BIOLOGICAL AND BIOCHEMICAL STUDY OF THE EFFECT OF CANAGLIFLOZIN AND SOME HERBAL COMBINATIONS ON MALE RATS WITH TYPE II DIABETES AND GOUT

Prof. Dr/ Mohamed Samir El-Dashlouty
Prof. of Nutrition and Food Science Ex-Dean of Faculty of Home Economics Menoufiya Universit

Prof. Dr / Mona Ibrahim Mohamed
Prof. of Nutrition and Food Science Faculty Specific Education Menoufiya University

Doa Hosni Mohammed Mansour
Submitted in partial fulfillment in the requirement for the degree of PhD. In Home Economics (nutrition & Food Science)

ABSTRACT

The main target of this study was to reduce the cost of treatment of diabetic and gout patients due to high drug prices. It was suggested to use herbal combinations (Ginger, Urtica Dioica (Nettle) Turmeric (Curcuma), Coffee (CoFFea), or DiLL (Anethum Graveolens), Melissa (Lemon Balm), Lemongrass (Cymbopogon Ciratus), Marjoram (Origanum Majorana)) with lowering the level of drug intake. Treatment cost calculated, and showed that drug decrease with giving herbs collection, especially the "B" collection reduced the cost of treatment. This was carried out on diabetic rats. Control "A" group (diabetic rats received plane diet without herbs or drug) showed higher, serum glucose, (VLDL), HDL, total protein, albumin, and SOD, and lower levels of triglycerides, cholesterol, LDL, ALT, AST, ALP, urea, uric acid, and creatinine. Nevertheless, feeding on the basal diet with drug 100 & 30, with combined herbs 100 or 300 mg reversed such changes. This was confirmed by the fewer histopathological changes. This indicated that suggested herbs especially the combined herb "A", may be used to lower the treatment cost of diabetics as calculation result revealed.

Keywords: canagliflozin - Ginger - Urtica Dioica - Turmeric - Coffee – Anethum Graveolens– Lemongrass - Origanum Majorana –Melissa - lipid profile – liver and renal function – insulin resistance.

INTRODUCTION

Canagliflozin lowers plasma glucose by lowering the renal threshold for glucose and increasing urinary glucose excretion, it is used to treat type 2 DM. As he reduces liver fat, triglyceride (TG), and glycogen contents and subsequently ameliorates hepatic steatosis. It is registrated in 100 mg & 300 mg film-coated tablets **(Palmer and Clegg, 2023).** Mechanism of canagliflozin acts by inhibiting the SGLT2 which accounts for more than 90% of renal glucose reabsorption **(Ferrannini *et al*., 2024).**

Ginger (Zingiber officinale Roscoe) is herbaceous perennial plant of the family Zingiberaceae**. Novakovic *et al*., (2024)** indicated that ginger was a promising therapy for T2DM and MetS through multiple targets and pathways. This positive effect may be resulting from its primary bioactive ingredients such as gingerols, shogaols, zingerone, and paradols. Ginger has been shown to have anti-diabetic activity through alpha glucosidase inhibition and presence β-Sesquiphell andrene which increases insulin sensitivity. Ginger is reduce the level of uric acid formation and gout disease.

Urtica dioica L. (common as stinging nettle) belongs to family Urticaceae which is used in the world as a herbal medicine. Is commonly known as medical herb for a long time in the world. Nettle powder had contained relatively high amounts of bioactive compounds as tannin, total phenolic (TP) and total dietary fractions. All parts of U. dioica has been reported to have some chemical materials such as histamine, formic acid, acetylcholine, acetic acid, butyric acid, lucoterians, 5-hydroxy tiryptamin and other stimulants. Nettle powders were showed a significant enhancement of insulin secretion thereby decreasing the blood sugar level **(Đurović *et al*., 2023).**

Cymbopogon citratus (DC.) Stapf belongs to family Poaceae. Cymbopogon citratus Stapf (Poacae) is commonly known as lemongrass is native. It is an aromatic grass-like plant. Is one of the largely cultivated medicinal plants for its essential oils, it contains 1-2% of-essential oil. The leaves of Lemongrass contains lemony characteristic flavour due presence of citral **(Kamaruddin *et al.,* 2022).** For several decades, lemongrass has been reported to be extensively used for a number of folkloric, cosmetic, and nutritional purposes. Lemongrass tea (LGT) is consumed for the treatment of DM and other related disorders such as hypertension, type 2 diabetic and obesity **(Dhayal *et al.,* 2023).**

The word coffee is derived from the name of the province Keffa where, prior to 1000 A.D. Coffee is one of the most frequently consumed beverages worldwide. It contains numerous bioactive chemicals, including phenolic compounds and caffeine. Caffeine is a central nervous system stimulant of the methylxanthine and plays an important role in increasing alertness, reducing fatigue, improving performance, and increasing mental functioning; it can also reduce blood glucose, protect the body from oxidative damage **(Ghavami *et al.,* 2021).**

Curcuma longa, the turmeric plant is an herbaceous plant of the family Zingiberaceae commonly utilized in food preparation as a spice. This plant is characterized by orange tuberous rhizomes and is known ‘yellow coloring agent. ’The singular characteristic of this plant is the presence of curcumin, which shows antioxidant and anti-inflammatory properties **(Emirik, 2020).**

Marjoram or Oregano (Origanum majoranum; OM) is a hardy perennial and herbaceous plant which belongs to family Labiatae It is generally called as "sweet marjoram" contains oleanolic and ursolic acids, flavonoids and hydroquinones, caffeic, rosemarinic, and lithospermic acids, tannins, and phenolic glycosides. Phenolic compounds of oregano represent 71% of the total oil. The essential oil is widely used as antihyperglycemic, **(Makrane *et al*., 2019).** Marjoram considered as antiseptic, antidiabetic, O. majorana leaves as aqueous extract leaves decreased blood glucose case. This practice reduced blood glucose and increased hemoglobin A1c (HbA1c) level, this also showed anti gout activity **(Gutiérrez *et al.,* 2022).**

Anethum graveolens L (commonly referred to as dill) is a herb commonly used both as a remedy and as a spice. In diabetic models, the administration of different extractions of A. graveolens seed had antioxidant, hypolipidemic and hypoglycemic effects. Randomized clinical trials showed that A. graveolens reduced total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) but did not change triglyceride or HDLC levels in patients with T2DM **(Aati *et al.,* 2022).**

Melissa officinalis (MO) is a species from Lamiaceaes family that also called Lemon balm because of its lemon like scent. is a well-known medicinal plant species used in perfumes, cosmetics, tea and food products in many countries. Scientific research haa revealed that Melissa officinalis possesses many beneficial effects such as reduced blood glucose and anti gout activity. Recently MO has been used to treat Alzheimer's disease. Among more than one hundred chemicals which have been identified in this plant, its main ingredients include citral, citronellal, geraniol, linalool and β-caryophyllene-oxide. The odor of the plant is mainly because of citral and citronellal **(Shin *et al.,* 2020).**

Finally it should be noted that price of canagliflozin 100mg is 436 L.E. of canagliflozin 300mg is 505 L.E. The price of drugs increased by 40% of original price (November, 2024) and may increase more in future time. Therefore, saving just 10% of the drug will mean something to the patient as will be seen reviewing the chapter of result & discussion since the new price of canagliflozin 100mg & 300mg will be 644 and 700 piasters respectively compared with price of herbs.

MATERIAL

1. Fructose purchased From EL-Gomhorya Company For Chemicals and Drugs, Cairo, Egypt.
2. STZ purchased From EL-Gomhorya Company For Chemicals and Drugs, Cairo, Egypt.
3. Fifty health adult male albino rats "Sprague Dawley Strain" weighting 160± 10g were obtained From the animal Colony, Helwan Farm, vaccine and Immunity Organization, Helwan Governorate, Egypt.
4. THe Herbs: Ginger, Urtica Dioica (Nettle) Turmeric (Curcuma), Coffee (CoFFea), DiLL (Anethum Graveolens), Melissa (Lemon Balm), Lemongrass (Cymbopogon Ciratus), Marjoram (Origanum Majorana) were obtained From Harraz Herbal Store, Helwan Governorate, Egypt.
5. Canagliflozin (SGLT2): Invokana (Alkana-gliflozin), At a Concentration of 100 mg and 300 mg were obtained From, EL-Ezaby, Pharmacy, Cairo, Egypt.
6. Chemicals and other materials: Casein">85% protein", corn starch, DL-methionine, choline chloride, vitamins, minerals and other required chemicals were obtained From Morgan Company For chemicals, Cairo, Egypt.

METHODS

Basal diet was prepared to give the efficiency for maintaining the growth of experimental animals. It is prepared From the Following ingredients per 100g diet were according to **(Reeves *et al.,* 1993).** It was consisted of 15% casein, 10% corn oil, 0.2% choline chloride, 0.3% methionine, 1% vitamin mixture, 4% salt mixture and 5% fiber (Cellulose). 65.5 Corn Starch, 14% protein **(Reeves *et al.,* 1993).**

Biological Experiment

Fifty healthy adult male albino rat's "Sprague Dawley Strain" weighting 160 ± 10 g kept in single wire cages with wire bottoms under hygienic conditions. The diet will be introduced to the rats in special food contains which avoid scattering of food. Also, water will be provided to the rats by glass tube projection through the wire cages. Food and water will be provided ad-libitum and checked daily.

The induction of experimental diabetes

After a fasting period of at least 8 h, DM was induced in male rats on these 9 groups by the intraperitoneal injection of STZ 40 mg/Kg body weight according to **(Dufrane, *et al* 2006).**

One week after the injection of STZ fasting blood samples were obtained to estimate fasting serum glucose 40 mg/dl rats which were considered diabetes **(Nine Group) (Akinola, *et al* 2012).**

The induction of experimental gout:

During this week male rats fed on t 30% fructose to inflict gout disease **(Nine Group). (Doa, 2016).**

Experimental Design

Fifty adult male albino rats "Sprague Dawley Strain" weighting 160+ Fed on basal diet for one week for adaptation. After this week, they were divided into ten main groups:

-**The First group:** Consists of 5 normal rats which Fed on basal diet only as a negative control group For seven weeks (49 day) **(Negative Control).**

After a fasting period of at least 8 h, DM was induced in male rats on these 9 groups by the intraperitoneal injection of STZ 40 mg/Kg body weight according to **(Dufrane, *et al* 2006).** One week after the injection of STZ fasting blood samples were obtained to estimate fasting serum glucose 40 mg/dl rats which were considered diabetes **(Nine Group) (Akinola, *et al* 2012).** During this week male rats fed on t 30% fructose to inflict gout disease **(Nine Group). (Doa, 2016).**

-**The second group:** consists of 5 normal rats which diet consists of basal diet with replacement of starch with 30% fructose for one week only, then fed on basal diet **(Positive Control).**

-**The Third group:** Consists of 5 normal rats which diet consists of basal diet with replacement of starch with 2.5% of Herbs A (ginger, urtica dioica (nettle), turmeric (curcuma), Coffee (Coffea).

-**The Fourth group:** Consists of 5 normal rats which diet consists of basal diet with replacement of starch with 2.5% of Herbs B (dill (Anethum Graveolens), Melissa (Lemon Balm), Lemongrass (Cymbopogon Citatus), Marjoram (Origanum Majorana).

-**The Fifth group:** Consists of 5 normal rats which diet consists of basal diet with replacement of starch with 2.5% Herbs A and canagliflozin 100mg/day).

-**The sixth group:** Consists of 5 normal rats which diet consists of basal diet with replacement of starch with 2.5% Herbs B and canagliflozin 100mg/day).

-**The seventh group:** Consists of 5 normal rats which diet consists of basal diet with replacement of starch with 2.5% Herbs A and canagliflozin 300mg/day).

-**The Eighth group:** Consists of 5 normal rats which diet consists of basal diet with replacement of starch with 2.5% Herbs B and canagliflozin 300mg/day).

-**The Ninth group:** Consists of 5 normal rats which diet consists of basal diet with replacement of starch with Canagliflozin 100mg/day (0.1gram).

-**The tenth group:** Consists of 5 normal rats which diet consists of basal diet with replacement of starch with Canagliflozin 300mg/day (0.3gram).

At the end of the experimental period (seven weeks), the animals (rats) sacrificed under ether anesthetized and blood samples collected in dry centrifuge tubes from hepatic portal vein. Also, the organs (liver, kidney and heart) removed by careful dissection, washed in saline solution (0.9%), dried using filter paper then weighed and the portion from liver put in 10% formaldehyde to examine histopathology. Serum will be separated by centrifugation of blood at 4000 rpm (round per minute) for 15 minutes at room temperature and kept in plastic vial at -20°C till analysis.

Biological Evaluation

Includes the determination of:

1. Feed intake and body weight gain:

Animals and food were weighed twice a week. At the end of experiment feed intake and body weight gain calculated as a mean ± SE for each group.

BWG = Final weight (g) - Initial weight (g) / Initial weight (g)

2. Feed efficiency ratio:

Calculated as a Follow according to **Eggum *et al*., (1973)**:

FER = Body weight gain (g) / Feed intake(g).

Biochemical Analysis:

Fasting plasma glucose level was determined by an enzymatic colorimetric method of **Sharp, (1972),** The quantitative enzymatic colorimetric determination of triglycerides in determined according to **Wahlefeld, (1974).** Determination of total cholesterol and HDL cholesterol in serum using kits Stanbio laboratory according to **Stein, (1986).** Low-density lipoprotein (LDL) cholesterol calculated according to **Friedewald *et al.,* 1972).** Aminotransferase (ALT and AST) were determined according to **Bergmeyer and Hordor, (1980).** Alkaline phosphatase (ALP) was determined according to **Bowers and MC-Comb, (1966).** Blood Urea Nitrogen (BUN) was estimated according to **Tabacco *et al.,* (1979).** Method was determined of uric acid according to **Fossati *et al.,* (1980).** Kinetic method determined of Creatinine according to **Hout, (1985).**

Histopathological Examination Of Organs:

Liver, Heart and kidney specimen from each rat were fixed in buffered 10% formalin solution. Organ samples embedded in paraffin wax and prepared for histobiological examination by sectioning and staining with hematoxylin and eosin, according to **Lambergton and Rothstein, (1988).**

Statistical Analysis:

Statistical analysis will be carried out using the programme of Cost Analysis Statistics (COSTAT). The results were expressed as mean ± standard error (mean ± SE). Data were analyzed using one-way classification, analysis of variance (ANOVA). The differences between means were tested for significance using the least significant difference (LSD) test at $p<0.05$. An independent t-test was also used to determine the statistical difference between the two means

When a significant main effect was detected, the means were separated with the Student-Newman-Keuls test. Differences between treatments ($P\leq0.05$) were considered significant **(SAS, 2002).**

Discussion

The results and discussion are divided into items, biological (Feed intake, body weight gain and feed efficiency ratio); biochemical analysis (Glucose, lipid profile, liver and kidney functions) and histological examination.

Fifty adult male albino rats divided into 10 groups. First group as negative control fed basal diet only. After a fasting period of at least 8 h, DM was induced in male rats on these 9 groups by the intraperitoneal injection of a single dose of alloxan monohydrate (150 mg/kg body weight), which was dissolved in normal saline. Blood glucose levels were measured using a glucometer 48 h after alloxan injection. Then, fed on 30% fructose to infestation gout disease for one week (Nine Group). Group two as positive control fed standard diet, Group three fed basal diet and replacement of corn starch with 2.5% of Herbs A (ginger, urtica dioica (nettle), turmeric (curcuma), Coffee (Coffea)) from diet, Group four fed standard diet and replacement of corn starch with 2.5% of Herbs B (dill (Anethum Graveolens), Melissa (Lemon Balm), Lemongrass (Cymbopogon Citatus), Marjoram (Origanum Majorana) from diet, Group five fed basal diet and replacement of corn starch with 2.5% of Herbs A from diet + canagliflozin 100mg/day, Group six fed basal diet and replacement of corn starch with 2.5% of Herbs B from diet + canagliflozin 100mg/day, Group seven fed basal diet and replacement of corn starch with 2.5% of Herbs A from diet + canagliflozin 300 mg/day, Group eight fed basal diet and replacement of corn starch with 2.5% of Herbs B from diet + canagliflozin 300 mg/day, Group nine fed basal diet and replacement of corn starch with Canagliflozin 100mg/day from diet, Group ten fed basal diet and replacement of corn starch with Canagliflozin 300mg/day from diet, for the whole period of experiment (7 weeks). and compare Normal control group results with others groups results.

5.1. Biological Evaluation:

Table (1) : FI, BWG and FER for rat fed control (-) control (+) herbs A, herbs B, Herbs A, B, + Canagliflozin 100 Herbs A, B + Canagliflozin 300, Canagliflozin 100, Canagliflozin 300

Parameters / Group	Feed intake (g/day)	BWG (g/day)	Feed efficiency ratio
Control A	$18.14^{ab} \pm 0.608$	$0.895^{a} \pm 0.054$	$0.049^{a} \pm 0.004$
Control B	$18.21^{ab} \pm 0.631$	$0.808^{a} \pm 0.200$	$0.044^{a} \pm 0.013$
Herbs A	$17.67^{ab} \pm 0.814$	$0.815^{a} \pm 0.145$	$0.046^{a} \pm 0.008$
Herbs B	$17.30^{ab} \pm 0.772$	$0.91^{a} \pm 0.021$	$0.052^{a} \pm 0.003$
Herbs A + Canagliflozin 100	$20.19^{a} \pm 1.556$	$0.928^{a} \pm 0.136$	$0.045^{a} \pm 0.0100$
Herbs B + Canagliflozin 100	$20.10^{a} \pm 1.309$	$1.027^{a} \pm 0.056$	$0.051^{a} \pm 0.006$
Herbs A + Canagliflozin 300	$19.56^{ab} \pm 1.132$	$1.061^{a} \pm 0.085$	$0.054^{a} \pm 0.005$
Herbs B + Canagliflozin 300	$19.48^{ab} \pm 2.260$	$0.965^{a} \pm 0.105$	$0.049^{a} \pm 0.006$
Canagliflozin 100	$17.08^{ab} \pm 0.727$	$0.840^{a} \pm 0.059$	$0.049^{a} \pm 0.004$
Canagliflozin 300	$16.61^{b} \pm 0.300$	$0.873^{a} \pm 0.1359$	$0.052^{a} \pm 0.008$
LSD (P≤ 0.05)	2.056	0.203	0.013

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

5.2. Biochemical Analysis:

Table (1) : Serum glucose for rat fed control (-), control (+), herbs A, herbs B, Herbs A, B, Canagliflozin 100, Herbs A, B, Canagliflozin 300, Canagliflozin 100, Canagliflozin 300

Parameters / Group	Glucose mg/dl
	M±SD
Control A	$133^{I} \pm 0.11$
Control B	$217^{a} \pm 0.57$
Herbs A	$198^{d} \pm 0.71$
Herbs B	$143^{g} \pm 0.88$
Herbs A + Canagliflozin 100	$175^{e} \pm 0.85$
Herbs B + Canagliflozin 100	$140^{h} \pm 0.05$
Herbs A + Canagliflozin 300	$172^{f} \pm 0.49$
Herbs B + Canagliflozin 300	$130^{J} \pm 0.76$
Canagliflozin 100	$213^{b} \pm 0.15$
Canagliflozin 300	$202^{c} \pm 0.81$
LSD (P≤ 0.05)	1.9

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

Table (1) show the levels of serum glucose as affected by the two herbs formulae and two levels of canagliflozin as administered to diabetic rats. Herbs formulae added to used drug to lower the levels of canagliflozin during treatment. The results of table (1) reveal the success of this attempt. Serum in glucose of during intake at 100-300mg without herbs was 202-213 mg/dl and with herbs A & B was 143-198 mg/dl only. Then herbs lowered the drug intake. Canagliflozin alone (202-213 mg/dl) or herbs alone (143-198 mg/dl) did not show the low serum

glucose found when both a combined together (130/175 mg/dl). This may indicate a synergistic effect when the drug combined with herbs**.**

The value of canagliflozin was not excluded from the combination. This drug causes significant loss of glucose in urine, reduces body weight gain, increases of LDL and HDL decreases **(Mahaffey *et al*., 2018).** Many authors **(Mukandi *et al* 2017)** reported the value of used herbs as anti-diabetics it was pointed to the deleterious effect of therefore on glucose metabolism and insulin sensitivity indeed a high fructose diet increased glucose and insulin responses to sucrose loud**.**

Table (2) : Triglycerides (TG) for rat fed control (-), control (+), herbs A, herbs B, Herbs A, B + Canagliflozin 100, Herbs A, B + Canagliflozin 300, Canagliflozin 100 and Canagliflozin 300

Parameters / Group	Triglycerides mg/dl
	M±SD
Control A	$119^{h} \pm 1.63$
Control B	$160^{a} \pm 0.54$
Herbs A	$153^{c} \pm 0.29$
Herbs B	$156^{b} \pm 0.62$
Herbs A + Canagliflozin 100	$132^{e} \pm 4$
Herbs B + Canagliflozin 100	$129^{f} \pm 0.53$
Herbs A + Canagliflozin 300	$127^{g} \pm 0.88$
Herbs B + Canagliflozin 300	$115^{I} \pm 0.58$
Canagliflozin 100	$146^{d} \pm 0.53$
Canagliflozin 300	$152^{c} \pm 0.73$
LSD (P≤ 0.05)	2.9

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

The results of table (2) show the levels of TG in diabetic rats fed on herbs A,B and different levels (100 & 300 unit) of canaglofilozin it is evident that due to alloxan injection, TG was rasied in diabetic rats According to **Szkudelski, (2001)** diabetes mellitus reveal some disorders of lipids metabolism in bodies including the TG.

Table (3) : HDL for rat fed control control (-), control (+), herbs A, herbs B, Herbs A, B + Canagliflozin 100, Herbs A, B + Canagliflozin 300, Canagliflozin 100 and Canagliflozin 300

Parameters / Group	HDL mg/dl
	M±SD
Control A	$44^{c} \pm 0.35$
Control B	$34^{I} \pm 0.35$
Herbs A	$40^{e} \pm 4$
Herbs B	$35^{h} \pm 0.56$
Herbs A + Canagliflozin 100	$38^{f} \pm 0.60$
Herbs B + Canagliflozin 100	$36^{g} \pm 3$
Herbs A + Canagliflozin 300	$41^{d} \pm 0.16$
Herbs B + Canagliflozin 300	$47^{a} \pm 0.64$
Canagliflozin 100	$34^{I} \pm 0.19$
Canagliflozin 300	$46^{b} \pm 0.64$
LSD (P≤ 0.05)	0.9

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

Table (3) show the levels of HDL of diabetic rats as affected by herbs A, B intakes, canaglofilozin 100 & 300 and the mixture of both.it is Clear that due to diabetes mellitus HDL (called the good cholesterol) decreased When diabetic rats given herbs A, B formulae HDL improved somewhat reaching 40 &35 and 42 mg respectively. Canaglofilozin alone raised HDL to 46 mg/dl while at 100 mg/dl did not show such level (only to 34 mg/dl) which was at control (+) group combination of canaglofilozin 300 with herbs B revealed maximum increase of HDL (47 mg/dl) and this was the best group being also so for TG and TC **(Bode *et al*., 2015)**

Table (4) : LDL Level for rat fed control (-), control (+), herbs A, herbs B, Herbs A, B + Canagliflozin 100, Herbs A, B + Canagliflozin 300, Canagliflozin 100 and Canagliflozin 300

Parameters / Group	LDL mg/dl
	M±SD
Control A	$17.2^{I} \pm 0.58$
Control B	$21^{a} \pm 0.47$
Herbs A	$26.4^{d} \pm 0.24$
Herbs B	$29.8^{c} \pm 0.23$
Herbs A + Canagliflozin 100	$15.6^{j} \pm 0.17$
Herbs B + Canagliflozin 100	$24.2^{e} \pm 0.89$
Herbs A + Canagliflozin 300	$20.6^{f} \pm 0.04$
Herbs B + Canagliflozin 300	$18^{h} \pm 0.83$
Canagliflozin 100	$30.8^{b} \pm 0.83$
Canagliflozin 300	$19.6^{g} \pm 0.71$
LSD (P≤ 0.05)	1.0

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

The results of table (4) show the levels of LDL in diabetic rats as affected by administration of herbs A,B and canagliflozin 100 and 300 mg. It is obvious that due to diabetes mellitus LDL considerably increased (from 17.2 to 121 mg/dl). Nevertheless, herbs mixtures, herbs and the drug and also the plain drug induced the level of LDL, indicating causing of diabetes. For G8 (herbs B + canagliflozin 300) the level of LDL (0.8 mg/dl) was nearly the same as control (-) rats. This (G8) was the best group. This indicated that combination of herbs formula and the drug gave best results due to synergistic effect **(Li *et al.,* 2013).**

Table (5) : Liver enzymes; AST activity for rat fed control (-), control (+), herbs A, herbs B, Herbs A, B + Canagliflozin 100, Herbs A, B + Canagliflozin 300, Canagliflozin 100 and Canagliflozin 300

Parameters / Group	AST U/L
	M±SD
Control A	104 ^{I} ± 0.7
Control B	165 ^{a} ± 0.11
Herbs A	132 ^{e} ± 0.89
Herbs B	126 ^{g} ± 0.38
Herbs A + Canagliflozin 100	130 ^{f} ± 0.95
Herbs B + Canagliflozin 100	134 ^{e} ± 0.17
Herbs A + Canagliflozin 300	143 ^{c} ± 0.86
Herbs B + Canagliflozin 300	137 ^{d} ± 0.83
Canagliflozin 100	160 ^{b} ± 0.33
Canagliflozin 300	114 ^{h} ± 0.74
LSD (P≤ 0.05)	0.50

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

Table (5) show the AST enzymes activity of rats liver as affected by herbs mixtures and canagliflozin. It was observed that diabetes mellitus (alloxan injection) raised AST activity in serum indicating increased porosity of liver tissue and penetration of enzymes from into liver tissues at higher amounts **(Liu *et al.*, 2020).**

Table (6) : Liver enzymes, ALT activity for rat fed control (-), control (+), herbs A, herbs B, Herbs A, B + Canagliflozin 100, Herbs A, B + Canagliflozin 300, Canagliflozin 100 and Canagliflozin 300

Parameters / Group	ALT U/L
	M±SD
Control A	68 ^{I} ± 0.54
Control B	94 ^{a} ± 0
Herbs A	77 ^{g} ± 0.53
Herbs B	83 ^{f} ± 0.70
Herbs A + Canagliflozin 100	76 ^{h} ± 0.60
Herbs B + Canagliflozin 100	92 ^{b} ± 0.39
Herbs A + Canagliflozin 300	89 ^{c} ± 0.51
Herbs B + Canagliflozin 300	85 ^{e} ± 0.35
Canagliflozin 100	83 ^{f} ± 0.73
Canagliflozin 300	86 ^{d} ± 0.17
LSD (P≤ 0.05)	0.35

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

The results of table (6) show the ALT activity of rats serum as affected by herbs mixtures and canagliflozin. It could be observed. that

due to diabetes mellitus ALT activity was raised from 68 to 94 U/L . Meanwhile the intake of herbs A,B and plain drug lowered the ALT activity, provided that irregular order was noticed because the drug 300 plus herbs B showed high ALT activity (92 U/L) than that of herbs B + canagliflozin 300 (85U/L). This may be due to irregular porosity and penetration of the ALT Under these and conditions best group was that of herbs A and canagliflozin 100 (76 U/L). Nevertheless, the fact was clear that herbs and the drug lowered the activity of ALT (**DeFronzo *et al.*, 2013).**

Table (7) : Alkaline phosphatase (ALP) for rat fed control (-), control (+), herbs A, herbs B, Herbs A, B + Canagliflozin 100, Herbs A, B + Canagliflozin 300, Canagliflozin 100 and Canagliflozin 300

Parameters / Group	ALP U/L
	M±SD
Control A	$68^{j} \pm 0.95$
Control B	$103^{c} \pm 0.51$
Herbs A	$84^{h} \pm 0.26$
Herbs B	$91^{e} \pm 0.51$
Herbs A + Canagliflozin 100	$78^{I} \pm 0.07$
Herbs B + Canagliflozin 100	$96^{d} \pm 0.74$
Herbs A + Canagliflozin 300	$89^{f} \pm 0.05$
Herbs B + Canagliflozin 300	$87^{g} \pm 0.05$
Canagliflozin 100	$104^{b} \pm 0.55$
Canagliflozin 300	$125^{a} \pm 0.94$
LSD (P≤ 0.05)	0.51

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

ALP results are shown in table (7) The results showed that due to diabetes mellitus ALP activity was raised appreciably (from 68 to 103 U/L). Irregularity was also noticed to ALP This be caused herbs and the drug lowered ALP, except for drug plain groups (100 & 300), where ALP was even more than for the control (+) group (104 -125 and 103 U/L respectively). Nevertheless, for the groups herbs collection (A & B) Lowered the ALP. Herbs 300 tended to show more effect and less ALP than herbs 100 except for herbs A + drug best may was that of G5 (herbs A + drug 100) (78U/L). This may due to irregular tissue porosity and penetration. Anyhow, herbs and drug lowered the ALT activity-Fructose feeding caused damage of liver function as found be increased of AST, ALT and ALP **(Schindhelm *et al.*, 2005).**

Table (8) : Urea level for rat fed control (-), control (+), herbs A, herbs B, Herbs A, B + Canagliflozin 100, Herbs A, B + Canagliflozin 300, Canagliflozin 100 and Canagliflozin 300

Parameters / Group	Urea mg/dL M±SD
Control A	27 ^{e} ± 3
Control B	49 ^{a} ± 4
Herbs A	34 ^{e} ± 3.6
Herbs B	42 ^{c} ± 3.6
Herbs A + Canagliflozin 100	32 ^{e} ± 3.46
Herbs B + Canagliflozin 100	39 ^{d} ± 3
Herbs A + Canagliflozin 300	31 ^{e} ± 2
Herbs B + Canagliflozin 300	29 ^{e} ± 1.73
Canagliflozin 100	41 ^{c} ± 3.6
Canagliflozin 300	46 ^{b} ± 2
LSD (P≤ 0.05)	2.4

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

Table (8) Show the level of urea in serum of diabetic rats as affected by herbs and canagliflozin intakes. It could be observed that alloxan injected diabetic rats had much more urea in serum. (49 mg/dl) compared to control (-) group (27 mg/dl). Nevertheless, herbs intake lowered the urea level to 34 - 42mg/dl. The drug was less effective than herbs in reducing the urea content (41- 46 mg/dl). Hence it seems that combination of herbs with the drug was a successful practice **(Amini et al., 2021)**.

Table (9) : Creatinine level for rat fed control (-), control (+), herbs A, herbs B, Herbs A, B + Canagliflozin 100, Herbs A, B + Canagliflozin 300, Canagliflozin 100 and Canagliflozin 300

Parameters / Group	Creatinine mg/dL M±SD
Control A	0.5 ^{e} ± 0.2
Control B	1.9 ^{a} ± 0.36
Herbs A	1.6 ^{b} ± 0.36
Herbs B	1.0 ^{d} ± 0.45
Herbs A + Canagliflozin 100	1.1 ^{c} ± 0.1
Herbs B + Canagliflozin 100	1.0 ^{d} ± 0.1
Herbs A + Canagliflozin 300	0.8 ^{e} ± 0.26
Herbs B + Canagliflozin 300	0.7 ^{e} ± 0
Canagliflozin 100	1.1 ^{c} ± 0.26
Canagliflozin 300	1.0 ^{d} ± 0.72
LSD (P≤ 0.05)	0.10

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

The results of table (9) show creatinine level in serum as affected by herbs and canagliflozin intakes. Creatinine in Serum was raised from 0.5 to 1.9 mg/dl. When diabetic rats consumed herbs collection creatinine decreased from 1.9 to 1.0 - 1.6 mg/dl. Also canagliflozin lowered the creatinine of serum from 1.9 to 1.0 - 1.1 mg/dl. This improvement may be attributed to the anti-inflammatory and antioxidant properties of herbal components, which may help reduce glomerular damage and enhance tubular function **(Nasri & Rafieian-Kopaei, 2014).**

Best group was that of G8 (herbs B+ Canagliflozin 300), being 0.7 ± 0 mg/dl.

Table (10) : Uric acid level for rat fed control (-), control (+), herbs A, herbs B, Herbs A, B + Canagliflozin 100, Herbs A, B + Canagliflozin 300, Canagliflozin 100 and Canagliflozin 300

Parameters / Group	Uric acid mg/dL
	M±SD
Control A	$2.5^{b} \pm 0.26$
Control B	$4.4^{a} \pm 0.87$
Herbs A	$3.1^{b} \pm 0.4$
Herbs B	$3.2^{b} \pm 0.60$
Herbs A + Canagliflozin 100	$2.9^{c} \pm 0.1$
Herbs B + Canagliflozin 100	$2.4^{d} \pm 0.51$
Herbs A + Canagliflozin 300	$2.9^{c} \pm 0.26$
Herbs B + Canagliflozin 300	$2.1^{e} \pm 0.26$
Canagliflozin 100	$2.8^{c} \pm 0.36$
Canagliflozin 300	$2.3^{d} \pm 0.55$
LSD (P≤ 0.05)	0.20

Each value is represented as mean ± standard deviation
Mean under the same line bearing different superscript letters are different significantly ($p < 0.05$)

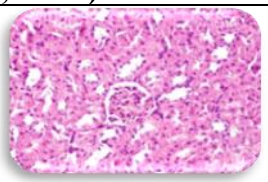
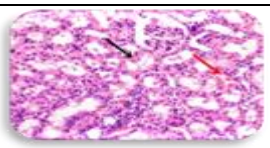
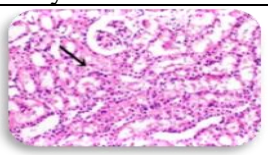
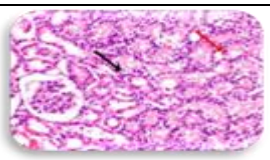
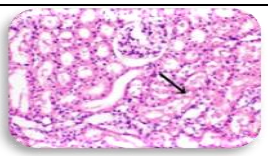
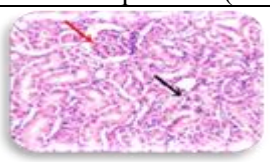
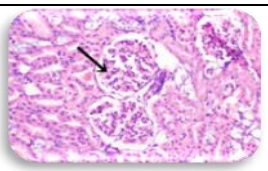
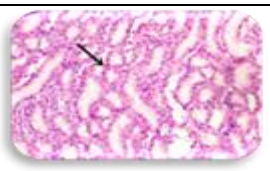
The results of table (10) show uric acid of diabetic rats as affected by herbs collections and canagliflozin intakes. It is obvious that alloxan injection raised significantly the level of uric acid in serum (from 2.5 to 4.4 mg/dl). Nevertheless, feeding on herbs collections A, B lowered uric acid in serum (from 4.4 to 3.1 - 3.2 mg/dl). Canagliflozin intake decreased also uric acid level (from 4.4 to 2.3-2.8 mg/dl). Combination of herbs with canagliflozin also lowered uric acid level to 2.3-2.8 mg/dl. Combination of the drug with herbs reduced also the uric acid level to 2.1-2.9 mg/dl **(Zhao *et al.*, 2020).**

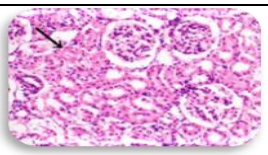
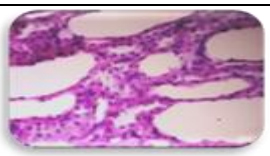
Best group was that of G8 (2.1 mg/dl) as regards the uric acid decreased. This was also recorded for urea & creatinine, indicating improvement of renal function.

Histopathological examination of Kidney:

kidney photo of rat fed control (-) control (+) herbs A herbs B Herbs A, B Canagliflozin 100 Herbs A, B Canagliflozin 300, Canagliflozin 100, Canagliflozin 300. The histopathological evaluation of kidney tissues across the ten experimental groups provides crucial insights into

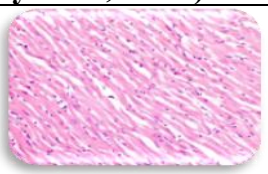
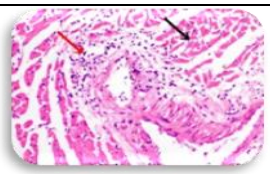
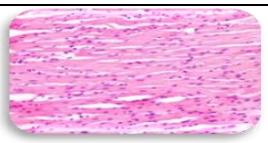
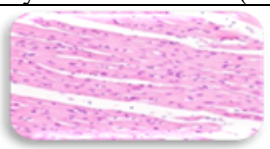
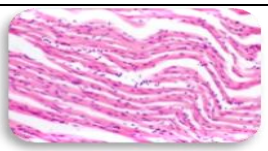
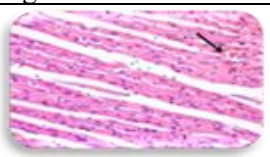
the degree of renal protection or damage induced by hyperglycemia, Canagliflozin, herbal treatments, and their combinations. The analysis, supported by hematoxylin and eosin (H&E) staining at ×400 magnification, reveals clear pathological distinctions among the groups, correlating strongly with the biochemical renal parameters **(Forbes & Cooper, 2013).**

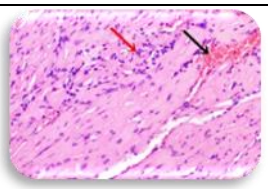
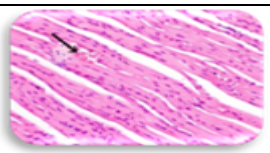
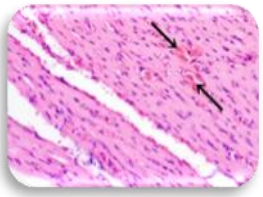
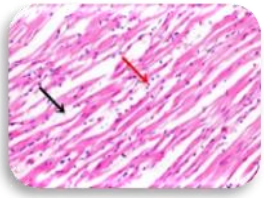
 **Photo. (1):** Photomicrograph of kidney of rat from group 1 (Control A) showing the normal histological structure of renal parenchyma.	 **Photo. (2):** Photomicrograph of kidney of rat from group 2 (Control B) showing necrobiosis of epithelial lining renal tubules (black arrow) and congestion of intertubular blood capillaries (red arrow).
 **Photo. (3):** Photomicrograph of kidney of rat from group 3 (Herbs A) showing vacuolar degeneration of epithelial lining renal tubules (black arrow).	 **Photo. (4):** Photomicrograph of kidney of rat from group 4 (Herbs B) showing vacuolization of epithelial lining renal tubules (black arrow) and congestion of intertubular blood capillaries (red arrow).
 **Photo. (5):** Photomicrograph of kidney of rat from group 5 (Herbs A + Canagliflozin 100) showing vacuolar degeneration of epithelial lining renal tubules (black arrow).	 **Photo. (6):** Photomicrograph of kidney of rat from group 6 (Herbs B + Canagliflozin 100) showing vacuolization of epithelial lining renal tubules (black arrow) and congestion of glomerular tuft (red arrow).
 **Photo. (7):** Photomicrograph of kidney of rat from group 7 (Herbs A + Canagliflozin 300) showing congestion of glomerular tufts (arrow).	 **Photo. (8):** Photomicrograph of kidney of rat from group 8 (Herbs B + Canagliflozin 300) showing slight congestion of intertubular blood capillaries (arrow).

 **Photo. (9):** Photomicrograph of kidney of rat from group 9 (Canagliflozin 100) showing necrobiosis of epithelial lining some renal tubules (black arrow).	 **Photo. (10):** Photomicrograph of Kidney of rat from group 10 (Canagliflozin 300) showing cystic diletation of renal tubules.

Histopathological examination of Heart:

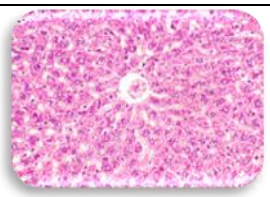
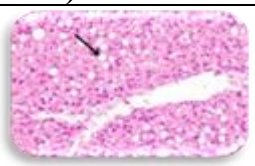
The histopathological examination of heart tissues from the different treatment groups offers key insights into the **cardioprotective or cardiotoxic effects** of herbal treatments, Canagliflozin, and their combinations under hyperglycemic conditions. Photomicrographs stained with H&E at 400× magnification reveal variable alterations in myocardial structure, vascular integrity, and inflammatory infiltration **(Cherney *et al.*, 2014).**

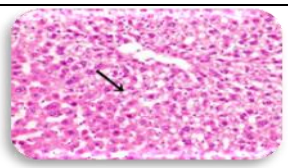
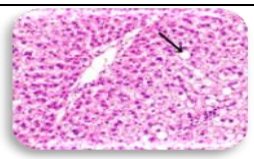
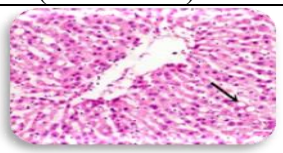
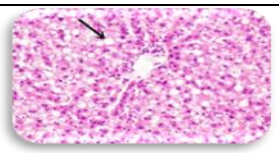
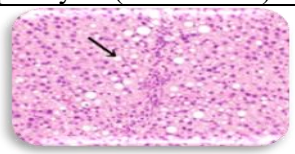
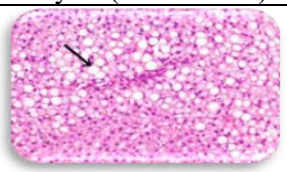
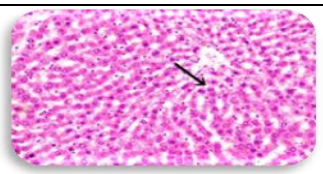
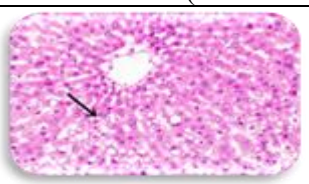
 **Photo. (11):** Photomicrograph of heart of rat from group 1 (Control A) showing the normal histological structure of cardiac myocytes.	 **Photo. (12):** Photomicrograph of heart of rat from group 2 (Control B) showing vacuolation of the sarcoplasm of cardiac myocytes (black arrow) and perivascular inflammatory cells infiltration (red arrow)**.**
 **Photo. (13):** Photomicrograph of heart of rat from group 3 (Herbs A) showing no histopathological alterations.	 **Photo. (14):** Photomicrograph of heart of rat from group 4 (Herbs B) showing no histopathological alterations.
 **Photo. (15):** Photomicrograph of heart of rat from group 5 (Herbs A + Canagliflozin 100) showing no histopathological alterations.	 **Photo. (16):** Photomicrograph of heart of rat from group 6 (Herbs B + Canagliflozin 100) showing congestion of myocardial blood vessels.

 **Photo. (17):** Photomicrograph of heart of rat from group 7 (Herbs A + Canagliflozin 300) showing congestion of myocardial blood vessel (black arrow) and focal inflammatory cells infiltration (red arrow).	 **Photo. (18):** Photomicrograph of heart of rat from group 8 (Herbs B + Canagliflozin 300) showing congestion of myocardial blood vessel (black arrow).
 **Photo. (19):** Photomicrograph of heart of rat from group 9 (Canagliflozin 100) showing congestion of myocardial blood vessel (black arrow).	 **Photo. (20):** Photomicrograph of heart of rat from group 10 (Canagliflozin 300) showing slight intermyocardial edema (black arrow) and few intermuscular inflammatory cells infiltration (red arrow).

Histopathological examination of liver:

The histopathological examination of the liver tissue in rats across various experimental groups provides essential insights into the hepatic alterations induced by diabetes, herbal treatments, and the administration of Canagliflozin, as well as their potential for hepatoprotection or hepatotoxicity. The results, as demonstrated by the H&E-stained liver sections, reveal varying degrees of hepatocellular steatosis (fatty liver) and other hepatic changes, which offer a clearer understanding of the impacts of these treatments **(Vasilenko *et al.*, 2020).**

 **Photo. (21):** Photomicrograph of liver of rat from group 1 (Control A) showing the normal histological architecture of hepatic lobule.	 **Photo. (22):** Photomicrograph of liver of r from group 2 (Control B) showin hepatocellular steatosis (arrow).

 **Photo. (23):** Photomicrograph of liver of rat from group 3 (Herbs A) showing hepatocellular steatosis of some hepatocytes (black arrow).	 **Photo. (24):** Photomicrograph of liver of rat from group 4 (Herbs B) showing hepatocellular steatosis of some hepatocytes (black arrow).
 **Photo. (25):** Photomicrograph of liver of rat from group 5 (Herbs A + Canagliflozin 100) showing steatosis of some hepatocytes (black arrow).	 **Photo. (26):** Photomicrograph of liver of rat from group 6 (Herbs B + Canagliflozin 100) showing steatosis of some hepatocytes (black arrow).
 **Photo. (27):** Photomicrograph of liver of rat from group 7 (Herbs A + Canagliflozin 300) showing hepatocellular steatosis (black arrow).	 **Photo. (28):** Photomicrograph of liver of rat from group 8 (Herbs B + Canagliflozin 300) showing hepatocellular steatosis (black arrow).
 **Photo. (29):** Photomicrograph of liver of rat from group 9 (Canagliflozin 100) showing small vacuoles in the cytoplasm of some hepatocytes (black arrow).	 **Photo. (30):** Photomicrograph of liver of rat from group 10 (Canagliflozin 300) showing steatosis of some hepatocytes (black arrow).

Conculsion:

Regarding to the finding in the present study, Herbal combination with replace not only completely the drug canagliflozin to reduce the diabetic and gout disease, and drug canagliflozin have side effect on the health so we try to reduce the usage. The best group is G8 in the transactions, and In the Histopathological kidney (herbs A, Herbs A + Canagliflozin 100, Herbs B + Canagliflozin 300) Heart (Herbs A, Herbs B), Liver (Herbs A, Herbs B, Herbs A and B 100)

Reference

Aati, H. Y.; Perveen, S.; Aati, S.; Orfali, R.; Alqahtani, J. H.; Al-Taweel, A. M.; Wanner, J. and Aati, A. Y. (2022): Headspace solid-phase microextraction method for extracting volatile constituents from the different parts of Saudi Anethum graveolens L. and their antimicrobial activity. *Heliyon.,* **8, e09051.**

Akinola, O. B., Martins, E. A. & Dini, L. (2012): Chronic treatment with ethanolic extract of the leaves of *Azadirachta indica* ameliorates lesions of pancreatic islets in streptozotocin diabetes. *Int. J. Morphol.* **28, 291–302.**

Amini, L., *et al.* (2021): Medicinal plants with potential renoprotective effects in diabetic nephropathy: A review. *Journal of Ethnopharmacology*, **271, 113870.**

Bergmeyer, H. U. & Horder, M. (1980): Methods for the measurement of catalytic concentration of enzymes, J. Clin. Chem. Clin. Biochem., **18:521-534.**

Bode, B.; Stenlöf, K. Harris, S. *et al*. (2015): Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55 to 80 years with Type 2 diabetes. Diabetes. Obes. Metab., **17(3), 294–303.**

Bowers, G. N. J. r. & McComb, R. B. (1966): A continuous spectrophotometric method for measuring the activity of serum alkaline phosphatase, Clin. Chem., Feb; **12(2):70-89.**

Cherney, D. Z. I., Perkins, B. A., Soleymanlou, N., *et al.* (2014): Renal hemodynamic effect of sodium–glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*, **129(5).**

DeFronzo, R. A. *et al.* (2013): Canagliflozin: A novel therapeutic option for patients with type 2 diabetes. *Diabetes Care*, **36(Suppl 2), S307–S314.**

Dhayal, D.; Lal, K. & Khanna, M. (2023): Lemongrass an aromatic crop: Boost for farmers income. *The. Pharma. Innovation.,* **12 (1): 2440-2443.**

Doa, M. (2016): Biological and biochemical study the excessive Fructose intake which may causes high uric acid level and diabetes type II in vivo.

Dufrane, D.; van Steenberghe, M.; Guiot, Y.; Goebbels, R. M.; Saliez, A. and Gianello, P. (2006): Streptozotocin-induced diabetes in large animals (pigs, primates): role of GLUT2 transporter and β-cell plasticity. *Transplantation* **81:36–45.**

Đurović, S.; Pezo, L.; Gašić, U.; Gorjanović, S.; Pastor, F.; Bazarnova, J. G. *et al.* (2023): Recovery of biologically active compounds from stinging nettle leaves part II: processing of exhausted plant material after supercritical fluid extraction. *Food. Secur.,* **12:809.**

Eggum, B. O.; Villeggas, E. M. and Vasal, S. K. (1973): Progress in protein quality of maize, J. Sci. Food Agriculture., **30: 1148-1153.**

Emirik, M. (2020): Potential therapeutic effect of turmeric contents against SARS-CoV-2 compared with experimental COVID-19 therapies: in silico study. *J. Biomol. Struct. Dyn.,* **183-57 :19**

Ferrannini, E.; Solini, A.; Baldi, S.; Scozzaro, T.; Polidori, D. and Natali, A. *et al.* (2024): Role of glycosuria in SGLT2 inhibitor-induced cardiorenal protection: A mechanistic analysis of the CREDENCE trial. *Diabetes*., **73:250–9**.

Forbes, J. M., & Cooper, M. E. (2013): Mechanisms of diabetic complications. *Physiological Reviews*, **93(1), 137–188.**

Fossati, P.; Prencipe, L. and Berti, G. (1980): Use of 3, 5-dichloro-2-hydroxybenzene sulfonic acid /4-aminophenazone chromogenic system in direct enzymatic assay of uric acid in serum and urine. Clin. Chem., **26: 227-231.**

Friedewald, W. T.; Levy, R. I. and Fredriclsor, D. S. (1972): Estimation of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin. Chem., **18: 499-502.**

Ghavami, H. S.; Khoshtinat, M.; Sadeghi-Farah, S.; Kalimani, A. B.; Ferrie, S. and Faraji, H. (2021): The relationship of coffee consumption and CVD risk factors in elderly patients with T2DM. *BMC. Cardiovascular*. *Disorders.,* **21(1).**

Gutiérrez, R. M. P.; Jerónimo, F. F. M.; Soto, J. G. C.; Ramírez, A. M. and Mendoza, M. F. E. (2022): Optimization of ultrasonic-assisted extraction of polyphenols from the polyherbal formulation of Cinnamomum verum, Origanum majorana, and Origanum vulgare and their anti-diabetic capacity in zebrafish (Danio rerio). *Heliyon.,* **8(1), e08682.**

Hout, O. (1985): Interpretation of clinical laboratory tests, **P. P., 220-234.**

Kamaruddin, Z. H.; Jumaidin, R.; Selamat, M. Z. and Ilyas, R. A. (2022): Characteristics and properties of lemongrass (Cymbopogan citratus): a comprehensive review. *J. Nat. Fibers.,* **19: 8101-8118.**

Lambergton, S. & Rothstein, R. (1988): Laboratory manual of histology and cytology **2**nd Ed. pp.**137-140.** A.V.I. publishing company, Inc., west port Connecticut, USA.

Li, W. L., *et al.* (2013): Natural medicines used in the traditional Chinese medical system for the therapy of diabetes mellitus. *Journal of Ethnopharmacology*, **92(1), 1–21.**

Liu, Q., *et al.* (2020): Natural products for the treatment of liver diseases: Evidence from traditional medicine. *Frontiers in Pharmacology*, **11, 873.**

Mahaffey, K. W.; Perkovic, V.; de Zeeuw, D. *et al.* (2018): Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet. Diabetes. Endocrinol*., **6:691-704.**

Makrane, H.; Aziz, M.; Mekhfi, H.; Ziyyat, A.; Legssyer, A.; Melhaoui, A. *et al.* (2019): Origanum majorana L. extract exhibit positive cooperative effects on the main mechanisms involved in acute infectious diarrhea. *Journal. Of. ethnopharmacology.,* **239:111-503.**

Mukandi, M. (2017): Modelling of a Bioflocculant Supported Dissolved Air Flotation System for Fats Oil and Grease Laden Wastewater Pretreatment. Master's Thesis, Cape Peninsula University of Technology, Cape Town, South Africa.

Nasri, H., & Rafieian-Kopaei, M. (2014): Medicinal plants and kidney disease. *Iranian Journal of Kidney Diseases*, **8(3), 181–186.**

Novakovic, S.; Jakovljevic, V.; Jovic, N.; Andric, K.; Milinkovic, M.; Anicic, T.; Pindovic, B.; Kareva, E. N.; Fisenko, V. P.; Dimitrijevic, A. and Joksimovic Jovic, J. (2024): Exploring the antioxidative effects of ginger and cinnamon: A Comprehensive review of evidence and molecular mechanisms involved in polycystic ovary syndrome (PCOS) and other oxidative stress-related disorders. *Antioxidants. (Basel).,* **13(4): 392.**

Palmer, B. F. and Clegg, D. J. (2023): Kidney-protective effects of SGLT2 inhibitors. ***Clin. J. Am. Soc. Nephrol.,* 18:279–89.**

Reeves, P. G.; Nielsen, F. H. and Fahey, G. C. (1993): AIN-93 Purified diets for laboratory rodents: Final report of the American Institute of Nutrition Ad Hoc writing Committee on the Reformulation of the AIN-**76**. A Rodent diet. J. Nutr., **123: 1939-1951.**

SAS. (2002): Statistical Analysis System SAS/ Stat User's Guide version 9 SAS Institute. Inc. Gary. NC. USA.

Schindhelm, R. K.; Diamant, M.; Bakker, S. J.; vanDijk, R. A.; Scheffer, P. G.; Teerlink, T.; Kostense, P. J. and Heine, R. J. (2005): Liver alanine aminotransferase, insulin resistance and endothelial dysfunction in normotriglyceridaemic subjects with type 2 diabetes mellitus. Eur. J. Clin. Invest., **35(6):369- 374.**

Sharp, P. (1972): Interference in glucose oxidase peroxidase blood glucose methods. Clin. Chem. Acta., **40: 115-20.**

Shin, Y.; Lee, D.; Ahn, J.; Lee, M.; Shin, S. S. and Yoon, M. (2020): The herbal extract ALS-L1023 from Melissa officinalis reduces weight gain, elevated glucose levels and beta-cell loss in Otsuka Long-Evans Tokushima fatty rats. *J. Ethnopharmacol.,* **264, 113360.**

Stein, E. A. (1986): In text book of clinical chemistry, NW Tiez. ED. W. B. Sander, Philadelphia, PP., **879-886.**

Szkudelski, T. (2001): The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. Physiol. Res., **50:537–546.**

Tabacco, A.; Meiattini, F.; Moda, E. and Tarli, P. (1979): Simplified enzymatic / colorimetric serum urea nitrogen determination. Clin. Chem., **25: 336-337.**

Vasilenko, T.; Karapetian, S. & Kolesnik, N. (2020): Hepatic effects of sodium-glucose cotransporter 2 inhibitors: A review of clinical and experimental data. *Journal of Clinical Endocrinology & Metabolism*, **105(7), e2503-e2512.**

Wahlefeld, A. W. (1974): In methods of enzymatic analysis, vol. 5, HU Bergmeyer, ED. Academic Press, New York, PP., **1831-1835.**

Zhao, Y., *et al.* (2020): Natural products for the prevention and treatment of hyperuricemia: Mechanisms and applications. *Phytomedicine*, 68, 153169.

دراسة بيولوجية وكيميائية حيوية لتأثير كاناجليفلوزين وبعض التركيبات العشبية على ذكور الفئران المصابة بمرض السكري من النوع الثاني والنقرس

أ.د/ محمد سمير الدشلوطي
أستاذ التغذية وعلوم الأغذية عميد كلية الاقتصاد المنزلي– جامعة المنوفية سابقا

أ.د/ منى إبراهيم محمد
أستاذ التغذية وعلوم الأغذية قسم الاقتصاد المنزلي كلية التربية النوعية– جامعة المنوفية

دعا حسني محمد منصور
تم تقديمها استكمالاً جزئياً لمتطلبات الحصول على درجة الدكتوراة في الاقتصاد المنزلي (التغذية وعلوم الأغذية)

الملخص العربي

تزايد في الفترة الأخيرة تداول عقار الكانا جليفلوزين المعروف باسم " انفو كانا " كعلاج لمرض السكر من النوع 2 والنقرس أيضا. وتم استخدامه لدى البعض كوقاية خوفا من الإصابة بمرض السكر أو النقرس أو كلاهما. وكان ذلك هو الهدف والسبب الأساسي في عمل هذه الدراسة لمعرفة أضرار هذا العقار وإذا كان بالإمكان الاستغناء عنه والبحث عن بدائل ذات قيمة غذائية حيوية تعالج مرض السكر والنقرس معا.

ونجد في هذه الدراسة قسمت ذكور الجرذان البيضاء إلى10مجموعات تغذت المجموعة الأولى على الوجبة القياسية كمجموعة ضابطة سالبة. وتم حقن الـ9مجموعات بالألوكسان (150 مجم/ كجم من وزن الجسم)، لمدة أسبوع واحد فقط والتي تم إذابتها في محلول ملحي طبيعي ثم تم إطعامهم 30% فركتوز للإصابة بمرض النقرس لمدة أسبوع. وتغذت المجموعة الثانية على الوجبة القياسية كمجموعة ضابطة موجبة "وفي المجموعات الثماني تم استبدال 2.5% من النشا بالأعشاب أو بالأعشاب وعقار كاناجليفلوزين" وتغذت المجموعة الثالثة على الوجبة القياسية الممزوجة بتوليفة الأعشاب،أ، [زنجبيل، قراص، كركم، بن] وتغذت المجموعة الرابعة على الوجبة القياسية الممزوجة بتوليفة الأعشاب"ب" [الشبت، حشيشة الليمون، البردقوش، المليسا] وتغذت المجموعة الخامسة على الوجبة القياسية الممزوجة بتوليفة الأعشاب (أ)+ كانا جليفلوزين100 مجم /يوم وتغذت المجموعة السادسة على الوجبة القياسية الممزوجة بتوليفة الأعشاب (ب) + كانا جيلفلوزين 100 مجم/ يوم وتغذت المجموعة السابعة على الوجبة القياسية الممزوجة بتوليفة الأعشاب(أ)+ كانا جليفلوزين300 مجم/يوم وتغذت المجموعة الثامنة على الوجبة القياسية الممزوجة بتوليفة الأعشاب(ب) كاناجليفلوزين300 مجم/ يوم وتغنت المجموعة التاسعة على الوجبة القياسية+كاناجليفلوزين100 مجم /يوم وتغذت المجموعة العاشرة

على الوجبة القياسية + كاناجليفلوزين300 مجم/يوم وذلك لمدة 7 أسابيع وبنهاية مدة التجربة ثم عمل تقييم بيولوجى وعمل تحاليل بيوكيميائية (وظائف الكبد، الكلى، الجلوكوز، تحليل SOD الخاص بالأكسدة) وعمل فحص هستو باثولوجى أظهرت النتائج الزيادة في كمية الغذاء المتناول، وزن الجسم المكتسب أكثر من المجموعة الضابطة السالبة أما نسبة كفاءة الغذاء لم تظهر أي فروق معنوية عن المجموعة الضابطة السالبة. التحاليل البيوكيميائية أوضحت انخفاض الجلوكوز والبروتين منخفض الكثافة للغاية والكوليسترول النافع والبروتين الكلى والألبيومين وتحليل الأكسدة سوبر أكسيد ديسميوتاز SOD. وارتفاع الدهون الثلاثية والكوليسترول والكوليسترول السيئ وإنزيم ناقلة أمين الألانين وإنزيم ناقلة أمين الأسبارتات والفوسفاتاز القلوى واليوريا وحمض اليوريك والكرياتنين مقارنة بالمجموعة الضابطة السالبة. وقد استنتج من الدراسة أن بدائل العقار الغذائية كان لها تأثير ولهذا تنصح بتخفيض. نسبة العقار في العلاج لـ 10% وإن زادت النسبة سيكون أفضل على المريض لتقليل الآثار الجانبية المصاحبة له.

الكلمات المفتاحية: كاناجليفلوزين– الزنجبيل– القراص– الكركم– الشبت– القهوة– ميليسا– عشبة الليمون– بردقوش– ملف الدهون– وظائف الكبد والكلى– مقاومة الأنسولين