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Potential Effects of Curry (*Murraya koenigii*) and Walnut Leaves (*Juglans regia*) on Diabetic Rats Induced by Alloxan.

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Abstract:
Egypt is among the world's top 10 countries in the number of patients with diabetes mellitus (DM). Medicinal plants are used to treat diabetes to overcome hypoglycemic medications' cost and unwanted side effects. The current study investigated the potential effects of curry and walnut leaves powders (CLP and WLP) and their methanolic extracts (CLEx and WLEx) on diabetic rats. Sixty male albino rats weighing (150±10g) were divided into two main groups. The first main group (group 1=6 rats): as control (-ve) fed on the basal diet BD. The second main group (diabetic rats, 54 rats): was injected with alloxan to induce DM and divided into nine subgroups, six rats for each as follows: group (2): as control (+ve) fed on BD, groups (3-6): fed on BD containing (5.0 and 7.0 %, w/w) of CLP and WLP; and groups (7-10): fed on BD and orally administered with (200 and 400 mg/kg/d) of CLEx and WLEx, for 42 days respectively. Results showed that alloxan induced a significant (P≤0.05) decrease in insulin, HDL-c, Superoxide dismutase (SOD), Glutathione peroxidase (GPX), and Catalase (CAT) levels; and significantly increased blood glucose level, liver and kidney functions parameters, lipid profile and malondialdehyde content (MDA). Treatment of diabetic rats with CLP, WLP, CLEx and WLEx at the tested concentrations improved all indicated markers. In conclusion, these findings may provide a basis for utilizing curry and walnut leaves, or foods fortified with them, for the prevention/treatment of DM instead of/beside synthetic medications that may have adverse effects.

Keywords*: Curry leaves, Walnut leaves, Phenolic compounds, Diabetes mellitus, Antioxidants enzymes activities, Malondialdehyde.*

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both [1]. Egypt is the eighth leading country regarding the prevalence of DM [2].

Diabetes affects around 15.56% of adults aged 20 to 79 in Egypt, with diabetes accounting for 86,478 deaths annually. Diabetes prevalence in Egypt has risen dramatically over a relatively short period, from an estimated 4.4 million in 2007 to 7.5 million in 2013. This number is expected to increase to 13.1 million by 2035 [3]. Diabetes significantly burdens society through increased medical expenditures, lost productivity, early death, and insensible costs such as decreased quality of life [4]. There are multiple commercial medications for diabetes treatment; however, their long-term usage may result in undesired side effects on the kidney, liver, stomach, etc. [5]. Therefore, the world's focus began to shift to the phytotherapy method for managing diabetes [6]. Medicinal plants are utilized to prevent and control diabetes to alleviate the population's financial burden from the high expense of traditional pharmaceuticals [7].

The curry leaves (*Murraya koenigii*) have well-established therapeutic potentials like hypolipidemic, nephroprotective, hepatoprotective, and cardioprotective effects in experimental animals [8]. The therapeutic activities of *M. koenigii* are related to multiple chemical components of distinct carbazole alkaloids and other significant metabolites, including terpenoids, flavonoids, phenolics, carotenoids, vitamins, and nicotinic acid from various parts of the plant [9]. The walnut leaves (*Juglans regia*) contain phenolic acids, tannins, essential fatty acids, ascorbic acid, flavonoids, caffeic acid, and paracomaric acid [10]. Pharmacological evidence has linked the positive benefits of *Juglans regia* L. leaf extract to a broad range of biological activities, particularly anti-oxidative, anti-inflammatory, anti-carcinogenic, antimicrobial, and antifungal effects [11].

This study aimed to evaluate the effect of curry, and walnut leaves powders at concentrations of (5.0 and 7.0% w/w of BD) and their methanolic extracts (200 and 400 mg/kg/d) on diabetic rats induced by alloxan.

Material and Methods

Materials

Curry (*Murraya koenigii*) and walnut (*Juglans Regia*) leaves were obtained from the local market of Shebin El-Kom, Menoufia Governorate, Egypt.

Chemicals and Kits

Alloxan, (pure chemical fine product) was obtained from SIGMA (USA), and used for induction of diabetes mellitus among rats. Casein, vitamins mixture, salt mixture, cellulose, L-Cystine, choline chloride and methanol were purchased from El-Gomhoriya Company, Cairo, Egypt. Kits used to determine the biochemical analysis were obtained from Gamma Trade Company, Cairo, Egypt.

Experimental animals

Normal sixty (60) adult male albino rats of Sprague Dawley Strain, weighing (150±10g) were bought from the Medical Insects Research Institute, Dokki, Cairo, Egypt.

Methods

Preparation of curry and walnut leaves powders (CLP & WLP) and their extracts (CLEx. & WLEx.)

All plant leaves were dried in a vacuum oven at 40°C then ground into fine powder by using an electric grinder and kept in dark glass bottles in a cool and dry place till use according to Russo [12].

Powders of curry (*Murraya koenigii*) and walnut tree leaves (*Juglans Regia*) (400g) were soaked in 1000 ml of distilled methanol for five days (three times) with occasional shaking. After maceration, the mixtures filtered through Whatman (No.1) filter paper to separate the filtrate from residues. The resulting filtrates were evaporated to a constant weight on a rotay evaporator with the recovery of (15.1) g and (22.6) g of extracts, respectively. Extracts were subsequently dissolved in distilled water to the desired concentrations to be studied (200 and 400 mg/kg. bwt/d) for each extract [13].

Determination of proximate chemical composition, total phenolic content, and phenolic compounds

Concentrations of moisture, total protein, fat, fiber, and ash were determined in curry leaves and walnut leaves according to AOAC [14], while total carbohydrates were estimated by differences. Carbohydrates (%) = 100 - (% moisture + % protein + % fat + % Ash + % fiber). Total phenolic content was determined spectrophotometrically according to Folin–Ciocalteu colorimetric method as reported by Haq et al., [15]. Some phenolic compounds of the tested materials were determined according to the method described by Crozier et al., [16].

The Biological experiment

Ethical approval

The biological experiments conducted in this study were granted ethical approval by the Scientific Research Ethics Committee (Animal Care and Use), Faculty of Home Economics, Menoufia University, Shebin El-Kom, Egypt (Approval no. 24-SREC-10-2019).

Preparation of the basal Diet (BD)

The basal diet was formulated in accordance with AIN, [17].

Induction of diabetes mellitus

Diabetes was induced in healthy albino rats via intraperitoneal injection of alloxan 150 mg/kg body weight as described by by Desai and Bhide [18]. Fasting blood samples were collected one week following the alloxan injection to determine fasting serum glucose. Rats with more than 200 mg/dl of blood glucose were considered diabetics [19]

Experimental design

The experiment was carried out at the Faculty of Home Economics, Menoufia University, Shibin El-Kom, Egypt. The rats were kept in separate stainless steel cages during the experiment under standard ambient temperature conditions and a 12-hour light-dark cycle. For acclimation, all rats were fed the basal diet (BD) for a week prior to the experiment.

After one week, the rats were separated into two main groups: The first group (Group 1): 6 rats as a negative control group and was fed on the BD. The second main group (diabetic rats, 54 rats) was fed BD. and injected with a single dose of freshly prepared alloxan solution (150 mg/kg B.W.) to induce DM, and then divided into nine subgroups of six rats each as

follows: Group (2): as a positive control group, fed on BD; Groups (3-6): fed on BD containing (5.0 and 7.0 %, w/w) of CLP and WLP; and Groups (7-10): were fed on BD, and received an oral dose of (200 and 400 mg/kg/d) of CLEx and WLEx, respectively. All rats had unrestricted access to food and water. The treatments lasted a total of 6 weeks.

Biological evaluation

Feed consumption was documented daily during the experiment, and body weight was recorded weekly. Body weight gain (BWG) g/d, feed intake (FI) g/day/rat, and feed efficiency ratio (FER) were calculated following Chapman *et al*. [20] using the following formulas:

BWG = (Final weight – Initial weight)

FER = Body weight gain (g/42 day)/ feed intake (g/42 day).

Blood sampling

At the end of the experiments, the rats were fasted for 12 hours before being sacrificed. Blood was obtained from the portal vein of each rat and separated into two samples. A sample was kept in clean, dry centrifuge tubes for 30 min until clotted before being centrifuged at 3000 rpm for 15 min to separate the serum. The serum was cautiously extracted, placed in clean Eppendorf tubes, and then frozen at -20 ^{o}C until the assay [21]. The other blood sample was placed in an EDTA anticoagulation tube to determine the levels of antioxidant enzymes (catalase CAT, superoxide dismutase SOD, and glutathione peroxidase GSH-Px) in red blood cells RBCs.

Biochemical analysis

Blood glucose and serum insulin levels

Enzymatic determination of serum glucose was performed calorimetrically in accordance with the method reported by [22]. Serum insulin was determined according to [23].

Serum lipid profile

Serum triglycerides (TG) were estimated by the enzymatic method described by, [24]. Determination of serum total cholesterol (TC) was carried out according to the method described by [25]. High-density lipoprotein (HDL-c) was evaluated according to the methods reported by [26]. Very low-density lipoprotein (VLDL-c) and Low-density lipoprotein (LDL-c) were computed as described by [27] as follows:

VLDL-c (mg/dl) = Triglycerides/5

LDL-c (mg/dl) = Total cholesterol – (HDL-c + VLDL-c)

Liver function parameters

Serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and serum alkaline phosphatase (ALP) were determined according to the methods described by [28 and 29].

Kidney functions

Serum urea and serum creatinine were estimated following the methods described by [29 and 30]. While serum uric acid was measured using the technique reported by [31].

Malondialdehyde concentration (MDA) and antioxidant enzymes activities

MDA (a biomarker of lipid peroxidation) in the serum was evaluated as thiobarbituric acid reactive substances (TBARS), as explained by [32]. Glutathione peroxidase (GSH-Px) activity was determined following the method described by [33]. The activity of superoxide dismutase

(SOD) was estimated following the procedure reported by [34]. At the same time, the technique described by [35] was used to evaluate catalase (CAT) activity.

Statistical Analysis

One-way ANOVA was employed to analyze the data statistically using Computerized Costate Software. The results were presented as a mean ± standard deviation (SD). Variations among treatments, at a significance level of (P≤0.05), were regarded as statistically significant [36].

Results and Discussion

Proximate chemical composition, total phenolic content, and selected phenolic compounds of curry and walnut leaves

Table (1) reflects the proximate chemical composition, total phenolic content, and some phenolic compounds of curry and walnut leaves. The obtained data illustrated that the moisture, total protein, crude fat, crude fiber, ash and total carbohydrate contents were 7.58, 16.93, 3.79, 5.23, 11.25 and 55.22% (for curry leaves) and 6.18, 13.15, 4.53, 7.80, 13.10 and 55.24% (for walnut leaves) respectively. The data indicated a high total phenolic content TPC of walnut leaves and curry leaves (61.44 and 44.53 mg/g) respectively. Analysis of some phenolic compounds demonstrated that curry and walnut leaves contained a vital phenolic compounds like, pyrogallol, gallic, catechol, caffeic, vanillic, oleuropin, ferulic, ellagic and coumarin.

Jain *et al*., [37] found that the nutrient value of (*Murraya koenigii*) fresh curry leaves as per 100gram (protein 6g, fat 1g, carbohydrate 18.7g) and dry curry leaves (protein 12g, fat 5.4g, carbohydrate 64.31g). Abeysinghe *et al*., [38] reported that, total polyphenol content (TPC) of curry leaves (*M. koenigii*) was 101±1 mg GAE/g. Igara *et al*. [39] discovered that the coumarins and flavonoids of catechin and rutin were antioxidants and anticancer components among the non-alkaloidal active ingredients in curry leaves (*M. koenigii*). Moreover, the polyphenolic components ferulic acid, gallic acid, and vanillic acid have been shown to boost the antioxidant capacity of curry leaves (*M. koenigii*). Taha and Alwadaan [40] indicated that walnuts are a nutrient-dense food because of their abundant fat, protein, vitamin, and mineral content. They also contain high amounts of flavonoids, sterols, pectin compounds, phenolic acids, and other polyphenols. Ebrahimi *et al*. [41] reported that walnut leaves had many phenolic compounds, including coumaric acid, vanillic acid, ellagic acid, myricetin, juglone, and rutin.

The components mentioned above in curry and walnut leaves may be essential from a nutrition perspective. Therefore, the fortification of various food products by CLP and WLP could improve the nutritional quality of the products more than many other food sources. Additionally, these leaves' total phenolic contents and phenolic components make such food an essential functional food.

Table 1. Proximate chemical composition, total phenolic, and selected phenolic compounds of curry and walnut leaves

Component	Curry Leaves	Walnut Leaves
Proximate chemical composition		
Moisture (g/100g)	7.577	6.181
Total protein (g/100g)	16.929	13.150
Crude fat (g/100g)	3.79	4.53
Ash (g/100g)	11.254	13.102
Total carbohydrate (g/100g)	55.22	55.24
Crude fiber (g/100g)	5.23	7.80
Total phenolic content TPC		
Total Phenolic (mg/g)	44.53	61.44
Selected phenolic compounds (ppm)		
Pyrogallol	38.82	138.46
Gallic	5.76	34.13
3-OH-Tyrosol	80.82	ND*
Catechol	6.57	586.53
4-Aminobenzoic	102.95	9.87
Catechein	129.79	ND*
Chlorogenic	20.59	ND*
P-OH-benzoic	39.52	347.82
Benzoic	72.99	ND*
Caffeic	45.27	204.48
Vanillic	100.45	141.27
Caffeine	260.11	214.95
Oleuropin	32.88	ND*
Ferulic	38.82	593.04
Ellagic	5.76	1945.24
Coumarin	80.82	82.77

** ND, not detected.*

The effect of CLP, WLP, CLEx, and WLEx on body weight gain (BWG), feed intake (FI), and feed efficiency ratio (FER) of diabetic rats.

Data in Table (2) showed the effect of CLP, WLP, CLEx, and WLEx on body weight gain (BWG), feed intake (FI) and feed efficiency ratio (FER) of diabetic rats. The data showed that the positive control group had lower mean values of BWG, FI, and FER compared to the negative control group, with a significant difference (P≤0.05) which were (1.51 Vs. 2.95 g/day/rat, 15.31 Vs. 15.56 g/day and 0.10 Vs. 0.19), respectively. Treatment of the diabetic rats with CLP and WLP (5.0 & 7.0%, w/w); and CLEx and WLEx (200 & 400 mg/kg/d) resulted in significant increases (P≤0.05) in the mean values of FER when compared with the positive

control group. The highest mean value of FER was recorded for the diabetic group treated with CLEx (200 mg/kg/d). In contrast, the lowest mean value was recorded for the groups fed on CLP and WLP (7.0%) of the BD with significant differences (P≤0.05).

Rajkumar et al. [42] and Matough et al. [43] reported that weight loss in diabetic rats may be due to the breakdown or degradation of protein structure. It seems reasonable that in the absence of insulin, cells, particularly skeletal muscle cells, cannot use glucose for energy but instead rely on intracellular proteins[43]. Birari *et al*. [44] found that dichloromethane (MKD) and ethyl acetate (MKE) extracts of curry (*Murraya koenigii*) leaves significantly reduced body weight gain. The anti-obesity and activity of these extracts were linked to the carbazole alkaloids Mahanimbine. According to Rabiei *et al*. [45], ingesting walnut (*J. regia*) leaves extract resulted in a marked drop in body weight, and a similar approach was observed by Rock *et al*. [46] in obese men and women who received a walnut-enriched diet.

Table 2. Effect of curry and walnut leaves powders and their methanolic extracts on body weight gain (BWG), feed intake (FI) and feed efficiency ratio (FER) of diabetic rats

Groups	BWG (g/day/rat)	FI (g/day)	FER
Control (-ve)	2.95^{a}±0.24	15.56^{d}±0.12	0.19^{a}±0.01
Control (+ve)	1.51^{d}±0.30	15.31^{e}±0.08	0.10^{d}±0.02
CLP (5.0%, w/w)	2.25^{bc}±0.19	16.79^{b}±0.14	0.13^{c}±0.01
CLP (7.0%, w/w)	1.72^{d}±0.44	12.82^{i}±0.21	0.13^{c}±0.03
WLP (5.0%, w/w)	2.23^{bc}±0.40	13.89^{h}±0.19	0.16^{abc}±0.03
WLP (7.0%, w/w)	1.87^{cd}±0.44	14.07^{g}±0.09	0.13^{c}±0.03
CLEx. (200 mg/kg/d)	2.61^{ab}±0.34	14.22^{f}±0.07	0.18^{a}±0.02
CLEx. (400 mg/kg/d)	2.82^{a}±0.23	17.16^{a}±0.18	0.16^{ab}±0.02
WLEx. (200 mg/kg/d)	2.58^{ab}±0.13	16.57^{c}±0.08	0.16^{bc}±0.01
WLEx. (400 mg/kg/d)	2.50^{ab}±0.32	17.09^{a}±0.09	0.15^{bc}±0.02
LSD	0.41	0.13	0.03

Each value was represented as mean ± standard deviation. Means in the same column with different letters are significantly different at p≤0.05. CLP, curry leaves powder; WLP, walnut leaves powder; CLEx, curry leaves extract and WLEx, walnut leaves extract.

The effect of CLP, WLP, CLEx, and WLEx on serum glucose and insulin levels

The data in Table (3) demonstrated the effect of CLP, WLP, CLEx, and WLEx on the diabetic rats' serum glucose and insulin levels. The data collected revealed that injected rats with the alloxan caused damage in pancreas cells, causing a significant decrease (P≤0.05) of insulin which led to a significant increase (P≤0.05) of serum glucose level for the control (+ve) group when compared with the control (-ve) group (60.10 Vs. 231.52 µIU/ml) and (245.91 Vs. 116.49 mg/dl) respectively. Treatment of the hyperglycemic rats with CLP and WLP (5.0 & 7.0%, w/w); and CLEx and WLEx (200 & 400 mg/kg/d) resulted in a significant reduction (P≤0.05) of mean values of serum glucose and a significant (P≤0.05) elevation of insulin levels as compared to the positive control group. The lowest mean serum glucose level was recorded for the WLEx-treated hyperglycemic group (400 mg/kg/d), and the highest mean

was recorded for the CLP-supported group (5.0%, w/w) of BD with a significant difference (P≤0.05). The lowest mean value of serum insulin level was recorded for the hyperglycemic group supported with CLP (5.0%, w/w) of the BD, and the highest mean value was recorded for the group treated with WLEx (400 mg/kg/d) with significant differences (P≤0.05). It is worth noting that the mean serum glucose levels of diabetic-treated groups with CLEx and WLEx (400 mg/kg/d) revealed insignificant differences comparing to the normal control group.

Table 3. Effect of curry and walnut leaves powders and their methanolic extracts on serum glucose and serum insulin levels of diabetic rats

Groups	Glucose (mg/dl)	Insulin (µIU/ml)
Control (-ve)	116.49 ^{g} ± 18.34	231.52 ^{a} ± 11.27
Control (+ve)	245.91 ^{a} ± 21.98	60.10 ^{i} ± 4.10
CLP (5.0%, w/w)	223.17 ^{b} ± 11.00	80.00 ^{h} ± 6.32
CLP (7.0%, w/w)	203.84 ^{cd} ± 6.36	107.00 ^{f} ± 5.43
WLP (5.0%, w/w)	211.01 ^{bc} ± 9.34	91.25 ^{g} ± 6.42
WLP (7.0%, w/w)	187.95 ^{d} ± 12.58	156.50 ^{d} ± 6.80
CLEx. (200 mg/kg/d)	159.49 ^{e} ± 11.52	138.25 ^{e} ± 9.28
CLEx. (400 mg/kg/d)	123.69 ^{fg} ± 11.24	164.75 ^{d} ± 5.07
WLEx. (200 mg/kg/d)	140.18 ^{f} ± 15.64	186.75 ^{c} ± 11.76
WLEx. (400 mg/kg/d)	119.20 ^{g} ± 9.18	218.37 ^{b} ± 11.30
LSD	16.87	10.63

Each value was represented as mean ± standard deviation. Means in the same column with different letters are significantly different at p≤0.05. CLP, curry leaves powder; WLP, walnut leaves powder; CLEx, curry leaves extract and WLEx, walnut leaves extract.

Alloxan has two damaging pathological effects: it downregulates glucose-induced insulin secretion by specifically inhibiting glucokinase, the beta cell's glucose sensor, and it induces insulin-dependent diabetes by stimulating species-reactive oxygen (ROS) formation, resulting in specific necrosis of beta cells. Both of these effects may be attributed to alloxan's distinct chemical characteristics, with the common denominator being preferential cellular absorption and accumulation of alloxan by beta cells [47]. Handral *et al*. [48] reported that mahanimbine, a chemical ingredient found in curry (*M. koenigii*) leaves, has been proven to lower blood sugar levels by improving the action of insulin, whether by enhancing peripheral glucose absorption or via releasing the Langerhans islets of pancreatic beta cells. Mahanimbine also demonstrated a substantial alpha-amylase inhibitory effect compared to acarbose, raised the levels of glucose-6phosphate dehydrogenase enzyme, and regulated hepatic and muscular glycogenesis, resulting in adequate glucose utilization. Kawser Hossain *et al*. [49] stated that the quercetin and kaempferol components present in walnut leaf extract serve as antioxidants and free radical scavengers, play a role in beta cell regeneration, and protect pancreatic islets. Also, Pereira *et al*. [50] indicated that the antihyperglycemic activity of walnut extract could be attributed to phenolic compounds, including gallic acid and caffeoylquinic acid. Jelodar *et al*. [51] showed that the mechanism involving in the

hypoglycemic effect of walnut *(J. regia*) leaves could be due to increased insulin production from remnant and/or regenerated β-cells, restoration of insulin sensitivity, intervention with dietary carbohydrate uptake in the small intestine, and facilitation of glucose utilization by peripheral tissues via an insulin-dependent pathway glucose transporter.

The effect of CLP, WLP, CLEx, and WLEx on serum lipid profile

The effect of CLP, WLP, CLEx, and WLEx on serum lipid profile levels of the diabetic rats are presented in Table (4). The results illustrated that the mean values of serum TC, TG, LDL-c, and VLDL-c levels of the positive control group were significantly (P≤0.05) higher than those of the negative control group. On the other hand, the mean HDL-c value in the positive control group decreased significantly (*P≤0.05*) when compared with the normal control group (30.14 and 45.05 mg/dl), respectively. Treatment of the diabetic rats with CLP and WLP (5.0 & 7.0%, w/w); and CLEx and WLEx (200 & 400 mg/kg/d) significantly (*P≤0.05*) improved the serum lipid profile levels. The highest mean values of TG and VLDL-c levels were recorded for the group fed on CLP (5.0%, w/w) of the BD (175.58 and 35.12 mg/dl) while the lowest mean values were recorded for the group treated with WLEx (400 mg/kg/d) (71.38 and 14.28 mg/dl) with a significant difference (*P≤0.05*). Regarding, HDL-c, the highest mean value was observed for the group treated with WLEx (400 mg /kg/d), while the lowest mean value recorded for the group supported with CLP (5.0%, w/w) of the BD with a significant difference (*P≤0.05*). On the other side, It was found that there were no statistically significant changes between the normal control group and the diabetic groups treated with WLEx (200 and 400 mg/kg/d) with respect to TC, TG, and VLDL-c.

The increase in serum lipids can be attributed to a variety of mechanisms including metabolic changes caused by insulin deficiency [52]. Bardini et al. [53] noted that in the absence of insulin, it is reasonable for the activity of hormone-sensitive lipase in adipocytes to increase, resulting in disturbances in lipid metabolism. Furthermore, El Senosi et al. [54] explained that hypertriglyceridemia can be attributed to the liver producing triglyceride-rich VLDL at higher rates and peripheral tissues, primarily adipose tissue and muscle, having decreased TG removal. Insufficient insulin leads to elevated TG production and subsequent packaging of VLDL. The reduced activity of lipoprotein lipase may account for the lower HDL-C levels in diabetes.

Our findings were consistent with those of El Amin *et al*. [55], who observed that curry leaves (*Murraya koenigii*) had a powerful hypolipidemic impact, that could be attributed to the existence of antioxidants like carbazole alkaloids (Mahanimbine) and polyphenols. Treatment with *Juglans regia* extracts also caused a marked drop in LDL, triglycerides, and total cholesterol and a significant improvement in HDL levels [56]. Shimoda *et al*. [57] stated that polyphenol-rich walnut extract had been shown to have hypotriglyceridemic effects in the liver through improving peroxisomal fatty acid β-oxidation and clarified that tellimagrandin I had an essential role in the process of hypotriglyceridemia.

Table 4. Effect of curry and walnut leaves powders and their methanolic extracts on serum lipid profile level of diabetic rats

Groups	TC (mg/dl)	TG (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
Control (-ve)	94.14^{e}±2.97	68.06^{f}±1.28	45.05^{a}±1.34	35.48^{e}±2.78	13.61^{f}±0.26
Control (+ve)	192.11^{a}±18.54	221.61^{a}±17.9	30.14^{e}±1.57	117.65^{a}±13.52	44.32^{a}±3.58
CLP (5.0%, w/w)	170.65^{b}±17.6	175.58^{b}±12.4	35.25^{d}±0.91	100.29^{b}±18.1	35.12^{b}±2.48
CLP (7.0%, w/w)	130.42^{c}±10.74	142.55^{c}±7.73	35.87^{cd}±0.91	66.04^{c}±10.32	28.51^{c}±1.55
WLP (5.0%, w/w)	175.30^{b}±6.36	152.41^{c}±10.29	36.85^{c}±0.97	107.97^{ab}±6.44	30.48^{c}±2.06
WLP (7.0%, w/w)	119.85^{cd}±7.44	122.17^{d}±13.9	39.00^{b}±0.68	56.42^{cd}±5.97	24.43^{d}±2.78
CLEx. (200 mg/kg/d)	130.38^{c}±12.95	142.48^{c}±11.29	39.45^{b}±1.16	62.43^{c}±11.54	28.49^{c}±2.26
CLEx. (400 mg/kg/d)	118.06^{cd}±11.4	103.83^{e}±7.02	39.32^{b}±0.99	57.97^{cd}±10.26	20.77^{e}±1.40
WLEx. (200 mg/kg/d)	107.61^{de}±7.48	74.29^{f}±6.16	40.30^{b}±1.00	52.45^{cd}±7.32	14.86^{f}±1.23
WLEx. (400 mg/kg/d)	101.68^{e}±5.55	71.38^{f}±4.12	40.47^{b}±1.34	46.93^{de}±6.61	14.28^{f}±0.82
LSD	13.80	13.10	1.40	12.61	2.62

Each value was represented as mean ± standard deviation. Means in the same column with different letters are significantly different at p≤0.05. CLP, curry leaves powder; WLP, walnut leaves powder; CLEx, curry leaves extract and WLEx, walnut leaves extract. (TC) Total cholesterol – (TG) Triglycerides – (HDL-c) High Density lipoprotein cholesterol – (LDL-c) Low Density lipoprotein cholesterol – (VLDL-c) Very Low-Density lipoprotein cholesterol.

The effect of CLP, WLP, CLEx, and WLEx on liver enzymes activities

Table (5) indicates the effect of CLP, WLP, CLEx, and WLEx on liver enzymes activities (aspartate aminotransferase AST, alanine aminotransferase ALT, and alkaline phosphatase ALP) of diabetic rats. It was obvious that, the mean values of AST, ALT and ALP for the control (+ve) group were significantly (*P≤0.05*) higher when compared to the control (-ve) group (200.72 *Vs* 89.17, 101.31 *Vs* 38.14 and 321.29 *Vs* 110.35 U/L), respectively. Treatment of hyperglycemic rats with CLP and WLP (5.0 & 7.0%, w/w); and CLEx and WLEx (200 & 400 mg/kg/d) caused a significant decrease (*P≤0.05*) in the liver enzymes activities when compared with the control (+ve) group. The highest mean values of liver enzymes activities were recorded for the hyperglycemic group fed on CLP (5.0%, w/w) of the BD and the lowest mean values were recorded for the group treated with WLEx (400 mg/kg/d) with a significant difference (*P≤0.05*).

Stanely et al. [58] demonstrated that since ALT is present in considerably higher concentrations in the liver compared to other parts of the body, an increase in ALT activity specifically indicates damage to the liver, which is a common occurrence in diabetes and may be attributed to the leakage of enzymes into the bloodstream. To certain limits, AST and ALT levels serve as markers for the normal functioning of the liver. Moreover, Toma et al. [59] reported that diabetes and hyperlipidemia also cause damage to cells by altering the architecture of the cell membrane, thereby leading to increased activities of ALP in diabetic rats.

Table 5. Effect of curry and walnut leaves powders and their methanolic extracts on liver enzymes activities of diabetic rats

Groups	AST (U/L)	ALT (U/L)	ALP (U/L)
Control (-ve)	89.17^{g} ±11.14	38.14^{h} ± 4.82	110.35^{e} ±18.95
Control (+ve)	200.72^{a} ±19.28	101.31^{a} ± 7.99	321.29^{a} ± 38.86
CLP (5.0%, w/w)	182.44^{b} ± 20.26	90.53^{b} ± 9.42	265.88^{b} ± 11.18
CLP (7.0%, w/w)	131.13^{cd} ± 9.13	80.94^{cd} ± 6.16	231.12^{c} ± 12.83
WLP (5.0%, w/w)	181.26^{b} ± 12.39	87.09^{bc} ± 8.98	256.01^{b} ± 20.35
WLP (7.0%, w/w)	119.17^{de} ± 6.81	59.32^{e} ± 5.02	187.55^{d} ± 22.27
CLEx. (200 mg/kg/d)	134.04^{c} ± 8.47	73.86^{d} ± 11.75	216.09^{c} ± 16.06
CLEx. (400 mg/kg/d)	106.55^{ef} ± 4.03	55.65^{ef} ± 6.03	186.00^{d} ± 16.72
WLEx. (200 mg/kg/d)	100.21^{fg} ±7.02	49.15^{fg} ± 4.65	169.33^{d} ± 15.21
WLEx. (400 mg/kg/d)	91.16^{g} ± 4.97	40.83^{gh} ± 6.72	133.36^{e} ± 8.73
LSD	13.94	9.43	23.32

Each value was represented as mean ± standard deviation. Means in the same column with different letters are significantly different at p≤0.05. CLP, curry leaves powder; WLP, walnut leaves powder; CLEx, curry leaves extract and WLEx, walnut leaves extract. (AST) Aspartate Aminotransferase – (ALT) Alanine Aminotransferase - (ALP) Alkaline Phosphates.

The obtained results are aligned with those found by Sathaye *et al*. [9] who discovered that the hepatoprotective nature of *M. koenigii* leaves extract resulted from the combined effect of carbazole alkaloids, including girinimbine, mahanine, mahanimbine, isomahanimbine, murrayazolidine, murrayazoline, as well as ascorbic acid, and α-tocopherol. Hydroethanolic leaves extract of *Murrya koenigii* in dosages of 200, 400, and 600 mg/kg b.w exhibited a significant reduction in ALT, AST, ALP, and total bilirubin levels in CCl_4-treated hepatotoxic rats. According to Eidi *et al*. [60] walnut leaf extract treatments (varying from 0.2 to 0.4 g/kg b.w) substantially reduced serum ALT, AST, and ALP levels in CCl_4-treated rats. Moreover, the antioxidant enzymes superoxide dismutase and catalase were enhanced by walnut leaves extract. Also, Shimoda *et al*. [57] reported that polyphenolic compounds, such as tellimagrandins I and II, rugosin C, and casuarictin, are key ingredients with a potential hepatoprotective against oxidative damage.

The effect of CLP, WLP, CLEx and WLEx on kidney function

The effect of CLP, WLP, CLEx, and WLEx on kidney functions (serum creatinine, uric acid, and urea) in diabetic rats is presented in Table (6). The obtained results demonstrated that Alloxan injection in rats induced a significant (P≤0.05) increase in mean serum creatinine, uric acid, and urea levels for the positive control group compared to the normal control group (1.21 *Vs* 0.53, 7.01 *Vs* 3.60 and 65.09 *Vs* 17.95 mg/dl), respectively. Treatment of diabetic rats with CLP and WLP (5.0 & 7.0%, w/w); and CLEx and WLEx (200 & 400 mg/kg/d) caused significant decreases (*P≤0.05*) in kidney functions when compared with the positive control group. The highest mean values of creatinine, uric acid and urea were recorded for the group supported with WLP (5.0%, w/w) of the BD while the lowest mean values were recorded for the hyperglycemic group treated with WLEx (400 mg/kg/d), with a significant difference at (*P≤0.05*) when compared with the control (+ve) group.

Diabetic nephropathy is a diabetic microvascular complication. The aggregation of glycogen granules in the distal tubules, which causes renal hypertrophy, is a significant morphological alteration related to persistent hyperglycemia as reported by Kang *et al*. [61].

Table 6. Effect of curry and walnut leaves powders and their methanolic extracts on kidney functions level of diabetic rats

Groups	Creatinine (mg/dl)	Uric acid (mg/dl)	Urea (mg/dl)
Control (-ve)	0.53 f ± 0.05	3.60 f ± 0.47	17.95 h ± 4.61
Control (+ve)	1.21 ^{a} ± 0.11	7.01 ^{a} ± 0.21	65.09 ^{a} ± 7.19
CLP (5.0%, w/w)	0.94 ^{b} ± 0.07	6.35 ^{b} ± 0.20	57.23 ^{b} ± 5.45
CLP (7.0%, w/w)	0.81 ^{c} ± 0.06	5.70 ^{c} ± 0.29	47.74 ^{c} ± 3.61
WLP (5.0%, w/w)	0.96 ^{b} ± 0.07	6.58 ^{b} ± 0.17	57.70 ^{b} ± 3.78
WLP (7.0%, w/w)	0.67 ^{de} ± 0.04	5.05 ^{d} ± 0.35	39.63 ^{de} ± 2.98
CLEx. (200 mg/kg/d)	0.74 ^{cd} ± 0.04	5.38 ^{cd} ± 0.68	43.89 ^{cd} ± 2.47
CLEx. (400 mg/kg/d)	0.73 ^{d} ± 0.06	5.26 ^{cd} ± 0.36	38.71 ^{ef} ± 2.70
WLEx. (200 mg/kg/d)	0.60 ^{ef} ± 0.05	4.34 ^{e} ± 0.32	34.03 ^{fg} ± 2.80
WLEx. (400 mg/kg/d)	0.55 ^{f} ± 0.05	3.65 ^{f} ± 0.25	30.61 ^{g} ± 3.76
LSD	0.07	0.43	4.88

Each value was represented as mean ± standard deviation. Means in the same column with different letters are significantly different at p≤0.05. CLP, curry leaves powder; WLP, walnut leaves powder; CLEx, curry leaves extract and WLEx, walnut leaves extract.

The results are in agreement with those of Bhandri., [62] who discovered that, oral administration of aqueous extract of *Murraya koenigii* leaves in a daily manner for 30 days in streptozotocin-induced diabetes in male rats were found a significant reduction in serum urea and creatinine levels and promote tissue regeneration in the kidney. Jain *et al*., [37] found that, *Murraya koenigii* contains koenimbidine which has reno-protective activity against unilateral renal ischemia. Furthermore, Noureddini and Rezaee-Joshogani. [63] reported that the impact of walnut leaves' ether, ethanol, and cyclohexane extracts on biochemical blood markers in diabetic rats was studied and the findings confirmed a reduction in glucose, cholesterol, triglycerides, and blood urea nitrogen levels (BUN).

The effect of CLP, WLP, CLEx, and WLEx on antioxidant status

Data in Table (7) indicated the effect of CLP, WLP, CLEx, and WLEx on malondialdehyde MDA (a marker of oxidative stress) concentration and selected antioxidant enzymes activities, glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and catalase (CAT) in hyperglycemic rats. Data revealed that the mean values of GSH-Px, SOD, and CAT activities in the positive control group were significantly lower (P≤0.05) when compared with the negative control group. On the other side, the mean value of MDA concentration in the positive control group (234.8 nmol/ml) increased significantly (P≤0.05) when compared with the corresponding value in the normal control group (26.4 nmol/ml). Treatment of the diabetic rats with CLP and WLP (5.0 & 7.0%, w/w); and CLEx and WLEx (200 & 400 mg/kg/d) significantly (P≤0.05) decreased MDA concentration and improved the antioxidant enzymes activities (GSH-Px, SOD, and CAT) activities when compared with the control (+ve) group. The

highest mean values of GSH-Px, SOD, and CAT activities were achieved for the diabetic group treated with WLEx (400 mg/kg/d) (36.2, 50.4, and 83.00 U/gHb), respectively. The lowest mean values were noted for the group fed on CLP (5.0%, w/w) of the BD (15.00, 15.00, and 28.8 U/gHb), respectively, with a significant difference (P≤0.05) when compared to the positive control group. Regarding MDA concentration, the lowest mean value was reported for the group treated with WLEx (400 mg/kg/d). In contrast, the highest mean value was obtained for the group supported with CLP (5.0%, w/w) of the BD with a significant difference (P≤0.05). It is worth mentioning that no significant differences were noticed between the control (-ve) group and the diabetic group treated with WLEx (400 mg/kg/d) concerning CAT, GSH-Px activities, and MDA concentration.

Aloulou et al. [64] have reported that the diabetic effect of alloxan can be attributed to the overabundance in the production of free radicals. This surplus leads to toxicity in the cells of the pancreas, which subsequently diminishes the synthesis and release of insulin. Additionally, Giacco and Brownlee [65] have observed that the increase in the generation of free radicals and the heightened levels of oxidative stress, attributed to the depletion of the activity of enzymes responsible for scavenging free radicals caused by chronic hyperglycemia, are evident in both human and experimental animal models of diabetes. The elevated level of MDA, serving as a biomarker for lipid peroxidation, found in diabetic control rats is indicative of the inadequacy of antioxidant defenses in combating damage caused by ROS (reactive oxygen species), as indicated by Jelodar et al. [51].

Ningappa *et al*. [66] reported that treating diabetic rats with curry leaves can mitigate the adverse effects of oxidative stress, prevent diabetic complications and enhance the heart's mitochondrial function. This is owing to the powerful antioxidant properties of curry leaves, which are beneficial in reducing membrane damage and related activities mediated by ROS. Jain *et al*. [37] indicated that curry leaves have antioxidative properties due to their composition of mahanimbine and koenigine, which elevate GSH activity and reduce malondialdehyde concentration in the liver. Mani *et al*. [67] found that total alkaloid extracts from *Murrya koenigii* leaves at doses of (20 and 40 mg/kg p.o.) significantly increased levels of protective antioxidant enzymes and lowered lipid peroxidation in brain homogenate of aged mice. Zhao *et al*. [68] detected that the leaves of *Juglans regia* L. have a high concentration of phenolic compounds known to be free radical scavengers. The major phenolic components found in the fresh leaves of *Juglans regia* L. are phenolic acids, naphthoquinones, and flavonoids. Alkhalidy *et al*. [69] discovered that the quercetin and kaempferol compounds in walnut leaves extract serve as potent antioxidants and free radical scavengers and are essential for beta cell regeneration and pancreatic islet protection. Teimoori *et al*. [70] illustrated that administering walnut leaf extract to diabetic rats improved glutathione peroxidase, superoxide dismutase, and catalase activities in red blood cells while significantly lowering MDA levels.

Table 7. Effect of curry and walnut leaves powders and their methanolic extracts on malondialdehyde concentration and antioxidant enzymes activities of diabetic rats

Groups	MDA (nmol/ml)	GSH-Px (U/gHb)	SOD (U/gHb)	CAT (U/gHb)
Control (-ve)	26.4 ^{f} ± 3.71	38.8 ^{a} ± 4.55	53.8 ^{a} ± 4.02	86.2 ^{a} ± 8.07
Control (+ve)	234.8 ^{a} ± 31.94	8.2 ^{h} ± 0.84	7.2 ^{i} ± 0.84	16.00 ^{g} ± 3.00
CLP (5.0%, w/w)	156.00 ^{b} ± 16.6	15.00 ^{g} ± 1.22	15.00 ^{h} ± 1.22	28.8 ^{f} ± 4.55
CLP (7.0%, w/w)	105.2 ^{d} ± 11.86	21.5 ^{e} ± 0.61	24.4 ^{f} ± 1.34	44.4 ^{d} ± 4.10
WLP (5.0%, w/w)	135 ^{c} ± 13.10	18.2 ^{f} ± 0.84	20.8 ^{g} ± 1.64	37.6 ^{e} ± 1.34
WLP (7.0%, w/w)	67.6 ^{e} ± 10.04	25.05 ^{cd} ± 0.87	34.8 ^{d} ± 2.05	54.8 ^{c} ± 2.17
CLEx. (200 mg/kg/d)	89.4 ^{d} ± 11.84	22.8 ^{de} ± 1.25	27.2 ^{e} ± 2.05	47.2 ^{d} ± 3.83
CLEx. (400 mg/kg/d)	63.2 ^{e} ± 4.09	25.7 ^{c} ± 1.20	36.6 ^{d} ± 1.34	58.8 ^{c} ± 2.17
WLEx. (200 mg/kg/d)	42.2 ^{f} ± 8.17	32.2 ^{b} ± 2.59	44.00 ^{c} ± 1.22	74.4 ^{b} ± 1.67
WLEx. (400 mg/kg/d)	28.4 ^{f} ± 1.67	36.2 ^{a} ± 2.09	50.4 ^{b} ± 2.51	83.00 ^{a} ± 3.00
LSD	17.78	2.69	2.44	4.67

Each value was represented as mean ± standard deviation. Means in the same column with different letters are significantly different at p≤0.05. CLP, curry leaves powder; WLP, walnut leaves powder; CLEx, curry leaves extract and WLEx, walnut leaves extract. (MDA) Malondialdehyde – (GSH-Px) Glutathione Peroxidase – (SOD) Superoxide Dismutase – (CAT) Catalase.

Conclusion

Plants naturally possess a wide range of bioactive and therapeutic constituents, although their characteristics may differ based on the specific plant. This study provides corroborative evidence regarding the potential anti-diabetic effect of curry and walnut leaves. The constituents present in curry and walnut leaves may hold vital significance from a nutritional standpoint. Hence, the incorporation of these leaves into certain food products would augment the nutritional value of the product more effectively than many ordinary food sources. Additionally, the total phenolic content and phenolic compounds found in these leaves confer significant value upon such food as a pivotal functional food for the prevention or co-treatment of diabetes.

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التأثيرات المحتملة للأوراق الكاري والجوز على الفئران المصابة بالسكر المستحث بالألوكسان

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الملخص العربي:
مصر من بين الدول العشرة الأولى في العالم من حيث عدد مرضى البول السكري، تستخدم النباتات الطبية للوقاية أو لعلاج مرض السكر للتغلب على التكلفة والآثار الجانبية غير المرغوبة لأدوية السكر. تهدف الدراسة الحالية لاستكشاف التأثيرات المحتملة لمسحوق أوراق الكاري والجوز ومستخلصاتهما الميثانولية على الفئران المصابة بالسكري. تم تقسيم ستين من ذكور فئران الألبينو وزنها (150±10جم) إلى مجموعتين رئيسيتين. المجموعة الرئيسية الأولى (مجموعة 1 = 6 فئران): وهي المجموعة الضابطة السالبة، وتم تغذيتها على الوجبة الأساسية. المجموعة الرئيسية الثانية (54 فأر): تم حقنها بالألوكسان لإحداث الإصابة بالبول السكري، تم تقسيم هذه المجموعة إلى تسع مجموعات تتكون كل مجموعة من (6 فئران) كالتالي: مجموعة (2): وهي المجموعة الضابطة الموجبة وتغذت على الوجبة الأساسية، المجموعات من (3-6) تغذت على الوجبة الأساسية التي تحتوي على مسحوق أوراق الكاري والجوز بتركيز 5.0، 7.0% (وزن/وزن)، المجموعات من (7-10) تغذت على الوجبة الأساسية مع إعطائها المستخلص الميثانولى لأوراق الكاري والجوز عن طريق الفم بتركيز 200، 400 (ملجم/كجم من وزن الجسم/اليوم) لمدة 42 يوم. أظهرت النتائج أن الحقن بالألوكسان أدي إلى انخفاض معنوي ($P\leq0.05$) ملحوظ فى مستوى الأنسولين، الليبوبروتينات مرتفعة الكثافة، سوبر أوكسيد ديسميوتيز، الجلوتاثيون بيروكسيديز والكاتاليز، وارتفاع ملحوظ في مستوى سكر الدم، مؤشرات وظائف الكبد والكلى، مستوي الدهون في الدم بالإضافة الى تركيز المالونالدهيد. أدت معاملة الفئران المصابة بالسكري بمسحوق أوراق الكاري والجوز، وكذلك مستخلصاتهما الميثانولية بالتركيزات المختبرة إلى تحسن في جميع هذه المؤشرات. الخلاصة: توفر هذه النتائج أساسا لاستخدام أوراق الكاري والجوز -أو الأغذية التي يمكن تدعيمها بهما- للوقاية أو للعلاج من مرض البول السكري بدلا من أو بجانب الأدوية الاصطناعية التي قد يكون لها آثار جانبية غير مرغوبة.

الكلمات المفتاحية: أوراق الكاري، أوراق الجوز، المركبات الفينولية، مرض البول السكري، نشاط الإنزيمات المضادة للأكسدة، المالونالدهيد