# Preventive Effect of *Cichorium Intybus* L. Two Extracts on Cerulein-induced Acute Pancreatitis in Mice

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## ABSTRACT

**Objectives:** Acute pancreatitis is an inflammatory condition of pancreas with sudden onset, high mortality rate and multiple organ failure characteristics. It has been shown that oxygen free radicals have an important role in development of pancreatitis and its complications. Antioxidant, anti-inflammatory, anti-hepatotoxicity and gastroprotective properties of *Cichorium intybus* L. suggest that this plant may have beneficial effects in the management of acute pancreatitis.

**Methods:** Five intraperitoneal (i.p.) injection of cerulean (50 μg/kg at 1 h intervals) in mice resulted in acute pancreatitis, which was characterized by edema, neutrophil infiltration, as well as increases in the serum levels of amylase and lipase in comparison to normal mice. Different doses of *C. intybus* root (CRE) and aerial parts hydroalcoholic extract (CAPE) orally (50, 100, 200 mg/kg) and intraperitoneally (50, 100, 200 mg/kg) were administrated 1.0 and 0.5 h respectively before pancreatitis induction on separate groups of male mice ($n$=6). Control groups treated with normal saline (5 ml/kg) similarly.

**Results:** Both extracts in greater test doses (100 mg/kg and 200 mg/kg, i.p.) were effective to decrease amylase (23-36%) and lipase (27-35%) levels. In oral route, the dose of 200 mg/kg showed a significant decrease in levels of amylase (16%) and lipase (24%) activity while the greatest dose (200 mg/kg, i.p.) was only effective to diminish inflammatory features like edema and leukocyte infiltration in pancreatitis tissue ($P$<0.01). Vacuolization was not significantly reduced in extracts treated groups.

**Conclusions:** These data suggest that *C. intybus* hydroalcoholic extracts were effective to protect against experimental acute pancreatitis and the efficacy was partly dependent to the dose and was more significant after parenteral administration.

**Keywords:** Animal model, *Cichorium intybus* L., inflammation, pancreatitis, plant extracts, preventive therapy

Original Article

## INTRODUCTION

Acute pancreatitis is a sudden inflammation of the pancreas with high mortality and limited specific therapy.[1] Circulatory

shock, cardiac insufficiency, renal, respiratory and hepatic failure are the most important causes of death.[2]

Alcohol beverage drinking and biliary tract disorders are the most common etiologies of pancreatitis. Viral infections such as mumps and hepatitis type A and B, drugs such as tetracyclines, furosmide and estrogens, as well as hypertriglyceridemia and hypercalcemia are the other etiologic factors for acute pancreatitis.[3]

It has been shown that activation of intracellular digestive enzymes and auto-digestion of the pancreas induces local and systemic injuries as well as organ failure.[4] Oxidative stresses such as hydrogen peroxide ($H_2O_2$), superoxide and hydroxyl radicals have been shown to be involved in the pathophysiology of acute pancreatitis, where oxygen free radicals and lipid peroxidation play important roles in the development of pancreatic inflammation.[5] It is believed that many factors are involved in the progression of this illness from acinar cell injuries to a fetal systemic reactions, such as activated leukocytes and releases of cytokine and chemokine mediators like interlukin-1, interlukine-6 and tumor necrosis factor (TNF-α).[6,7] So the use of drugs with antioxidant and anti-inflammatory properties could be proposed as a potential therapeutic intervention in acute pancreatitis.[8] Cichory (*Cichorium intybus* L.) (Asteraceae) an important traditional remedy is widely used in Iran as a liver and digestive tract protective. It has been implemented in folk medicine in Iran for several centuries. Roots have been recently recognized as an important source of dietary fibers (inulin and oligosaccharide). It is believed that these fibers possess anticarcinogenic, diuretic and laxative properties.[9] Moreover, the roots are the major source of sesquiterpene lactones (SQLs), with strong anti-inflammatory effects.[10] SQLs have been found as prostaglandin E2 synthesis inhibitors. This was caused by inhibitory effects on cyclooxygenase 2 expression by the pro-inflammatory agent TNF-α. Moreover, they have been shown to possess a wide variety of pharmacological properties such as antimicrobial, anti-tumoral, and anti-inflammatory activities.[11] Also, Cichory has a potent hepatoprotective, antioxidant, hypoglycemic, diuretic, anti-testicular toxicity and immune-modulatory effects.[12-14] The present study was designed to study the protective effects of *C. intybus* root (CRE) and aerial parts hydroalcoholic extracts (CAPE) in a murine model of acute pancreatitis caused by cerulein administration. In order to have a better insight into the mechanism(s) of action of the observed anti-inflammatory effects of Cichory extract on pancreatitis, we investigated the effects of Cichory on serum amylase and lipase levels, tissue edema, leukocyte infiltration and vacuolization.[15]

## METHODS

### Plant material and extraction

The roots and herbal aerial parts of *C. intybus* were collected from the plants grown wild in Shalamzar (Charmahal-e Bakhtiari province, Iran) during June, 2009. The plant was identified by Dr. Iraj Mehregan, (Department of Biology, Tehran Islamic Azad University, Tehran, Iran) and a voucher sample encoded 1,392 was deposited in Pharmacognosy Department of Isfahan School of Pharmacy, Isfahan, Iran.

For preparation of hydroalcoholic extract, dried and finely powdered herbs (500 g) was soaked in adequate volume of ethanol : water (70: 30) and the extraction was undertaken for 48 h to obtain full extract using percolator apparatus. The product was then shaken, filtered and evaporated in a rotary evaporator to obtain semisolid extract under reduced pressure.[16]

### Total phenol assay of the extract

The total phenols in the CRE and CAPE were determined by the Folin-Ciocalteua method with some modifications. Results are given as gallic acid equivalent (GAE)/g of the extract.[17]

### Induction of pancreatitis

For biological testing total hydroalcoholic extracts (CRE and CAPE) were dispersed in normal saline solution as vehicle.

Acute pancreatitis was induced by five intraperitoneal (i.p.) injection of 50 µg/kg body weight of cerulein (Sigma, St. Louis, MO, USA) with 1 h intervals according to the method was previously demonstrated by Mazzon *et al*.[18] in which edematous pancreatitis with leukocyte infiltration, as well as increased serum levels of amylase and lipase activity were prominent.

### Animals

Male mice weighting 25–30 g and bred in animal house of Isfahan School of Pharmacy, Isfahan, Iran were used in this study. Animals

were kept in uniform environmental conditions of temperature, humidity and light/dark cycles (12/12 h) and allowed free access to rodent chow and tap water. The study was approved by the local Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran.

### Groupings

Animals were randomly assigned into following 16 groups ($n$=6).

Sham groups: Normal mice pretreated with normal saline (5 ml/kg p.o. and i.p.).

Negative control groups: Mice with acute pancreatitis were pretreated with normal saline (5 ml/kg p.o. and i.p).

CRE groups: Mice with acute pancreatitis were pretreated with CRE (50, 100, 200 mg/kg) as a single dose (p.o. and i.p.).

CAPE groups: Mice with acute pancreatitis were pretreated with CAPE (50, 100, 200 mg/kg) as a single dose (p.o. and i.p.). Test doses of Cichory extracts were chosen because they were suggested as hepatoprotective by Zafar *et al*.[19]

Intraperitoneal (i.p.) and oral (p.o.) treatments were carried out 0.5 and 1 h before pancreatitis induction, respectively. Mice were sacrificed 4h after last injection of cerulein. Blood samples were obtained by directed intracardiac puncture under generalized anesthesia induced by diethyl ether inhalation and stored at -60° for biochemical analysis.[18] Pancreas were removed immediately and fixed in formaldehyde (10%) for histological examination.

### Biochemical analysis

Serum lipase and amylase activity were determined by using commercially available lipase and amylase kits (Pars-Azmoon Company, Tehran, Iran).

### Histological examination

Paraffin-embedded pancreas samples were sectioned (5 μm), stained with hematoxylene and eosin (H and E) and examined by an experienced co-worker pathologist unaware from experimental protocol.

The histological grading of edema was made using a scale ranging from 0 to 3 (0=no edema, 1=interlobular edema, 2=interlobular and moderate intralobular edema, and 3=interlobular edema and severe intralobular edema). Leukocyte infiltration was also graded from 0 to 3 (0=absent, 1=scarce perivascular infiltration, 2=moderate perivascular and scarce diffuse infiltration, 3=abundant diffuse infiltration). Grading of vacuolization was based on the appropriate percentage of acinar cells involved: 0=absent, 1=less than 25%, 2=25–50% and 3=more than 50% of acinar cells.[15]

### Statistical analysis

Biochemical results are expressed as mean±SEM. Statistical analysis was carried out by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. Nonparametric data was analyzed by Mann-Whitney U test. The minimal level of significance was considered at $P$<0.05.

## RESULTS

### Total phenolic content

Phenolic content of CRE and CAPE were 2.5 and 6.5% of 100 g galic acid respectively.

### Effects of CRE on the serum levels of amylase and lipase

Cerulein-induced pancreatitis in vehicle-treated mice was associated with significant rises in the serum levels of amylase and lipase. The increase in amylase and lipase was markedly reduced in cerulein-treated mice which had been pre-treated with CRE in doses of 100, 200 mg/kg by i.p. injection and in dose of 200 mg/kg by oral route [Figures 1a and b].

### Effects of CAPE on the serum levels of amylase and lipase

The effects of CAPE on the serum levels of amylase and lipase were same as root extracts. The groups that were received extract in doses of 100, 200 mg/kg by an i.p. injection showed a significant decrease in levels of amylase and lipase. In oral route the group that received extract in the dose of 200 mg/kg showed a significant decrease in levels of amylase and lipase activity too [Figures 2a and b].

### Effects of CRE and CAPE on the histological parameters

In normal saline treated mice, pancreas did not show any tissue injury at light microscopic level (×10 magnification). Administration of cerulein

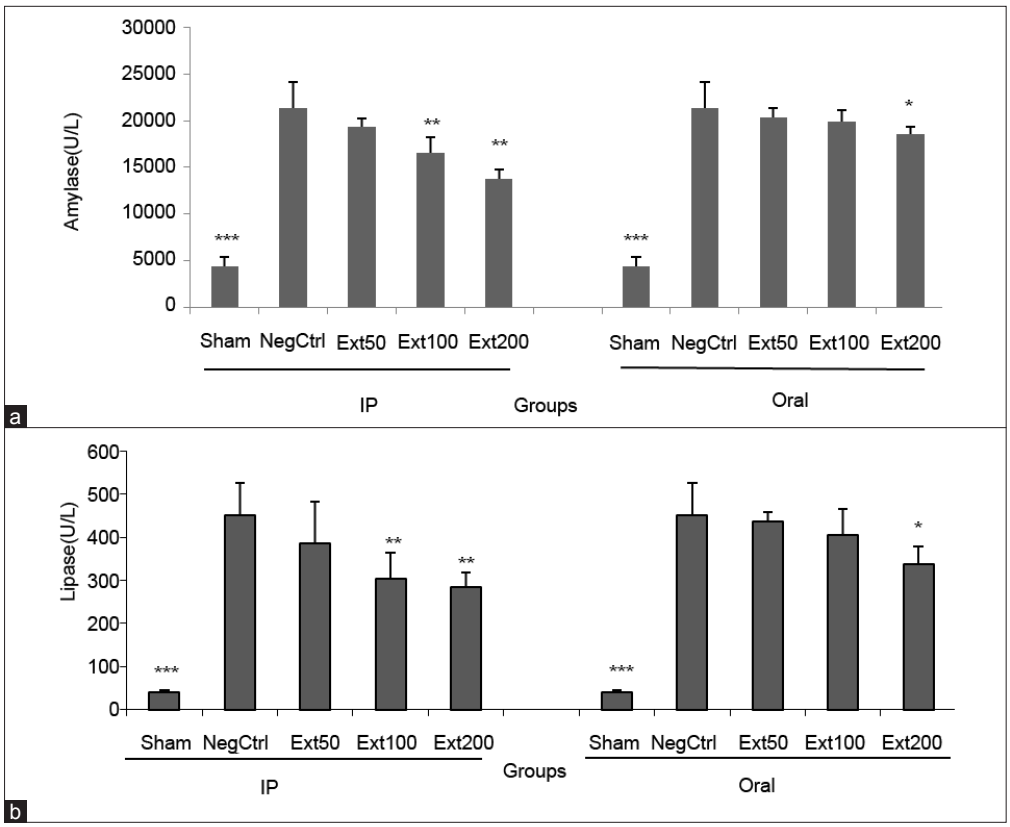


**Figure 1:** (a) Effect of CRE on serum amylase level (U/L) of cerulein-induced acute pancreatitis in mice. Sham: normal mice treated with normal saline (5 ml/kg), NegCtrl: Negative control treated with normal saline (5 ml/kg), Ext: *C. intybus* root extract (50, 100, 200 mg/kg), IP: Intraperitoneal. Data are shown as means ± SEM of 6 animals for each group. **P*<0.05, ***P*<0.01, ****P*<0.001 versus negative control (ANOVA). (b) Effect of CRE on serum lipase level (U/L) of cerulein-induced acute pancreatitis in mice. Sham: normal mice treated with normal saline (5 ml/kg), NegCtrl: Negative control treated with normal saline (5 ml/kg), Ext: *C. intybus* root extract (50, 100, 200 mg/kg), IP: Intraperitoneal. Data are shown as means ± SEM of 6 animals for each group. **P*<0.05, ***P*<0.01, ****P*<0.001 versus negative control (ANOVA)

induced acute edematous with severe leukocytic infiltration pancreatitis in all mice tested. The pancreas was grossly swollen and enlarged with a visible collection of edematous fluid. Prominent interlobular and severe intralobular edema was also accompanied with moderate perivascular and abundant diffuse inflammatory infiltration. Vacuolization was also observed in 25 to more than 50% of acinar cells but no necrosis or hemorrhages were observed.

In groups that received extracts in the dose of 200 mg/kg by i.p. injection, the severity of edema and leukocytic infiltration significantly reduced compared to normal saline treated group (interlobular edema, scarce perivascular infiltration). Vacuolization was not significantly reduced in extracts treated groups. Lower test doses (50 and 100 mg/kg) of both extracts (CRE and CAPE) were not effective to reduce pathological tissue injures compared to controls [Table 1].

## DISCUSSION

In the present study, results showed that CRE and CAPE had good potential to attenuate pancreatitis in mice as indicated by biochemical and histological evaluations. Biochemical assays confirmed that administration of CRE and CAPE reduced amylase and lipase activity, both of which are markers of pancreatitis.[6] Interestingly CRE and CAPE, especially at doses of 100 mg/kg and 200 mg/kg i.p. and 200 mg/kg p.o., showed significant protection against pancreatitis compared to control groups. Regarding to the histological results, administration of CRE and CAPE showed an effective protection in a manner was partly dependent to the dose and route of administration. The highest doses of CRE and

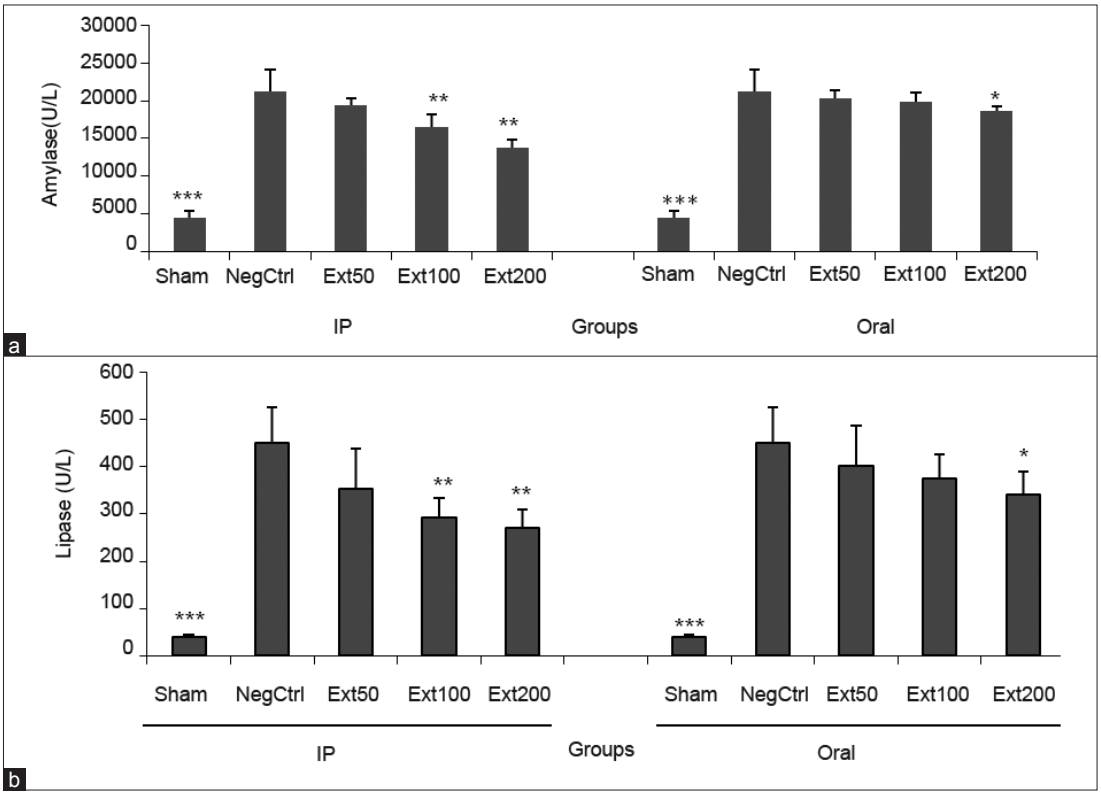


**Figure 2:** (a) Effect of CAPE on serum amylase level (U/L) of cerulein-induced acute pancreatitis in mice. Sham: normal mice treated with normal saline (5 ml/kg), NegCtrl: Negative control treated with normal saline (5 ml/kg), Ext: *C. intybus* areal part extract (50, 100, 200 mg/kg), IP: Intraperitoneal. Data are shown as means ± SEM of 6 animals for each group. **P*<0.05, ***P*<0.01, ****P*<0.001 versus negative control (ANOVA). (b) Effect of CAPE on serum lipase level (U/L) of cerulein-induced acute pancreatitis in mice. Sham: normal mice treated with normal saline (5 ml/kg), Neg. Ctrl: Negative control treated with normal saline (5 ml/kg), Ext: *C. intybus* areal part extract (50, 100, 200 mg/kg), IP: Intraperitoneal. Data are shown as means ± SEM of 6 animals for each group. **P*<0.05, ***P*<0.01, ****P*<0.001 versus negative control (ANOVA)

**Table 1:** Effect of *C. intybus* extracts on pathological scores in cerulein-induced acute pancreatitis in mice

| Group | Route | Edema | Leukocyte infiltration | Vacuolization |
|---|---|---|---|---|
| Sham | i.p/p.o. | 0.00 | 0.00 | 0.00 |
| NegCtrl | i.p. | 2.50 ± 0.22 | 2.16 ± 0.30 | 0.62 ± 0.22 |
| CRE50 | i.p. | 2.10 + 0.31 | 2.00 ± 0.29 | 0.50 ± 0.24 |
| CRE100 | i.p. | 1.80 ± 0.28 | 1.83 ± 0.30 | 0.51 ± 0.15 |
| CRE200 | i.p. | 1.16 ± 0.16** | 1.00 ± 0.25** | 0.42 ± 0.21 |
| CRE50 | p.o. | 2.30 ± 0.25 | 2.10 ± 0.25 | 0.64 ± 0.24 |
| CRE100 | p.o. | 2.00 ± 0.24 | 1.84 ± 0.26 | 0.66 ± 0.23 |
| CRE200 | p.o. | 2.16 ± 0.29 | 2.00 ± 0.29 | 0.51 ± 0.26 |
| CAPE50 | i.p. | 2.30 ± 0.30 | 2.10 ± 0.27 | 0.65 ± 0.27 |
| CAPE100 | i.p. | 1.80 ± 0.30 | 1.66 ± 0.29 | 0.51 ± 0.29 |
| CAPE200 | i.p. | 1.00 ± 0.25** | 0.66 ± 0.21** | 0.57 ± 0.20 |
| CAPE50 | p.o. | 2.54 ± 0.21 | 2.17 ± 0.31 | 0.66 ± 0.27 |
| CAPE100 | p.o. | 2.00 ± 0.25 | 2.20 ± 0.29 | 0.61 ± 0.30 |
| CAPE200 | p.o. | 1.80 ± 0.31 | 1.87 ± 0.32 | 0.60 ± 0.28 |

Sham = normal, NegCtrl = negative control, CRE = *C. intybus* root extract (50, 100, 200 mg/kg), CAPE = *C. intybus* aerial parts extract (50, 100, 200 mg/kg), i.p. = intraperitoneal, p.o = oral. Data are shown as Mean ± SEM, *n*=6 (Mann-Withney U test), ***P*<0.01: significant difference compared to negative control group

CAPE (200 mg/kg) that were administered intraperitoneally had significant effects compared to the respected control groups.

In biochemical examination, the results showed that the lowest doses of oral extracts (50 and 100 mg/kg) were not effective to suppress pancreatitis and neither of doses had significant effects on serum levels of amylase and lipase activities. This is in accordance with the results obtained by Zhao *et al*.[20] The authors demonstrated that the higher dose of rhubarb hydroalcoholic extract (150 mg/kg, twice daily, p.o.) was effective to protect against cerulein-induced acute pancreatitis while the lower test dose (75 mg/kg) was not effective.

Examination of total phenolic content of extracts showed that the amount of total phenols in the CAPE was about twice rather than in the CRE but interestingly biochemical and histological results showed that CAPE and CRE had same effects in same doses as well as route of administration. It could be suggested that both extracts exerted their protective effect through mechanisms are not essentially dependent to phenolic contents of extracts. Moreover compared to the roots, the aerial parts which are easily harvested and found as renewable source had same potential to be considered as a useful source for anti-inflammatory and pancreatitis protective compounds. The hepatoprotective activity of *C. intybus* L. root and root callus extracts has investigated by Zafar *et al*.[19] The results showed that root callus extract had better activity against carbon tetrachloride hepatotoxicity as compared with natural root extract. They suggested that metabolites present in cultured cells were more potent as anti-hepatotoxic as compared to constituents present in natural root extract. The results also indicated that natural root extract especially by 150 mg/kg as the highest test dose was effective to markedly prevent necrosis in liver tissue, however lower doses of 50 and 100 mg/kg were only effective to reduce milder forms of hepatic injures like fatty changes and bilirubin content.

Administration of medicinal herbs that possess anti-inflammatory and antioxidant properties is a new approach to attenuate inflammatory-related disorders.[19] In this regard the effects of *Ginko biloba* extract on acute pancreatitis has been studied by Zeybek *et al*.[21] The results demonstrated that *Ginko biloba* extract in 100 mg/kg administered i.p. was able to decrease significantly in serum amylase and lipase levels as well as histopathologic scores in sodium taurocholate-induced pancreatitis. The beneficial effects had attributed to the oxygen radical scavengering potential of *Ginko biloba* flavonoids contents. Flavonoids with anti-inflammatory, antioxidant and gastro-protective effects are widely distributed in plant kingdom. Stimulation of prostaglandins, suppression of histamine secretion and inhibition of *Helicobacter pylori* growth are the main causes of gastroprotective effects of flavonoids.[22]

*C. intybus* is considered as a promising source of flavonoids with various beneficial biological effects. Hepatoprotective, gastroprotective, free radical scavenging and anti-inflammatory actions are the most important properties of *C. intybus* that assumed to be related to its flavonoids.[23] As we know aqueous and alcoholic extracts of *C. intybus* L. showed anti-inflammatory activity against formalin-induced paw edema in mice.[24] Moreover *C. intybus* has immunomudulatory, apoptotic and osteoporosis preventive properties for which fructans derivatives and fermented preparations have been shown to be involved (butyrate derivatives).[9,25] In addition, roots are the source of sesquiterpene lactones that have been showed to act as powerful inhibitors of cyclooxygenase-2 enzyme (Cox-2)[26] that can dramatically reduce the inflammation.[27] Various mechanisms might be involved in beneficial protective effects of Cichory in this study and total extracts have many different components for which wide variety of pharmacological effects has been mentioned. Thus, further experimental studies are necessary to isolate and identify the active principles present in CRE and CAPE fractions which are responsible for the protective effects on pancreatitis.

## CONCLUSION

We demonstrated that *C. intybus* hydroalcoholic extracts possess protective therapy in cerulein-induced acute pancreatitis in mice and may suggest a therapeutic potential for pretreatment in this inflammatory disease condition in clinical setting.

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