doi.org/10.36721/PJPS.2025.38.6.REG.13426.1

Cardioprotective, lipid-lowering and glucose-lowering properties of edible seeds from the Cucurbitaceae family

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Abstract: Diabetes mellitus impairs carbohydrate, protein, and lipid metabolism, increasing the risk of metabolic dysfunction and associated complications. This study aimed to evaluate the glucose-lowering and cardioprotective effects of selected edible seed extracts by assessing fasting blood sugar and lipid levels in rabbits. The seed extracts were prepared using a conventional extraction process, seeds of *Cucumis melo*, *Citrullus lanatus*, *Cucurbita maxima*, and *Cucumis sativus* were selected for the investigation. All extracts significantly reduced LDL-C, triglycerides, and total cholesterol levels, while HDL cholesterol levels increased, indicating strong cardioprotective potential. After 30 and 60 days of treatment, All the extracts produced a marked improvement in cardiovascular risk indices. On day 60, *C. lanatus* (200 mg) and *C. maxima* (200 mg) notably decreased the atherogenic index of plasma (AIP). Similarly, after 30 days, the combination group of all extracts at 100 mg dosages showed a significant reduction in AIP. These findings suggest that seeds of *C. melo*, *C. lanatus*, *C. maxima*, and *C. sativus* could be promising natural sources of anti-diabetic and hypocholesterolemic agents, capable of correcting biochemical abnormalities in both normoglycemic and hyperglycemic conditions, thereby reducing cardiovascular risk indices.

Keywords: Cardiovascular disorders; Cardio-protection; Diabetes; Edible seeds; Glucose lowering effects

Submitted on 18-09-2024 – Revised on 02-12-2024– Accepted on 03-03-2025

INTRODUCTION

Diabetes mellitus is a chronic medical condition caused by an insulin imbalance that ultimately results in excessive blood glucose and glucosuria, manifested as polydipsia, polyphagia and polyuria. (Ramachandran, 2014). In accordance with the International Diabetes Federation's recent update in 2021, there are 537 million cases of diabetes globally, with NIDDM Type II diabetes mellitus accounting for 91% of cases (T2DM) and 6.7 million fatalities, with a high prevalence rate in developing countries and Asia. (Zheng *et al*., 2018, Cousin *et al*., 2022) and America (Cousin *et al*., 2022, Fortis-Barrera *et al*., 2017). Diabetes affects people of all ages, including newborns, pregnant women and the elderly and its incidence is rapidly rising (Jwad and Neamah, 2022).

According to the American association of diabetes, there are various types of diabetes (Association, 2005) such as Insulin-dependent diabetes mellitus a type I DM (IDDM); non-insulin-dependent diabetes mellitus a type II DM(NIDDM II) and gestational diabetes mellitus (GDM). IDDM is characterized by a complete loss of pancreatic insulin secretory cells, resulting in no insulin in the body to control metabolism. It is managed through the daily administration of insulin at different dosage as per the level of blood sugar of the patient. Type II diabetes a most common type of diabetes (90-95%) began with insulin resistance, with a gradual decline in insulin production as age progressed (Goyal and Jialal, 2021). The aetiology of diabetes and cardiovascular disease is complicated, involving reversible risk factors such as smoking, obesity, sedentary lifestyle and overeating, as well as irreversible risk factors such as age and genetic predisposition, the most significant of which are nutrition and lifestyle (Zheng *et al*., 2018). The development of atherosclerosis and its consequences is greatly influenced by insulin resistance and hyperglycemia. As a result of metabolic abnormalities, reactive oxygen species are generated in excess that triggers diabetic vascular disease through endothelial dysfunction (Sena *et al*., 2013) and inflammation (Incalza *et al*., 2018).

CVS disorders are usually linked to increased consumption of saturated fats in the form of meat and dairy products, which causes blood vessel narrowing and hardness owing to defective phospholipids. Increased phospholipid synthesis unbalances the coagulating and anticoagulant components without causing initial blood vessel rupture. The activation of the coagulation system in a healthy artery is caused by the deposition of atherogenic lipoproteins this can lead to serious cardiovascular disorders such as atherosclerosis, angina, ischemic heart disease, heart failure and even stroke. (Ezihe-Ejiofor and Hutchinson, 2013).

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The pathogenesis of diabetes-related cardiovascular events involves changes in vasculopathy brought on by endothelial and smooth muscle cell dysfunction, stimulation of platelets and creation of a pro-thrombotic or a pro-inflammatory state that ultimately results in atherothrombosis. (Prandi *et al*., 2022). According to a cross-sectional study conducted in Pakistan in 2019, Type II diabetes and cardiovascular comorbidities co-exist especially in the younger age group (Raza *et al*., 2019). Understanding nutritional knowledge, attitudes and behaviors significantly enhance wellbeing by minimizing the onset of diabetes. (Chawla *et al*., 2019).

Anti-diabetic medications widely used to treat hyperglycemia include biguanide (metformin), thiazolidinediones (Pioglitazone or Rosiglitazone), sulfonylureas (glyburide or glimepiride) and enzyme alpha-glucosidase inhibitors (acarbose or miglitol) used with or without insulin (Padhi *et al*., 2020, Nathan *et al*., 2009). Because of unfavorable side effects, complications and high rates of treatment failure, it is critical to identify or synthesize effective anti-diabetic medications with fewer side effects and a significant reduction of complications (Mahankali *et al*., 2022). Traditional anti-diabetic medicinal herbs are the quickest approach to studying safer and more effective oral hypoglycemic treatments. (Rahmasuha *et al*., 2022).

The current study's goal was to assess the cardioprotective and anti-diabetic characteristics of four Cucurbitaceae seed extracts, as well as their combination. The seeds of selected plants were *Cucumis melo, Citrullus lanatus, Cucurbita maxima* and *Cucumis sativus.* All these seeds are available individually as well as in a blended mixture in Pakistan termed as *Charomaghaz.* Plants of the Cucurbitaceae family have nutritional and medicinal benefits.

MATERIALS AND METHODS

Chemicals

The Karachi-based Multi Chem Sigma-Aldrich Corporation provided all blood testing Kits (Blue and Red top), chemicals, standards dimethyl sulfoxide (99.9%) for this research.

Plant seeds

The seeds were provided by local medicinal herb dealer and identified at the University of Karachi's Herbarium, Center for Plant Conservation. The general herbarium number (GH#) assigned to each plant are mentioned in table 1.

Preparation of ethanolic extract

Seeds were macerated for 21 days, in 95 percent ethanol at a ratio of 1 Kg in 1.5 liters. The extract was filtered and the ethanol was evaporated with a rotary evaporator. Solvent was completely removed by freeze drying. The process was repeated for their 3 consecutive extractions after the soaking of same seeds. The extracts was kept in firmly sealed bottles at 4°C once the extraction procedure was complete (Joshua *et al*., 2022).

Animals

The animals were procured form the animal house of Department of Pharmacology, University of Karachi, animals were randomly allocated into 14 groups: The weight of the animals ranged between 1100g to 1300g, the control group was given 5% DMSO, ethanol extracts of four seeds were administered to 12 test groups at 3 different doses i.e., 50, 100 and 200 mg/kg; additionally, one group was given 100 mg/kg dosages of a combination of all four extracts. The treatment was continued for 2 months daily at 12.00 pm. At day 30 and 60, the blood samples were taken after 12-14 hours of fasting, from all rabbits to measure the lipid profile and FBS (Jiang, 2022). Each rabbit's blood sample (about 10ml) was obtained at two intervals through cardiac puncture (Ghanaati *et al*., 2018) i.e., 30^{th} day and 60^{th} day of dosing.

Blood glucose level

The GOD-PAP technique was used to find out blood glucose, which is an enzymatic colorimetric assay for quantifying the blood glucose level without deproteinization (Barham and Trinder, 1972). Normal fasting blood sugar is defined as less than 99 mg/dL, prediabetes as 100-125 mg/dL and diabetes as 126 mg/dL or more. However, a study reveals that while fasting blood sugar levels between 80 and 90 mg/dl are ideal, fasting plasma glucose levels between 90 and 99 mg/dL in healthy individuals gradually increase the risk of type 2 diabetes. (Munekawa *et al*., 2022). In a different study, the lowest risk was found in the range of 85 to 99 mg/dL, while fasting glucose levels and CVD risks often showed J-shaped associations. Increasing fasting glucose levels above 100 mg/dL raised the risk of ischemic heart disease, myocardial infarction, thrombotic stroke and cardiovascular disease. (Park *et al*., 2013).

Lipid profile

Lipid clearing factor and enzymes were used in a colorimetric method to quantify the cholesterol and triglycerides while a precipitant method was used to measure HDL cholesterol in the supernatant (Romaszko *et al*., 2023). Each serum sample's LDL level was determined indirectly using the equation below.

$$\text{LDL Cholesterol} = \text{TC} - [\text{HDL} - (\frac{\text{TG}}{5})]$$

Where TC is total Cholesterol, HDL is high density lipoprotein and TG is Triglyceride level. The risk of cardiovascular diseases is raised by low HDL cholesterol levels, or elevated levels of LDL-C, TGs and TC. (Lee and Siddiqui, 2021).

Cardiac parameters

Some cardiovascular risk indicators with a link to cardiovascular comorbidities were calculated based on the results of lipid profile. These indices include the Atherogenic Index of Plasma (AIP), the Cardiovascular Risk Index 1 also known as atherogenic or Castelli index (TC/HDL) and the Cardiovascular Risk Index 2 (LDL/HDL). Compared to the isolated normal levels of lipoproteins, the cholesterol/HDL ratio and the LDL/HDL cholesterol ratio are superior risk indicators with stronger predictive values for risk of the development of cardiac issues (Millán *et al*., 2009).

$$\text{Cardiovascular risk index 1} = \frac{\text{TC levels}}{\text{HDL - C levels}}$$

$$\text{Cardiovascular risk index 2} = \frac{\text{LDL - C levels}}{\text{HDL - C levels}}$$

$$\text{AIP} = \log\left(\frac{\text{TG}}{\text{HDL - C}}\right)$$

Where HDL-C stands for high-density lipoprotein, LDL-C for low-density lipoprotein, TC for total cholesterol and TG for triglycerides. Key risk levels and desired ratios are summarized in table 2. High cardiovascular risk is indicated by values over 0.24, medium cardiovascular risk by values between 0.1 and 0.24 and low cardiovascular risk by values between -0.3 and 0.1. (Sein and Latt, 2014, Niroumand *et al*., 2015).

Cardiac enzymes

Cardioprotective activity was analyzed by measuring the levels of cardiac enzymes along with lipid profiles (Khalil *et al*., 2015) . Humazym M-Test was used to calculate creatinine kinase (CK Nac) (Szasz *et al*., 1976). Lactate dehydrogenase (LDH) was determined by catalytic activity with minor alterations (Prandi *et al*., 2022).

Statistical analysis

The data was analyzed using SPSS software version 26. To compare the test results to the control, one way ANOVA was used, followed by Dunnet post hoc testing. The results were declared significant at $p < .05$ and very significant at $p<0.01$.

RESULTS

Glucose level

The effect of seed extracts and extract combinations from the Cucurbitaceae family on fasting blood sugar levels is displayed in table 3. Each seed extract lowered fasting blood sugar levels, though there were some differences. After 30 and 60 days of chronic treatment, the group that received *C. melo* seed extract at dosages of 50 mg/kg and 100 mg/kg demonstrated a significant decrease in FBS in comparison to the control group. The group that received 200 mg/kg of *C. melo* showed a significant decrease in FBS after 30 days and a significant decrease in blood glucose after 60 days of therapy when compared to the control group. However, the fasting level of FBS exceeded the 100 mg/dl upper limit after 60 days.

Compared to the control *C. lanatus*, 100mg/kg and 200mg/kg, both groups demonstrated a significantly substantial reduction in FBS after 30 and 60 days of medication, however, fasting levels exceeds 100mg/dl. Despite this, the fasting level of FBS approached the upper limit of 100 mg/dl.

C. maxima and *C. sativus* seed extracts at 50mg/kg, 100mg/kg and 200mg/kg dosages, as well as a combined group of all four seed extracts at 100mg/kg dose, showed a highly significant drop in blood glucose level after 30 and 60 days of therapy. C. maxima had the greatest glucose reducing effects among all studied extracts as compared to the control at the dosages of 50mg/kg, 100mg/kg and 200mg/kg.

Lipid profile

Table 4 reveal the effect of different seed extracts on the lipid profile after 30 and 60 days of chronic treatment. All seed extracts were found to have the capacity to reduce blood levels of cholesterol, triglycerides (TGs), low-density lipoprotein (LDL-C) and very low-density lipoprotein (VLDL-C), while serum levels of HDL cholesterol were found to be raised, indicating cardioprotective benefits. Individual effects for each seed extract are mentioned below.

C. melo at each doses revealed highly significantly reduction in the serum levels of Total cholesterol, LDL-C, TGs and VLDL-C after 30 days as well as 60 days of dosing while revealed highly significant elevation in serum levels of HDL-C after dosing for duration of 30 days as well as 60 days.

After 30 days of chronic dosing, *C. lanatus* 50mg/kg showed a significant decrease in serum levels of TGs, while serum levels of total cholesterol, LDL-C and VLDL- C showed a highly significant decrease after 30 and 60 days of dosing. Following 30- and 60-day dosing, there was a highly significant increase in HDL-C serum levels.

C. maxima 50mg/Kg revealed significant reduction in VLD-C at 60th day, while at each doses revealed highly significantly reduction in the serum levels of total cholesterol, LDL-C and VLDL-C and TGs after 30 days and 60 days of chronic dosing. *C. maxima* 100mg/Kg and 200mg/Kg revealed highly significant reduction in TGs, total cholesterol, LDL-C and VLDL-C after 30 days and 60 days respectively. There was highly significant increment in HDL-C after the dosing for duration of 30 days as well as 60 days at all three doses.

Table 1: General herbarium number assigned to plant

S#	Name of Plant	General Herbarium number (GH#)
1.	*C. melo*	94494
2.	*C. lanatus*	9462
3.	*C.maxima*	9501
4.	*C. sativus*	94589

Table 2: Cardiovascular risk ratios

Risk index	Risk level		Required ratios	
	Men	Women	Men	Women
Cardiovascular risk index 1(CH/HDL)	> 5.0	> 4.5	<4.5	<4.0
Cardiovascular risk index 2 (LDL/HDL)	>3.5	>3.0	<3.0	<2.5

Table 3: Effects of seed extracts on fasting blood sugar level

Groups and Doses (mg/Kg)	Fasting Blood sugar Day 30 (mg/dl)	Fasting Blood sugar Day 60
Control	115.75 ± 3.58	124.0 ± 3.69
C. melo 50	94.8 ± 2.34**	91.58 ± 2**
C. melo 100	89.68 ± 2.15**	94.8 ± 2**
C. melo 200	94.25 ± 4.37**	100.9 ± 0.92**
C. lanatus 50	107.22 ± 5.14	110.46 ± 5.8
C. lanatus 100	99.64 ± 3.02**	95.34 ± 8.69**
C. lanatus 200	102.33 ± 3.41*	101.00 ± 1.9**
C. maxima 50	64.06 ± 4.04**	78.3 ± 2.59**
C. maxima 100	74.82 ± 0.64**	78.62 ± 4.8**
C. maxima 200	78.46 ± 1.16**	76.34 ± 3.94**
C. sativus 50	74.18 ± 4.37**	72.34 ± 3.83**
C. sativus 100	85.36±3.67**	96.04 ± 2.08**
C. sativus 200	84.56±2.96**	95.9±2.83**
COM 100	81.4±1.53**	89.38±6.04**

n=10, Mean ± SEM. COM 100= Combination of all 4 Seeds extract 100 mg each. *P<0.05 significant while ** P<0.01 highly significant reduction as compared to control.

At day 30, *C. sativus* 50 mg/kg showed a substantial increase in HDL-C, whereas at days 30 and 60, there were extremely significant decreases in TGs, cholesterol, LDL-C and VLDL-C. At day 60, there is a very noticeable increase in HDL-C levels. Following dosage for 30 and 60 days, *C. sativus* 100 mg/kg and 200 mg/kg shown a highly significant decrease in serum levels of TGs, LDL-C and VLDL-. Following the administration of *C. sativus* at all three doses for 30 and 60 days, there was a highly significant increase in the serum level of HDL-C. The group that got 100 mg/kg of a mixture of all four seed extracts showed an extremely significant decrease in TGs, cholesterol, LDL-C and VLDL-C. There is highly significant increment in HDL-C after dosing for duration of 30 days as well as 60 days at all three doses.

Cardiac parameters

The impact of several seed extracts on cardiac risk factors following 30 and 60 days of chronic dosing is shown in table 5. All seed extracts and the combination group had atherogenic index of plasma (AIP) values below the danger limit (-0.06-0.13). AIP was significantly reduced at day 60 by *C. lanatus* 200 mg/kg, *C. maxima* 200 mg/kg and C. sativus. At day 30, there was a noticeable drop in AIP in the group that was given a dose of 100 mg/kg of a combination of all four seed extracts.

The results also revealed that the chosen seed extracts significantly reduced the cardiovascular risk indexes HDL/LDL and total cholesterol/HDL after 30 and 60 days of dosage. The HDL/LDL ratio of all seeds extract and combination groups was found to be less than the risk limit indicated above, 4.5 (1.4- 2.00), indicating that these seeds have cardioprotective properties.

It was confirmed that these seeds had cardioprotective properties when the total cholesterol/HDL ratio determined for all seeds extract and the combination group was also found to be below 3.0/2.5 (0.11-0.53).

Cardiac enzymes

Table 6 shows the impact of Cucurbitaceae family seed extract on cardiac enzymes on days 30 and 60 of chronic dosage. According to the data, all seed extracts showed lower LDH and ckNac levels than the control. Following 30 days of dosage, the levels of ckNac were considerably

reduced after treatment with *C. melo* at all doses, *C. lanatus* at 50 mg/kg and 200 mg/kg and *C. sativus* at 50mg/kg. After 30 days of dosage, *C. lanatus* 100 mg/Kg, *C. maxima* 200mg/kg and *C. sativus* 100 mg/kg showed a substantial decrease in ckNac.

DISCUSSION

The current study's findings regarding the determination of fasting blood sugar (FBS) levels, lipid profile and cardiovascular risk indices revealed that these edible seeds have significant glucose lowering and hypocholesteremic effects with an increment in HDL levels and a decline in cardiovascular risk indexes. Among the four examined seeds, *C. maxima* exhibit the strongest blood glucose-reducing characteristics at all dosages.

According to results achieved after 30 and 60 days of treatment, FBS was significantly reduced by all seed extracts, but *C. maxima* had the strongest glucose-lowering impact across all doses. Similar to *C. maxima*, the combination group likewise had a significant hypoglycemic response. These findings imply that phytochemicals enhance insulin sensitivity and glucose consumption in concert.

As compared to the control group, the combination group had a comparable glucose lowering impact. *C.melo* and *C.lanatus* similarly demonstrated a significant reduction in FBS at 100 mg/kg, but at higher dosages, a notable anti-diabetic effect on lowering FBS was not seen, which might be related to the presence of glucose or carbohydrate in their seeds. The effects on glucose were detected in the following sequence. *C.maxima> COM > C. sativus> C. melo > C. lanatus.*

Results of our study showed that treatment with all extracts increased HDL-C and significantly decreased TC, LDL-C, VLDL-C, and TG levels, suggesting strong hypolipidemic action. The most consistent outcomes across doses and time periods were shown by *C. maxima* and *C. sativus*. Their potential to lower atherogenic risk in diabetic circumstances is highlighted by improvements in lipid profiles.

With an increase in HDL cholesterol and a decrease in cardiovascular risk indices, the seed extracts exhibit impressive hypocholesterolemic effects. A higher risk of CVD is substantially correlated with normoglycemic glucose levels. Blood sugar levels measured during a fast may help identify individuals who appear healthy but have early metabolic abnormalities and are more likely to develop cardiovascular disease before prediabetes and obvious diabetes mellitus (CVD). (Shaye *et al*., 2012). Diabetes is also associated with lower levels of HDL cholesterol and higher levels of total cholesterol, LDL cholesterol, VLDL cholesterol and TG (Krauss, 2004).

According to data received following treatment, AIP values were below the high-risk threshold; at 60 days, there were notable decreases for *C. lanatus* (200 mg), *C. maxima* (200 mg), and *C. sativus*. The cardioprotective function of these seed extracts was confirmed by the constant reduction of the TC/HDL and LDL/HDL ratios.

C. melo is an important plant with seeds that have considerable nutritional and therapeutic properties. It includes cucurbitacin B and E (Chen *et al*., 2005), phenolic glycosides (De Marino *et al*., 2009), trypsin-inhibitors i.e. CMeTI-A, CMeTIB , melonin, cucumisin in the fruit, important minerals such as magnesium, potassium, calcium and sodium (Bouazzaoui and Mulengi, 2018), chromone derivatives such as beta-amyrin, beta-sitosterol and beta-sitosterol-3-O-betaglucopyranoside (Ibrahim, 2010), vitamins like A and C and antioxidants like gallic acid, ferulic acid, ellagic acid and caffeic acid (Peng and Gnsman, 2008, Vella *et al*., 2019).

Beta-sitosterols and its analogue subgroup of the steroids, are reported to have an anti-inflammatory, anticancer, increased insulin secretory and cholesterol lowering effects (Ivorra *et al*., 1988, Bin Sayeed and Ameen, 2015)., COX inhibitor, hypocholesteremic, antidiabetic, angiogenic, chemo preventive for cancer, immunomodulatory, analgesic, antimutagenic properties (Saeidnia *et al*., 2014).

In type 2 diabetic rats, gallic acid improves kidney functioning through blocking the p38 MAPK. (Ahad *et al*., 2015). Isolated glycolipids are mono and diacylglycerol and digalactosyldiacylglycerol, β-Carotenes and apocarotenoids, phosphatidylcholine, phosphatidyl-ethanolamine were also isolated. It's seeds also contain amentoflavone a bioflavonoid having antioxidant, cyclooxygenase enzyme inhibitor, induced nitric oxide synthase and inhibit phospholipase A2 inhibition, as well as the suppression of degranulation and arachidonic acid from neutrophils (Mallek-Ayadi *et al*., 2018).

A study regarding the determination of antidiabetic and antihyperlipidemic activities was conducted using fruit of *C. melo* in streptozocin model of diabetes (Srivastava *et al*., 2020). The results were synchronized to our study revealing hypoglycemic and hypocholesteremic effects.

C. lanatus also contains high concentrations of several micro-nutrients such as pro-vitamin A (carotene), Vitamin B2 (riboflavin), vitamin C, vitamin K, riboflavin and minerals like iron, iodine, sodium, calcium and potassium (Nnenne *et al*., 2020). Beside these, *C. lanatus* has significant amount of several types of alkaloids, phenolic compounds, such as citrulline, lycopene, arginine, b-glutamine and C-Aspartic acid, coumarin and phytochemicals such as cucurbitacin E, triterpenes like antioxidant.

Table 4: Effects of seed extracts on Lipid Profile

Groups and Doses (mg/Kg)	Cholesterol		Triglycerides		HDL-C		LDL-C		VLDL-C	
	mg/dl									
	Day 30	Day 60	Day 30	Day 60	Day 30	Day 60	Day 30	Day 60	Day 30	Day 60
Control	59.00 ± 1.34	58.93 ± 1.33	93.0 ± 4.3	92.88 ± 4.88	13.88 ± 0.44	12.13 ± 0.74	26.53±0.99	28.23 ±2.03	18.6 ±0.86	18.58±0.98
C. melo 50	47.00 ± 1.58	48.8 ± 1.5	59.7 ± 3.7**	66.94 ± 3.00	27.6 ± 1.12*	29.2 ± 1.97**	3.80±0.64**	7.74 ± 1.15**	11.95± 0.74**	13.39±0.9**
C. melo 100	49.3 ± 0.4	45.22 ± 0.59*	61.7±3.29*	58.0 ± 3.62**	32.48 ± 1.04**	30.4 ± 0.64**	7.72±1.15**	5.4±1.04**	12.34±0.66**	11.60±0.72*
C. melo 200	42.40 ± 0.73**	43.65 ± 2.41**	59.7± 3.52*	57.42 ± 3.83**	29.63 ± 1.79 **	31.10 ± 1.59**	7.06±0.87**	6.80±1.07**	11.94±0.72**	11.48±0.77**
C. lanatus 50	38.04 ± 2.02**	37.40 ± 1.76**	56.8 ± 6**	51.40 ± 2.84**	22.60± 1.66*	20.26 ±1.07	4.08±0.42**	6.86±2.28**	11.36±0.68**	10.28±0.57**
C. lanatus 100	36.9 ± 1.65**	40.30 ± 1.07**	50.8 ± 3.36*	50.5 ± 3.47**	23.11 ± 1.2**	26.10 ±1.18**	3.63±0.82**	4.10±0.49**	10.16±0.67**	10.10±0.69**
C. lanatus 200	38.80 ± 2.19**	43.7 ± 0.97**	49.76 ± 4.56**	39.20 ± 1.33**	23.09 ± 2.76**	29.30 ±1.01**	5.76±0.25**	6.56±0.58**	9.95±0.91**	7.84±0.27**
C. maxima 50	47.50 ± 1.17	47.20 ± 1.62	76.7 ± 3.52	60.74 ± 6.41*	24.48 ± 0.47**	24.70 ±1.61*	7.68± 0.83**	10.35±2.45**	15.35*± 0.70	12.15**± 1.28*
C. maxima 100	46.20 ± 2.97*	46.70 ± 1.07*	52.68± 4.3**	57.40 ± 3.93**	28.3 ± 1.57**	26.19 ±0.35**	7.36± 1.22**	9.03± 1.13**	10.54±1.4**	11.9±1.4**
C. maxima 200	43.00 ± 3.02*	45.40 ± 0.48*	50.94 ± 1.91**	43.76 ± 6.26**	21.30 ± 2.44*	27.10 ±0.43**	11.51± 4.42**	9.55±0.70**	10.49± 0.38 **	11.73±0.57**
C. sativus 50	41.70 ± 1.41**	47.55 ± 1.60	52.46 ± 1.91**	58.64 ± 2.84*	20.90 ± 0.77*	25.10±0.99**	10.31±1.82**	10.72± 2.11**	10.49±0.38**	11.73±0.57**
C. sativus 100	41.0 ± 4.0	47.3 ± 3.20	47.32 ±3.09**	54.78 ± 1.05**	24.5 ± 3.07**	24.8±4.2**	6.8±0.9**	11.4±1.8**	9.7±1.06**	11.1±1.2**
C. sativus 200	44.60 ± 1.11	42.90 ± 1.13**	54.70 ± 1.32**	54.78 ± 1.05**	26.24 ± 2.14**	27.60± 0.78**	7.42±2.00**	4.34± 0.83**	10.94±0.26**	10.96±0.26**
COM100	46.90 ± 0.78**	43.30 ± 0.63**	57.73±3.6**	59.46 ± 2.54*	32.10 ± 1.07**	28.10±1.34**	3.25±0.63**	3.31±0.54**	11.55±0.72**	11.89±0.51**

n=10, Mean ± SEM. COM 100= Combination of all 4 Seeds extract 100 mg each. *P<0.05 significant; ** P<0.01 highly significantly different as compared to control.

Table 5: Effects of seed extracts on cardiac risk parameters

Groups and	AIP index		CH/HDL Ratio		LDL/HDL Ratio	
Doses (mg/Kg)	Day 30	Day 60	Day 30	Day 60	Day 30	Day 60
Control	0.2±0.03	0.20±0.04	4.28± 0.14	5.0±0.34	1.91±0.05**	2.41±0.24
C. melo 50	0.1±0.02	0.13±0.02	1.73±0.10**	1.74±0.13**	0.14±0.02**	0.31±0.09**
C. melo 100	0.08±0.02	0.1±0.02	1.53±0.05**	1.5±0.03**	0.24±0.03**	0.16±0.031**
C. melo 200	0.14±0.03	0.11±0.01	1.50±0.12**	1.41±0.01**	0.27±0.05**	0.23±0.04**
C. lanatus 50	0.17±0.01	0.13±0.04	1.71±.04**	1.89±0.12**	0.2±0.03**	0.37±0.13**
C. lanatus 100	0.13±0.03	0.13±0.03	1.6±0.01**	1.57±0.06**	0.15±0.03**	0.17±0.02**
C. lanatus 200	0.10±0.06	-0.07±0.03**	1.77±0.08**	1.5±0.02**	0.27±0.02**	0.23±0.02**
C. maxima 50	0.2±0.01	0.09±0.05	1.95±0.05**	2.00±0.17**	0.32±0.04**	0.48±0.13**
C. maxima 100	0.05±0.03**	0.08±0.03	1.63±0.02**	1.79±0.05**	0.25±0.03**	0.35±0.05**
C. maxima 200	0.09±0.02*	-0.04±0.6**	2.53±0.54**	1.68±0.03**	0.93±0.42**	0.35±0.02**
C. sativus 50	0.1±0.01	0.09±0.02	2.04±0.14**	1.94±0.15**	0.53±0.11**	0.46±0.11**
C. sativus 100	0.07±0.02*	0.08±0.02	1.7±0.04**	2.03±0.14**	0.31±0.03**	0.53±0.09**
C. sativus 200	0.09±.01	-0.04±0.02**	1.8±0.14**	1.56±0.02**	0.36±0.11**	0.16±0.03**
COM100	0.08±0.02**	0.06±0.05	1.47±0.03**	1.56±0.04**	0.11±0.03**	0.12±0.02**

n=10, Mean ± SEM; AIP= Atherogenic index of Plasma; COM 100= Combination of all 4 Seeds extract 100 mg each. *P<0.05 significant; ** P<0.01 highly significantly different as compared to control.

Table 6: Effects of seeds extracts on cardiac enzymes

Groups and Doses	ckNac (U/L)		LDH (U/L)	
(mg/Kg)	Day 30	Day 60	Day 30	Day 60
Control	174.5±12.3	189.0±20.2	173.5±19.8	177.1±21.8
C. melo 50	115.8±12.3**	138.0±25.3	101.9±26.9	61.3±13.8**
C. melo 100	114.4±4.7**	99.4±14.9	135.2±7.5	84.9±15.0*
C. melo 200	129.7±10.2**	125.6±11.0	130.7±11.5	67.4±17.0**
C. lanatus 50	114.9±7.9**	213.3±47.5	153.7±6.7	85.1±15.0
C. lanatus 100	134.6±12.9*	193.0±32.5	103.6±16.9	65.0±12.6**
C. lanatus 200	113.4±2.8**	183.0±39.1	191.1±44.0	63.9±13.8**
C. maxima 50	128.1±7.8**	136.1±15.3	153.5±10.5	110.4±16.6
C. maxima 100	140.3±15.9	294.8±43.2	138.9±14.6	118.7±6.4
C. maxima 200	129.9±7.7*	141.4±12.3	135.1±6 .7	135.2±31.8
C. sativus 50	126.8±7.3**	136.0±3.5	62.0±10.0**	120.2±19.7
C. sativus 100	110.0±5.5*	114.9±4.5	80.7±20.3**	107.2±17.1
C. sativus 200	137.0±8.9	134.3±7.9	117.4±21.3	96.6±15.0*
COM100	103.9±4.9**	97.0±8.9	59.4±12.9**	74.1±14.8**

n=10, Mean ± SEM; COM 100= Combination of all 4 Seeds extract having 100 mg of each. *P<0.05 significant; ** P<0.01 highly significantly different as compared to control.

Due to these vital phytochemicals, it has several pharmacological characteristics (Ismael *et al*., 2022). The seed also have significant concentration of oleic acid, linoleic acid (61.75%) and sterol along with some saturated fatty acids contents as well (Lucky *et al*., 2012, Eke *et al*., 2021). Oliec acid and linoleic acid, n-6 fatty acids, are found to be linked to lower the incidence of type 2 diabetes by increasing insulin sensitivity while n-3 fatty acid failed to increase insulin sensitivity in several clinical trials (Belury *et al*., 2018).

In an alloxan-induced diabetic model, a study evaluated the methanolic extract of *C. lanatus* rind at doses of 100, 200, and 500 mg/kg (Ajiboye *et al*., 2020). This study confirmed the significant reductions in triglycerides, low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C), along with an increase in high-density lipoprotein cholesterol (HDL-C). Significant hypoglycemic effects were also documented with *C. lanatus* rind, emphasizing its role in the amelioration of biochemical derangement (Kolawole *et al*., 2016). Another study evaluated the seed extract of *C. lanatus* in a cardiovascular disease model supplemented with 400 mg/kg of cholesterol daily. Administration of *C. lanatus* at a dose of 120 mg/kg significantly reduced LDL-C, total cholesterol, and VLDL levels, while markedly increasing HDL-C levels, even in the presence of a high-fat diet (Messaoudi *et al*., 2019). The hypocholesterolemic effect may be attributed to reduced cholesterol absorption mediated by the presence of squalene and phytosterols. The antidiabetic activity of *C. lanatus* is associated with its content of flavonoids,

polyphenols, and citrulline, a precursor of arginine. Dietary arginine has been shown to lower plasma glucose levels, enhance glucose uptake by muscles, improve dyslipidemia, decrease fat mass and increase insulin sensitivity (Fu *et al*., 2005).

Fruit of *C. maxima* contains is also a good source of polyunsaturated fatty acids along with sterols. It is also suggested for children growth and melioration of their immunity as rich in protein and carbohydrate content (Mansour *et al*., 1999) (Torkova *et al*., 2018). It's ethanolic extract of seed and leaves contains secondary phytochemicals alkaloids such as flavonoids, alkaloids, carotenoids, γ-amino butyric acid, (Matus *et al*., 1993, Murkovic *et al*., 2002), tannins, 11E-octa decatrienoic acid, saponins and terpenoids (Muchirah *et al*., 2018) phenolic glycosides (Glew *et al*., 2006). Phytosterols of *C.maxima* have hypercholesteremic properties (Aguilar *et al*., 2011).

C. maxima pulp and seed's oil, have been also considered as anthelmintic, hypoglycemic, hypotensive and antiperoxidative properties (Nkosi *et al*., 2006), improve symptoms of benign prostatic hyperplasia and anxiety in limited clinical trials (Gossell-Williams *et al*., 2006). Pectin isolated from *C. maxima* has maximum antioxidant effect, hypoglycemic, anti-inflammatory, cytoprotective and anti-cancerous effect (Caili *et al*., 2006, Adams *et al*., 2011).

C. sativus is consumed as a salad. Its various parts including the stem, leaf, fruit and seeds have various therapeutic benefits. It has undergone extensive research and is primarily used in several skin formulations for fading age spots (Mukherjee *et al*., 2013, Mukherjee *et al*., 2011). Its fruits also have high nutritional value due to presence of carbohydrates like starch, sugars, pectin, protein, amino acids and fats (Peng and Gnsman, 2008). Beside it, several phytochemicals are found in its fruit such as Cucurbitacin A-D, terpenoids, flavonoids, carotenoid, saponins, cucmerin A and B, several vitamins such as vitamin A, C, E and K, minerals (Kumar *et al*., 2010), enzymes, polyphenols, Vitexin and isovitexin, orientin and isoorientin, traces of essential oil, glycosides including some cyanogenic, tannins (Wang *et al*., 2007, Uzuazokaro *et al*., 2018).

Additionally, *C. sativus* contains phytoestrogens such as lignin matairesional, lignin secoisolariciresinol, formononetin, glycitein and isoflavones genistein, biochanin coumestrol and daidzein. (Jun-Hua *et al*., 2008) and phytosterols such as β-sitosterol, campesterol, stigmasterol, campestanol and β-sitostanol (Fishwick *et al*., 1977). *C. sativus* is mainly used for its antioxidant, anti-aging, anti-cancerous, antimicrobial, hypolipidemic, anti-diabetes, antiparasitic activities, analgesic, mild anti-inflammatory and ulcer protective and (Mukherjee *et al*., 2013). Additionally, the juice of this plant can be used to cure anuria, bleeding and jaundice (Uzuazokaro *et al*., 2018). In a study, *Cucumis sativus* antidiabetic potential was assessed through β-glucosidase inhibitory effect which yielded the highest value of 96.81%.These effect might be due to the presence of phenolic acids such as coumaric and syringic acids (Jamal *et al*., 2011).

Levels of CK-Nac and LDH were significantly reduced in most treatment groups, especially with the combination extract and *C. melo* seeds. This decline indicates membrane stabilization and protection of cardiac tissue from oxidative damage, supporting the cardioprotective claims of these extracts.

A recent literature review that seeds of Cucurbitaceae family contains α-spinasterol a phytosterol that has been found in seeds of *C. lanatus*, *C. maxima* and *C sativus* that can cross blood brain barrier. It has a range of important pharmacological characteristics, including anti-diabetic, anti-inflammatory, hypolipidemic, anti-ulcer, neuroprotective, analgesic and anticancerous activity (Majeed *et al*. 2022).

Cucurbitacin A, B, C, D, I and some newer types of triterpenoids present in these seeds has been reported to have antidiabetic activity besides their potent anti-inflammatory, anticancerous activities (Hernández Navia *et al*., 2022, Kanani and Pandya, 2022). Cucurbitacin I, B and E has been found to possess glucose lowering and antidiabetic characteristics besides its antioxidant and other pharmacological effects (Attar *et al*., 2022). Cucurbitacin B and E showed reduction of atherosclerosis by inhibiting lipid oxidation products including 4-hydroxynonenal (4-HNE) and malonaldehyde (MDA) (Tannin-Spitz *et al*., 2007) in turn alteration of lipoproteins (Saba and Oridupa, 2010), enhances blood circulation (Kaushik *et al*., 2015). In a study, 23, 24-dihydrocucurbitacin D (DHCD) had shown potent anti-inflammatory activity. Inducible NO synthase's protein and mRNA levels were lowered by DHCD (iNOS). Nuclear factor-B (NF-B) activation that required for the transcriptional activation of iNOS, was effectively prevented by DHCD (Park *et al*., 2004).

There have been claims that a 23, 24-dihydrocucurbitacin F analogue possesses strong hypoglycemic and antihyperglycemic properties. The possible mechanisms underlying the antihyperglycemic effects include the regulation of hepatic glycogen metabolism and the stimulation of insulin release.

CONCLUSION

The seeds of *C. melo, C. lanatus, C. maxima and C. sativus* are an excellent source of antidiabetic and hypocholesteremic drugs that rectify biochemical abnormalities in individuals who are either

normoglycemic or hyperglycemic, resulting in a considerable reduction in cardiovascular risk indices.

Significant drops in LDH and CK-Nac levels also suggest that cardiac tissue is protected and myocardial damage is avoided. A multi-targeted mode of action combining antioxidant, membrane-stabilizing and insulin-sensitizing pathways is suggested by the combined effects on glucose, lipids and cardiac biomarkers. These results demonstrate the potential of Cucurbitaceae seeds as affordable, all-natural antidiabetic and cardioprotective medicines. Their clinical usefulness in human populations and active phytoconstituents may be investigated in future research.

Acknowledgement
The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through large group Research Project under grant number RGP2/384/46.

Authors' contributions
Shahana Wahid conceived and designed the study, performed data interpretation, and drafted the manuscript. Taha Alqahtani. Ali Alqahtani and Yahya I. Asiri contributed to funding and statistical analysis. Nausheen Hameed Siddiqui critically revised the manuscript and provided overall guidance. Azra Riaz contributed to the study design and literature review. Ejaz Basheer facilitated extraction procedures. All authors read and approved of the final manuscript.

Funding
There was no funding.

Data availability statement
The datasets collected and analyzed during the current study are available from the corresponding author upon request.

Ethical approval
The study was approved by the Institutional Bioethical Committee (IBC), University of Karachi; Approval No. IBC KU-121/2020.

Conflict of interest
The authors declared no conflict of interest.

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