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BIOMEDICAL SCIENCES

Water-soluble lectin (WSMoL) from *Moringa oleifera* seeds treatment recovers glycemic levels and improves left ventricular ejection fraction on Type-2 Diabetes mice model

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Abstract: *Moringa oleifera,* a plant widely used in traditional medicine as well as for water purification, contains a lectin on its seeds named WSMoL which modulates several immune characteristics and has shown cardiac safe properties. Here, we tested the hypothesis that WSMoL is able to recover fasting glucose levels and to improve the cardiac left ventricular (LV) function in a type 2 diabetes mellitus (T2DM) mice model. T2DM was induced in adult C57BL/6 mice by combining a high fat diet and low doses of Streptozotocin. Mice were randomly divided in two groups: i. received WSMoL for 21 consecutive days by gavage (T2DM + WSMoL) and ii. received saline solution (T2DM). Metabolic parameters and LV function were assessed. WSMoL was able to reduce fasting blood glucose levels in T2DM mice after 2 weeks of treatment, when compared to T2DM untreated group. Regarding to cardiac LV function, the T2DM + WSMoL group depicted ejection fraction values comparable to non-diabetic group. Our results show: i. WSMoL treatment presented a potent hypoglycemic effect decreasing insulin resistance and ii. WSMoL was able to improve cardiac LV ejection fraction. Collectively, the results presented here show WSMoL as a potential hypoglycemic agent to be tested in T2DM patients.

Key words: *Moringa oleifera*, WSMoL, diabetes, hypoglycemic, insulin resistance, ejection fraction.

INTRODUCTION

Moringa oleifera Lamarck (MO - Moringaceae) is a tree that, even though is native from southern Himalayan region, it is widely found in northeastern Brazilian regions (Coelho et al. 2009, Moura et al. 2015, 2017, Ferreira et al. 2011, Rodriguez-de-Yurre et al. 2019, Santos et al. 2015). It has been especially used for its nutritional content, but also has been widely used in traditional medicine for its vast medicinal properties (Ferreira et al. 2011, Santos et al. 2015, Hassan & Ibrahim 2013). This plant seeds are used for water purification (Santos et al. 2015) and roasted seeds as nourishment (Villasenor et al. 1989).

Several works have investigated the mechanisms and the therapeutic potential of MO upon medicinal features, using either powder, infusion or extracts from leaves and seeds. Seeds have been used to treat respiratory diseases such as asthma, and a clinical study using seed powder showed significant improvement in pulmonary function (Agrawal & Mehta 2008). In this regard, several investigations in animal

models and also in patients have proved the potential hypoglycemic effect of MO treatment (Divi et al. 2012, Gupta et al. 2012, Efiong et al. 2013, Kumari 2010, El Latif et al. 2014, Jaiswal et al. 2009). However, at the time, at least to our knowledge, the mechanisms of this effect and the molecules responsible for these findings are unclear.

Our group has extensively studied the different properties of the water-soluble lectin (WSMoL) purified from *Moringa oleifera* Lam. seeds. WSMoL was previously characterized showing a molecular mass: 60 kDa and Isoelectric point: 5.5 (Moura et al. 2016). In addition, the sequence of peptide mass (2130.10) was QAVQLTHQQQGQVGPQQVR, which compared with known sequences in the NCBInr database showed significant (score 70%) similarity with M02.1 and M02.2 (identification number gi|127215) proteins from *M. oleifera* seeds (Coelho et al. 2009). In this sense, previous works have demonstrated that WSMoL reduces turbidity and bacterial contamination of lake water, prevents biofilm development from various bacteria (Moura et al. 2015, 2017, Ferreira et al. 2011) and promotes immunomodulation in human peripheral blood mononuclear cells (Coriolano et al. 2018). In our most recent work, we demonstrated that treatment with WSMoL for 21 consecutive days was metabolically and cardiologically safe for mice (Rodriguez-de-Yurre et al. 2019).

It is well known that Type 2 diabetes mellitus (T2DM) is an important health problem worldwide accounting about 90 % of all cases of diabetes. As a consequence of the sustained hyperglycemic levels, different comorbidities are commonly diagnosed. The cardiac function is one of the most impaired systems in T2DM (Jia et al. 2018). Therefore, significant efforts are being performed in order to find a novel T2DM treatment that not only reduce the glycemic levels, but also preserve the cardiac function or revert the cardiac damage induced by T2DM (Chan 2014).

Thus, in the present work we tested the hypothesis that WSMoL reduces glycemic levels and improves the cardiac left ventricular function in a T2DM mice model.

MATERIALS AND METHODS

Plant material and lectin isolation

Seeds of *Moringa oleifera Lam.* (Moringaceae Family) (voucher specimen deposited under number 73,345 at the herbarium Dardano de Andrade Lima from the Instituto Agronomico de Pernambuco) was collected in Recife city (Brazil) and sample storage was performed as previously described by Rodriguez de Yurre et al. (2019). WSMoL was isolated from seed powder according to the protocol previously described by Coelho et al. (2009). Briefly, the protocol consists of extracting proteins in distilled water and, after filtration and centrifugation, the extract is treated with ammonium sulfate at 60% saturation (Green & Hughes 1955) for 4 h at 28 °C. After a second centrifugation, the precipitate is resuspended in water and dialyzed for 8 h against distilled water (4 h) and 0.15 M NaCl (4 h). The dialyzed fraction (100 mg of proteins) is then loaded onto a chitin column (equilibrated with 0.15 M NaCl (20 mL/h flow rate)) and WSMoL is eluted with 1.0 M acetic acid. Finally, the isolated lectin is dialyzed against distilled water (with three liquid changes, for eluent elimination).

Ethical approval

All experiments were conducted in accordance with the internationally accepted principles for laboratory animal use and care as found in the Ethical Principles in Animal Research adopted by the Brazilian College of Animal Experimentation, and the applied protocols

received approval from the Committee on Ethics in Animal Research of Federal University of Rio de Janeiro, under protocol number DFBCICB041.

Adult male C57BL/6 mice were used and maintained at the Carlos Chagas Filho Biophysics Institute of Federal University of Rio de Janeiro under controlled conditions of temperature (23 °C), in a standard light/dark cycle of 12h/12h and free access to food and water.

Animals and experimental protocol

The 2-month-old male C57BL/6 mice were induced to T2DM with a combination of a high fat diet (HFD, 45% fat) and two low doses of streptozotocin (STZ, 40 mg/kg/I.P.; Sigma-Aldrich, USA) 15 and 16 days after the protocol started respectively (Rodriguez-de-Yurre et al. 2020).

After 6 weeks of protocol initiation, fasting blood glucose (FBG) was assessed and the animals with FBG higher than 140 mg/dL were considered diabetic. Those animals were randomly separated in two groups: T2DM group (n = 11), which received daily by gavage 0.2 ml of NaCl 0.9%; and T2DM + WSMoL group (n = 11), which was treated by gavage (same volume as the T2DM group) with the lectin purified protein – WSMoL - 5 mg/kg body weight (equivalent to 0.2 mg/ml) (Rodriguez-de-Yurre et al. 2019) for 21 days. A group of mice that did not receive the combination of HFD-STZ and received daily by gavage 0.2 ml of NaCl 0.9% (and was age matched with diabetic mice), was used as control group (CTRL) (n = 11).

Fasting blood glucose, intraperitoneal glucose tolerance test, and intraperitoneal insulin tolerance test

FBG concentrations were determined from tail vein blood using an automated glucometer (Accu-Chek Active Roche, Germany) after 6 h of fasting. For intraperitoneal glucose tolerance test (IPGTT, n = 11) and intraperitoneal insulin tolerance test (IPITT, n = 11), mice were fasted for 6 h and 4 h, respectively. After the fasting period, animals received intraperitoneally 2 g/kg of glucose for IPGTT or 0.5 IU/kg of insulin for IPITT and glucose levels were monitored 0, 15, 30, 60, 120 min after injection from a tail snip. The area under the curve (AUC) was calculated using all the time points in each animal evaluated.

Ventricular function assessment

Cardiac ventricular function was evaluated after 21 of treatment with WSMoL (n = 9) or vehicle (T2DM n = 8; CTRL n = 5) by *in vivo* echocardiography (ECHO) using the Vevo 770 High-Resolution Imaging System (VisualSonics, Canada) coupled to a 30 MHz transductor, under isoflurane anesthesia. Images were acquired in bidimensional mode and analyzed by a blinded investigator. Left ventricular (LV) mass corrected, fractional shortening, ejection fraction, stroke volume and end-systolic and end-diastolic volume were calculated using Simpson's method, as described previously (Benavides-Vallve et al. 2012).

Statistical analysis

The results are presented as mean ± standard deviation (SD). Mean comparisons were performed between groups with ANOVA. Importantly, data showing non-Gaussian distribution (Kolmogorov-Smirnov test) were compared by the "Kruskal-Wallis test". Differences between variables were considered significant when $p < 0.05$. All analyses were performed using GraphPad Prism 8.0 (GraphPad Software, USA).

RESULTS

WSMoL and body weight

After 9 weeks, the combination of HFD and two low STZ injections, was not able to induce differences on body weight among groups (Fig. 1a). However, both epididymal and retroperitoneal fat were higher in the T2DM treated and untreated WSMoL groups, when compared to CTRL non-diabetic mice (Fig. 1b and 1c).

WSMoL treatment and metabolic parameters

Several reports suggest that the intake of water containing seeds of *Moringa oleifera* improves the glycemic levels in animals and diabetic patients (Divi et al. 2012, Gupta et al. 2012, Efiong et al. 2013, Kumari 2010, Al-Malki & El-Rabey 2015).

Here we tested the hypothesis that the treatment for 21 consecutive days with a water soluble-lectin (WSMoL) purified from *Moringa oleifera* seeds improves the glycemic levels in a T2DM mice model. Therefore, WSMoL treatment was able to decrease the glycemic levels after 2 weeks (Fig. 2a) when compared to T2DM untreated group. This effect was maintained, at least, for one more week (Fig. 2a).

Altogether, the WSMoL treatment induced 37.5 ± 3.9 % of reduction in the FBG levels when performed the delta of glycemic values between the last day and the first day of treatment (Fig. 2b). The CTRL group showed almost no variation in the glycemic levels throughout the three weeks of the study, as expected (Fig. 2a).

In order to better understand the mechanism involved in the WSMoL-induced hypoglycemic effects, both, IPGTT and IPITT were performed.

In regard to IPGTT, at the end of treatment period, the T2DM and the T2DM+WSMoL group were significantly different to CTRL group (Fig. 2c). Thus, the area under the curves (AUCs) were higher than the CTRL group and similar between them (Fig. 2d).

Interestingly, after three weeks of treatment, WSMoL was enough to drastically decrease the insulin resistance in the T2DM group, showing also lower insulin resistance than the CTRL non-diabetic group (Fig. 2e). In addition, these results were clearly reflected in the values obtained in the AUC of this group (Fig. 2f).

WSMoL treatment and cardiac left ventricular function

It is well accepted that T2DM patients are more prone to develop cardiac disease. In this context,

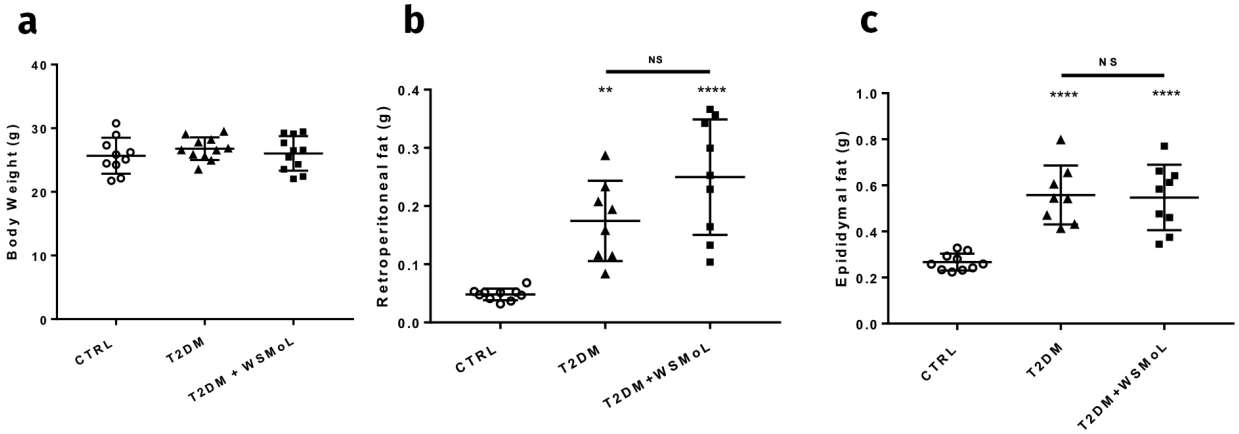

Figure 1. WSMoL does not modify body weight in type 2 diabetic mice model. a. Body weight (g). b. Retroperitoneal fat (g). c. Epididymal fat (g). CTRL (n = 5 - 11) vs T2DM (n = 7 - 11) vs T2DM + WSMoL (n = 6 - 11). ** p < 0.01, **** p < 0.0001 vs CTRL, ns: non-significative difference between T2DM vs T2DM + WSMoL.

a "diabetic cardiomyopathy" was previously described by Rubler et al. (1972, Pappachan et al. 2013) and is a fact that T2DM increases the risk of other cardiovascular diseases as myocardial infarction (Laakso 2001). In the present work, the left ventricular (LV) structure and function were evaluated by echocardiography. The T2DM model presented here did not depict differences neither on left ventricular mass nor on LV corrected mass (Fig. 3a and Fig. 3b). However, the animals treated with WSMoL showed an improvement in the LV ejection fraction and

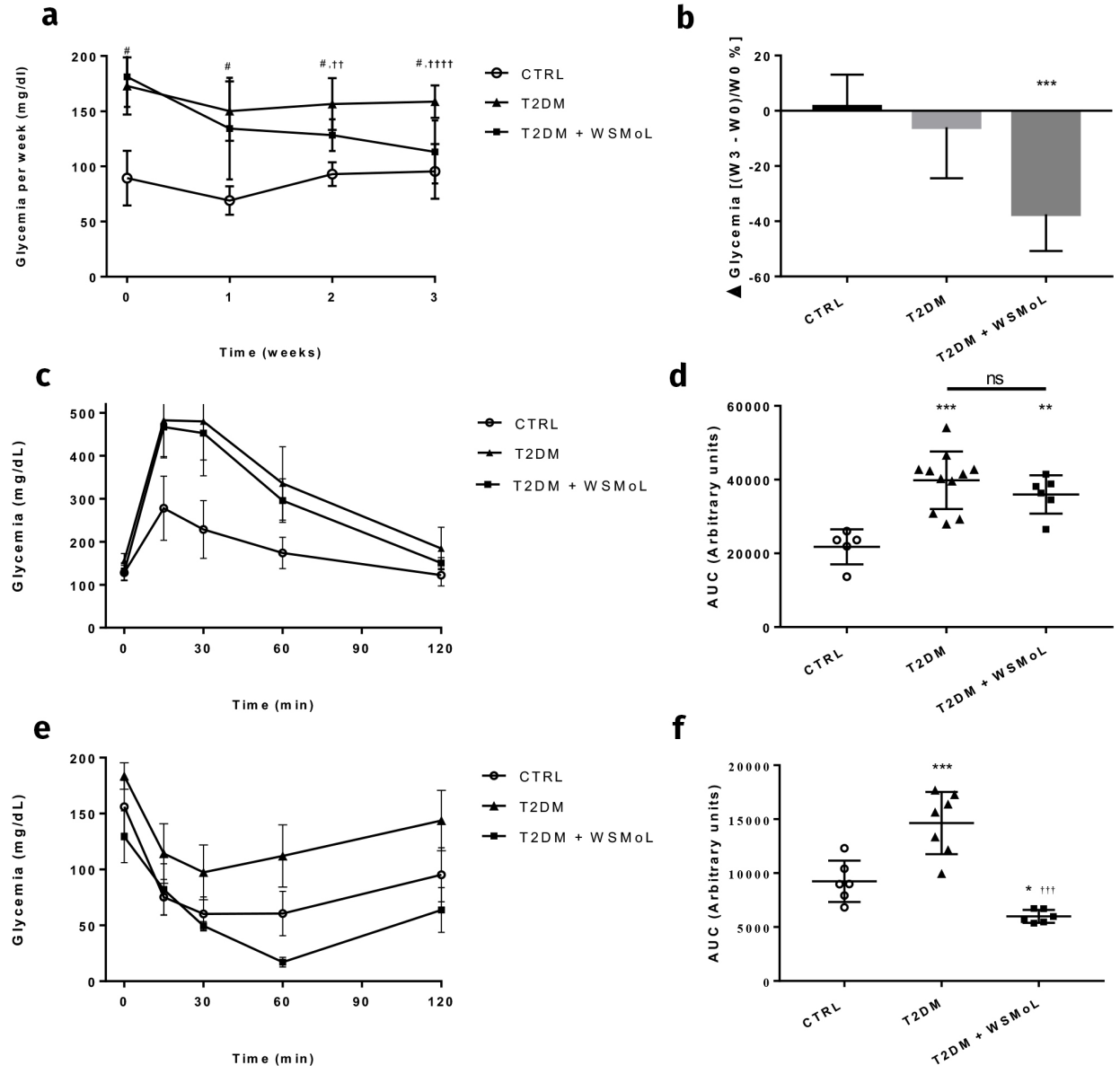

Figure 2. WSMoL treatment improves metabolic parameters in type 2 diabetic mice. a. Weekly measured glycemia values (mg/dl). b. Differences in fasting glycemia between the third week glycemia (W3) and the initial glycemia (W0), expressed as percentage of W0. c. Intraperitoneal glucose tolerance test (IPGTT). d. Area under the curve (AUC) of IPGTT. e. Intraperitoneal insulin tolerance test (IPITT). F. AUC of IPITT. CTRL (n = 5 - 11) vs T2DM (n = 7 - 11) vs T2DM + WSMoL (n = 6-11). * p < 0.05, ** p< 0.01, *** p < 0.001 (vs CTRL), ns : non-significative difference between T2DM vs T2DM + WSMoL # p < 0.0001 (T2DM vs CTRL) †† p < 0.01 ††† p < 0.001, †††† p < 0.0001 (T2DM vs T2DM + WSMoL).

in the end diastolic volume when compared to T2DM untreated group (Fig. 3c and Fig. 3f). Also, the T2D + WSMoL presented lower end systolic volume than T2DM untreated mice (Fig. 3e). Furthermore, the end systolic volume values of T2DM-Wsmol were similar to control group. Fractional shortening and Stroke Volume were similar among studied groups (Fig. 3a, Fig. 3b and Fig. 3d).

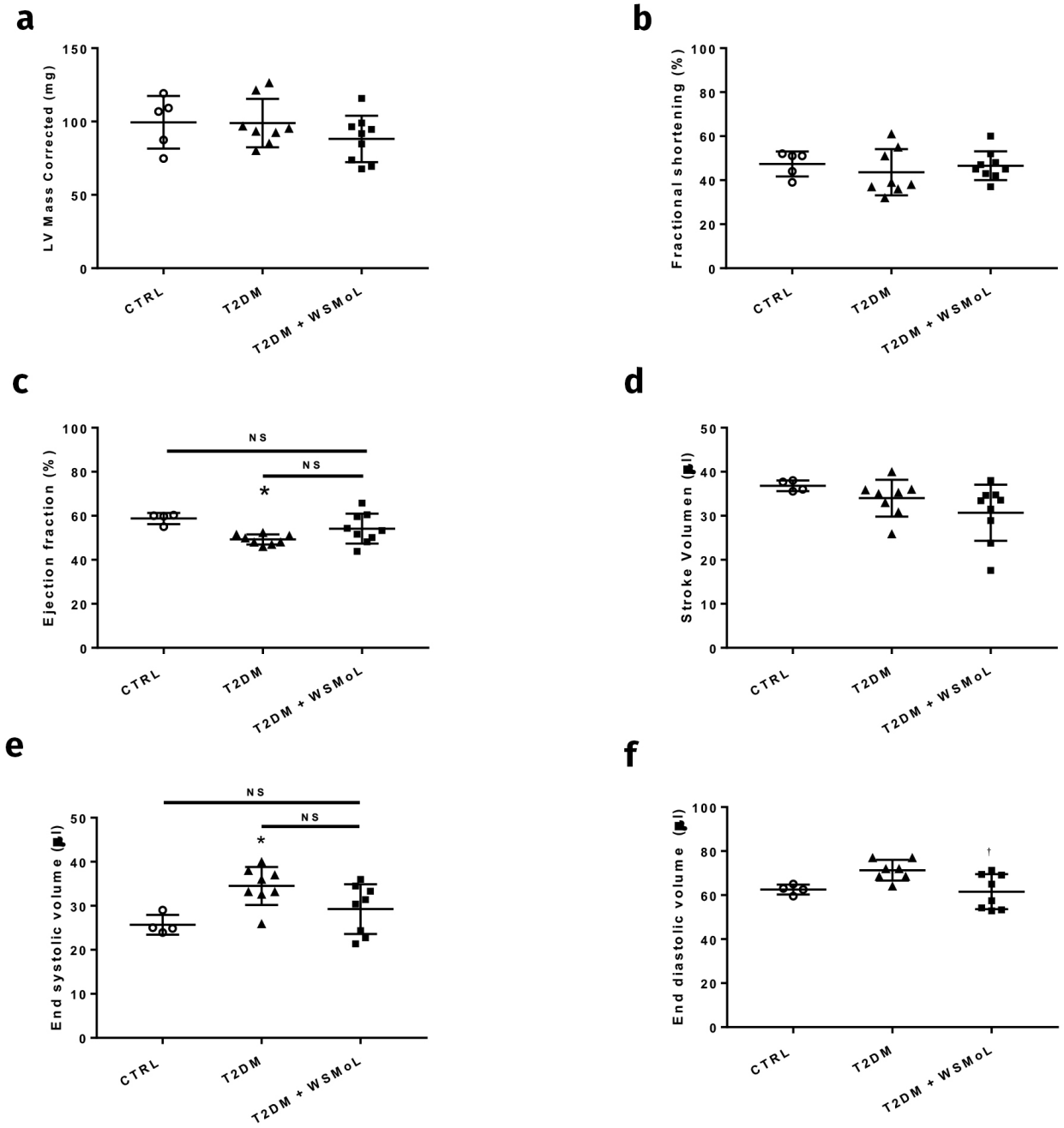

Figure 3. WSMoL treatment improves cardiac left ventricular function. a. Left Ventricular (LV) Mass Corrected (mg). b. Fractional shortening (%). c. Ejection fraction (%). d. Stroke Volume (µl). e. End systolic volume (µl). f. End diastolic volume (µl). CTRL (n = 4 - 5) vs T2DM (n = 7 - 8) vs T2DM + WSMoL (n = 8 - 9) * p < 0.05 (vs CTRL). † p < 0.05 (T2DM vs T2DM + WSMol).

DISCUSSION

Several works have depicted the potential hypoglycemic role played by MO, in animal models and also in humans (Jaiswal et al. 2009,Kumari 2010, Divi et al. 2012, Gupta et al. 2012, Efiong et al. 2013, El Latif et al. 2014). In this regard, in alloxan-induced diabetes female rats, the treatment with MO aqueous extract from the leaves was able to decrease the glucose levels, reaching similar levels to control group after 18 days of treatment (El Latif et al. 2014). In this direction, also aqueous extract of MO leaf showed antihyperglycemic effect in STZ induced diabetic rats, in which after 60 days of treatment the FBG decreased to similar values to those of the control group (Divi et al. 2012). Here we observed similar results, though, after 21 days of treatment with WSMoL. Other work, which used methanol extracts of MO pods, has obtained also hypoglycemic effect in STZ-induced diabetic albino rats treated for 21 days. However, the FBG levels were higher than those in non-diabetic animals (Gupta et al. 2012). It is important to remark that in our study WSMoL brings the glycemic levels close to the levels observed in non-diabetic mice.

Another treatment option previously used was the *MO seed powder*. Therefore, the treatment of STZ-induced diabetic rats, with different doses of *MO seeds powder* for 4 weeks, significantly decreased the FBG in the serum. Interestingly, the glucose levels were also higher than the non-diabetic control values (Al-Malki & El-Rabey 2015).

The works described above used the whole MO products, but other works also tested the hypoglycemic potential of MO isolated extracts. In order to test the potential hypoglycemic effect of MO ethanolic extract, Efiong et al. (2013) used a higher dose of MO, treating the STZ-induce diabetic rats with 500 mg/kg body weight of MO twice a day (12 h) for 28 consecutive days orally. The authors observed a significant reduction in FBG levels and the reduction was comparable with that obtained with the standard hypoglycemic drug treatment (glibenclamide) (Efiong et al. 2013). Importantly, both, the hypoglycemic and the LV function results obtained here with WSMoL, were achieved administrating 5 mg/kg/body weight.

In this line, Jaiswal et al. (2009) demonstrated that aqueous extract of MO leaves (200 mg/kg/body weight) not only decreased the FBG levels, but also induced a maximum fall of 31.1 % during oral glucose tolerance test (OGTT) after 21 days of treatment (Jaiswal et al. 2009). Conversely with this data, the treatment with WSMoL was not able to improve the IPGTT. This discrepancy could be due to the different dose used, since Jaiswal et al used 200 mg/kg while we used 5 mg/kg of purified lectin. Also, we cannot discard that WSMoL, even at a higher dose, may not have this beneficial effect by itself, suggesting that this effect could be the result of the action of different compounds present in the extract.

Regarding to insulin response, we demonstrated that after treatment with WSMoL T2DM mice showed decreased insulin resistance when compared with T2DM untreated group. In fact, the WSMoL group depicted much better response than non-diabetic group. In another study, it was shown that aqueous extract of MO leaves induced higher fasting insulin levels (Divi et al. 2012) (109.6 %) in treated diabetic rats when compared with diabetic non treated group. However, the insulin recovery was partial, as the insulin levels did not reach control levels. In this direction, Chinedu et al. (2015) demonstrated that ethanolic leaf extract of MO (250 and 500 mg/kg/day) in HFD/STZ induced diabetic rats for 2 weeks, showed a significant improvement on insulin resistance (HOMA-IR) (Chinedu et al. 2015), showing similar outcome with our study,

reducing the insulin resistance in the WSMoL treated group.

The therapeutic potential of MO also was tested in humans. In this context, one study in T2DM patients demonstrated that oral treatment with MO leaves powder (8 g) for 40 consecutive days was able to decrease the FBG values from 162 ± 9.0 to 117 ± 21.3 and the post prandial glycemia from 219 ± 77.4 to 163 ± 49.4 (Kumari 2010). However, it was not clear which molecule present in the powder was the responsible for this hypoglycemic effect. Or, if that effect was a consequence of an additive action of a group of molecules present in the MO leaves powder.

T2DM treatment is a priority in world health since 10.7% of the world mortality is caused by this disease (Cho 2017) and it is important to reach a control in the hyperglycemia and cardiovascular disease derived therefrom (Chan 2014, Laakso 2001). The effectiveness of interventions for the primary prevention of T2DM (Knowler et al. 2002, Tuomilehto et al. 2001) has widely been demonstrated among individuals who have impaired glucose tolerance. Thus, WSMoL could be considered in the objective to optimize the glycemic control in some T2DM patients in order to reduce atherosclerotic cardiovascular disease risk factors (ADA 2020a) and in those patients whom have not developed yet diabetes but present high FBG levels.

Diabetes cardiomyopathy was initially described by Rubler et al. (1972) characterized by the presence of myocardial changes which cannot be attribute to major coronary arterial involvement, hypertension, valvular or neuromuscular disease (Rubler et al. 1972). In a previous review, the diabetic cardiomyopathy was defined as a clinical condition of ventricular dysfunction that occurs in the absence of coronary atherosclerosis and hypertension in patients with diabetes mellitus (Tuomilehto et al. 2001). In the second stage of diabetic cardiomyopathy the cardiac diastolic dysfunction is more advanced which later on leads to a reduced ejection fraction (Jia et al. 2018).

Besides diabetes cardiomyopathy, a vast literature has pointed out that T2DM patients have several cardiac comorbidities, which usually are not reverted or prevented by hypoglycemic conventional therapy. Also, prediabetes is an increased risk for diabetes and cardiovascular disease (CVD) that needs to be correctly treated (ADA 2020b). Moreover, the perspective to find a new hypoglycemic compound must include also a beneficial effect on other organs, like heart. This was tested in the empagliflozin study, were T2DM patients, after a median observation time of 3.1 years, had a lower death rate due to cardiovascular causes, while there were no significant differences between-groups in the myocardial infarction or stroke rates (Zinman et al. 2015).

Interestingly, even though that several works were performed in order to test the hypoglycemic potential of MO, no work at the time, at least in our knowledge, has explored the beneficial effect of MO on T2DM-induced cardiac impairment. A previous work of our group consistently demonstrated that the oral gavage with the purified lectin of MO, WSMoL, demonstrated to be cardiologically safe (Rodriguez-de-Yurre et al. 2019). Here, we showed that WSMoL was able to improve the cardiac LV function in a T2DM mice model improving the LV ejection fraction and the end diastolic volume in the T2DM treated group when compared to T2DM untreated group.

Here, we consistently demonstrated that 21 consecutive days of treatment with WSMoL was able not only to recover the normal glycemic levels, but also to partially revert the LV function.

The present work demonstrates that the treatment with WSMoL, a purified soluble lectin from *Moringa oleifera* seeds, for 21 consecutive

days was able to: i. brings the glycemic levels to those values comparable to non-diabetic mice; ii. drastically decrease the T2DM-induced insulin resistance, and iii. partially improve the left ventricular function.

Taken together, these data depicted that WSMoL is one of the "active principles" present in the MO seeds that induces hypoglycemic action. Additionally, these findings open a new venue to deepen study the cellular and molecular mechanisms of these phenomena and positioned the WSMoL as a potential candidate to be a "*natural*" hypoglycemic compound.

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EM and PMGP conceived the project, designed the experiments and contributed to manuscript writing and financial obtaining. NVN and ARY performed the experiments, analyzed the data, prepared the figures and wrote the manuscript. Both, NVN and ARY contributed equally to this work. JDFS and MKST isolated the purified lectin from *Moringa oleifera* seeds. IPR performed echocardiographic analysis and interpreted the data obtained. EM, NVN, ARY, THN, PMGP and LCBBC wrote the manuscript and made critical revisions of the manuscript for intellectual content. NVN and ARY contributed equally to this work. The authors declare that they have no conflict of interest.