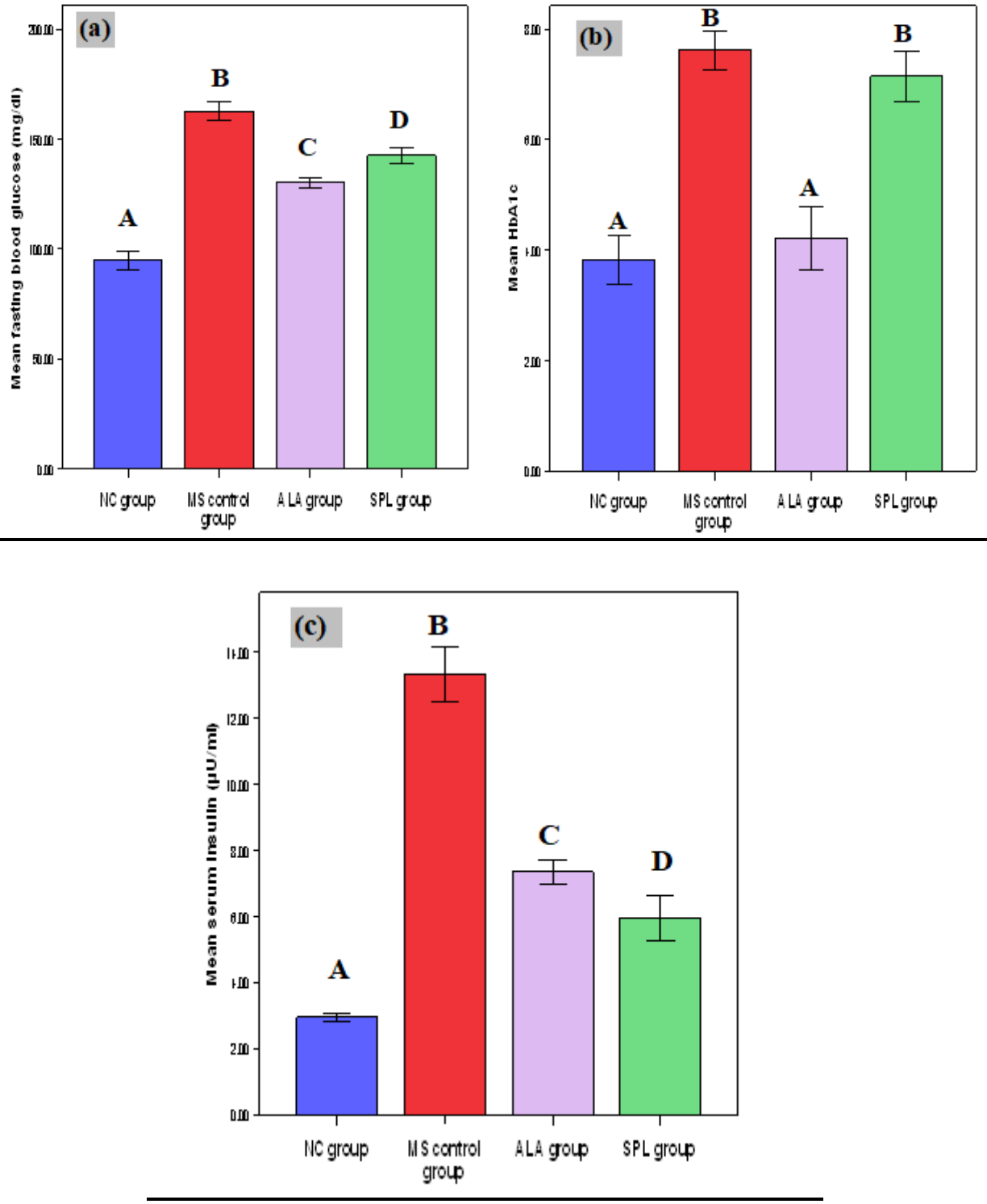

Figure (1): Effect of administration of single daily oral dose of 10 mg/kg alagebrium and 50 mg/kg spironolactone for 6 weeks on (a) fasting blood glucose (mg/dl) (b) glycated hemoglobin level HbA1c (%) (c) Serum insulin levels (µU/ml)
(Different capital letters are significantly (P<0.05) different, **NC**: normal control group, **MS**: metabolic syndrome control group, **ALA:** alagebrium treated group, **SPL:** spironolactone treated group, **HbA1c**: glycated hemoglobin level)

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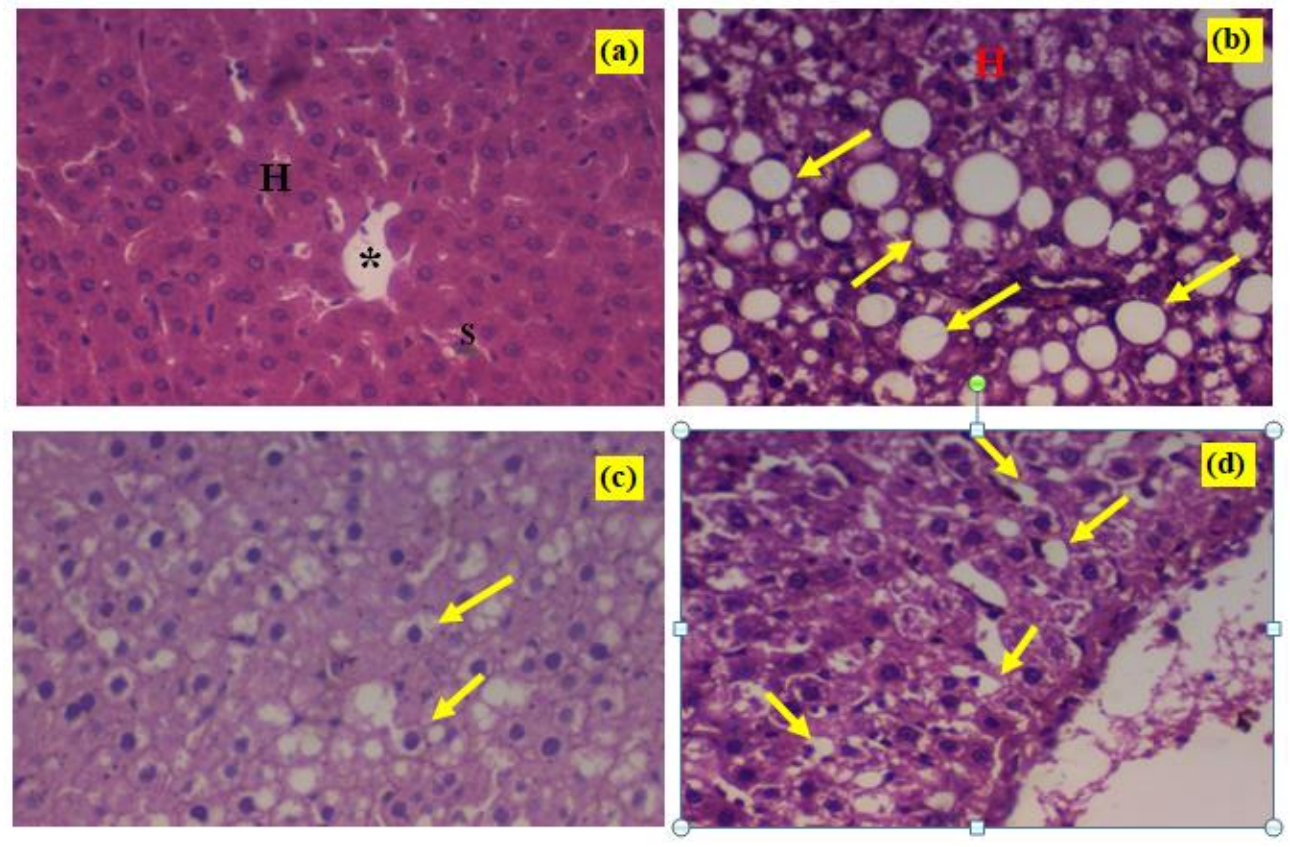

Figure (2): Effect of ALA and SPL treatment on hepatic histopathological sections (a) normal control group (NC) showing classic hepatic lobule-containing central vein (*) and radiating cords of hepatocytes (H) with central nuclei and abundant eosinophilic cytoplasm. The narrow blood sinusoids (s) lies in between the hepatocytes (b) liver section of MS control group exposed to HCFD showing severe fatty changes of hepatocytes with vaculated cytoplasm (yellow arrows) and other hepatocytes appeared with darkly stained nuclei (H) (c) liver section of alagebrium (ALA) treated group showing improvements of the fatty changes of the hepatocytes with some vaculated hepatocyte cytoplasm (yellow arrows) (d) liver section of spironolactone (SPL) treated group showing mild improvement of fatty changes of the hepatocytes as regarding steatotic changes and ballooning (Photomicrographs H&E ×400)

- values represent mean ± SE, values in the same column with different superscript capital letters are significantly ($p<0.05$) different
- **NC**: normal control group, **MS**: metabolic syndrome control group, **ALA:** alagebrium treated group, **SPL**: spironolactone treated group, **MDA**: malondialdehyde, **TNF-α:** tumor necrosis factor alpha, **n**: number of rats in each group).

DISCUSSION

The current study demonstrated that ALA and SPL given to rats with induced MS improved the disturbed lipid profile; lowered serum liver enzymes, reduced hepatic TNF-α production, enhanced antioxidant defense and improved liver histopathology when compared to that of MSCG.

In the present study ALA treatment produced no significant change in rats' BW; similar results were reported by **Park et al** [15] on diabetic rats**.** The present work demonstrated that, SPL treatment produced significant reduction in BW. Such finding is in agreement with **Machado et al** [16] in rats with MS. This effect was explained by **Caprio et al** [17] as being due to the decreased expression of PPAR-γ, a key transcriptional mediator of adipogenesis.

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ALA treatment significantly reduced MABP; similar finding was reported by **Zhang et al** [18] in diabetic-hypertensive rats. The author explained antihypertensive effect of ALA as being due to decrease of AGEs (that inhibit synthesis and release of NO and prostacyclin "PGI_2"), thereby restore the normal function of NO and PGI_2 by vascular endothelial cells [18].

The present study demonstrated that SPL treatment significantly reduced MABP, which agrees with **Liu et al** [19], in hypertensive-diabetic rats. The mechanism of BP lowering effect of SPL include the action of the drug in both the central and peripheral mineralocorticoid receptors (MR) as both are involved in hypertension[20].

The present work demonstrated that ALA significantly reduced FBG, serum insulin and HbA1c levels. These results are in line with **Harcourt et al** [21] obese mice.

SPL treatment reduced the FBG and serum insulin these results are in line with **Wada et al** [9] in mice with MS. The author explained the mechanism of this effect as being due to both SPL induced enhanced expression of phosphor-enol-pyruvate-carboxy-kinase, a hepatic gene for gluconeogenesis, and the SPL blocking action on aldosterone receptors [17]. However, SPL didn't change HbA1c levels, similar finding were observed **Mayyas et al** [23]. On the contrary, **Griffin et al** [24] confirmed the role of the renin-angiotensin-aldosterone system activation and poor glycemic control evidenced by high HbA1c in diabetes.

ALA treatment significantly reduced serum LDL and TGs with no effect on HDL. These results are parallel to that of **Watson et al** [25] in diabetic mice, who attributed this to the ALA induced reduction of advanced lipoxidation end products (ALEs) by breaking of their cross links, in analogy to AGEs.

SPL treatment reduced LDL and HDL serum levels with no effect on TGs. Similar results were obtained by **Long et al** [8] in MS rats, who attributed these results to the inhibited activation of MR by SPL which ameliorate the impaired lipid metabolism induced by MR activation.

The present study demonstrated that treatment with ALA significantly reduced liver enzymes ALT and GGT. These results agreed with that of **Fernando et al** [26] in mice with non-alcoholic steatohepatitis, and attributing these findings to the inhibition the activated AGE/RAGE pathway.

SPL treated group demonstrated significant reduction in both AST and ALT serum liver enzymes. These results are in accordance with **Pérez et al** [27] in rats treated by SPL.

Regarding the oxidative stress in the present work, ALA treatment significantly decreased hepatic MDA levels. These results are in line with **Dhar et al** [28] and attributed this effect to its scavenging action on AGEs.

Treatment with SPL in the present study resulted in significantly lower MDA levels. These findings are parallel to **Pérez et al** [27] who found that SPL improved total antioxidants activity in Wistar rats.

The present work demonstrated that ALA treatment resulted in significant lower level of hepatic TNF-α. Such finding confirms the work of **Coughlan et al** [22] in diabetic rodents, and attributed this effect to AGEs cross linkage breaking action of ALA.

ALA improved the liver histopathological features in the present study, which in agreement with the work of **Fernando et al** [26]. This effect is confirmed in the present study by ALA improvement in the liver function tests, metabolic parameters as well as to decreased TNF-α.

SPL treatment significantly decreased the liver histopathological changes, these results are in accordance with that of **Pérez et al** [27] in Wister rats and explained this effect together with decreased serum levels of AST & ALT as being due to the antioxidant activity of SPL, which was also confirmed in the present work.

Conclusion, ALA and SPL proved to be beneficial in treatment of MS evidenced by improvement of the metabolic parameters, enhancement of the anti-oxidant status and reduction of inflammatory mediators with improvement in the histopathological derangements. In comparison between both drugs, ALA was superior in decreasing FBG,

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serum TGs, serum ALT and hepatic TNF-α and mitigating the liver histopathology. However, SPL was superior in reducing BP, BW, serum insulin and LDL cholesterol, and increasing HDL cholesterol as well as improving antioxidant status.

Conflict of interest: No
Financial disclosure: No

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