Scientific Research Publishing

Food and Nutrition Sciences, 2020, 11, 23-31
https://www.scirp.org/journal/fns
ISSN Online: 2157-9458
ISSN Print: 2157-944X

A New Supplement for the Treatment of Metabolic Syndrome in Postmenopausal Women

Annamaria Giacobbe[1], Alessandra Bitto[2], Vincenzo Arcoraci[2], Roberta Granese[1], Rosario D'Anna[1*]

[1]Department of Human Pathology, University of Messina, Messina, Italy
[2]Department of Experimental Medicine of Messina, Messina, Italy
Email: *rdanna@unime.it

How to cite this paper: Giacobbe, A., Bitto, A., Arcoraci, V., Granese, R. and D'Anna, R. (2020) A New Supplement for the Treatment of Metabolic Syndrome in Postmenopausal Women. *Food and Nutrition Sciences*, **11**, 23-31.
https://doi.org/10.4236/fns.2020.111003

Received: November 29, 2019
Accepted: January 4, 2020
Published: January 7, 2020

Abstract

Background: Metabolic Syndrome (MS) is considered a cluster of metabolic abnormalities whose pathogenesis is principally attributable to insulin resistance. Lack of estrogens occurs in postmenopausal women and worsening insulin resistance and lipid profile, predispose to MS. The aim of the study was to show whether a new supplement containing cinnamon, corosolic acid and glycyrrhizic acid may counteract MS manifestations. **Methods:** A total of 60 postmenopausal women were enrolled in a randomized, controlled trial; the active treatment group was taking the new supplement for 3 months and was on a hypocaloric diet, control group was only on diet. At the beginning and after 3 months, metabolic variables were evaluated. **Results:** After 3 months, a significant difference in the treated group was observed for glucose, HOMA, total cholesterol and HDL-cholesterol; whereas, in the control group, a significant difference was shown only for glucose. After 3 months, a significant difference between groups was highlighted only for HDL-cholesterol. **Conclusion:** This study has shown the naturally occurring components of this new supplement may improve insulin resistance and lipid profile in a small sample of postmenopausal women.

Keywords

Metabolic Syndrome, Postmenopause, Insulin Resistance, Cinnamon, Corosolic Acid, Glycyrrhizic Acid

1. Introduction

Metabolic Syndrome (MS) is considered a cluster of metabolic abnormalities and

a complex condition which predicts future development of type 2 diabetes mellitus (DM) and cardiovascular disease [1]. It is defined by four clinical manifestations: central obesity, glucose intolerance, dyslipidemia and high blood pressure. Several risk factors have been identified, mainly excessive calorie intake, sedentary lifestyle and genetic predisposition. Pathogenesis of MS is largely attributable to insulin resistance [2] while the onset of complications like cardiovascular diseases is closely linked to chronic, systemic pro-inflammatory and pro-coagulation state [3]. Menopausal transition may predispose to MS being usually associated with changes in body composition, due to the prevalence of androgens over estrogens, and a reduction in physical activity. Furthermore, lack of estrogens increases insulin resistance and changes in lipid profile predispose to atherogenesis [4]. Adipose tissue, in particular visceral fat, is an important source of inflammatory markers, which contributes to the development of a pro-inflammatory state. Conversely, it has been ascertained that high levels of physical activity and exercise have an anti-inflammatory effect [5]. MS is usually treated with statins and/or metformin, but these drugs taken for long periods may cause tiresome side effects. There is actually an increased request of natural compounds to prevent or to treat metabolic disorders too. Some of these substances are Corosolic Acid, Glycyrrhizic Acid and Cinnamon. These supplements were already individually used in oriental traditional medicine as a remedy for various illnesses and ailments, particularly for lowering blood glucose levels, reducing body weight and treating metabolic diseases, such as DM. Corosolic Acid (CA) has been identified from the red leaves of *Lagerstroemia speciosa*, commonly known as *Banaba*; it grows widely in tropical countries, including Philippines, India, Malaysia, China and Australia [6]. Glycyrrhizic Acid (GA), a triterpenoid saponin found in abundance in the root of genus *Glycyrrhiza glabra*, commonly known as liquorice, has shown some compelling therapeutic activities in counteracting MS [7]. Extracts of cinnamon contained consistent amounts of procyanidin that has insulin-potentiating properties and may be involved in the alleviation of the signs and symptoms of diabetes and cardiovascular disease-related to insulin resistance and MS [8]. A large number of studies have demonstrated that MS correlates with chronic and low-grade inflammation with massive secretions of pro-inflammatory cytokines [9]. High Mobility Group Box 1 (HMGB1) is a new potential biomarker of inflammation, acting as a "danger signal" that positively correlates with insulin resistance [10]. Based on literature reports, this study aims to show if the association of the above supplements could improve MS in post-menopausal women.

2. Materials and Methods

A prospective, randomized, controlled, open-label study was carried out in the Obstetrics and Gynaecology Unit, University Hospital of Messina. A total of 60 women were selected from a cohort of postmenopausal outpatient women affected by MS. All subjects gave their informed consent for inclusion before they

participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Messina (project identification code n. 64/17). Inclusion criteria were: a) amenorrhea for at least 12 months, b) an age between 45 and 65 years old, c) women affected by MS, diagnosed in accordance with the National Cholesterol Educational Program Adult Treatment Panel III 2015 criteria which are: fasting glucose ≥ 110 mg/dl; triglycerides ≥ 150 mg/dl; blood pressure ≥ 130/85 mmHg; abdominal obesity (waist circumference > 88 cm); HDL-cholesterol < 50 mg/dl. For diagnosing MS at least 3 of the above criteria were needed. Exclusion criteria were principally current treatments with hypoglycaemic (metformin) or anti-cholesterol drugs (statins).

At enrolment (t0) and after 3 months (t1), blood pressure, waist circumference, weight and BMI were recorded for each participant. Moreover, a modified life-style, such as moderate aerobic physical activity (duration ranging from 20 to 50 minutes at least three times per week) and a hypocaloric diet (1400 kg/cal divided in 50% carbohydrates, 30% lipids and 20% proteins) was strongly suggested to all women. A blood sample to evaluate glycaemic (fasting glycaemia and insulin) and lipid profile, total cholesterol (TC), HDL-cholesterol (HDL-C), triglycerides, was taken to confirm diagnosis of MS. Insulin-resistance was evaluated as Homeostasis Model Assessment (HOMA) index. In addition, thyroid function was evaluated (TSH, Ft3, Ft4, AbTg, AbTPO) as well as an inflammatory marker as serum HMGB1 too. Participants were then randomly divided into two groups using a computer-generated randomization. Two soft gel capsules per day were administered to each participant of the treated group (TG) before lunch and dinner, for 3 months. Each capsule contained corosolic acid 480 mcg, glycyrrhizic acid 38 mg and procyanidin (methyl hdroxicalcone) 2.4 mg. No supplements were administered to the control group (CG), only a modified life-style and diet as for the other group. After 3 months (t2), blood pressure, waist circumference, weight and BMI, glycaemic and lipid profiles, HOMA Index, HMGB1 and thyroid pattern were re-evaluated.

CLINICAL TRIAL REGISTRATION: https://www.clinicaltrials.gov/, NCT 03813914.

Statistical Analysis

Data are expressed as mean (standard deviation) for continuous variables and as percentages for categorical variables. The means of independent groups were compared using the Student's t-test after checking for normal distribution. For parameters that did not have normal distribution, we used the Mann-Whitney test. Intra-group differences were evaluated with the Wilcoxon test. A p-value of 0.05 or less was considered statistically significant. All analyses were performed using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

3. Results

A total of 56 women completed the study and were considered for the final evaluation; all reported a good adhesion to the hypocaloric diet suggested. In

each group 2 drop-outs (lack at the control after 3 months) have been recorded. The two groups were comparable for age: 55.8 ± 5.5 (TG) vs. 56.9 ± 5.6 years in the CG ($p = 0.5$), and time elapsed from the last period: 81.4 ± 61 months in the TG and 95.6 ± 66.7 months in the CG ($p = 0.4$). At baseline, there were no differences between groups for each measure considered (**Table 1**). At the end of the study, no statistically significant differences were found in the two groups regarding anthropometric variables, such as BMI and waist circumference, and for some metabolic measures such as insulin, triglycerides, but also blood pressure and thyroid profile (**Table 1**). After 3 months, a significant difference in the TG was highlighted for glucose (**Figure 1**), HOMA-IR (**Figure 2**), TC (**Figure 3**) and HDL-C (**Figure 4**).

In the control group, a significant difference was shown only for glucose. Furthermore, a significant difference between groups at the end of the study was highlighted only for HDL-cholesterol (**Figure 4**). HMGB1 values were comparable at the beginning of the study (TG 4.6 ± 2.2 vs. CG 4.4 ± 2.1 ng/ml, $p = 0.7$), but significantly different at the end of it (TG 2.6 ± 1.3 vs. CG 3.6 ± 1.7 ng/ml, $p = 0.01$); in the TG, the difference (T0 vs. T3) was significant ($p < 0.001$); instead, no difference between T0 vs. T3 in the CG ($p = 0.1$).

4. Discussion

This study has shown that an association of three natural substances (cinnamon, corosolic acid, glycirrhizic acid) well known by some eastern populations since ancient times may decrease fasting blood glucose, triglycerides and insulin resistance, increase HDL-cholesterol and thus improve the metabolic syndrome. One of the limitations of this study may be the time of treatment (3 months), probably too short to obtain resounding results. Furthermore, the substances used were natural compounds which usually need more time to show an appreciable effect. However, recent studies have demonstrated that cinnamon at high doses may determine similar results in a similar period of treatment: 2 and 4 months respectively [11] [12]. A possible mechanism of action for cinnamon may involve the reduction of post-prandial intestinal glucose absorption by inhibiting the activity of enzymes involved in carbohydrate metabolism [13], promoting cellular glucose uptake by membrane translocation of GLUT-4, stimulation of glycogen synthesis and inhibition of gluconeogenesis [14]. Furthermore, methylchalcone which is a procyanidin component of cinnamon enhances the triacylglycerol lipase activity that hydrolyzes dietary fat, the effect that may explain the decrease of body weight and fat body mass in subjects with type 2 DM [15]. All these experimental results have been confirmed by very recent small trials performed in humans [11] [12]. Commonly used anti-diabetic drugs up-regulate both glucose transport and lipid biosynthesis in adipocytes: weight gain is a frequent side effect, damaging the psyco-physical wellness of women in menopause; therefore, drugs with glucose-lowering activity with lacking adipogenic activity are highly desirable. An improvement of glucose and lipid profile (cholesterol and triglycerides) could be also the effect of the anti-adipogenic property

Table 1. General characteristics and outcomes measures.

	suppl t0	placebo t0	suppl t3	placebo t3
	p1	p2	p3	p4
BMI	26.8 ± 3.7	26.7 ± 3.7	26.3 ± 3.9	26.9 ± 3.7
	ns	ns	ns	ns
WC	100.1 ± 10.9	99.6 ± 10.7	98.2 ± 10.5	98.2 ± 10.3
	ns	ns	ns	ns
Glucose	102.5 ± 19.3	104.9 ± 22.3	90.1 ± 9.4	97 ± 14.2
	ns	ns	ns	ns
Insulin	11.1 ± 5.6	9.8 ± 3.9	8.6 ± 4.8	8.6 ± 4.8
	ns	ns	ns	ns
HOMA	2.8 ± 1.4	2.5 ± 1.1	1.9 ± 1.1	1.9 ± 0.8
	ns	ns	< 0.05	ns
Triglycerides	171.0 ± 58.4	169.6 ± 59	134.4 ± 48.7	149.4 ± 57.3
	ns	ns	ns	ns
Total-chol	222.8 ± 34.1	221.8 ± 34.3	195.3 ± 37.4	204.8 ± 39.3
	ns	ns	<0.05	ns
HDL-chol	49.8 ± 11.3	49.6 ± 10.7	71.5 ± 31	57.7 ± 11.3
	ns	<0.05	<0.05	ns
TSH	1.1 ± 0.6	1.2 ± 0.6	1.4 ± 0.8	1.5 ± 0.8
	ns	ns	ns	ns
FT3	3.6 ± 1.3	3.3 ± 0.7	3.7 ± 1.4	3.3 ± 0.9
	ns	ns	ns	ns
FT4	1.2 ± 0.6	1.2 ± 0.6	1.1 ± 0.5	1.1 ± 0.5
	ns	ns	ns	ns
AbTG	44.2 ± 45.5	28.0 ± 40.2	45.5 ± 91.2	30.1 ± 43
	ns	ns	ns	ns
AbTPO	8.3 ± 9.1	9.2 ± 10	6.2 ± 4.6	6.5 ± 5.2
	ns	ns	ns	ns

P1: supplement t0 vs. placebo t0. P2: supplement t3 vs. placebo t3. P3: supplement t0 vs. t3. P4: placebo t0 vs. t3.

of corosolic acid which has shown anti-obesity effect inhibiting adipocyte differentiation [16] and a stimulating activity on glucose transport and glucose uptake in adipocytes [17]. Experimental studies have shown that also glycyrrhizic acid may improve insulin sensitivity and lipid metabolic disorders by reducing circulatory stress hormones, normalizing gluconeogenesis and increasing muscular lipid uptake [7]. Furthermore, glycyrrhizic acid may inhibit the expression of High Mobility Group box 1 (HMGB1), an important mediator of the inflammatory response, improving renal injury in diabetic rats [18]. This last report

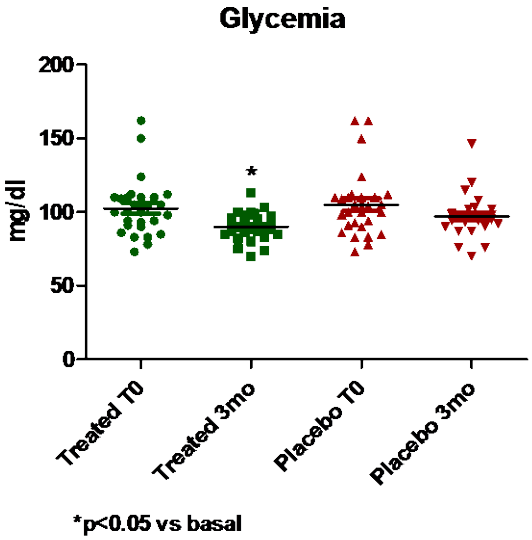

Figure 1. Glucose levels in both groups at baseline and after 3 months.

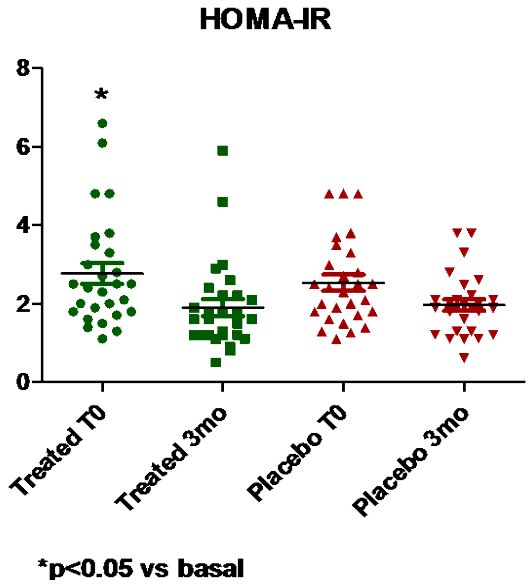

Figure 2. HOMA levels in both groups at baseline and after 3 months.

might be the reason for which a significant reduction of HMGB1 has been evidenced in the treated group; the statistically significant reduction of HMGB1 values in the treated group suggest that these natural compounds may decrease the oxidative stress status characteristic of MS, procrastinating the onset of complications such as cardiovascular diseases and diabetes. HMGB1 could be considered a new, effective tool for monitoring metabolic profile in MS. This is the first study which deals with this emergent biomarker of inflammation in menopausal women suffering by MS, treated with natural supplements.

In conclusion, our study suggests an association of three natural compounds as a new therapeutic approach for MS in a peculiar target of patients: women in

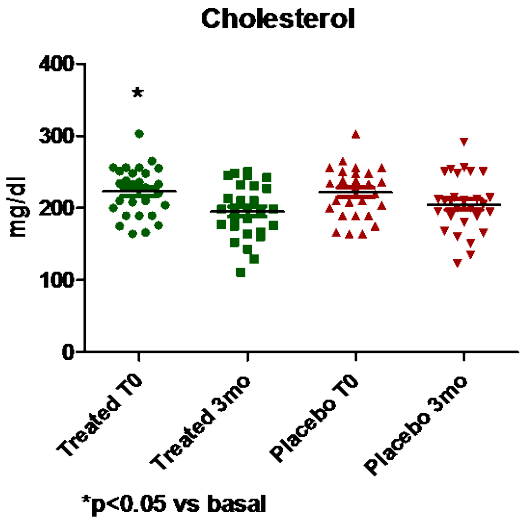

Figure 3. Total cholesterol levels in both groups at baseline and after 3 months.

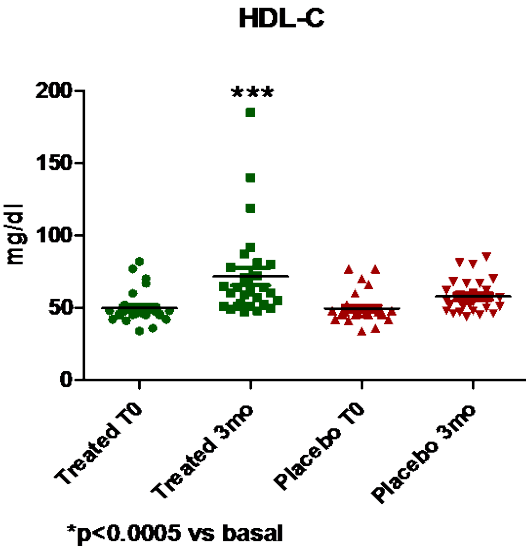

Figure 4. HDL-cholesterol levels in both groups at baseline and after 3 months.

post-menopause. As already known the study underlines the importance of a modified lifestyle and this was strongly recommended in both groups. The data obtained show that the association of these natural compounds determines metabolic effects, ameliorating some characteristics of MS, with benefits achieved only after 3 months of treatment. The association of corosolic acid, glycyrrhizic acid and cinnamon may represent an alternative choice to antidiabetic drugs to induce glucose uptake. Our data highlight the effectiveness of these ancient supplements with insulin-like and anti-adipogenesis, antioxidant and anti-inflammatory properties, to evaluate a possible application in medical practice. Further studies appear necessary in this field, and a larger study sample for a longer time is required to confirm our results.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Hunt, K.J., Resendez, R.G., Williams, K., Haffner, S.M. and Stern, M.P. (2004) National Cholesterol Education Program versus World Health Organization Metabolic Syndrome in Relation to All-Cause and Cardiovascular Mortality in the San Antonio Heart Study. *Circulation*, **110**, 1251-1257. https://doi.org/10.1161/01.CIR.0000140762.04598.F9

[2] Reusch, J.E. (2002) Current Concepts in Insulin Resistance, Type 2 Diabetes Mellitus, and the Metabolic Syndrome. *American Journal of Cardiology*, **90**, 19G-26G. https://doi.org/10.1016/S0002-9149(02)02555-9

[3] Brownlee, M. (2005) The Pathobiology of Diabetic Complications: A Unifying Mechanism. *Diabetes*, **54**, 1615-1625. https://doi.org/10.2337/diabetes.54.6.1615

[4] Roeters van Lennep, J., Westerveld, H.T., Erkelens, D.W. and van der Wall, E.E. (2002) Risk Factors for Coronary Heart Disease: Implications of Gender. *Cardiovascular Research*, **53**, 538-549. https://doi.org/10.1016/S0008-6363(01)00388-1

[5] Razmjou, S., Bastard, J.P., Doucet, E., Rabasa-Lhoret, R., Fellahi, S., Lavoie, J.M., *et al.* (2016) Effect of Menopausal Transition and Physical Activity Energy Expenditure on Inflammatory Markers: A MONET Group Study. *Menopause*, **23**, 1330-1338. https://doi.org/10.1097/GME.0000000000000716

[6] Judi, W.V., Hari, S.P., Stogsdill, W.W., Judi, J.S., Naguib, Y.N. and Passwater, R. (2003) Antidiabetic Activity of a Standardized Extract (Glucosol) from *Lagerstroemia speciosa* Leaves in Type II Diabetics. A Dose-Dependence Study. *Journal of Ethnopharmacology*, **87**, 115-117. https://doi.org/10.1016/S0378-8741(03)00122-3

[7] Cheng, H.S., Yaw, H.P., Ton, S.H., Choy, S.M., Kong, J.M. and Abdul Kadir, K. (2016) Glycyrrhizic Acid Prevents High Calorie Diet-Induced Metabolic Aberrations Despite the Suppression of Peroxisome Proliferator-Activated Receptory Expression. *Nutrition*, **32**, 995-1001. https://doi.org/10.1016/j.nut.2016.02.002

[8] Qin, B., Panickar, K.S. and Anderson, R.A. (2010) Cinnamon: Potential Role in the Prevention of Insulin Resistance, Metabolic Syndrome, and Type 2 Diabetes. *Journal of Diabetes Science and Technology*, **4**, 685-693. https://doi.org/10.1177/193229681000400324

[9] Lopez-Tinoco, C., Roca, M., Fernandez-Deudero, A., Garcia-Valero, A., Bugatto, F., Aguilar-Diosdado, M., *et al.* (2012) Cytokine Profile, Metabolic Syndrome and Cardiovascular Disease Risk in Women with Late-Onset Gestational Diabetes Mellitus. *Cytokine*, **58**, 14-19. https://doi.org/10.1016/j.cyto.2011.12.004

[10] Giacobbe, A., Granese, R., Grasso, R., Salpietro, V., Corrado, F., Giorgianni, G., *et al.* (2016) Association between Maternal Serum High Mobility Group Box 1 Levels and Pregnancy Complicated by Gestational Diabetes Mellitus. *Nutrition, Metabolism & Cardiovascular Diseases*, **26**, 414-418. https://doi.org/10.1016/j.numecd.2016.02.007

[11] Borzoei, A., Rafraf, M. and Asghari-Jafarabadi, M. (2018) Cinnamon Improves Metabolic Factors without Detectable Effects on Adiponectin in Women with Polycystic Ovary Syndrome. *Asia Pacific Journal of Clinical Nutrition*, **27**, 556-563.

[12] Gupta Jain, S., Puri, S., Misra, A., Gulati, S. and Mani, K. (2017) Effect of Oral Cinnamon Intervention on Metabolic Profile and Body Composition of Asian Indians

with Metabolic Syndrome: A Randomized Double-Blind Control Trial. *Lipids in Health and Disease*, **16**, 113. https://doi.org/10.1186/s12944-017-0504-8

[13] Adisakwattana, S., Lerdsuwankij, O., Poputtachai, U., Minipun, A. and Suparpprom, C. (2011) Inhibitory Activity of Cinnamon Bark Species and Their Combination Effect with Acarbose against Intestinal *α*-Glucosidase and Pancreatic *α*-Amilase. *Plant Foods for Human Nutrition*, **66**, 143-148. https://doi.org/10.1007/s11130-011-0226-4

[14] Anand, P., Murali, K.Y., Tandon, V., Murthy, P.S. and Chandra, R. (2010) Insulinotropic Effect of Cinnamaldehyde on Transcriptional Regulation of Pyruvate Kinase, Phosphoenolpyruvate Carboxykinase, and GLUT4 Translocation in Experimental Diabetic Rats. *Chemico-Biological Interactions*, **186**, 72-81. https://doi.org/10.1016/j.cbi.2010.03.044

[15] Jarvill-Taylor, K.J., Anderson, R.A. and Graves, D.J. (2001) A Hydroxycalcone Derived from Cinnamon as a Mimetic for Insulin in 3T3-L1 Adipocytes. *Journal of the American College of Nutrition*, **20**, 327-336. https://doi.org/10.1080/07315724.2001.10719053

[16] Liu, F., Kim, J., Li, Y., Liu, X., Li, J. and Chen, X. (2001) An Extract of *Lagerstroemia speciosa* L. Has Insulin-Like Glucose Uptake-Stimulatory and Adipocyte Differentiation-Inhibitory Activities in 3 T3-L1 Cells. *The Journal of Nutrition*, **131**, 2242-2247. https://doi.org/10.1093/jn/131.9.2242

[17] Klein, J., Kim, J., Himmeldirk, K., Cao, Y. and Chen, X. (2007) Antidiabetes and Anti-Obesity Activity of *Lagerstroemia speciosa*. *Evidence-Based Complementary and Alternative Medicine*, **4**, 401-407. https://doi.org/10.1093/ecam/nem013

[18] Zhang, H., Zhang, R., Chen, J., Shi, M., Li, W. and Zhang, X. (2017) High Mobility Group Box1 Inhibitor Glycyrrhizic Acid Attenuates Kidney Injury in Streptozotocin-Induced Diabetic Rats. *Kidney and Blood Pressure Research*, **42**, 894-904. https://doi.org/10.1159/000485045