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Antihyperlipidemic activity of hydroalcoholic seed extract of *Cucumis sativus* L in triton X-100 induced hyperlipidemic rats

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ABSTRACT

Hyperlipidemia is linked to an elevated risk of atherosclerosis disease and managing this risk factor is crucial. This study was aimed at investigation of high performance liquid chromatographic (HPLC) analysis and antihyperlipidemic effect of hydroalcoholic extract of seeds of the plant *Cucumis sativus* L in Wistar albino rats. The rats were divided into four groups A, B, C and D. All the groups except group A were administered with diet having high cholesterol and given intraperitoneal injection of Triton X-100 to induce hyperlipidaemia. Group A served as normal. Group B served as hyperlipidemic control. After one week of inducing hyperlipidaemia group C (standard) was given with simvastatin (10 mg/Kg) and group D (plant treated) was administered with hydroalcoholic extract of the plant (400 mg/Kg) daily for 7 days. The biochemical parameters of all the groups were estimated after one week of administration of plant extract using kits of Roche Cobas C111 chemistry analyser. Histological studies of liver and heart tissues were also done. HPLC study showed the presence of compounds in the extract. The plant decreased the levels of total cholesterol, triglycerides, alanine aminotransferase, low and very low-density lipoprotein cholesterol significantly. The plant may be used as dietary supplement in combating hyperlipidemia.

Keywords: *Cucumis sativus* L, HPLC, dyslipidemia, Triglycerides, Triton X-100, Simvastatin.

INTRODUCTION: Hyperlipidemia is a condition in which there are increased levels of total cholesterol-TC, triglycerides-TG, low density lipoprotein cholesterol-LDL-C and very low-density lipoprotein cholesterol (VLDL-C) with a decrease in the levels of high- density lipoprotein cholesterol (HDL-C). It is based on the disorders in lipid metabolism leading to cardiovascular (CV) diseases (Firdous *et al.*, 2021). The WHO has revealed that 40% of the population all over the world is suffering from higher levels of plasma cholesterol. Globally the most frequently health issues are diabetes mellitus (DM), cardiovascular diseases (CVDs) and myocardial infarction and these are much associated to hyperlipidemia. As hyperlipidaemia is linked to higher serum TC and TG levels, it may also result in major cardiac diseases like atherosclerosis. So, controlling this risk factor is crucial in preventing atherosclerosis. The use of synthetic therapeutic drugs like statins, bile acid sequestrants and fibrates can reduce the synthesis of lipids and their gastrointestinal absorption to treat hyperlipidaemia. However, the usage of these synthetic drugs may result a few persistent harmful side effects, mostly rhabdomyolysis, myopathy and increased risk of cancer. So the development of effective and novel natural hypolipidemic agents with minimal or undesired side effects is required on urgent basis (Aladaileh *et al.*, 2019). Various herbal medicines have been shown to be effective for treating dyslipidemia due to the components like flavonoids, vitamins, antioxidant, and polyphenols substances (Soltani *et al.*, 2014). WHO estimated that the population trust 80% of the use of herbal medicine in pathological conditions. This led to a tremendous increase in interest among the researchers in herbal and nutraceutical treatment with proved health benefits (Vogel, 2007). This plant (*Cucumis sativus* L.) belonging to the *Cucurbitaceae* family is widely cultivated in the tropical areas (Minaiyan *et al.*, 2011). Traditionally it has been utilized as diuretic, anti-diabetic, anti-inflammatory, anti-helmanthic and lipid lowering agent (Saeedi *et al.*, 2020). The seeds are rich in several constituents which includes fats (42.5%) and crude proteins (42%). The fatty acid components are stearic (16.2%), palmitic (0.63%), oleic acid (38.70%) and linoleic (40.11%). (Saeedi *et al.*, 2020). Extracts of *C. sativus* L seeds are found to have analgesic (Kumar *et al.*, 2010), antimicrobial (Begum *et al.*, 2019), anti-inflammatory (Vetriselvan *et al.*, 2013), anti-oxidant (Begum *et al.*, 2019), anti-diabetic and anti-ulcer activities (Minaiyan *et al.*, 2011). Hypoglycemic as well as hypolipidemic studies have been demonstrated on *C. sativus* L fruit in alloxan induced diabetic rats that reduced 72% triglyceride level (Sharmin *et al.*, 2013).

OBJECTIVES: Although seeds of *C. sativus* L are used traditionally as a lipid-lowering agent but no previous study is present which confirms this effect. No previous report is present about hypolipidemic effect of the seeds of this plant in Triton X-100 induced hyperlipidaemic rats. Also, no reports are present about HPLC analysis of hydroalcoholic extract of this plant. Therefore, the objectives of this study was (1) to analyse the phytochemical composition of hydroalcoholic extract of *C. sativus* L (var. pickling) seeds. (2) To investigate hypolipidemic activity of this extract in hyperlipidemic Wistar albino rats.

MATERIALS AND METHODS: Collection of plant: The fresh plant *C. Sativus* L was purchased from local arcade, Gulberg, Lahore, Pakistan. It was identified and authenticated by Professor Dr. Zaheer-ud-Din Khan, Department of Botany, G.C University, Lahore. A voucher specimen No. (GC. Herb. Bot. 3384) was submitted in the herbarium of same university.

Seeds were separated from ripened dried fruit of the plant and were properly dried.

Preparation of plant seed extract: Dried seeds (500 g) were reduced to fine powder with grinder. The powder was macerated in ethanol and water (hydroalcohol) in a ratio (75:25, v/v) respectively. Hydroalcoholic extract was passed through filter papers and dried using rotary (Heidolph Laborata 4002, Germany) under reduced pressure and extract was stored at -20°C in bottles after 72 h (Minaiyan *et al.*, 2011).

Phytochemical screening: Hydroalcoholic extract of the plant was subjected to phytochemical screening by following the standard methods (Shah, 2009). The extract was tested for alkaloids, flavonoids, phenols, saponins and tannins.

HPLC analysis: RP-HPLC analytical study of hydroalcoholic extract was done for the identification of bioactive compounds.

Preparation of mobile phase: Methanol and water (60: 40, v/v) was used as mobile phase in HPLC analysis and was run through the membrane filter (Millipore bedfoed MA, USA) having a pore size of 0.45µm. It was sonicated for 15 min. to remove the gases from the mobile phase.

Chromatographic conditions: Reverse phase high performance liquid chromatographic (RP-HPLC) analysis was performed using HPLC (Shimadzu Prominence HPLC instrument), with liquid chromatograph (LC 20A), column C18 (250×4.6mm, 5µm) (Shimadzu Prominence) and a quaternary solvent pump system (LC 20AT-VP). UV-Vis spectrophotometer detector, a loop injector (Rheodyne 7725) having an injection capacity (20 µL). Degasser (DGU-20A-5R) and Column oven (CTO-20A). Equilibration of column was done by passing the pure methanol for 30 min through the column before injecting hydroalcoholic extract. This extract (10 µL) was passed through a reverse phase (RP) C18 column using isocratic system and maximum wavelength (238 nm). The detector used for the analysis was UV (Photo diode array). The column (CTO-20A) temperature for operating was 30°C. Flow rate of mobile phase was adjusted at 1mL/minute and total volume of injection was 10µL. Run time for the mobile phase was 10 min. Shimadzu Lab Solution with Version (6.43 SPI) was the software used during HPLC analysis.

Antihyperlipidemic activity: Animals required for the study: Experimental methods were approved under Approval No. IREC-2019-79 Dated 28/03/2019 by the Animal Ethical Committee (AEC), The University of Lahore. The rats were obtained from Post Graduate Medical Institute (PGMI) and were stored in the animal house of Faculty of Pharmacy, The University of Lahore. The animals were maintained at 25±1°C in cages and were placed for 20 days under the standard lab conditions. The animals were allowed to take the standard pellet diet and water freely. They were maintained at the lab conditions before starting the study.

Acute toxicity studies: Following Organization for Economic Co-operation Development (OECD) test guidelines 425 acute oral toxicity study was done (OECD., 1994). Hydroalcoholic extract of *C. Sativus* L (2000 mg/kg) was given to wastar albino rats and observed for signs of toxicity after 14 days.

Induction of hyperlipidemia: Single Triton X-100 solution was prepared freshly in the saline solution prepared normally and was administered by intraparatonea (i.p.) injection at the dose (100 mg/kg) to all groups (B, C and D) after fasting for 18h. (Abdelgadir *et al.*, 2020).

Study design: Antihyperlipidemic activity was performed using male Wistar albino rats (20) weighing 170-250 g. Each group had 5 rats and allowed free access to water and diet. The rats were distributed into four group (A, B, C and D). All the group except group A were given i.p. injection of Triton X-100 after 72 h. Group A was treated as normal control and was given dry pellet diet, fresh water and normal saline taken orally for the whole study. Group B served as hyperlipidaemic control. This group received continuously heavy cholesterol diet and water without treatment and hyperlipidaemia was induced by Triton X-100 (100 mg/kg) injection (Sudha *et al.*, 2011). Group C was given the standard simvastatin at the dose (10 mg/kg/day) daily after 72 hours of inducing hyperlipidemia for seven days (Gorji *et al.*, 2014). Group D was given with hydroalcoholic extract (800 mg/Kg) of the plant seeds taken orally for seven days (Minaiyan *et al.*, 2011). The extract was given orally to the rats using a stomach tube having disposable syringe.

Sample collection: After the treatment protocols, anaesthesia was induced in all rats to collect samples. Blood samples were collected using cardiac puncture technique into tubes of gel clot activator for serum separation using centrifuge machine (3000 rpm/10min) (Keshetty *et al.*, 2009) and stored at -20°*C*.

Analysis of biochemicals: The levels of biochemicals (TC, TG, HDL-C, AST, and ALT) were estimated after 72 hours using kits of chemical analyser (ROCHE diagnostics Roche, USA).

Assay procedure: The sample was taken into false bottom tube (RD standard Cobas sample tube) and was put in a Cobas (C111) chemistry analyser. The specific test was chosen in the main menu and the readings were taken. Lipids, ALT, and AST serum levels were estimated using Cobas C 111 (ROCHE) chemistry analyser (Friedewald *et al.*, 1972). Using CHOD-PAP method, Cholesterol level was measured. Non-HDL-C, LDL-C and VLDL-C levels were estimated as given below:

Non-HDL-C = TC-HDL (Ridker *et al.*, 2005), LDL-C = TC-(HDL-VLDL) and VLDL-C = TG/5 (Friedewald *et al.*, 1972).

Histopathological studies: Liver and heart tissue samples were obtained and preserved in formalin (10%) solution for further histopathological studies. The tissues were fixed in formalin solution**,** paraffin embedded, consecutively cut with 5µm thickness, and treated for hematoxylin and Eosin staining (Abdelgadir *et al.*, 2020).

Statistical analysis: The readings were taken as mean ± SEM. The data was analysed using one way ANOVA which was followed by Tukey's multiple comparison test (Version: Graph pad Prism 7.02) as post hoc test. $P < 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION: Phytochemical screening: The results showed the presence of tannins, flavonoids, phenols, saponins, oil, fats, sterols and the absence of alkaloids in hydroalcoholic extract of *S. sativus* L. Preliminary phytochemistry of *C. sativus* L seeds in literature revealed the presence of fixed and volatile oils, saponins, steroids, flavonoids, carotenes, amino acids, flavones, tannins, resins and alkaloids (Begum *et al.*, 2019). The phytochemicals present in the seeds of plant justifies the medicinal use of this plant in treating different disorders. Phytochemical screening at preliminary level may be useful for detecting bioactive principles leading to the drug discovery. The plant may have different biological activities due to the phytochemical constituents present in the plant and it is used

pharmacologically in the development of health benefitting novel compounds.

HPLC analytical study of hydroalcoholic extract for determining different compounds: The HPLC analysis of hydroalcoholic extract of *C. sativus* L seeds exhibited different peaks of compounds with various retention times (RT). The height and specific area with specific retention times of HPLC peaks are given in table 1.

Peak No.	Retention Time	Area	Height
1	1.60	294260	10606
2	2.13	86440	3615
3	2.63	41248	3507
4	2.82	62116	7439
5	3.26	1492131	41754
6	4.87	283337	5747
7	5.25	199836	5390
8	5.98	300997	4866
9	7.43	213635	3227
10	9.03	238771	3205
Total		3212772	89357

Table 1: The HPLC analysis of hydralcoholic extract of *C. sativus* L. Different peaks of compounds with specific height and area are given with retention time.

The peaks with specific retention time show the presence of compounds in the extract. The area covered by each peak indicate the amount of compound present.

Toxicological studies: Single orally administered extract of *C. sativus* L did not cause clinical signs of toxicity or mortality in SD rats after 14 days. Thus, LD50 of hydroalcoholic extract of the plant was considered to greater than 2000 mg/kg and was unlikely to be toxic (United Nations, 2011).

Effects of hydroalcoholic extract of the plant on hyperlipidaemia: Effect of hydroalcoholic extract of the seeds of *C. sativus* L on biochemical parameters (mg/dl ± SEM) in hyperlipidaemic induced rats administered for 7 days are given in table 2. TC, TG-C, LDL-C, non-HDL-C, VLDL-C and alanine aminotransferase-ALT in serum levels of group D (hydroalcoholic extract of the plant) were shown to be decreased at significant ($P < 0.05$) level in comparison to hyperlipidemic control group. HDL-C levels were significantly ($P > 0.05$) increased in comparison to group B (hyperlipidemic control). There is non-significant ($P > 0.05$) decrease in the levels of aspartate transaminase-AST in serum of group D as compared to group B (hyperlipidemic control). The values are presented as mean ± SEM (n=3). Statistical analysis (one way ANOVA followed by Tukey Multiple Comparison test as post-hoc test) of lipid profile of standard and plant treated group in comparison to hyperlipidemic control group. TC, Total Cholesterol; TG, Triglycerides; LDL-C, low-density lipoproteins; HDL-C, high density lipoprotein cholesterol; VLDL-C, Very low-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine aminotransferase. Both significant and non-significant results were obtained when lipid profiles were compared to hyperlipidemic control.

Histopathological Examination of Liver: The effect of hydroalcoholic extract of seeds of *C. sativus* L on the liver and normal configuration of liver in normal control rats is shown in figure 1(a). There was severe congestion of blood vessels and fatty changes in hepatocytes in Triton X-100 induced rats (figure 1b). There were fatty changes in hepatocytes tissues by the fat accumulated in animals administered with standard simvastatin (figure. 1c). *C. Sativus* L seed extract treated rats showed moderate congestion and there was accumulation of inflammatory cells of liver present in the portal areas. There were no hyperlipidaemic signs (figure. 1d).

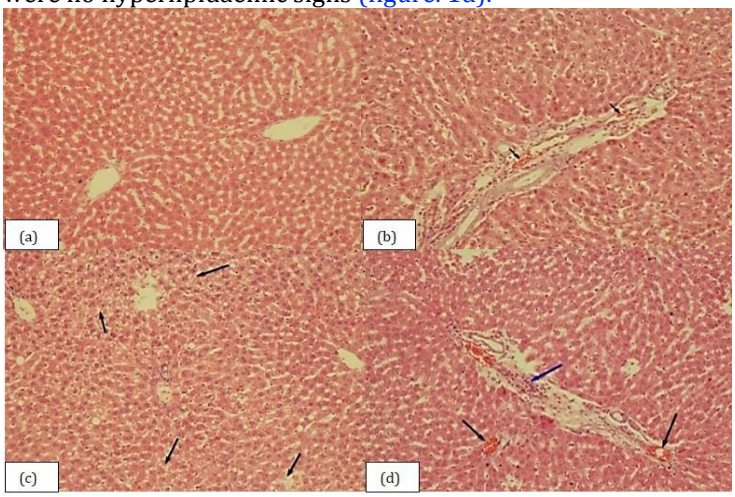

Figure 1: Histopathological changes occurred in the liver of rats stained by Haematoxylin and Eosin. Normal con Figureuration of the liver tissues of normal control rats (a). Clear congestion appeared in blood vessels (arrows) appeared in the liver tissues of untreated Triton X-100 induced hyperlipidaemic rats (b). Mild fatty changes (arrows) in hepatocytes of liver tissue of simvastatin treated rats (c). Moderate congestion of hepatic blood vessels (black arrows) and accumulation of inflammatory cells in the portal areas (blue arrow) in the liver tissue of *C. sativus* L treated rats (d).

Histopathological examination of heart: Effect of hydroalcoholic extract of seeds of *C. sativus* L on the heart is exhibited in figure 2.

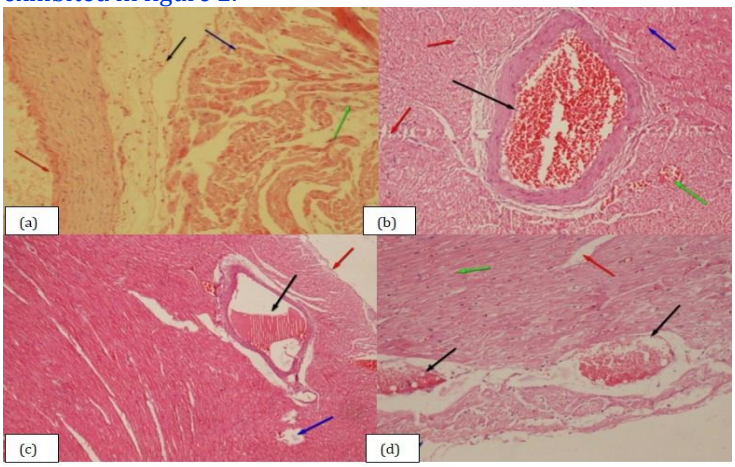

Figure 2: Histopathological changes in transverse section of hearts of animals administered with hydroalcoholic extract of *C. sativus* L seeds (a). Pericardium, epicardium, myocardium, and coronary artery appear normal in normal control group. Coronary blood arteries appeared severely congested (black arrow), necrosis of cardiac myocyte (red arrow) with myocardia haemorrhages (blue arrow) of hyperlipidemic (diseased control) group (b). Normal mesothelium (red coloured arrow), slight congestion of coronary vessels in epicardium (black coloured arrow) and few number of necrotic foci (blue arrow) of simvastatin treated group (c). Mesothelium sloughed off indicated by blue coloured arrow, dilated blood

vessels in epicardium indicated by black arrow, necrosis in myocardium as shown by red arrow with moderate haemorrhages as shown by green arrow were noticed in *C. sativus* L treated group (d).

Parameter	Group A Normal Control rats	Group B Hyperlipidemic Control rats	Group C Hyperlipidemic standard Simvastatin	Group D Hyperlipidemic *C. sativus* L
TC (mg/dl)	55.6 ± 4.22	100.6 ± 7.83	55 ± 2.12[b]	63.6 ± 4.69[b]
TG (mg/dl)	79.2 ± 12.78	255.2 ± 58.69	81 ± 7.19[b]	86.4 ± 7.50[b]
LDL-C (mg/dl)	30.04 ±3.13	103.72 ± 21.66	27 ± 3.13[b]	39.68 ± 3.10[b]
VLDL-C (mg/dl)	15.84 ±2.55	51.04 ± 11.73	16.2 ± 1.43[b]	17.28 ± 1.50[b]
HDL-C (mg/dl)	41.4 ± 3.10	22.96 ± 5.97	44.2 ± 3.51[b]	41.2 ± 3.36[a]
Non-HDL-C (mg/dl)	14.2 ±1.20	77.64 ± 11.50	10.8 ± 1.93[b]	22.4 ± 2.71[b]
AST (IU/dl)	122.8 ±13.01	183.0 ± 14.60	138.6 ± 13.21[ns]	193 ± 14.32[ns]
ALT (IU/dl)	43 ±3.36	70.6 ± 6.55	38.6 ± 3.48[b]	37.8 ± 2.78[b]

Table 2: Effect of C. sativus L seeds on total cholesterol, triglycerides, HDL-C, LDL-C, Non-HDL-C, VLDL-C, ALT and AST levels in triton X-100 induced rats after 7 days of hydroalcoholic extract adminitration.

Severe hyperlipidaemic conditions i.e., severe congestion of blood vessels, necrosis of cardiac muscles was seen in hearts of group B rats in comparison to group A normal control rats. The rats administered with the standard in simvastatin exhibited congestion of blood vessels with mild hyperlipidemic condition. Group D treated with *C. sativus* L had dilated blood vessels with no lipidemic condition. There was no evidence of the storage of lipid droplets. The biologically active compounds that are present in seed extract of *C. sativus* L show various biological functions. To check whether the activity might be antihyperlip-idemic, the effect of plant extract on the lipid profile was investigated compared to the standard simvastatin. Fruit extract of *C. sativus* L fruit was proved to have reducing effect on TG level up to 72% in alloxan induced diabetic rat model (Sharmin *et al.*, 2013). Similar results were reported from adult hypolipidemic patients using clinical trial of randomized double blinded placebo controlled where seeds extract of *C. sativus* elevated HDL concentration significantly (Soltani *et al.*, 2017). This activity is due to the active phytoconstituents in the plant responsible for antihyperlipi- demic activity. It has also been demonstrated that several plants with higher levels of unsaturated fatty acids, such as linoleic acid have lipid-lowering properties. The effects of fruit oil of *Cornus wilsoniana* containing unsaturated fattyacids on hypolipidemia in rats were investigated by Fu *et al.* (2012). The findings demonstrated that the oil dramatically lowers serum TG, LDL, and total cholesterol. According to an analysis unsaturated fatty acids, such as linoleic acid and -linolenic acid, were found in significant numbers (69.12 %) in this oil by chemical analysis. A clinical investigation found that taking 400 mg of pomegranate seed oil twice daily had a positive impact on HDL and TG levels. This oil contains 6–7% linoleic acid (Mirmiran *et al.*, 2010). Previously, a decrease in blood cholesterol, TG, and LDL was recorded (Berrougui *et al.*, 2003) to evaluate the impact of oil of *Argania spinosa* (containing linoleic acid and oleic acid) on serum lipids. Fatty acids such as myristic, lauric, stearic, oleic, palmitic, and linoleic acids are also present in cucumber. The composition (%) of fatty acid in the plant is stearic (16.2%), palmitic (0.63%), oleic (38.70%) and linoleic acid (40.11%) (Saeedi *et al.*, 2020). According to Rayees *et al.*, (2013) cucumber seed is high in fatty acids like monounsaturated (oleic acid, 7%) and polyunsaturated (linoleic acid, 71%) supporting its potential application in the management of hyperlipidemia. *Cucumis* seed extract contains phytosterols, which may also be the cause of its hypolipidemic effects. Due to its hydrophobic shape, cholesterol is poorly absorbed by humans and is dependent on the bile salts' emulsifying abilities to form tiny micelles. In order to prevent all of the cholesterol from being transported and expelled in the faeces, phytosterols with structures similar to those found in cholesterol have minimal enteric absorption (Kelishadi *et al.*, 2016). Different kinds of hypercholesterolemia, such as familial hypercholesterolemia, familial mixed hypercholesterolemia, and undefined hypercholesterolemia, have been linked to the reducing effects of plant sterols (Garaiova *et al.*, 2013). As per literature the plant contains a number of sterols like as codisterol, 25 (27)-dehydro-porifersterol, clerosterol, stigma-sterol, isofucosterol, 22-dihydrobrassicasterol, campesterol, sit-osterol, 25 (27)-hydrocondrillasterol, 25 (27)-dehydrofungiste-rol 24-β-ethyl-25 (27)-dehydrofungisterol, avenasterol, 24-methylenecolesterol, 22-dihydrispinosterol (Saeedi *et al.*, 2020). Abou-Zaid and colleagues previously analysed *C. sativus* seed. It has 5-sterols with structures related to cholesterol, such as 24-ethyl-cholest-5-en-3-ol, also 24-ethylcholesta7, 22-dien-3-ol and 4-ethylcholesta-7-en-3-ol.

CONCLUSION: The *C. Sativus* L exhibited a significant antihyperlipidemic activity in Triton X-100 induced hyperlipi-daemic rats that is comparable to those of the common cholesterol-lowering medication simvastatin, which prevents the synthesis of cholesterol. Chemical compounds present in this plant are responsible for hypolipidemic activity. Cucumber seed may therefore be used as a food supplement to treat dyslipidaemia. In order to determine the effectiveness and completely understand the mechanism of action underlying the observed antihyperlipidemic effect of the plant, more research is strongly advised. It is needed to establish the safety and efficacy for more clinical study. Further investigation is recommended for isolation, purification and characterization of the compounds responsible for hypolipidemic activity.

CONFLICT OF INTEREST: Authors have no conflict of interest.

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