

Citrullus colocynthis and Silbum Marian as therapeutic agent in metabolic syndrome Rrattus model

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Abstract

Background: Plants represent a treasure chest with many unrevealed medical applications that have made them traditionally used for thousands of years to treat different diseases. One of these applications is the hypoglycemic and antioxidant roles of some plants. A pathological condition characterized by hyperglycemia, insulin resistance, and dyslipidemia known as metabolic syndrome.

Objectives: This work focuses on examining the hypoglycemic effect of three plants on a metabolic syndrome-induced animal model and studying the role of the extracted phenolic compounds on different mitochondrial function genomic parameters. **Methods:** Citrullus colocynthis, Silbum Marian, and Rheum rhabarbarum phenolic compounds extracted and quantified using the Folin–Ciocalteu reagent, as described by Sánchez-Rangel et al. (2013). Forty albino rats were included in the work. They were divided into eight groups of five animals each as follows: negative control (normal), positive control (metabolic syndrome induced with fructose with no treatment), and metabolic syndrome treatment with Citrullus colocynthis, metabolic syndrome treatment with Silbum Marian, and metabolic syndrome treatment with Rheum rhabarbarum. Non-metabolic syndrome animals treated with Citrullus colocynthis Non-metabolic syndrome animals treated with Silbum Marian and non-metabolic syndrome animals treated with Rheum rhabarbarum Lipid profile, liver function tests, serum glucose, lactate, pyruvate, and molar lactate/pyruvate ratio. Mitotracker (green and red) used to study mitochondrial mass and action potential.

Results: The results of this work revealed that the three plants significantly reduce blood glucose in metabolic syndrome-induced rats. The three plants return serum lactate, pyruvate, and molar lactate: pyruvate ratio to normal control negative values. Mitochondrial mass and action potential significantly improve after treatment. In comparison to metabolic syndrome animals, the mitochondrial copy number of peripheral blood cells significantly increases after treatment with the three plants. metabolic syndrome significantly reduce mitochondrial genome copies number. The application of the ethanolic extract of Citrullus colocynthis and Silbum Marian.

Keywords: phenolic compounds, glycemic profile, mitochondrial copies number, action potential, lactate: pyruvate ratio.

phenolic compounds on different mitochondrial function and genomic parameters.

1. Introduction

Metabolic syndrome (MS) refers to a group of risk factors for cardiovascular disease that includes central-obesity, hyperglycemia, dyslipidemia, and hypertension (Frazier-wood & Wang, 2016). Various organizations have developed their own definitions of MS. However, these organizations later merged and created a new definition known as "harmonized criteria," which included central-obesity, high blood pressure, high serum triglyceride levels, low serum HDL cholesterol, presence of abnormally high serum glucose and/ or insulin resistance and hyperuricemia (Prakaschandra & Naidoo, 2022). Metabolic syndrome diagnosed when a patient has at least three of the conditions listed above. High-carbohydrate especially Fructose and/ or high-fat diets, as well as sedentary lifestyles, all contribute to the development of MS (Vatashchuk et al., 2022).

In our previous works, induction of MS by high fructose diet caused significant elevation in oxidative stress; induce apoptosis and /or necrosis in time dependent manner, in addition to the deteriorating effect on mitochondrial function and genome (Taqa et al., 2022). In some works, insulin resistance was correlate to abnormal mitochondrial activity (Sergi et al., 2019),(Patti & Corvera, 2010), while others works demonstrated how impaired mitochondrial function could lead to insulin resistance(Heo et al., 2021)(Ruegsegger et al., 2018). Sebastián et al. (2012) provided a critical description of the special coordination function of mitofusion proteins in mitochondria and endoplasmic reticulum function, which led to a modulation of insulin signaling and glucose homeostasis in liver-specific Mfn-2 KO-mice(Sebastián et al., 2012).

This work focuses on examining the hypoglycemic effect of three plants on induced-metabolic syndrome-rattus model and studying the role of the extracted

2. Methods and materials

Citrullus colocynthis, Silbum Marian, and Rheum rhabarbarum phenolic compounds extracted and quantified using the Folin–Ciocalteu reagent, as described by Sánchez-Rangel et al.(Sánchez-Rangel et al., 2013). GC analysis was conduct in College science – University of Mosul. Forty albino rats were included in the work. They were divided into eight groups of five animals each as follows: negative control (normal), positive control (metabolic syndrome induced with fructose with no treatment), and metabolic syndrome treatment with Citrullus colocynthis, metabolic syndrome treatment with Silbum Marian, and metabolic syndrome treatment with Rheum rhabarbarum. Non-metabolic syndrome animals treated with Citrullus colocynthis Non-metabolic syndrome animals treated with Silbum Marian and non-metabolic syndrome animals treated with Rheum rhabarbarum.

Serum glucose, lipid profile, liver function tests and some renal function parameters assessed by Fully-auto Biochemistry Analyzer, BA-A-160 (Bioveopeak). Indirect Mitochondrial function parameters as serum lactate, pyruvate determined by fluorescence-based methods of Cayman chemicals (700510 and 700470 respectively) and molar lactate/pyruvate ratio. Mitochondrial copy number was assayed using ND1 gene (Ahmed, 2018) and GAPDH as housekeeping gene.

3. Results

The GC-mass analysis for the phenolic extract contain the following compounds as showed in Table 1.

Plant extract	Compounds	Reten tion time	Molec ular Weight

Citru llus colocynt his	Diethyl Phthalate	20.55 5	222 152
	Phenol, 4- (ethoxymethyl)	22.12 1	240
	Cyclopentade canone, 2- hydroxy	27.04 1	194
	Alpha-D- Glucopyranoside , methy	28.74 3	
Silyb um marianu m	4H-Pyran-4- one, 2,3-dihydro- 3,5-dihydroxy-6- methyl	19.57 0	144 222
	4-Diethyl Phthalate	20.55 5	240
	4-Diethyl Phthalate	27.04 2	180
	Cyclopentade canone, 2- hydroxy	28.05 8	180
	(E)-4-(3- Hydroxyprop-1- en-1-yl)-2- methoxyphenol	28.05 8	
Benzene, 1- (butylthio)-4- methyl			
Rheu m ribes	Furaneol	17.03 1	128
	4H-Pyran-4- one, 2,3-dihydro- 3,5-dihydroxy-6- methyl-	19.56 6	144 142
	4H-Pyran-4- one, 5-hydroxy- 2-	19.75 4	222
	(hydroxymethyl)	20.55 2	126 152
	Diethyl Phthalate	21.79 6	206

			124
5- Hydroxymethylf urfura	23.63 2		194
Vanillin	25.96 9		
4-(p- Acetoxyphenyl)- 2-butanone	27.33 1		
Orcinol	28.73 8		
Alpha.-D- Glucopyranoside , methyl			

A significant increase was observed in the level of serum lactate in rats with positive control by (186%) compared to the negative control group at a significant level (0.01).

The group of rats with metabolic syndrome treated with ethanolic extract of Citrullus colocynthis showed significant decrease in the level of serum lactate by (37%) at a significant level (0.01) compared to the positive group. As for metabolic syndrome animals treated with ethanolic extract of Silbum Marian which shows significant decrease in serum lactate by (35%) at a significant level (0.01) compared to the positive group.

As for the two groups of animals without the metabolic syndrome, one of them was treated with the Citrullus colocynthis, and the second group was treated with the Silbum Marian . There was a significant decrease in the lactate by (44%) and (43%) respectively, at a significant level of 0.01, compared with the positive group.

The result of the work indicates a significant increase in the level of serum pyruvate in rats with metabolic syndrome by (340%) compared to the negative control group at a significant level (0.01).

Animals with the metabolic syndrome treated Citrullus colocynthis , there was a significant decrease (57%) in the level of pyruvate enzyme compared to the

positive group; As for rats with metabolic syndrome treated with Silbum Marian, there was a significant decrease in the level of pyruvate by (51%) compared to the positive group; at a significant level (0.01) for both groups.

The group of rats without metabolic syndrome dosed with *Citrullus colocynthis* showed significant decrease in the level of pyruvate by (67%) compared to the positive group at a significant level of (0.01); similarly, those animals dosed with Silbum Marian, pyruvate level decreased significantly by (65%) at a significant level 0.01 compared to the positive group.

Molar lactate to pyruvate ratio – as indirect mitochondrial function index - study indicated that; The comparison between the molar ratio of lactate to pyruvate in rat serum showed a significant decrease (44%) between the positive group (with metabolic syndrome) and the negative group (without metabolic syndrome) at a significant level of 0.05.

Metabolic syndrome animals treated with *Citrullus colocynthis* there was a significant increase (46%) compared to the positive control group at a significant level of 0.05; while those treated with Silbum Marian showed significant increase (11%) compared to the positive control group at a significant level of 0.05.

As for animals without metabolic syndrome (two groups), the group dosed with *Citrullus colocynthis* showed significant increase (28%), and those treated with Silbum Marian showed significant increase of (25%) compared to the positive control group at a significant level of 0.05.

The above data indicated significant effect for these two extract on mitochondrial function, Mitochondrial genome copies number recruited here to explain the changes in the different groups in this work, and the results shows that, the positive control group with the metabolic syndrome showed a significant decrease in the number of copies (mtDNA) by (101%) compared to the negative control group at a significant level (0.01).

In the first week of the experiment, metabolic syndrome animals treated with coloscythin, there was significant increase in the number of mtDNA copies by (77%) compared to the positive control group at a significant level (0.01). similarly, metabolic syndrome

treated with ethanolic extract of *Silbum* plant, showed significant increase in the number of (mtDNA) copies was observed by (73%) compared to the positive control group.

For the negative control group treated with ethanolic extract of *Citrullus colocynthis* plant and ethanolic extract of *Silbum Marian*, there was no significant effect of both plants on the mtDNA number copies.

In the second week of the experiment, there was an increase in the relative number of (mtDNA) copies of the group of rats with metabolic syndrome treated with ethanolic extract of *Citrullus colocynthis* by (42%) compared to the positive control group at a significant level (0.01). similarly, those treated with ethanolic extract of *Silbum* plant, showed increase in the number copies mtDNA by (74%) compared with the positive group at a significant level (0.01).

The results also showed that for the two groups of rats without metabolic syndrome and dosed with the ethanolic extract of *Citrullus colocynthis* and galangal, there was an increase in the relative number of (mtDNA) copies by (11% and (12%)), respectively, compared with the positive group, at a significant level (0.05).

In the third week, the results of the group of rats with the metabolic syndrome and treated with ethanolic extract of *Citrullus colocynthis* showed an increase in the relative number copies mtDNA by (33%) at a significant level (0.01). the metabolic syndrome treated with ethanolic extract of *Silbum Marian* showed an increase of (63%) at a significant level of 0.01 compared with the positive group.

Rats without the metabolic syndrome dosed with the ethanolic extract of the *Citrullus colocynthis* plant, as well as the group of rats without the metabolic syndrome dosed with the ethanolic extract of the *Silbum Marian*, an increase in the relative number copies mtDNA was observed by (31% and 14%), respectively, compared to the positive group.

In the fourth week; The results of the group of rats with the metabolic syndrome treated with ethanolic extract of *Citrullus colocynthis* showed an increase in the relative number copies of mtDNA by ((18%) at a significant level (0.05) compared with the positive

group; while the group of rats with the metabolic syndrome treated with the ethanolic extract of the *Silbum Marian* also showed an increase in the relative number copies mtDNA by (33%) at a significant level (0.01) compared with the positive group.

The two groups without metabolic syndrome and dosed with ethanolic extract of *Citrullus colocynthis* and *Silbum Marian*, respectively, showed an increase in the relative number of mtDNA copies by (34% and 12%) for each group, respectively, at a significant level (0.01) compared with the positive group.

In conclusion, metabolic syndrome significantly reduce mitochondrial genome copies number. The application of the ethanolic extract of *Citrullus colocynthis* and *Silbum Marian*.

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3

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