

Protective Effect of *Capparis spinosa* Hydroalcoholic Extract on the Integrity of Rat Pancreatic Islets

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Article Info

 [10.30699/jambs.28.129.204](https://doi.org/10.30699/jambs.28.129.204)

Received: 2020/04/18;

Accepted: 2020/07/15;

Published Online: 31 July 2020;

Use your device to scan and read the article online



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ABSTRACT

Background & Objective: *Capparis spinosa* L. belongs to the Capparaceae family for which biological roles such as antioxidant, anti-inflammatory, and antidiabetic effects have been reported. Some active chemical groups including flavonoids, phenols, alkaloids, tannins, and minerals have been detected in this plant. This study aimed to extract the *C. spinosa* alcoholic extract from different parts of the plant, measure the content of phenols and flavonoids, and evaluate the effects of bud extracts on the viability and oxidative state of the islets of Langerhans isolated from rat pancreas.

Materials & Methods: In this experimental setup, the hydroalcoholic extracts of different parts of the plant were obtained based on the maceration method. Folin-Ciocalteu and rutin were used as the standard reagents to measure phenols and flavonoids. The islets of Langerhans were isolated from the pancreas of male rats (n=16) and incubated for 24 hours. Then, the islets were exposed to the plant extract for 24 hours after which cellular viability and reactive oxygen species were measured.

Results: The *C. spinosa* bud alcoholic extract markedly increased the survival of the islet cells. This effect was dose-dependent, and the greatest effects were observed at 10^3 and 10^4 $\mu\text{g mL}^{-1}$. At the mentioned concentrations, ROS production was reduced by 37% and 72% respectively comparing to the control.

Conclusion: The results indicated that *C. spinosa* may have protective effects on the endocrine pancreas by increasing viability and decreasing ROS in the islets, and can thus be considered as a promising agent for prophylaxis and therapy in diabetes management.

Keywords: *Capparis spinosa* L, Diabetes, Pancreas, Insulin, Oxidative stress



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Introduction

Diabetes mellitus (DM) is known as the century's metabolic disease with different etiologies, affecting many organs (1) and causing several complications such as renal, ocular, and cardiovascular problems (2). The number of people suffering from DM is increasing; it is estimated that there are ~451 million people with diabetes worldwide, and this value is expected to reach 693 million by 2045 (3).

The exact pathophysiology of diabetes is related to the uncontrolled blood glucose concentration that can be due to a defect in the secretion or peripheral responsiveness of insulin. Disturbed cellular homeostasis in the organs responsible for glucose metabolism can deteriorate the pathophysiology of diabetes and related complications. The normal homeostasis of the living cells is determined by the ADP/ATP ratio and reactive oxygen species (ROS) level whose overproduction can saturate the antioxidant defense of the cell and lead to oxidative

stress. Oxidative stress occurs when radicals and ROS increase during metabolism and overwhelm antioxidant defensive molecules. ROS can damage cellular nucleic acids, proteins, and lipids, leading to cellular necrosis that has been known to be involved in age-related diseases such as neurodegeneration and diabetes (4,5). In this way, preventing the excess production of ROS in the cells by supporting antioxidant reservoirs is under comprehensive studies as a promising strategy for the treatment of the mentioned diseases. It has been shown that reducing ROS formation in the pancreatic cells by using antioxidants increases insulin gene expression, insulin release, and viability of Langerhans islets (6).

Currently, there exist some synthetic antioxidants in use which may have several adverse effects (7). Some plants contain molecules that can neutralize oxidative elements overproduced in the cells, and have been proposed as the natural sources of antioxidants (5).

Since antiquity, plants have been used to cure several diseases, and many medicinal plants show antidiabetic activities (8). *Capparis spinosa* L., known as capper, belongs to the Capparaceae family; there are some reports on the antimicrobial, antioxidant, anti-inflammatory, antimutagenic, and blood glucose-lowering effects of this family of plants (9). Phenols, flavonoids, alkaloids, tannins, and minerals are the main active chemical groups detected in capper (10). Among these, phenolic compounds have been demonstrated to scavenge free radicals in the cells. This is why the plants rich in phenolic compounds are considered as therapeutic candidates for human health problems due to their antioxidant and anti-inflammatory properties (11).

The present study aimed to measure the phenol and flavonoid content of the hydroalcoholic and methanolic extracts of the bud, roots, and leaf of *C. spinosa* obtained from the Moghan area in Ardabil Province, Iran, and screen the effect of bud ethanolic extract on the viability and oxidative markers of the rat islets of Langerhans.

Materials and Methods

Research Approval

This work is based on a thesis for a degree in pharmacy at the School of Pharmacy, Ardabil University of Medical Sciences, Ardabil, Iran. All the processes were approved by the Ethics Committee of Ardabil University of Medical Sciences (approval ID: IR.ARUMS.REC.1397.174).

Chemicals

Aluminum trichloride, bovine serum albumin (BSA), Dichloro-dihydro-fluorescein diacetate (DCFH-DA), Folin-Ciocalteu, gallic acid, HEPES sodium salt, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), rutin, and the RPMI 1640 medium were purchased from Sigma-Aldrich Co.

Plant Materials and Preparation

C. spinosa L. leaf, bud, and roots were used in this study. They were collected from the Moghan district of Ardabil, Iran, in June 2018. After cleaning the collected parts of the plant, they were dried under the shade at room temperature and then powdered. The maceration method was adopted to obtain alcoholic extracts of different parts of the plant. Briefly, 25 g of the plant powder from each part was treated with 250 mL of methyl alcohol (99%) in a tightly closed container for two days. The container was shaken one or two times a day. Then, the mixture was filtered and the solvent was removed by using a rotary evaporator. Hydroalcoholic extracts were also prepared by treating 25 g of the plant powder from each part with 250 mL of ethanol (80%) as the solvent, and the same procedures were followed. The residues were dissolved and used for the following experiments.

Phenolic Content Determination

The content of total phenols in the extracts was measured with the reagent Folin-Ciocalteu. In this experiment, 100 μ L of the plant extracts and 500 μ L of the Folin-Ciocalteu reagent were added to 1.5 mL of sodium carbonate (20%). After shaking the mixture, it was diluted with distilled water up to 10 mL and left for 2h. Subsequently, the absorbance of the mixture was determined at 765 nm. A standard curve was plotted from the different concentrations of gallic acid so that the content of total phenols would be expressed as mg/g gallic acid equivalents (GAE) (12).

Flavonoid Content Determination

We followed a method from the State Pharmacopoeia of USSR for the measurement of flavonoid content in the extracts by using rutin as the reference compound. Rutin, which was available in our lab, is a common flavonoid commonly used as a standard in the determination of total flavonoid content (13). Briefly, one drop of acetic acid was added to a mixture containing 1 mL of the extract in methanol (10 mg/mL) and 1 mL of aluminum trichloride in ethanol (20 mg/mL), and then made up to 25 mL by ethanol. After 40 mins, the absorbance of the mixture was determined at 415 nm. To prepare the blank samples, one drop of acetic acid was added to 1 mL of the extract and then ethanol was added to 25 mL. A standard solution containing rutin (0.5 mg/mL) in ethanol was used to plot the standard curve. The rutin equivalent (RE) was used to quantify the flavonoid content in the extracts according to the following formula; $X = (A * m_0) / (A_0 * m)$ where X means the content of flavonoids (mg/mg extract in RE), A and A_0 denote the absorbance of extract solution and standard solution, respectively, and m and m_0 express the weight of the plant extract (mg) and rutin (mg) in the solution, respectively (14).

Animals

Adult male Wistar rats weighting ~200-250 g were used (n=16); all the animal experimental procedures were approved by the Ethics Committee of Ardabil University of Medical Sciences (IR.ARUMS.REC.1397.174).

Isolation of Pancreatic Islets of Langerhans

Before starting the experimental procedure, a suitable period of time was given to the animals to spend in the lab environment. A solution containing ketamine and xylazine at a ratio of 10:1 (the administered dose of 100 mg/kg ketamine and 10 mg/kg xylazine) was intraperitoneally injected and, after anesthetization, the animals were subjected to laparotomy. The pancreatic duct was cannulated for perfusion with a cold and fresh Krebs buffer which made the pancreas swollen and easy to isolate from the other parts. Then, the pancreas was chopped and cut off into small pieces by using a small scissor in the cold Krebs buffer. Collagenase was added to the homogenate to breakdown the tissue around the islets. After the separation of fat tissues, the homogenate was washed with Krebs buffer in triplicate. Next, BSA was added and washed twice in order to stop digestion.

Finally, islets of Langerhans were picked up by using a sampler under the stereomicroscope, grouped based on similarity in size, and cultured in RPMI 1640. The cultured islets were incubated for 24 h at 37°C to overcome stressful conditions and restore their viability in the nourished and refreshed medium (15).

Pancreatic Islets' Treatment with the Plant Extract

After 24 h of pretreatment time, the islets were incubated with logarithmic concentrations of hydroalcoholic extracts of the bud, including $10, 10^2, 10^3, 10^4$ µg/mL in the RPMI medium for 24 h.

Viability Assay in the Pancreatic Islets

The MTT assay is based on the reducing capacity of yellow tetrazole into purple formazan by viable cells having the normal mitochondrial respiration. After 24 h of treatment of pancreatic islets with hydroalcoholic extracts, we removed the medium and washed the islets of Langerhans with Krebs buffer twice. Then, 50 µL of the MTT solution (0.5 mg/mL) was added to each vial of the islets and incubated for 4 h at 37°C. The islets having viable cells converted the yellow tetrazole into purple formazan, which was dissolved in the solution by adding DMSO and shaking for 30 min. Finally, a microplate reader was employed to read the absorbance of the samples at 570 nm (16).

ROS Assay in the Pancreatic Islets

The ROS level was measured using the DCFH-DA. ROS deacetylate and oxidize non-fluorescent DCFH-DA into the fluorescent DCF inside the cells. The islets of Langerhans were sonicated in 75 µL of the extraction buffer (containing 5 mM HEPES, 20 mM KCl, 1 mM EDTA, 0.25 mM sucrose) and 10 µL of the DTT solution (50 mM), and then centrifuged at 5000 rpm for 5 min. In the next step, we extracted 25 µL of the supernatant and mixed it with 80 µL of the assay buffer (containing 0.1 mM FeCl₃, 20 mM MgCl₂, 20 mM NaH₂PO₄, 130 mM KCl, 20 mM Tris-HCl, 0.1 mM NADPH, and 1.7 mM ADP). Finally, 5 µL of DCFH-DA was added to the mixture and incubated for

15 min at 37°C. During this time, DCFH-DA could enter the cells and be hydrolyzed by intracellular esterase to produce free DCFH. Measurement of the rate of DCF production through the oxidation of DCFH is an indicator of the amount of ROS in the cells. In this way, the absorbance of the mixture was read at an excitation of 485/20 and an emission of 528/20 every 5 min for 1 h with a fluorometer (Biotec, Tecan US, Inc.) (17).

Protein Assay in the Pancreatic Islets

The amount of total protein was assessed by the Bradford method in which BSA was used as the standard. Briefly, we added 100 µL of the Bradford reagent to 5 µL of each sample supernatant and standard solutions. After 20 min of incubation, we read the absorbance of the solutions by the spectrophotometer at 595 nm.

Statistical Analysis

The data were analyzed by SPSS and expressed as mean ± SEM with a replication number, n=4. The P-value of differences among the means were analyzed by one-way ANOVA followed by Tukey's test.

Results

In the first phase of the study, the phenol and flavonoid content of the methanolic and hydroalcoholic extracts of different parts of *C. spinosa* from the Moghan region were measured. In the second phase, the effects of the bud hydroalcoholic extract on the oxidative state and viability of rat pancreas were evaluated.

Calibration Curve for Plant Reagent Determination

We used gallic acid as the standard compound for the measurement of total phenolic content. The calibration curve of gallic acid was plotted with a regression of 0.9914 (Figure 1A). For determining flavonoid content, rutin was used as the standard compound, for which a calibration curve was drawn with a regression of 0.9848 (Figure 1B).

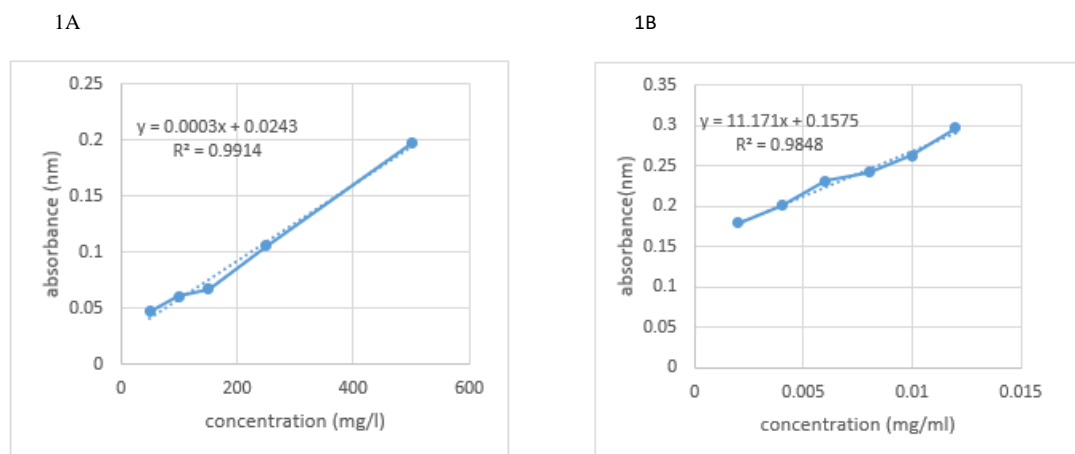


Figure 1. Calibration curve for gallic acid (A) and rutin (B).

Phenolic Content in Different Parts of the Plant

As shown in [Table 1](#), phenolic compounds had the highest content in the plant extract in comparison with others, and the leaf methanolic extract had the highest phenolic content (598.99 mg/g GAE). The root content of phenols was so low that it was ignored.

Flavonoid Content in Different Parts of the Plant

Flavonoids were less than phenols, and the amount of flavonoids in the leaf and bud had no significant differences ([Table 1](#)). The root content of flavonoids was also so low that could be ignored.

Table 1. Yield, total phenolic, flavonoid, and flavonol contents in the bud, leaf, and root methanolic and ethanolic extracts of *C. spinosa*

		Yield (%)	Total phenols mg/g plant extract (in GAE)	Total flavonoids mg/g plant extract (in RE)	Total flavonols mg/g plant extract (in RE)
Bud	Ethanolic	27.2	318.99±17.63	318.99±17.63	40.21±0.3
	Methanolic	26.28	328.99±29.06	328.99±29.06	34.49±0.16
Leaf	Ethanolic	18.8	534.55±18.36	534.55±18.36	32±2.23
	Methanolic	17.6	598.99±20.27	598.99±20.27	47.41±2.41
Root	Ethanolic	19.8	16.77±13.87	16.77±13.87	2.1±0.1
	Methanolic	11.88	130.11±8.39	130.11±8.39	2.31±0.1

Effect of the Plant Bud Extract on the Viability of Pancreatic Islets

Based on [Figure 2](#), the *C. spinosa* bud hydroalcoholic extract markedly increased the survival of the islet

cells. This effect was positively related to the concentration of the plant extract, and the greatest effect was observed at the concentration of $\sim 10^3$ and $10^4 \mu\text{g/mL}$ ($P < 0.001$).

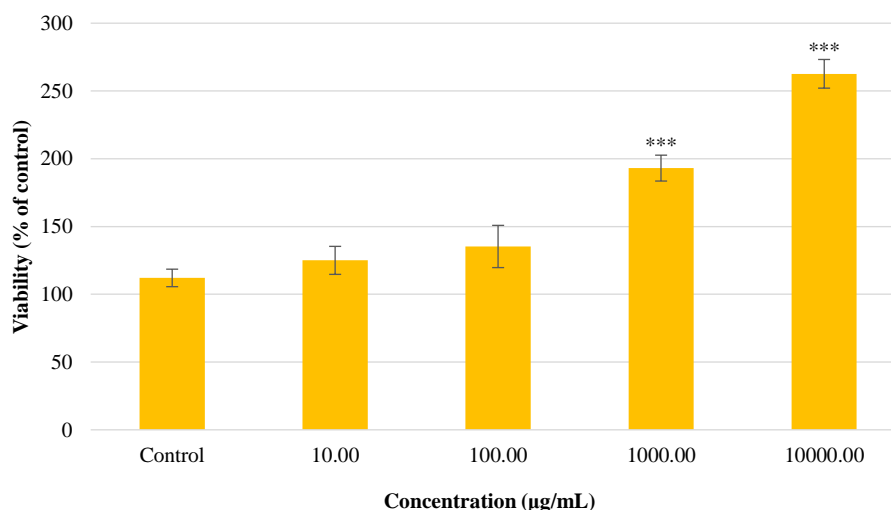


Figure 2. Effect of different concentration of *C. Spinosa* on the viability of islets of Langerhans isolated from the pancreas of rat after 24 h of exposure. Values are expressed as mean \pm SEM with a replication number, $n = 4$. ***significantly different from the control at P -value < 0.001 .

Effect of the Plant Bud Extract on ROS Level in the Pancreatic Islets

As seen in [Figure 3](#), there were remarkable reductions in ROS production compared with the control when the plant extract was used at the concentrations of $10^3 \mu\text{g/mL}$ ($P < 0.01$) and $10^4 \mu\text{g/mL}$

($P < 0.001$). The rate of decrease in ROS production was estimated to be 37% and 72% of the control in the mentioned treated groups, in that order.

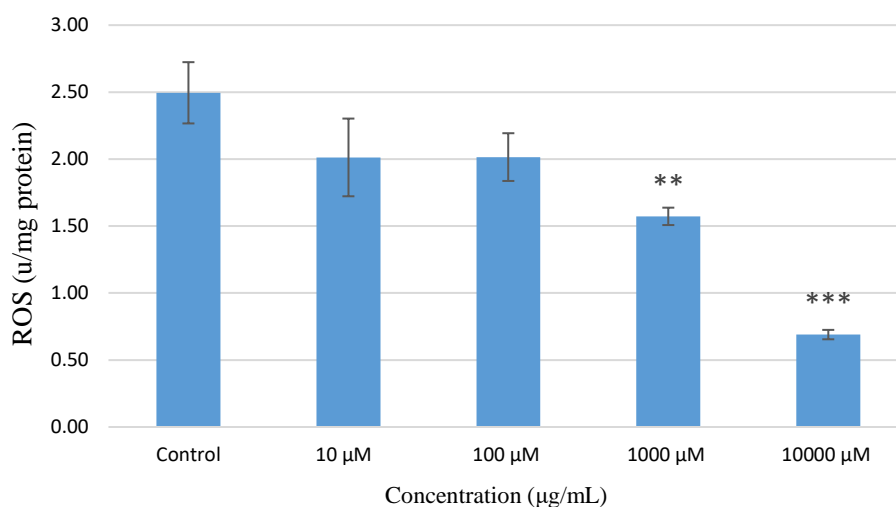


Figure 3. Effect of different concentration of *C. Spinosa* on the level of ROS in the islets of Langerhans isolated from the pancreas of rat after 24 h of exposure. Values are expressed as mean \pm SEM with a replication number, $n = 4$. **significantly different from the control at P-value < 0.01 , ***significantly different from the control at P-value < 0.001 .

Discussion

Diabetes is one of the most prevalent diseases in the current century and is expected to increase more quickly in developing countries (18). Apart from the changed lifestyle and diet, it has been proved that exposure to some environmental pollutants can increase the risk of diabetes in susceptible people. Heavy metals and pesticides have been identified as the major diabetogenic toxicants for which the probable relationship between environmental release and the risk of diabetes has been well documented by determining biochemical and molecular mechanisms (19-21). Therefore, presenting new therapeutic strategies from natural sources based on the recently known etiologies of the disease can be a promising approach to both the prevention and treatment of diabetes.

Diabetes has many etiologies, including the damage and destruction of pancreatic β -cells. There has been sufficient evidence on the occurrence of oxidative stress parameters in the biological samples of patients with diabetes (22). Oxidative stress caused by excessive free radicals and hyperglycemia is believed to damage cellular macromolecules in the islets of Langerhans and disrupt insulin gene expression and insulin release. Thus, antioxidants can improve the viability and function of islets by counteracting overproduced oxidants and maintaining cellular homeostasis (23). In fact, sustained hyperglycemia due to uncontrolled diabetes can gradually lead to glucose toxicity

manifested by oxidative stress and inflammatory responses. It has been reported that under such conditions, some intracellular compensatory cascades are activated, including the JNK pathway that has been shown to be involved in the dysfunction of pancreatic β -cell and induction of insulin resistance in peripheral tissues, both of which can deteriorate hyperglycemia and lead to following events (24,25).

Plants are one of the main natural sources of antioxidants and are rich ineffective ingredients with a high capacity for scavenging free radicals and ROS. Evidence has suggested that antioxidant compounds from natural sources such as plants can positively affect a wide range of biological functions in the cells by virtue of their radical scavenging properties (13). Polyphenols are considered as the secondary metabolites of plants and act as potent antioxidants that can provide defense against overproduced oxidants and oxidative stress. Polyphenol-rich diets have been reported to protect against the development of many pathological conditions with chronic progress, such as diabetes (26).

C. spinosa L. is a known polyphenol-rich plant that exhibits good antioxidant activities (27). Glucose-lowering effects have also been reported for this plant in experimental and clinical studies. The hypoglycemic and hypolipidemic effects of the *C. spinosa* extract in laboratory animal models of diabetes caused by insulin deficiency and insulin resistance have been documented

in different studies (28-33). The inhibitory effect of the *C. spinosa* extract on the activity of pancreatic alpha-amylase has also been confirmed. Drugs inhibiting the enzymatic activity of α -amylase and α -glucosidase are helpful in the treatment of diabetes by lowering postprandial glucose (34). This evidence suggests the protective role of ingredients in the *C. spinosa* extract on the metabolic profile of carbohydrates and lipids. Moreover, histological studies have demonstrated that the *C. spinosa* extract can decrease cell necrosis and tissue damage in diabetic laboratory animals. This effect can be mediated by the active ingredients of the plants, most commonly phenols and flavonols that have antioxidant and anti-inflammatory activities (35).

The present study is the first report on the protective effects of *C. spinosa* on the pancreatic islets whose integrity and function are essential for the maintenance of glucose metabolism since the pancreas is the only source of insulin production in the body. The *C. spinosa* extract increased the viability of rat pancreatic islets of Langerhans in a dose-dependent manner. Moreover, the amount of ROS, which is the main indicator of oxidative stress, was decreased in the islets treated with the *C. spinosa* extract. Oxidative stress plays a major role in depleting cellular ATP and initiating cell death procedures, especially in pancreatic β -cells that are highly sensitive to oxidants and reactive metabolites. In this way, the agents having antioxidant capacity have been proposed to be useful against β -cell damage and insulin synthesis and secretion disruption. Previous research has also reported anti-inflammatory activities for the *C. spinosa* extract in different animal models of experimental setups (36). Of course, these effects are predictable since oxidative stress and inflammation develop together in the cells and most of their elements interact with and augment one another. Given that the pathogenesis of diabetes involves the activation of both oxidative and inflammatory pathways, agents having antioxidant and anti-inflammatory effects can be helpful in the treatment of the disease. According to previous evidence on the glucose-lowering activity of *C. spinosa*, as well as its protective effects on the isolated islets of Langerhans observed in this study, it is concluded that the active ingredients of this plant can be regarded as a promising adjuvant therapy for the prophylaxis and management of diabetes, and merit further research to uncover the exact mechanisms responsible for this action.

Conclusion

The present findings showed that the *C. spinosa* bud extract from the Moghan region is a source of

polyphenol and can enhance the viability and reduce the production of ROS in the islets of Langerhans. Accordingly, *C. spinosa* can be evaluated for use in the prophylaxis and treatment of diabetes.

Acknowledgments

The authors wish to thank the Department of Toxicology and Diseases, The Institute of Pharmaceutical Sciences (TIPS) at Tehran University of Medical Sciences, Tehran, Iran for technical support.

Conflict of Interest

Authors declared no conflict of interest.

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How to Cite This Article:

Azad M, Mohammadi P, Bohlooli S, Mostafalou S. Protective Effect of *Capparis spinosa* Hydroalcoholic Extract on the Integrity of Rat Pancreatic Islets. *J Adv Med Biomed Res.* 2020; 28 (129) :204-211

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