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Full Length Research Paper

Nigella sativa L. oil ameliorates insulin resistance caused by dexamethasone treatment in male Wistar rats

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Dexamethasone is an anti-inflammatory glucocorticoid that may alter glucose and lipid homeostasis depending on the dose and/or duration of administration. *Nigella sativa* oil (NSO) can be used as potential modulator of intermediary glucose and lipid metabolism. Herein, the authors evaluated the dose-dependent effects of NSO (0.2 and 0.4 ml/kg body weight) supplementation on plasma glucose, insulin and triglyceride concentration in rats treated with dexamethasone (1 mg/kg body weight) for 5 days. Adult male Wistar rats (150 to 200 g) were housed and treated in the animal holding facility of the Faculty of Basic Medical Sciences, University of Ilorin, Ilorin. Animals were randomly distributed into 4 groups: control (normal saline, 1 ml/kg), DEX (dexamethasone 1 mg/kg), DEX + NSO 0.2 ml/kg and DEX+ NSO 0.4 ml/kg. All drugs were administered intraperitoneally. To assess insulin resistance, an insulin tolerance test was performed in addition to fasting glucose and insulin measurements used in calculating the homeostatic model assessment of insulin resistance index (HOMA-IR). Insulin-induced glucose lowering was improved following NSO supplementation during the insulin tolerance test ($p<0.05$). Likewise, there was a reduction in fasting hyperinsulinemia (50%; $p<0.05$) and HOMA-IR index. Dexamethasone induced hypertriglyceridemia which was not significantly reduced following NSO supplementation. Furthermore, NSO had no significant effect on liver alanine aminotransferase enzyme activity in rats treated with dexamethasone. In conclusion, it is shown that 5 days therapy with dexamethasone can be used as a model of insulin resistance and NSO supplementation for 5 consecutive days attenuates hyperglycemia and insulin resistance induced by dexamethasone treatment.

Key word: Dexamethasone, insulin resistance, *Nigella sativa* oil.

INTRODUCTION

It is generally observed that in most diabetic patients, there is the presence of insulin resistance prior to the development of frank diabetes which is marked by beta cell failure (Martin et al., 1992). Insulin resistance defines

a relative loss or reduction in response of target cells or tissues to insulin. The primary insulin sensitive tissues are skeletal muscle, liver and adipose tissue. Insulin resistance is prevalent in both non-metabolic (hypertension) and metabolic diseases including Cushing's disease-hypercortisolism (Bonora et al., 1998). In humans, the endogenous glucocorticoid, cortisol (corticosterone in rats) plays a vital role in virtually all physiological systems particularly immune, endocrine, metabolic and cardiovascular systems. Dexamethasone is a synthetic glucocorticoid widely prescribed in the treatment of rheumatoid arthritis, asthma and certain hematological malignancies due to its anti-inflammatory and immunomodulatory properties (Cain and Cidlowski, 2015). However, glucocorticoid therapy may alter glucose and lipid metabolism when administered in high doses or for prolonged periods thus limiting its long term use. In rodent studies, administering 1 mg/kg of dexamethasone for five days induces hyperglycemia, hyperinsulinemia, insulin resistance and hyperlipidemia (Rafacho et al., 2014). However, these effects are not observed at smaller doses administered for the same duration indicating that effects are dose dependent (Rafacho et al., 2008). Animal studies have provided insights into the mechanisms by which glucocorticoids induce glucose metabolism dysregulation including expression of key gluconeogenic enzymes which leads to increased glucose production as well as reducing peripheral glucose uptake (Pasieka and Rafacho, 2016). These studies are important in identifying potential mechanisms by which the adverse effects of glucocorticoids may be ameliorated. Thus, there is a continuous need to further search for agents capable of ameliorating glucocorticoid induced metabolic side effects.

The authors have identified *Nigella sativa* also known as "black seed" as a potential agent capable of ameliorating glucocorticoid adverse metabolic effects. *N. sativa* oil (NSO) is rich in both unsaturated and saturated fats (Wajs et al., 2008).

Thymoquinone is identified as one of the most active ingredients of the plant and has been isolated from the oil (Sarwar and Latif, 2015). NSO has several pharmacological activities including antibacterial, antifungal, anti-neoplastic, neuroprotective and antihyperglycemic activities (Ahmad et al., 2013; Imam et al, 2016). NSO may play a therapeutic protective role in streptozotocin-induced model of diabetes (Kanter et al., 2004). Also, in a high fat diet model of hyperglycemia, NSO exhibited glucose lowering and insulin sensitizing effects (Alsaif, 2008). Considering the pharmacological effects of NSO in these metabolic disease models, it is possible that NSO has therapeutic effects on the adverse metabolic effects of dexamethasone.

Therefore, in this study, the authors investigated the effects of NSO on insulin tolerance, alterations in plasma lipid, and glucose and insulin concentration in male Wistar rats induced by a 5-day dexamethasone treatment. The hypothesis tested was that NSO would ameliorate the metabolic effects of dexamethasone.

MATERIALS AND METHODS

Animals, drugs and *N. sativa* oil

All experiments were conducted in conformity with guidelines approved by the Institutional Animal Care and Use Committee of the University of Ilorin and were conducted following the Guide for the care and Use of laboratory animals, 8th edition.

Forty one male Wistar rats weighing 180 to 200 g were purchased from Department of Pharmacology and Therapeutics, University of Ilorin, Ilorin animal facility. These animals were acclimatized in the animal holding facility of the Faculty of Basic Medical Sciences, University of Ilorin, Ilorin for at least one week prior to the experiments. All animals had free access to commercial sterilized standard rodent feed and tap water. They were housed under ambient temperature and 12:12 h light and dark cycle.

Pharmaceutical grade dexamethasone sodium phosphate injection (4 mg/mL) (Wuhan Grand Pharmaceutical group, Wuhan, China) and *N. sativa* oil (Baruten, 100%) were used in this study. In the first experiment, twenty six animals were randomized into 4 groups with n=7 per group except the normal control: a control group, received normal saline group (n=5), dexamethasone group, received 1 mg/kg dexamethasone, Dex + NSO 0.2, received 0.2 ml/kg NSO followed by dexamethasone and Dex+ NSO 0.4 group received 0.4 ml/kg NSO prior to dexamethasone treatment.

All animals received daily intraperitoneal administration of either normal saline or dexamethasone (1 mg/kg body weight) (Rafacho et al., 2014) for 5 consecutive days, whereas rats in the DEXNSO 0.2/0.4 received intra-peritoneal injections of *NSO* also for 5 days. NSO was administered thirty minutes prior to dexamethasone administration. All drug administrations were carried out between 8:00 and 10:30 am daily.

Animals were sacrificed on the sixth day, twenty four hours after the last dexamethasone dose by the use of intramuscular injection of ketamine/xylazine followed by cervical dislocation (American Veterinary Medical Association, 2013). Blood was collected from the heart via a cardiac puncture and immediately transferred into heparinized bottles. Blood was centrifuged at 2000 ×g for 20 min and plasma separated. Plasma was stored until biochemical analysis.

To determine effect of NSO on insulin resistance, an insulin tolerance test was performed as previously described (Woo et al., 2014; Barbosa et al., 2015). Briefly, 15 animals were randomized into 3 groups, with 5 animals per group: a normal saline group that received 1 ml/kg (0.9% NaCl), a control group receiving 1 mg/kg bodyweight of dexamethasone and a treated group receiving dexamethasone (1 mg/kg) and *N. sativa* (DEXNSO 0.4ml/kg) for 5 days. Twenty-four hours after the last dose, an insulin tolerance test was performed.

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Metabolic, hormonal and biochemical measurements

Insulin tolerance test (ITT), glucose measurement and insulin resistance

An ITT was performed as previously described (Rafacho et al., 2014). On the 6th day, after a 4 h fast, an insulin tolerance test was conducted. Fasting blood glucose was obtained from rats' tail (time 0) following which animals were administered 1 unit/kg of Insulin (Actrapid, Novo-Nordisk) intraperitoneally. Blood was thereafter collected from tail at 15, 30, 45, 60 and 90 min following insulin administration. Blood glucose was measured using a hand held glucometer (Accuchek, Roche, Germany).

Insulin resistance was assessed using the homeostatic model assessment (HOMA) for insulin resistance (Levy et al., 1998). This model uses the fasting blood glucose and insulin values to estimate insulin resistance as shown below:

$$\text{HOMA-IR} = \frac{\text{Fasting blood glucose (mg/dl)} * \text{fasting insulin (U/ml)}}{405}$$

Lipid profile measurement

Commercial kits (Agappe Diagnostics, USA) were used in determining the plasma levels of total triglyceride, low-density lipoprotein and high-density lipoprotein fractions following manufacturer's instruction. The assay exploits lipid-specific enzymatic reactions resulting in the detection and measurement of individual lipid species. The end-point collor change was measured colorimetrically using a microplate spectrophotometer (Spectromax Plus 384, Molecular devices, California).

Liver enzyme assay

To assess integrity of liver, alanine aminotransferase (ALT) was assayed according to the method of Reitman and Frankel (1957). ALT (Agappe Diagnostics) was assayed via a colorimetric assay. The assay works on the principle of kinetics of enzyme catalysis.

Plasma insulin measurement

Plasma insulin concentrations were measured with a sensitive Insulin ELISA immunoassay kit (Calbiotech, USA) according to manufacturer's instruction. Briefly, the assay uses monoclonal antibodies directed against distinct epitopes of insulin. A detector monoclonal antibody labeled with horseradish peroxidase (HRP) is added. After an incubation period, the microtiter plate is washed to remove unbound enzyme-labeled antibody and a substrate solution is added and incubated. The reaction is stopped with HCl and the microtiter plate is read spectrophotometrically. The intensity of color is directly proportional to the concentration of insulin in the original specimen and was measured using a microplate spectrophotometer (Spectromax Plus 384, Molecular devices, California).

Statistical analysis

All data are presented as means ± SEM. Significant differences between multiple groups were determined by ANOVA, followed by Tukey's post-hoc analysis (GraphPad Prism v6). Statistical significance was determined at $P < 0.05$.

RESULTS

Blood glucose and serum insulin

Fasting blood glucose was significantly increased (175%, $p < 0.05$) in dexamethasone treated animals as compared to the control (Figure 1A). *Nigella sativa* oil at the lower 0.2 ml/kg dose did not reduce fasting blood glucose unlike the higher 0.4 ml/kg dose that reduced blood glucose to values comparable to normal control animals (Figure 1A). Fasting plasma insulin levels revealed 1.7, 1.8 fold increases for Dex and Dex+ NSO 0.2 ml/kg, respectively, compared to control ($P < 0.05$, Figure 1B). Plasma insulin levels were comparable in normal and NSO 0.4 ml/kg treated rats. Homeostatic model assessment for insulin resistance (HOMA-IR) indicates that while insulin sensitivity was impaired in dexamethasone treated rats, the higher NSO 0.4 ml/kg but not 0.2 ml/kg was able to restore insulin sensitivity comparable to normal animals (Figure 1C).

Circulating fasting triglyceride (TG) concentration

No significant differences were observed in the TG concentration in fasted Dex, Dex NSO 0.2 ml/kg and Dex NSO 0.4 ml/kg treated rats (Figure 2). However, these values were elevated 1.6, 1.3 and 1.4-fold as compared to normal values ($P < 0.05$). These observations show that unlike effects on glucose, NSO does not inhibit dexamethasone induced hypertriglyceridemia.

Insulin tolerance test

Dexamethasone treatment for 5 days in rats has been established to induce a relative loss of response to insulin in an insulin tolerance test. All dexamethasone treated rats exhibited higher blood glucose values at most time points as compared to normal animals. NSO 0.4 ml/kg significantly reduced blood glucose levels at 15 and 30 min post insulin administration ($n=5$, $P < 0.05$, Figure 3). The capacity to prevent insulin induced hypoglycemia was not lost in NSO treated rats despite improvement in early response to insulin.

Effect on hepatic enzyme

No significant differences were observed in liver alanine aminotransferase enzyme activity in any of the dexamethasone treated groups though there was a tendency for decrease in hepatic enzyme activity in animals treated with dexamethasone (Figure 4).

DISCUSSION

The main finding of the current study is that *N. sativa* oil

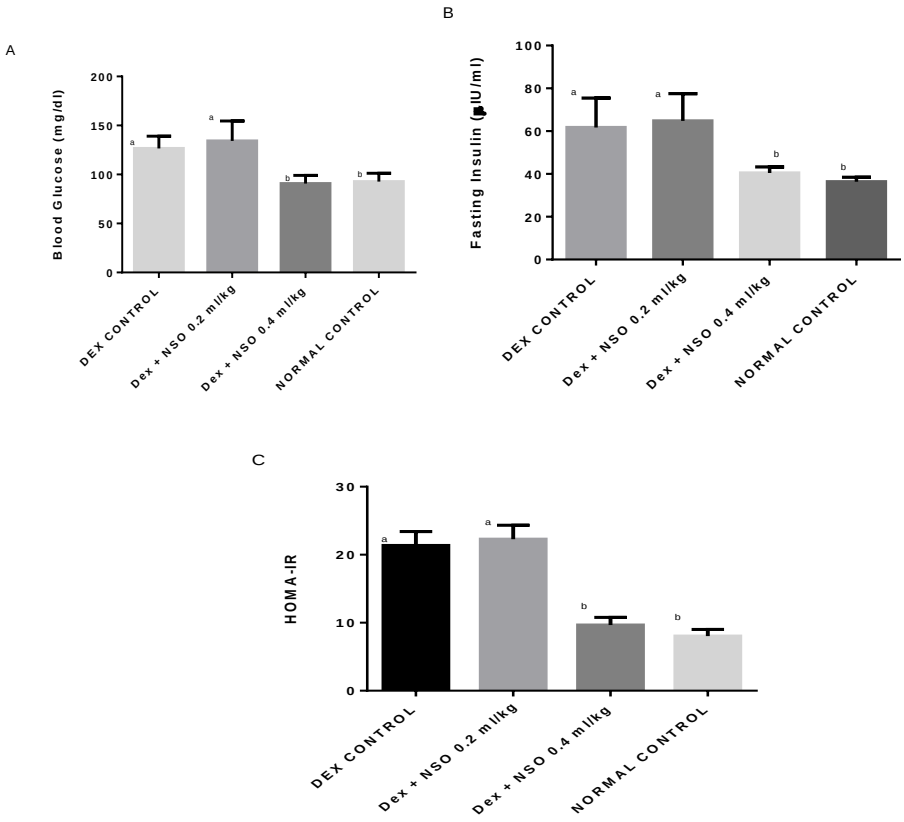

Figure 1. Simultaneous NSO administration dose-dependently improves markers of insulin resistance during 5 days of dexamethasone treatment in male Wistar rats. Comparison of fasting blood glucose levels (A), fasting plasma insulin (B), and HOMA index values obtained on the day of euthanasia. Values are means ± SEMs from 5 animals. Labeled means without a common letter differ, $P < 0.05$. Dex, Dexamethasone; NSO, *Nigella sativa* oil.

(NSO) improves fasting hyperglycemia and insulin tolerance in an animal model of insulin resistance. This model of dexamethasone treatment for five days has been reported to induce glucose intolerance, insulin intolerance, fasting hyperglycemia, hyperinsulinemia, hypertriglyceridemia and insulin resistance (Rafacho et al., 2007). It is a useful model in studying features of pre-diabetes as well as compensatory mechanisms in response to development of insulin resistance. Likewise, further studies in investigating the mechanisms of glucocorticoid induced insulin resistance can be undertaken using this model. While some plant products have been evaluated previously in this model (Phanse et al., 2014; Gao et al., 2007), this is the first report of insulin sensitizing effect of NSO in dexamethasone treatment.

During fasting, the liver is a major source of plasma glucose primarily via hepatic gluconeogenesis. Hepatic gluconeogenesis requires the co-activation of glucocorticoid receptors expressed in liver and these receptors are central to the control of expression of key gluconeogenic enzymes (Yoon et al., 2001). Dexamethasone, the most potent agonist at the glucocorticoid receptor mimics endogenous glucocorticoids in induction of fasting hyperglycemia (Patel et al., 2011) via increasing expression of a number of enzymes involved in hepatic gluconeogenesis (Pasieka and Rafacho, 2016). It has been shown that for dexamethasone induced disruption of glucose homeostasis, hepatic glucocorticoid receptor (GR) activation is required as liver-specific GR knockout mice did not develop hyperglycemia (Bose et al., 2016). Glucagon, which also induces elevation in glucose, has also been implicated as hyperglucagonemia was reported in this model (Rafacho et al., 2014). In the study by Rafacho et al. (2014), several metabolic derangements were normalized following administration of glucagon antagonist suggesting the pivotal role of glucagon in hyperglycemia as occur in this model. Reduction of hepatic gluconeogenesis may play a vital role in the blood glucose lowering effect of NSO. In support of this, NSO has been reported to decrease hepatic gluconeogenesis (Fararh et al., 2004).

The hyperinsulinemia observed in dexamethasone

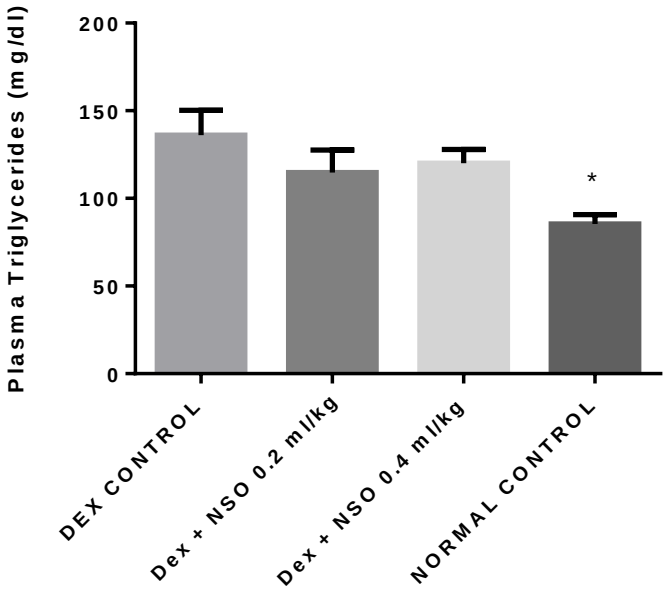

Figure 2. Comparison of effects of dex and/or *N. sativa* oil on circulating plasma triglycerides. Values are means ± SEMs from 5 animals. *Significant difference as compared to dex control, $P < 0.05$. Dex, Dexamethasone; NSO, *N. sativa* oil.

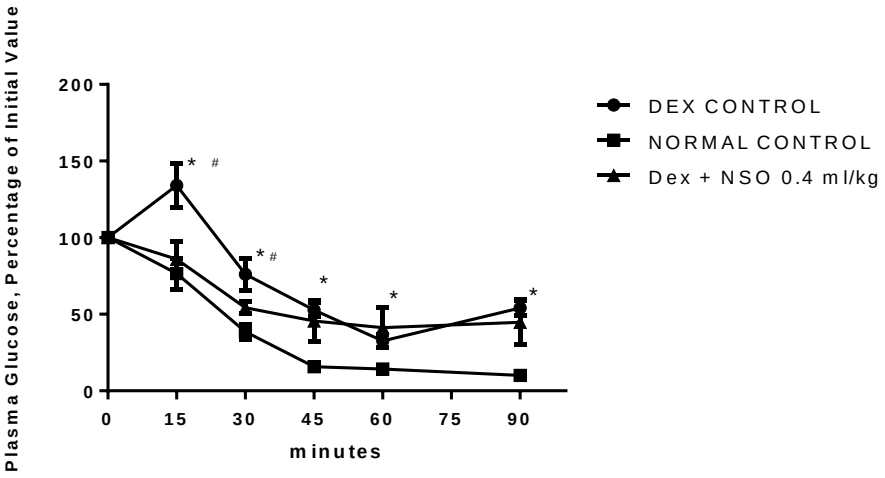

Figure 3. Simultaneous short-term *N. sativa* Oil (0.4 ml/kg body weight) administration improves insulin tolerance in dexamethasone-treated rats. Comparison of ITT results in terms of percentage changes normalized to the initial blood glucose value. Values are means ± SEMs; n=5. *Significant as compared to normal control, #Significant as compared to *Nigella* treated group, $P < 0.05$. DEX, Dexamethasone; NSO, *N sativa* oil; ITT, insulin tolerance test.

treated rats has been attributed to enhanced glucose induced insulin secretion and augmented beta cell proliferation (Protzek et al., 2016). These are seen as compensatory responses by beta cells to ameliorate insulin resistance. Direct effect of insulin on beta cells has been implicated in beta cell compensatory response (Okada et al., 2007). Furthermore, the hyperinsulinemia observed may be as a result of decreased insulin degrading enzyme activity in liver since dexamethasone impairs insulin binding to the enzyme (Harad et al., 1996). Hyperinsulinemia is thus both a consequence as well as a marker of insulin resistance.

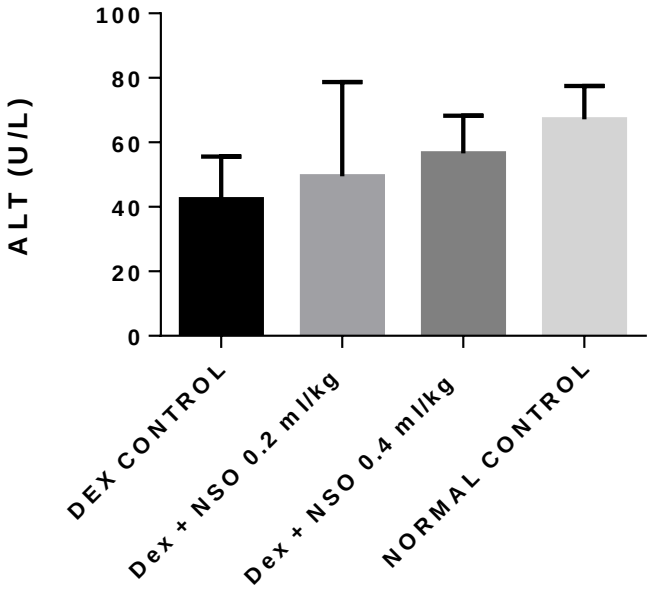

Figure 4. Effect of Dex and/or NSO on hepatic ALT enzyme activity. ALT activity tended to decrease in all dexamethasone treated animals with no significant NSO effect. Values are means ± SEM, P > 0.05. Dex, Dexamethasone; NSO, *N. sativa* oil; ALT, alanine aminotransferase.

So what causes insulin resistance in this model? Following insulin administration or release, the major chunk of glucose is shunted into the skeletal muscle. In response to insulin, insulin receptors induce the translocation of glucose transporters to the membrane allowing glucose entry. Dexamethasone impairs this insulin mediated glucose uptake via decreased insulin receptor substrate 1, a key mediator of insulin receptor signaling both in skeletal muscle and fat cells (Pasieka and Rafacho, 2016). Increased concentration of fatty and amino acids induced by glucocorticoids may also directly induce insulin resistance (Ferris and Kahn, 2012). Likewise, loss of insulin sensitizing hormones including adiponectin (Bönisch et al., 2016) may be implicated. Adiponectin acts on its receptors to modulate cellular and tissue response to insulin and in the absence of adiponectin, key insulin actions are markedly reduced (Kadowaki et al., 2006). Lastly, adenosine monophosphate kinase (AMPK) activity is associated with increased insulin sensitivity. The ability of *N. sativa* to modulate peripheral insulin sensitivity was associated with its ability to modulate AMPK phosphorylation thus suggesting a potential mechanism of action for NSO in this model (Benhaddou-Andaloussi et al., 2011).

Paradoxically, while NSO improves insulin sensitivity by reducing both fasting blood glucose and insulin mediated glucose uptake, effect on triglyceridemia was blunted. Insulin inhibits lipolysis thus favoring lipid storage. Recent insights into insulin resistance suggest that selective insulin resistance may occur (King et al., 2016). Thus, while glucose mediated insulin actions may be restored or maintained by therapy, other insulin mediated actions may be blunted. This may explain why NSO had no effect on hypertriglyceridemia in our study. Previous studies have also shown a non-consistent effect of NSO on lipid profile. Furthermore, a recent study did not observe NSO effect on adiponectinemia (Benhaddou-Andaloussi et al., 2011). Thus, NSO may not ameliorate insulin resistance in adipose tissue.

This study therefore suggests that the actions of NSO are not context dependent. Rather, NSO may be useful in ameliorating glucose dysregulation induced by dexamethasone. More reaching implication is the possibility that the limitation on anti-inflammatory efficacy of dexamethasone imposed by its steep effects on glucose metabolism may be ameliorated by NSO and since NSO itself has anti-inflammatory effects, it may potentiate the anti-inflammatory effects of glucocorticoids within the context of anti-inflammatory therapy.

Chemical characterization of the components of NSO has previously been conducted and suggests that thymoquinone and p-cymene were the most abundant chemical moieties (Sarwar and Latif, 2015). Thymoquinone has been shown to reduce blood glucose in various models of diabetes (Darakhshan et al., 2015) and this is likely to be via its ability to modulate enzymes involved in hepatic gluconeogenesis (Fararh et al., 2005; Pari and Sankaranarayanan, 2009) thereby suggesting that thymoquinone may play an important role in mediating the antihyperglycemic effects of NSO in this

model.

This needs confirmation and may be direction for further studies. Likewise, mechanisms involved in NSO effect particularly role of adiponectin may be subject for future investigations.

Conclusion

It can be concluded from this study that NSO could improve metabolic derangements induced by dexamethasone in Wistar rats, thus suggesting its antihyperglycemic potential.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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