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ABSTRACT

This study aims to study the effect of combining curcumin (*CUR*) with black pepper in different proportions on obese diabetic rats. Thirty-six adult male albino rats weighing 150 ± 10 g were used and divided into 6 groups (each group 6 rats) and the duration of the experiment was 4 weeks. The first group, the negative control group, was fed the basal diet. The main group (30 rats) were fed for two weeks on a high-fat diet (HFD) to induce obesity and injected with alloxan 150 g/kg of body weight to induce diabetes, and they were divided into 5 groups. (Each group 6 rats). The second positive group were fed the basal diet, the third group were fed the main diet with 2.5% CUR, the fourth group were fed the basal diet with 5% CUR, the fifth group were fed the basal diet with 2.5% CUR and 1.5% black pepper. The sixth group were fed the basal diet with 5% CUR and 5% black pepper. The results showed a decrease in the weights of the groups ($P < 0.05$) that were fed CUR and black pepper. The serum glucose level decreased in the group (G5) who fed 2.5% with 1.5% black pepper (131 ± 9.89) compared to the positive control group (255.5 ± 12.02) and the total cholesterol levels decreased in the group of rats fed 5% CUR with 5% black pepper (171 ± 9.89) compared to the positive control group (285.5 ± 7.77), and the results showed a decrease in the level of triglycerides in the group fed on 5% CUR and 5% black pepper (136.5 ± 23.3) compared to the positive control group (G2) (199 ± 4.24), so the study recommended combining CUR with black pepper in proportions moderate to get Good results in lowering serum glucose and fat levels

Key words: Glucose - lipid profile- liver enzymes

INTRODUCTION

Curcumin (CUR) is a natural polyphenol extracted from turmeric and has received considerable attention in recent decades because of its potential utility in the prevention and therapeutic treatment of a variety of cancers ***(Wang et al., 2017)*** and The bright yellow color is expressed because of the fat-soluble polyphenols that are known as curcuminoids ***(Brewer, 2011)*** Its molecular formulation is $C_{21}H_{20}O_6$ with a molecular weight of 368.37g/mol. CUR is soluble in natural solvents such as ethanol, methanol, dimethylsulfoxide (DMSO), acetone and acetonitrile however not in water ***(Anand et al., 2007)***

Research on turmeric has suggested that its medicinal properties and ability to neutralize redox reactions are owed to, its active ingredient ***(Aftab and Vieira, 2009).***. CUR has been proven to be many really useful do which include antioxidant, anti-inflammatory, anticoagulant, antitumor and hepatoprotective things to ***do (Anand et al., 2008).*** CUR has a confined to use as a drug to deal with the sickness due to the fact of its negative solubility in water and its low oral bioavailability ***(Prasad et al., 2014) & (Siviero et al., 2015)***

Despite massive lookup and development, bad solubility of curcumin, due to its hydrophobic property and preferential interplay with lipid membranes, stays a fundamental barrier in its bioavailability and scientific efficacy ***(Lacerda et al., 2010)***

CUR proved to be probably high quality in the prevention and cure for fibroblasts injury inside the cochlear tissues ***(Tengku Siti Hajar Haryuna et al., 2015).*** Based on repeated security and toxicity studies, turmeric is Generally Recognized As Safe (GRAS) via the Food and Drug Administration, and CUR was granted a desirableevery day consumption (ADI) degree of 0.1–3 mg/kg physique weight by means of the Joint FAO/WHO Expert Committee on Food Additives (***National Cancer Institute., 1996)*** CUR showed beneficial effects in several types of cancer in animals and human subjects. In animal models, oral administration of CUR inhibited cancers of the lungs ***(Cheng KW et***

al., 2013), buccal cavity (***Yu-Chuan Lin et al., 2010),*** liver (***Yoysungnoen et al., 2006),*** mammary gland, lymphocytes ***(Huang et al., 1998),*** familial adenomatous polyposis (***Sarah et al., 2002)*** and intestinal polyps ***(Pettan-Brewer et al., 2011)***. In humans, CUR (1–6 g/day) showed promising results in patients with dermatitis ***(Ryan et al.,2013),*** Crohn's disease (***Holt et al.,2005)***, and ulcerative colitis(***Hanai and Sugimoto.,2009).***Overall, the impact of CUR remedy is well-known and shows promising results in the scientific research investigating its impact on intestine inflammation. Thus, the use of CUR in opposition to intestine irritation is now not except for limitation. Animal research has proven that CUR is hastily metabolized, conjugated as glucuronide in the intestinal mucosa, transported lower back to the lumen and excreted in the feces ***(Pan et al., 1999))*** and ***(Ireson et al.,2001)*** Consumption of the CUR supplement, alongside drug therapy, is related to considerable enhancement of the scientific outcomes, with mild-to- moderate (ulcerative colitis) (***Sadeghi et al.,2020)***The potential benefits of CUR supplementation as an adjunct to statin therapy were found in patients with SAMS, as well as in individuals with residual cardiovascular risk***.(Sahebkar et al.,2017)***

Piperine *(PIP)*, one of the foremost alkaloids of black *(Piper nigrum L.)* and lengthy pepper *(Piper longum L.)* has been said to adjust intra-enterocyte glucuronidation ***(Bhardwaj et al., 2002)***.There are two ways in which piperine can enhance the bioavailability of CUR. The first way is by increasing curcumin's absorption by stimulating biliary excretion ***(Bhat, 1987)***. CUR is a lipid-soluble molecule, thus by increasing biliary excretion; it enhances lipid absorption, together with dissolved curcumins. ***(Zayed et al., 2020)*** Another study in rats showed that PIP (20 mg/kg orally) when co-administered with CUR (2 g/kg orally) enhanced the 20 bioavailability of CUR by 20-fold***(Sharma et al.,2010)*** The outcomes of the research carried out in rodent models translated properly into human trials as CUR bioavailability used to be accelerated through 2000% after forty five minutes of co-administering CUR orally with PIP***(Shoba et***

al.,1998) .The combination of piperine and CUR was found to inhibit osteoclastogenesis in vitro except for cytotoxic results in periodontal ligament cells. These results support its practical treatment programs for the prevention and treatment of alternative resorption in implanted teeth ***(Martins et al., 2015)***.

The research aims to study the effect of combining CUR and black pepper and their ratios in reducing diabetes and obesity in obese rats with diabetes.

MATERIALS AND METHODS

Materials:

- Basal diet used to be set up its substances from casein 10%,corn oil 10%, mineral's combination 4%, vitamin's combination 1%, fiber 4% and corn starch up to a hundred percent in accordance to ***(Campbell, 1961)*** and ***(Reeves et al., 1993)***
- Curcumin was obtained from the (Shana company in Shepen Elkom, Monofia, Egypt
- Ground black pepper was purchased from Rajab Al-Attar in Ataba.
- Casein, vitamins, minerals, cellulose, alloxane and choline chloride were purchased from El-Gomhoriya Company for Trading Drugs, Chemicals and Medical Instruments in Cairo, Egypt
- Corn starch and beef tallow were purchased from the local market, in Cairo, Egypt.
- **Animals;** Thirty-six male albino rats (Sprague-Dawley strain) (150 ± 10 g) were obtained from the animal house of the Institute of Ophthalmology - Giza – Egypt
- **Induction of diabetes and obesity**; The second main group (30 rats) was fed for two weeks on a high fat diet (HFD) to induce obesity, according **to *Min et al., (2004),*** and injected in the second main group with alloxan (150 mg alloxan/kg body weight) to induce diabetes according to the method described **by *Kumar et al (2010).*** Blood samples were

collected from the eyes of all rats to determine glucose levels to ensure induction diabetes.

- Conditions and fed on a basal diet for adaptation for at least seven days before experiments. The rats were divided into (6) main groups (6 rats each):
- Group (1) rats were fed on basal diet.

The other obese rats were injected with alloxan and then divided into 5 groups:

- Group (2) positive group fed on basal diet.
- Group (3) rats were fed on basal diet plus 2.5% of CUR
- Group (4) rats were fed on basal diet plus 5% of CUR
- Group (5) rats were fed on basal diet plus 2.5% of CUR and 1.5% ground black pepper
- Group (6) rats were fed on basal diet plus 5% of CUR and 5% ground black pepper

Methods:

Biological evaluation:

During the experimental period (28 days), body weight was recorded every week. Feed intake (FI) was determined, feed efficiency ratio (FER), body weight gain (BWG %) and organs relative weight were calculated according to ***Chapman et al., (1959).***

Biochemical analysis:

At the end of the experiment the rats were fasted overnight and then anesthetized and sacrificed, and blood samples were collected from the aorta. Blood samples were centrifuged and serum separated for quantification of some biochemical variables, such as serum cholesterol ***(Allain et al., 1974)***, triglycerides ***(Foster and Domain, 1973),*** and high-density lipoprotein (HDL-c) ***(Lopes-Virella et al., 1977)***. Low-density lipoprotein (LDL-c) and VLDL-c (***Friedwald et al., 1972***), serum *glucose* ***(Trinder, 1959).***

Statistical analysis:

(Mean ± standard deviation and one-way ANOVA) using the SAS package and compared with each other using the appropriate test (at least significant differences at (P≤ 0.05) ***(SAS, 2006)***

Histopathological examination;

Specimens from of the liver, heart, and kidney were taken immediately after weighing the organ of the rats and immersed in 10% neutral buffered formalin. The fixed specimens were then trimmed, washed, and dehydrated in ascending grades of alcohol, then cleared in xylene, stained with Hematoxylin and Eosin (H&E) and examined microscopically according *to* ***(Bancroft and Gamble, 2008)***

RESULTS AND DISCUSSION

Effect of CUR and black pepper on Body Weight, Feed Intake and Feed Efficiency Ratio of obese diabetic rats:

The data in table no. (1) showed that the percentage of body weight decreased significantly ($p<0.05$) in (G3) (G4) (195±0) by comparing to the positive control group (G2) (225±7.07) and the best results were in (G6) (185±0) where it was combined 5% CUR + 5% black pepper and the reason for the decrease in the body weight of rats is The interaction of CUR with black pepper, where it was found in a study ***(Susan and Douglas 2017)*** that the combination of Piperine, which is the main active ingredient of black pepper, with CUR increased the bioavailability by 2000%.

Table (1): Effect of CUR and black pepper on Body Weight, Feed Intake and Feed Efficiency Ratio of obese diabetic rats

Treatment/Parameter		BWG%	FI (g/day/rat)	FER
		Mean± SD		
(G1)	Control (-ve)	226.6^{a}±10.4	12.60^{b} ±. 53	12.97^{b} ±.0.59
(G2)	Control (+ve)	225^{a}±7.07	13.19^{a} ± 0.86	11.01^{bc} ± 0.31
(G3)	2.5% Cur	195^{b}±0	9.22^{c} ±.733	16.56^{a} ±1.19
(G4)	5% Cur	195^{b}±0	13.24^{a} ±.546	11.65^{b} ± 0.97
(G5)	2.5% Cur +1.5% black pepper	190^{b}±0	12.10^{b} ± 0.51	12.22^{b} ± 0.79
(G6)	5% Cur + 5% black pepper	185^{b}±0	12.86^{b} ± 0.63	12.49^{b} ± 1.15

***Values are expressed as means ±SD. BWG; body weight gain. FI: Feed intake. FER: Feed efficiency ratio**
***Values at the same column with different letters are significant at P<0.05**
*** Significant at p<0.05 using one way ANOVA test**

Effect of CUR and black pepper on the weight of the internal organs in obese rats with diabetes:

As a result of the changes in the relative weight of members shown in Table No. (2), where groups G3, G4, G5, and G6 showed a decrease in the weight of the heart (0.67 ± 0.14) (0.60 ± 0.06) (0.61 ± 0.04) and (0.51 ± 0.02) respectively compared to the positive control group (0.81 ±0.01) This is likely due to the rapid metabolism of CUR and its excretion ***(Shabbir et al., 2021)*** .There was no significant difference in the weight of kidneys and livers for all groups

Table (2) Effect of CUR and black pepper on the weight of the internal organs in obese diabetic rats

groups		Organ weight/body weight (Mean±SD)		
		Liver (%)	**Heart** (%)	**Kidney** (%)
(G1)	Control (-ve)	6.30 ^{a} ± 0.52	0.78 ^{a} ±0.05	1.26 ^{a} ±0.26
(G2)	Control (+ve)	5.68 ^{a} ±0.21	0.81 ^{a} ±0.01	1.25 ^{a} ± 0.09
(G3)	2.5% Cur	6.65 ^{a} ± 1.06	0.67 ^{b} ± 0.14	1.34 ^{a} ±0.08
(G4)	5% Cur	6.38 ^{a} ± 0.09	0.60 ^{b} ± 0.06	1.25 ^{a} ± 0.14
(G5)	2.5% Cur +1.5% black pepper	5.99 ^{a} ± 0.99	0.61 ^{b} ± 0.04	1.38 ^{a} ± 0.12
(G6)	5% Cur + 5% black pepper	5.62 ^{a} ± 0.75	0.51 ^{b} ± 0.02	1.27 ^{a} ± 1.27
LSD		1.5793	0.1577	0.3957

Values are expressed as means ± SD.
Values at the same column with different letters are significant at (P≤0.05)

Effect of CUR and black pepper on the level of glucose and Lipid profile in obese rats with diabetes:

The results of Table (3) showed the serum glucose level in the positive control group (255.5±12.02) increased significantly (P≤0.05). Compared to the negative control group (88 ±6.0), and all treatments showed a significant decrease. (p≤0.05) in serum glucose compared to the positive group, This agrees with a study ***(Den Hartogh et al., 2020)*** Who reported that CUR has an antidiabetic effect by promoting glucose uptake and improving pancreatic beta-cell function. In addition, turmeric contributes to reducing the process of gluconeogenesis and increasing Glucokinase activity. The highest decrease in serum glucose for group (G5) was 131 ± 9.89 where they fed 2.5% CUR + 1.5% black pepper in addition to the usual Diet. Followed by group (G4) 143 ± 8.48 who fed 5% of CUR in addition to their regular diet. This explains the effect of combining CUR with black pepper in reducing serum sugar concentration

The mean values of cholesterol, triglycerides, low-density lipoprotein and very low-density lipoprotein were increased in the positive control group (285.5± 7.77) (199±4.24) (208.7 ± 7.21) and (39.80 ±0.84) respectively compared to the positive control

group (112.3 ±8.14) (84.6 ±12.22) (58.06 ±5.89) and (14.93±1.40) respectively. Serum whole LDL cholesterol elevation might also be due in phase to extended biosynthesis of cholesterol by means of up-regulation of the HMG-CoA reductase enzyme (***Liang et al., 2005 and Ghelani et al., 2019).***

The results showed a decrease in Lipid profile (T.CHO-TG-LDL-VLDL) for the Treated groups, A study showed ***(Tossetta et al., 2021)*** who revealed that CUR has anti-lipid effects where T.CHO in the group G2 was (285.5± 7.77) and it became (187.5±4.94) in the G3 group that fed 2.5% CUR. The level of T.CHO became (180±11.31) in the G4 that fed 5% CUR, and it became (175.5 ±10) in the G5 group that fed2.5% CUR +1.5% black pepper, and it decreased more and became (171 ±9.89) in the G6 group that fed 5% CUR + 5% black pepper .

There was also a decrease in the concentration of TG for the groups G3-G4-G5-G6 compared to G2, A decrease in TG was found when comparing Control (+ve) (G2) (199±4.24) to (G3) fed on 2.5% CUR (132±9.89), and a decrease in VLDL-C was found when compared with (Control (+ve)) (G2) (39.8±0.84) by (G3) fed on 2.5% CUR (26.40 ± 1.97) and this agrees with the study ***(Seo et al., 2008).*** The use of CUR effectively reduced triglycerides in the blood and VLDL along with Along with triglycerides in the liver and there was a decrease in the concentration of LDL for the groups G3-G4-G5-G6 compared to G2. These results are consistent with a study ***(Wang et al.2017)*** Who reported that CUR reduces high cholesterol in the Western diet caused by chronic inflammation and associated metabolic diseases (including obesity).There was no difference in the level of HDL-c between all groups

Table (3): Effect of CUR and black pepper on the level of glucose and lipids in obese diabetic rats.

Groups		Glucose	T.CHO	TG	HDL-c	LDL-c	VLDL-c
		(mg/dl)					
(G1)	Control (-ve)	$88^{D} \pm 6.00$	$112.3^{C} \pm 8.14$	$84.6^{D} \pm 12.22$	$39.3^{A} \pm 1.52$	$58.06^{D} \pm 5.89$	$14.93^{E} \pm 1.40$
(G2)	Control (+ve)	$255.5^{A} \pm 12.02$	$285.5^{A} \pm 7.77$	$199^{A} \pm 4.24$	$37^{A} \pm 1.4$	$208.7^{A} \pm 7.21$	$39.80^{A} \pm 0.84$
(G3)	2.5% Cur	$161^{B} \pm 4.24$	$187.5^{B} \pm 4.94$	$132^{C} \pm 9.89$	$38.5^{A} \pm 2.12$	$122.6^{B} \pm 4.80$	$26.40^{D} \pm 1.979$
(G4)	5% Cur	$143^{CB} \pm 8.48$	$180^{B} \pm 11.31$	$157.5^{BC} \pm 7.77$	$35.5^{A} \pm 2.12$	$113^{BC} \pm 7.63$	$31.50^{BC} \pm 1.55$
(G5)	2.5%Cur +1.5% black pepper	$131^{C} \pm 9.89$	$175.5^{B} \pm 10.60$	$169^{B} \pm 2.82$	$38.5^{A} \pm 2.12$	$103.2^{C} \pm 12.16$	$33.80^{B} \pm 0.56$
(G6)	5% Cur + 5% black pepper	$154^{B} \pm 9.89$	$171^{B} \pm 9.89$	$136.50^{C} \pm 23.3$	$38^{A} \pm 4.2$	$105.70^{BC} \pm 9.47$	$27.30^{CD} \pm 4.6$
LSD		19.47	20.48	27.84	5.36	18.23	4.99

Values are expressed as means ± SD.

Values at the same column with different letters are significant at (P≤0.05).

Effect of CUR and black pepper on the Kidneys functions and Serum Liver Functions in obese rats with diabetes:

The results of Table No. (4) showed the curative effect of CUR and black pepper on kidney function (concentrations of urea, creatinine and uric acid in the serum)and Serum Liver Functions in obese diabetic mice, the blood urea concentration increased significantly (35 ± 4.24) mg/dl in the positive control group compared to In the negative control group (22±4.58), CUR supplementation with black pepper showed a decrease in serum urea levels up to (29.5±0.7) in (G6) fed with 5% CUR + 5% black pepper.

Table (4) showed that in the positive control group, the mean creatinine increased (4.24 ± 0.69) compared to the negative control group (0.02 ± 0.6), while all treated groups showed non-significant changes in serum creatinine compared to the negative

control group, and this corresponds to ***(Sara and tasneem 2021)*** and in the same table, the level of uric acid was high in all groups treated with CUR and black pepper, and in a study ***(Mazzali et al., 2001)*** it was demonstrated that increased serum uric acid could cause glomerular hypertrophy and systemic/glomerular hypertension through an accrystal-independent mechanism., and this is likely due to the effect of combining CUR and black pepper.On the other hand, the effect of CUR and black pepper on liver enzymes including glutamic-oxalic transaminase (GOT) and (GPT) Glutamate-pyruvic transaminase for obese rats with diabetes are shown in Table (4). Mean liver enzyme values (GOT) increased significantly ($p \leq 0.05$) in the positive control group (G2) (67.50 ± 4.94) compared to the negative control group (G1) (18.66 ± 2.081), and (Gpt) significantly increased ($p \leq 0.05$) in the positive control groups (G2) (57± 8.48) compared to the negative control group (G1) (19± 2). The results in this table showed that the use of 2.5% of CUR (G3) caused a significant ($p \leq 0.05$) decrease (39.50± 2.12) in (GOT) compared to the positive control group (G2) (67.50 ± 4.94) and also caused the use of 2.5 % of CUR (G3) had a significant ($p \leq 0.05$) decrease in (GPT) (30.50 ±2.12) compared to the positive control group (G2) (57± 8.48)This agrees with the study of ***(Farzaei et al., 2018)*** who reported that CUR and turmeric have many health benefits, including strong antioxidant and anti-cancer properties, so it is a popular choice for the prevention of liver disease Accordingly,

Table (4): Effect of CUR and black pepper on the Kidneys functions and Serum Liver Functions in obese rats with diabetes

groups		Uric acid	Urea nitrogen	Creatinine	Got	Gpt
		mg/dl			IU/L	
(G1)	Control (-ve)	$3.1^{B} \pm 0.3$	$22^{C} \pm 4.58$	$0.6^{D} \pm 0.02$	$18.6^{D} \pm 2.08$	$19^{D} \pm 2$
(G2)	Control (+ve)	$3.5^{B} \pm 0.14$	$35^{AB} \pm 4.24$	$0.69^{DC} \pm 4.24$	$67.5^{A} \pm 4.94$	$57^{B} \pm 8.4$
(G3)	2.5%Cur	$5.0^{A} \pm 0.14$	$26.5^{BC} \pm 4.94$	$0.7^{BC} \pm 0.01$	$39.5^{C} \pm 2.12$	$30.5^{C} \pm 2$
(G4)	5% Cur	$5.3^{A} \pm 0.56$	$36.5^{A} \pm 2.12$	$0.7^{AB} \pm 0.04$	$49.5^{B} \pm 2.12$	$44.5^{B} \pm 2$
(G5)	2.5% Cur +1.5% black pepper	$5.5^{A} \pm 0.77$	$34.5^{AB} \pm 4.94$	$0.8^{A} \pm 0.04$	$54^{B} \pm 5.65$	$40.5^{B} \pm 0.7$
(G6)	5% Cur + 5% black pepper	$5.50^{A} \pm 0.42$	$29.5^{ABC} \pm 0.7$	$0.78^{AB} \pm 0.03$	$51^{B} \pm 2.82$	$46^{B} \pm 2.82$
LSD		0.99	9.27	0.08	7.87	8.57

Values at the same column with different letters are significant at ($P \leq 0.05$)
Values were expressed as means ± SD

Effect of CUR and black pepper on complete blood picture levels in in obese diabetic rats:

The data summarized in Table 5 indicates that increase in complete blood picture levels (Hb, PLT,HCT,MCV and MCH) in Positive control (G2) as compared to negativecontrol (G1), while showing a significant decrease in WBC (x103) in Positive control (G2) as compared Negative control (G1) the study by ***(Rinkunaite et al., 2021***)showed that CUR reduced the levels of white blood cells, while the values of the untreated control increased with CUR and piperine, while in our current study the use of CUR and black pepper led to a decrease in white blood cells in (G5) (6.95±0.2) and (G6) (5.65±0.63) compared to (G2) (7.7±1.9) and the Values at the same column with different letters are significant at ($P \leq 0.05$)

Table (5) Effect of CUR and black pepper on complete blood picture levels in in obese diabetic rats

groups		HB g/dl	WBC (x103)	PLT	HCT %	RBC 106 cell/µL	MCV	MCH	MCHC
(G1)	Control (-ve)	$13.43^{BC}\pm 0.6$	$9.03^{A}\pm 1.201$	346.67 ± 44.27	$41.1^{C}\pm 2.65$	$5.09^{B}\pm 0.205$	$80.6^{D}\pm 1.527$	$26.33^{B}\pm 0.577$	$32.6^{A}\pm 1.154$
(G2)	Control (+ve)	$14.90^{A}\pm 0.28$	$7.70^{AB}\pm 1.979$	$376.5^{A}\pm 20.50$	$44.75^{AB C}\pm 1.909$	$5.20^{B}\pm 0.282$	$86^{CD}\pm 1.414$	$28.50^{A}\pm 0.707$	$33.5^{A}\pm 0.70$
(G3)	2.5%Cur	$13.70^{BC}\pm 0.141$	$7.90^{AB}\pm 0.989$	$312.5^{AB}\pm 40.30$	41.65^{BC}	$4.80^{B}\pm 0.141$	$87^{BC}\pm 1.414$	$28.50^{A}\pm 0.707$	$33^{A}\pm 0$
(G4)	5% Cur	$14.20^{AB}\pm 0.141$	$9.35^{A}\pm 1.202$	$327.5^{AB}\pm 89.8$	$47.30^{A}\pm 1.555$	$5.10^{B}\pm 0.141$	$92.5^{A}\pm 0.707$	$28.^{AB}\pm 0$	$30.5^{B}\pm 0.7$
(G5)	2.5%Cur +1.5% black pepper	$13.70^{BC}\pm 0.282$	$6.95^{AB}\pm 0.212$	$260.5^{B}\pm 19.09$	$45.75^{AB}\pm 2.05$	$5.00^{B}\pm 0.141$	$91.5^{AB}\pm 2.121$	$27.50^{AB}\pm 0.707$	$29.5^{B}\pm 0.7$
(G6)	5% Cur + 5% black pepper	$12.95^{C}\pm 0.212$	$5.65^{B}\pm 0.636$	$381.5^{A}\pm 14.84$	$49.10^{A}\pm 0.989$	$5.95^{B}\pm 0.212$	$82.5^{CD}\pm 4.949$	$22^{C}\pm 1.41$	$26^{C}\pm 0$
LSD		0.86	2.23	105	4.40	4.40	5.36	1.77	1.77

*Values are expressed as means ±SD. Means in the same column with different superscript letters are significant different at P≤0.05

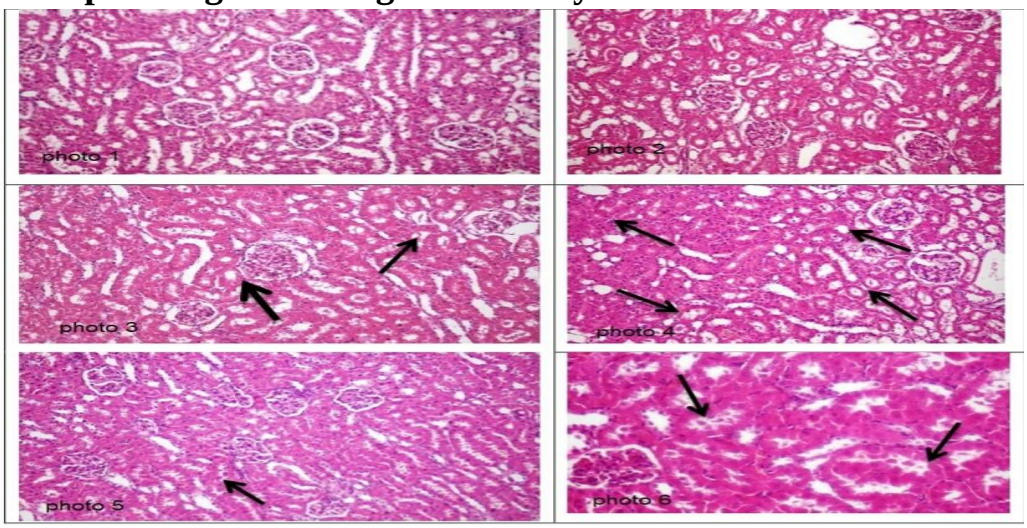
Histopathological examination:

Kidney

Kidney tissues of negative control group revealed normal histological structure (photo. 1). While the control positive group (G2) showing diffuse degeneration, necrosis and desquamation (arrow) of the renal tubular epithelial linings, with appearance of renal cast (dashed arrow) in the lumen of some tubules (photo. 2). On the other hand G 3 that treated with 2.5% CUR showing moderate degree of degeneration and necrosis (arrow) of the renal tubular epithelium, presence of eosinophilic granular cast (dashed arrow) in the lumen of some tubules(photo. 3). And the kidney of rats treated with 5% CUR (G 4) showed that mild swelling and degeneration of the renal tubular epithelium and few granular casts in the lumen of some tubules (dashed arrow) with scars

degenerated glomeruli (photo. 4) This is consistent with (Ghelani et al., 2019) that the traditional use of CUR prevents kidney damage.. And treated with combined 2.5% CUR and +1.5% black pepper (G5) showing few desquamated tubular epithelial linings (arrow). (photo. 5). While(G6) treated with combined 5% CUR + 5%black pepper showing mild tubular epithelial swelling, some desquamated cells (arrow) with attempts for hyaline cast (dashed arrow) formation in the lumen of few tubules. (photo. 6).

Histopathological Changes of Kidney tissues:

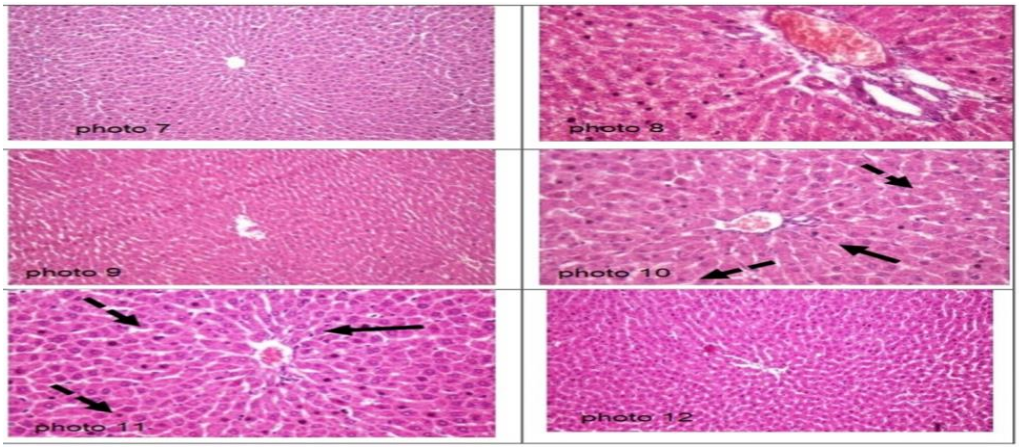


Histopathological Changes of liver:

liver tissues of negative control group showing normal central vein (CV) and hepatic cells (Hc) **(photo. 7)** While the control positive group (G2) showing congestion (Co) of the portal vessels, portal edema (Ed) and mild proliferation (arrow) of the bile duct epithelium, notice the hepatocellular necrobiotic changes and Kupffer cells activation (dashed arrow) **(photo. 8).** On the other hand G 3 that treated with 2.5% CUR showing mild necrobiotic changes of the hepatic parenchymal cells **(photo. 9).**and (G4) treated with 5% CUR showing mild congestion of the portal vessel (arrow) as well as mild swelling and necrobiotic changes (dashed arrow) of the hepatic cells **(photo. 10)** This agrees with the study (Chang et al., 2021) that giving CUR to rats led to a reduction in liver fat and fat cells.. Liver of control positive rat and treated with combined 2.5% CUR +1.5% black pepper (G5)

showing mild sinusoidal dilatation (arrow) and scattered necrotic hepatocytes**(photo. 11).**while - Liver of control positive rat and treated with combined 5% CUR + 5% black pepper (G6) showing good restoration of the hepatic parenchyma **(photo. 12).** This improvement in liver tissue agrees with the results of biochemical analyzes, where we find that in (G6) who fed 5% CUR + 5% black pepper, it led to a decrease in GOT and GPT (51± 2.82 ((46±2.82) respectively compared to (Control) (+ve) (G2) which is (67.5±4.94) (57±8.4) respectively

Histopathological Changes of liver tissues:

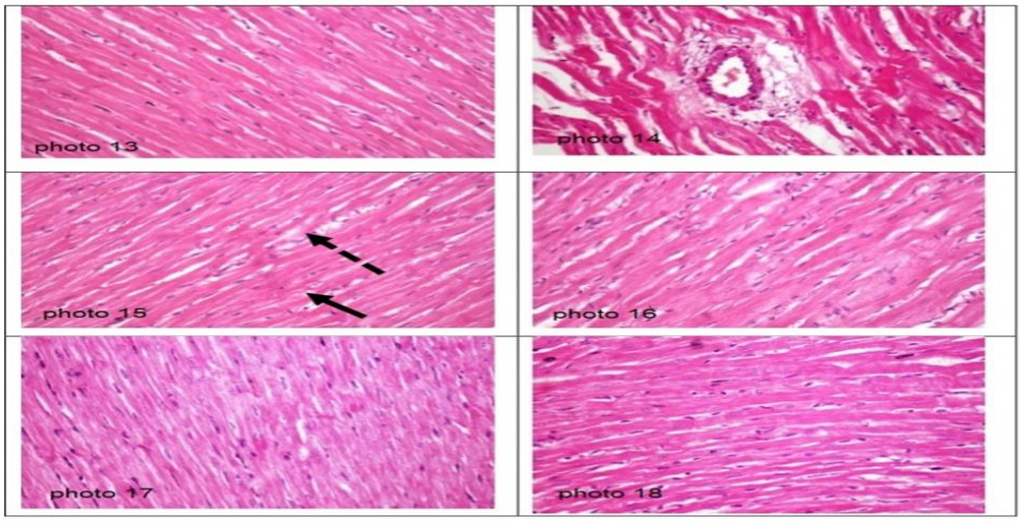


Histopathological Changes of heart:

Heart of control (-ve) (G1) showing normal cardiac muscle fibers **(photo. 13).**while show Higher magnification of heart of control positive rat showing vasculitis characterized by mononuclear inflammatory cells infiltration, focal hyalinization (arrow) of the blood vessel's wall and marked edema (Ed) in the blood vessel wall and perivascular also. Notice the hyalinization (dashed arrow) and necrosis of the muscle **fibers (photo. 14).** And treated with 2.5% CUR (G3) showing good degree of restoration with few necrotic muscle fibers (arrow) and very mild intermuscular edema (dashed arrow**). (photo. 15).** Heart of control positive rat and treated with 5% CUR (G4) showing mild granular degeneration of the muscle fibers, mild intermuscular edema and scars necrotic fibers **(photo. 16)** And it was found in a study (Ghelani et al., 2019) that CUR significantly reduces the risk

indicators of atherosclerotic lesions and coronary atherosclerosis. and treated with combined 2.5% CUR +1.5% black pepper (G5) showing few muscle fibers with granular degeneration (arrow) and scars necrotic cells **(photo. 17).**while heart of control positive rat and treated with combined 5% CUR+ 5% black pepper showing(G6) good restoration of the cardiac muscle fibers **(photo. 18)**

Histopathological Changes of heart tissues:



Conclusion and Recommendations

In conclusion, a diet containing 5% CUR + 5% black pepper can help to reduce the level of glucose, levels of total cholesterol, triglycerides and LDL cholesterol in serum. The results indicated that the administration of CUR in combination with black pepper in moderate proportions led to a significant improvement in the decrease in the level of sugar caused by the injection of alloxan and the decrease in the level of lipids caused by following a diet rich in fat in rats. The study recommended of combining CUR with black pepper in moderate proportions to obtain good results in lowering serum sugar and fat levels.

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دراسة تأثير دمج الكركمين والفلفل الأسود بنسب مختلفة على الفئران البدينة المصابة بالسكرى

المستخلص

تهدف هذه الدراسة إلى دراسة تأثير الجمع بين الكركمين (CUR) والفلفل الأسود بنسب مختلفة على الفئران البدينة المصابة بداء السكري. تم استخدام ستة وثلاثين من ذكور الجرذان البيضاء البالغة وزنها 150 ± 10 جم وقسمت إلى 6 مجموعات (كل مجموعة 6 فئران) وكانت مدة التجربة 4 أسابيع. المجموعة الأولى ، المجموعة الضابطة ، تم إطعامها بالنظام الغذائي الأساسي. المجموعة الرئيسية (30 جرذاً) تم إطعامها لمدة أسبوعين على نظام غذائي عالي الدهون (HFD) للحث على السمنة وحقنت بالألوكسان 150 جم / كجم من وزن الجسم للحث على مرض السكري ، وتم تقسيمهم إلى 5 مجموعات. (كل مجموعة 6 فئران). المجموعة الثانية تم تغذيتها على العليقة القاعدية ، المجموعة الثالثة غذيت على العليقة الرئيسية و 2.5٪ CUR ، المجموعة الرابعة غذيت على العليقة القاعدية و 5٪ CUR ، المجموعة الخامسة غذيت على العليقة القاعدية و 2.5٪ CUR و 1.5٪ فلفل اسود. المجموعة السادسة تم تغذيتها على العليقة القاعدية و 5٪ CUR و 5٪ فلفل اسود. أظهرت النتائج انخفاضاً في أوزان المجموعات (P <0.05) التي تغذت على الكركمين والفلفل الأسود. انخفض مستوى الجلوكوز في الدم في المجموعة (G5) التي تغذت 2.5٪ مع 1.5٪ فلفل أسود (131 ± 9.89) مقارنة بمجموعة التحكم الموجبة (255.5 ± 12.02) وانخفض مستوى الكوليسترول الكلي في مجموعة الفئران التي تمت تغذيتها بنسبة 5٪. CUR مع 5٪ فلفل أسود (171 ± 9.89) مقارنة بالمجموعة الضابطة الموجبة (285.5 ± 7.77) ، وأظهرت النتائج انخفاضًا في مستوى الدهون الثلاثية في المجموعة التي تم تغذيتها على 5٪ CUR و 5٪ فلفل أسود (136.5 ± 23.3) مقارنة بالمجموعة الضابطة الإيجابية (199±4.24) (G2) ، لذلك أوصت الدراسة بدمج CUR مع الفلفل الأسود بنسب معتدلة للحصول على نتائج جيدة في خفض مستويات الجلوكوز والدهون في الدم

الكلمات االمفتاحية: الجلوكوز - الدهون - أنزيمات الكبد