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Research Article

Effects of *Aloe vera* leaf gel extract on rat peritonitis model

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ABSTRACT

Objectives: The aim of this study was to investigate the antibacterial, anti-inflammatory, and antioxidant activities and probable toxic effects of *Aloe vera* (AV) in a rat peritonitis model.

Materials and Methods: Rats were divided into five groups: (1) Control group, (2) AV group, (3) peritonitis group (P), (4) peritonitis + AV group (P + AV), and (5) peritonitis + antibiotherapy group (P + Ab). Ultrafiltration (UF) rates were determined and colony and leukocyte counts were calculated in the dialysate. Glucose, blood urea nitrogen (BUN), creatinine levels, and alanine transaminase (ALT) activities were studied in blood. Glucose, interleukins (IL-1β, IL-6), and prostaglandin E2 (PGE2) were studied in dialysate and peritoneal tissue for the assessment of the anti-inflammatory effect. Copper/zinc superoxide dismutase (Cu, Zn-SOD), malondialdehyde (MDA), and nitric oxide (NO) were also investigated in peritoneal tissue.

Results: *Aloe vera* increased the UF rate and lowered leukocyte numbers in the peritonitis group. There was no significant difference in blood and dialysate glucose, BUN, creatinine levels and ALT activity among control and AV groups. AV decreased IL-1β, IL-6 and PGE2 in peritonitis, showing good anti-inflammatory effect. AV showed antioxidant effect on the chosen antioxidant parameters Cu, Zn-SOD, MDA, and NO.

Conclusion: It was concluded that, AV might be used in peritonitis for its probable UF increasing, anti-inflammatory, and antioxidant effects.

KEY WORDS: *Aloe vera*, antioxidant enzymes, cytokines, peritonitis, ultrafiltration

Introduction

Peritoneal dialysis (PD) is a choice of treatment in children with chronic renal failure due to advantages of easy application at home, allowing school attendance, and lesser frequency of blood contamination and anemia. However, peritonitis is a major complication of PD and recurrent peritonitis attacks may alter dialysis capacity and also enhance the cost of therapy.

In the pathogenesis of peritonitis, bacterial invasion is followed by the activation of inflammatory cells, mainly neutrophils, in a few hours. Tissue damage in inflammatory conditions is caused primarily by the host's effector cells, rather than by bacteria.[1,2] Free radicals generated during inflammatory disorders are necessary for bactericidal reaction, to damage cellular membrane by lipid peroxidation, and to increase leukotriene and prostaglandin levels and arachidonic acid turnover.[3]

Aloe vera (AV) (L.) Burm. fil (*A. barbedensis* Miller; Aloaceae) is a tropical cactus formerly attributed to the lily family and has been used for therapeutic potential effects for centuries by different cultures. The AV leaf gel contains biologically active compounds like mannose-6-phosphate, carboxypeptidase, glutathione peroxidase, and superoxide dismutase.[4-7] These compounds have been claimed to have anti-inflammatory, antioxidant, immunostimulatory, antibacterial, hypolipidemic, wound healing activity and hypoglycemic properties. In addition to well-documented positive effects of the plant, there have also been reports of toxic effects such as hepatitis and acute renal failure.[7-10]

The aim of this study was to investigate the antibacterial, anti-inflammatory, antioxidant activities and probable toxic effects of AV leaf gel in a rat peritonitis model.

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Materials and Methods

Preparation of the Aloe vera Leaf Gel Extract

Aloe vera leaf gel was prepared by Can *et al*.[11] at Istanbul University, Faculty of Pharmacy. Specimens of AV were collected

from Antalya, Turkey and cultivated in the greenhouse of Istanbul University Alfred Heilbronn Botanical Garden. AV leaves were weighed and cut in the middle; the gel was separated by scratching with a spoon. The gel (400 g = 2.5 g dry matter, 10 mL = 63 mg) was homogenized in a Waring blender, then diluted with an equal volume of phosphate buffered saline (pH: 7.4) and homogenized for a 2nd time. The extract was kept at 4°C overnight, and then filtered through cloth. The clear filtrate was kept at −20°C in small portions. Before use, the filtrate was sterilized by Co-60 gamma ray at Gamma-Pak ray center in Kocaeli, Turkey.

Experimental Animals

Male Wistar rats weighing 150-200 g were used for the study. The rats were housed in polycarbonate cages, at 24°C room temperature with 12 h light/dark cycle and were fed with commercial rat feed and water *ad libitum*.

The experimental protocol (protocol number: 2005/0021) was approved by the Animal Experimentation Committee of Adnan Menderes University, Faculty of Medicine.

Bacterial Strain

Staphylococcus aureus ATCC 25923 strain was incubated at bloody agar medium for 18-24 h at 37°C. Cultured colonies were kept at brain-heart infusion, after an overnight incubation, bacterial inoculum containing 10^9 CFU/mL was obtained.

Peritonitis Induction

Bacterial inoculum containing 10^9 CFU/mL *S. aureus* was administered intraperitoneally (IP) to rats.

Animal Groups and Study Design

Animals were divided into four study groups and a control group:

- Group 1: Control group (*n*:6): 20 mL of 3.86% PD solution (Dianeal: Eczacıbaşı-Baxter Healthcare, Istanbul, Turkey) was injected IP to healthy control rats
- Group 2: AV group (*n*:8): 100 mg/kg of AV gel was given IP in a 3.86% PD solution
- Group 3: Peritonitis (P) group (*n*:8): 1.5×10^9 CFU/mL *S. aureus* was injected and 3 h after bacterial inoculation, 20 mL of 3.86% PD solution was given IP
- Group 4: Peritonitis + AV (P + AV) group (*n*:8): 1.5×10^9 CFU/mL *S. aureus* was injected IP. After 3 h of bacterial inoculation, 100 mg/kg of AV in 20 mL of 3.86% PD solution was given IP
- Group 5: Peritonitis and antibiotherapy (P + Ab) group (*n*:8): 1.5 × 109 CFU/mL S. aureus was injected IP. After 3 h of bacterial inoculation, 100 mg/kg cefazolin (Sefazol, Mustafa Nevzat, Istanbul, Turkey) was administered intramuscularly and 20 mL of 3.86% PD solution was given IP. The dose of cefazolin was adjusted regarding the pharmacokinetics of the drug.[12]

At 1 h after the administration of 20 mL 3.86% PD solution, dialysate samples were taken through a midline incision, using a shortened dialysis catheter to prevent leakage of dialysate under aseptic conditions, and ether anesthesia. Net ultrafiltration (UF) rate was determined by calculating the difference between the instilled and drained volumes. Immediately after dialysate samples were taken, leukocytes were counted with a Thoma slide, incubation for colony counts, and Gram stains were performed and glucose levels were examined. Blood samples were collected by cardiac puncture. Glucose, blood urea nitrogen (BUN), creatinine levels and alanine aminotransferase (ALT) activity were studied in the serums of control and AV groups to determine the toxic and hypoglycemic effects. Interleukins (IL-1β, IL-6), and prostaglandin E2 (PGE2) were studied in dialysate and peritoneal tissue. Copper/zinc superoxide dismutase (Cu, Zn-SOD), malondialdehyde (MDA), and nitric oxide (NO) were determined in peritoneal tissue.

Preparation of Peritoneal Tissue

Tissues were homogenized in lysis buffer (pH: 7.6) containing protease inhibitor, phenylmethylsulfonyl fluoride (100 μg/mL), aprotinin (1 μg/mL), 0.001 EDTA, 0.01 M Tris-HCl, 0.1 M NaCl at 4°C using a Polytron homogenizer (B. BRAUN, Melsungen, Germany). For MDA determination whole tissue homogenate was used. Then the homogenate was centrifuged at 14.000 rpm for 10 min at 4°C. The resultant supernatant was used for measurement of NO (nitrite + nitrate), Cu, Zn-SOD, IL-6, IL-1β and PGE2.

Microbiological Assessment

Dialysate samples were incubated to bloody agar and Eosin-methylene blue agar at 37°C for 18-24 h. Gram stain was also done. For identification of the microorganism, catalase and coagulation tests, incubation to mannitol salt agar and DNAse media were done by using BBL Crystal Commercial Test System.

Biochemical Analyses

Blood samples were stored at −85°C up to analysis. Glucose, BUN, creatinine and ALT were studied in an autoanalyzer (Architect C8000, Abbott).

Interleukin-1β

Interleukin-1β levels were determined through commercial rat ELISA kit (IBL Co., Ltd., Hamburg, Germany), catalog number 27193.

Interleukin-6

Interleukin-6 levels were determined through commercial rat ELISA kit (IBL Co., Ltd. Hamburg, Germany) catalog and lot numbers were 17194 and OL-527.

The test results for IL-1β, IL-6 were calculated by BIOELISA reader El × 800 using a standard curve.

Prostaglandin E2

High sensitive prostaglandin determination was done through commercially kit assay design enzyme immunoassay kit (ELISA), catalog number was 930-001 (Assay Design, Inc., 800 Technology Drive, Ann Arbor, MI 48108, USA).

Copper/Zinc Superoxide Dismutase

Superoxide dismutase assay reagent (2.45 mL) was added to each tube; afterwards, 0.5 mL of pure Cu, Zn-SOD (0-270 ng), or samples were added. Subsequently, the rack of tubes was placed into a water bath adjusted to 25°C, 50 μl of Xanthine oxidase solution was added to each tube at 30 s intervals and each tube was incubated for 20 min. The reaction was terminated by adding $CuCl_2$. The production of formazan was determined at 560 nm using Shimadzu UV-160 spectrophotometer. Under these conditions, the absorbance at 560 nm of the Blanc tube was about 0.25. The percentage of inhibition was calculated as

follows: inhibition% = $(A_{blank} - A_{sample})/A_{blank} \times 100$. Cu, Zn-SOD activity was calculated via using a standard curve.[13]

Malondialdehyde or Thiobarbituric Acid Reactive Substances

The MDA production and hence lipid peroxidation were assessed in the tissues by the method of Ohkowa.[14] MDA forms a colored complex in the presence of thiobarbituric acid, which is detectable by measurement of absorbance at 532 nm. Absorbance was measured with Shimadzu UV-160 spectrophotometer. 1,1′,3,3′ Tetraethoxypropane was used as a standard and the results were expressed as nmol/g wet tissue.

Nitric Oxide

Nitric oxide (nitrite + nitrate) was assayed by a modification of cadmium-reduction method.[15] The samples were analyzed spectrophotometrically using a microplate reader and quantified automatically against KNO_3 standard curve and the results were expressed as μmol/L.

Histological Examination

The peritoneal membrane, renal and liver samples were fixed in 4% formalin and embedded in paraffin. Paraffin blocks were divided into 5-μm sections and were then stained with hematoxylin and eosin and Masson trichrome. All samples were examined by the same pathologist, who was unaware of the nature of the groups from which the samples originated. Peritoneal thickness (mean of three different measurements) was measured with an ocular micrometer. Inflammation was defined by counting capillaries and mononuclear cells per high-power field at ×400 magnification. Inflammatory cell infiltrations were scored as 0 (none), 1 (moderate), 2 (severe). Nephrotoxicity was scored through the severity of the histopathological changes (0: No nephrotoxicity, 1: Mild = low-grade tubular necrosis without interstitial nephritis, 2: Moderate = low-grade tubular necrosis with interstitial nephritis, 3: Severe = high-grade tubular necrosis with interstitial nephritis).

Statistical Analysis

All data were evaluated with SPSS 15.0 for Windows Software Package(SPSS Inc., Chicago;IL). The results were expressed as mean ± standard deviation. One-way ANOVA test with Tukey's correction for multiple comparisons was used. Kruskal-Wallis test together with Mann-Whitney U-test were performed to compare inflammatory histological scores.

Results

Ultrafiltration was calculated for each animal after 1 h dialysis with 20 mL of 3.86% PD solution. UF results were given in Table 1. The difference between groups was significant ($P < 0.001$).

No colonies cultured from dialysate samples of control and AV groups. The colony counts of groups with peritonitis were given in Table 1. There was no statistically significant difference in colony numbers cultured from dialysates among all peritonitis groups ($P = 0.16$).

The leukocyte numbers of dialysate samples were significantly different among the groups ($P = 0.01$). Leukocyte count in dialysate at P + AV group was significantly lower than peritonitis group ($P = 0.04$) [Table 1].

Serum glucose, ALT, BUN, and creatinine results were given in Table 2. The difference between control and AV groups for glucose, creatinine and BUN levels were not significant.

Dialysate cytokine levels were given in Table 3. Statistically significant difference was found among groups regarding IL-1β, IL-6, and PGE2 levels with ANOVA analysis ($P < 0.001$ for all comparisons). IL-1β, IL-6, and PGE2 levels in the peritonitis group were higher than that of control group ($P < 0.001$ for all comparisons). IL-1β, IL-6, and PGE2 levels in the dialysate samples of P + AV group were also significantly lower when compared to peritonitis group ($P = 0.01$, $P = 0.001$, and $P < 0.001$, respectively).

Levels of peritoneal tissue cytokine levels and oxidative markers were given in were given in Table 4.

The difference among groups was significant for tissue Cu, Zn-SOD, MDA, and NO levels ($P < 0.001$ for all comparisons).

Peritonitis group tissue Cu, Zn-SOD, MDA, NO, levels were higher than control group ($P < 0.001$ for all comparisons). Tissue Cu, Zn-SOD, MDA, NO levels in P + AV group were lower than peritonitis group ($P = 0.003$, $P = 0.001$, and $P = 0.002$, respectively).

The liver, renal tissues and peritoneal membrane from each group were examined histologically. Renal histologies were examined for the presence of tubular necrosis and interstitial nephritis. There were minimal changes (low-grade tubular necrosis without interstitial nephritis) at one slide in the P + Ab group, and one slide at P + AV group which were acceptable as minimal changes. There were no significant histological differences between groups for renal tissues. The liver histologies were evaluated for necrotic changes which were markers of toxic effects. The histologies of the peritonitis and control group were normal. There were confluent necrosis areas in the AV group, but these areas were not widespread and could be acceptable as minimal

Table 1:

UF, colony counts and leukocyte numbers and glucose levels of dialysates for all groups

Groups	UF (mL)	Colony count/mm³	Leukocyte count/mm³	Glycose level (mg/dL)
Control	9.48±2.34	No any colony	461.67±264.38	728.50±42.10
AV	3.85±2.71	No any colony	343.75±166.64	556.25±240.74
P	−15.95±6.92[a]	25714±0.9759	7828.75±10171.00	1348.71±311.33[e]
P+AV	7.80±1.28[b,c]	30000±0.9258	1185.00±845.90[d]	879.25±241.82[f]
P+Ab	−14.49±2.89	30000±0.7951	2751.25±1930.40	1200.50±251.52
P_{ANOVA}	<0.001	0.16	0.01	<0.001

[a]*P*<0.001 versus control, [b]*P*<0.001 versus peritonitis, [c]*P*<0.001 versus P+Ab, [d]*P*=0.04 versus peritonitis group, [e]*P*<0.001 versus control, [f]*P*=0.004 versus peritonitis. UF = Ultrafiltration rate, AV = *Aloe vera*, P = Peritonitis, P+AV = Peritonitis+*Aloe vera*, P+Ab = Peritonitis+antibiotheraphy

changes [Figure 1]. Focal necrosis which could be detected in also healthy cases was also determined in restricted areas at all groups. The peritoneal membrane thickness of the control group, AV group, P group, P + AV group and P + Ab group were 7.82 ± 2.89 mm, 9.58 ± 5.71 mm, 9.55 ± 3.56 mm, 11.14 ± 6.06 mm, 10.25 ± 5.83 mm, respectively and were similar (P_{ANOVA} = 0.78).

Discussion

Aloe vera gel extract enhanced the UF rate when used in peritonitis. This effect was better than antibiotherapy alone. When admitted to healthy rats, AV itself did not alter the ultrafiltration. Regarding to the data that one of the main factors effecting the UF rate is glucose content of the dialysate, dialysate glucose concentrations were examined. AV decreased glucose concentrations in peritonitis so that the effect of AV on UF rate was independent of glucose concentrations.

Inhibition of neutrophil migration into the peritoneal cavity by AV was reported previously.[16] In this study, AV decreased the leukocyte count in dialysate in comparison to the peritonitis group. This result was suggestive for anti-inflammatory effect of the gel.

Antimicrobial effect of AV was reported previously.[17] The colony count of peritonitis group was significantly higher than control proving that the peritonitis was done successfully. However, the difference between other groups was not significant and no antimicrobial effect of AV gel was shown.

The glucose reducing effect of the AV gel was reported in the diabetic rats.[18,19] Hyperglycemic effect of the AV leaf gel was also reported and the glucose, sorbitol, galactose components of the plant were claimed for that hyperglycemic effect.[20,21] The glucose reducing effect of the AV gel vary in regard to the part of the plant used (leaf pulp, leaf gel, leaf juice).[18] In this study, acute treatment with AV leaf gel did not alter the serum glucose levels in AV group when matched with the healthy control. This result was in concordance with previous studies done with nondiabetic rats.

Acute renal failure secondary to compounds named aloeresin in *Aloe* preparations was reported in the literature.[10] AV leaf gel did not effect BUN and creatinine levels in comparison to the healthy control group. No nephrotoxic effect was seen in this study. AV induced hepatitis due to chronic ingestion was reported in literature and hepatitis resolved completely after

Table 2:

Serum glucose, BUN, creatinine levels and ALT activity values for groups

Groups	Glucose (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	ALT (mg/dL)
Control	127.33±21.53	52.67±9.40	0.40±0.11	54.50±7.94
AV	160.88±40.73	41.25±9.07	0.33±0.07	59.88±19.07

BUN = Blood urea nitrogen, ALT = Alanine aminotransferase, AV = *Aloe vera*

Table 3:

Dialysate cytokine values for all groups

Groups	IL-1β (pg/mL)	IL-6 (pg/mL)	PGE2 (pg/mL)
Control	3.80±1.96	4.25±1.47	15.23±6.42
AV	2.59±1.22	2.88±1.32	13.93±3.24
P	24.82±16.18[a]	31.55±19.02[b]	61.74±10.08[c]
P+AV	11.96±6.03[d]	12.79±6.72[e]	20.03±6.75[f]
P+Ab	3.11±3.66[g]	4.12±1.86[h]	19.79±6.57[i]
P_{ANOVA}	0.001	0.001	0.001

[a]*P*<0.001 versus control, [b]*P*<0.001 versus control, [c]*P*<0.001 versus control, [d]*P*=0.001 versus P group, [e]*P*=0.001 versus P group, [f]*P*<0.001 versus P group, [g]*P*<0.001 versus P group, [h]*P*<0.001 versus P group, [i]*P*<0.001 versus P group. AV=*Aloe vera*, P=Peritonitis, P+AV=Peritonitis+*Aloe vera*, P+Ab=Peritonitis+antibiotheraphy, PGE2=Prostaglandin E2, IL=Interleukins

Figure 1: Confluent necrosis areas in the liver histologies of *Aloe vera* group

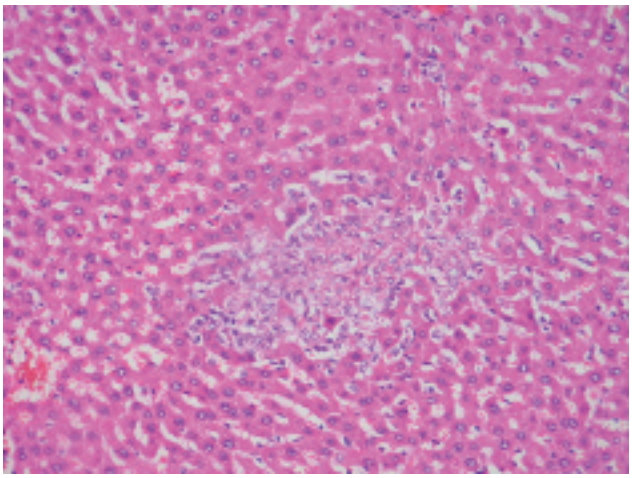


Table 4:

Peritoneal tissue cytokine levels and oxidative stress markers for all groups

Groups	IL-1β (pg/g tissue)	IL-6 (pg/g tissue)	PGE2 (pg/g tissue)	Cu, Zn-SOD (ng/g)	MDA (nmol/g)	NO (μmol/g)
Control	82.52±32.57	73.35±27.35	87.07±15.97	305.11±37.05	31.30±6.33	0.07±0.01
AV	124.93±90.53	59.54±29.74	155.28±33.64	322.81±102.1	28.91±7.77	0.07±0.04
P	149.22±99.37	149.17±93.50	404.06±73.45[c]	781.70±275.63[f]	77.31±26.94[h]	0.16±0.06[j]
P+AV	54.05±30.69	46.56±27.68[a]	124.54±36.76[d]	353.51±42.63[g]	33.57±7.66[i]	0.07±0.01[k]
P+Ab	51.40±41.80	36.20±20.97[b]	54.96±20.31[e]	370.28±67.7[9]	41.64±16.20	0.05±0.01
P_{ANOVA}	0.08	0.01	<0.001	0.08	0.01	<0.001

[a]*P*=0.02 versus peritonitis group, [b]*P*=0.01 versus peritonitis group, [c]*P*<0.01 versus control group, [d]*P*<0.01 versus peritonitis group, [e]*P*<0.01 versus peritonitis group, [f]*P*<0.001 versus control, [g]*P*=0.003 versus peritonitis group, [h]*P*=0.001 versus control, [i]*P*=0.001 versus peritonitis group, [j]*P*=0.01 versus control, [k]*P*=0.002 versus peritonitis group. AV = *Aloe vera*, P=peritonitis, P+AV=Peritonitis+*Aloe vera*, P+Ab=Peritonitis+antibiotheraphy, PGE2=Prostaglandin E2, MDA=Malondialdehyde, NO=Nitric oxide, IL=Interleukins, Cu, Zn-SOD=Copper/zinc superoxide dismutase

discontinuing medication.[10] Serum ALT levels were not altered in AV group in comparison to healthy control group. However, this study was an acute model and could be insufficient to denote toxic effects during chronic treatment.

Kinetics of peritoneal infection model was reported by Welten *et al*.[2] and Walley *et al*.[1] The 4 h interval was appropriate for evaluating peritoneal lavage cytokine levels. Determination of cytokine levels permits the evaluation of anti-inflammatory effects of drugs. It has been reported that AV gel reduced the serum IL-6 levels in infected or wounded rats.[17,22] Langmead *et al*.[23] also reported the inhibitory effect of the AV gel on colorectal PGE2 and IL-8 production. Immunostimulatory effects of AV gel were also reported as significant increase in IL-6, tumor necrosis factor-alpha, IL-1 levels.[24,25] In this study, AV gel administration to peritonitis group reduced the increased levels of IL-1β, IL-6, and PGE2 in dialysate and peritoneal tissue thus showing the anti-inflammatory effect of the gel.

Superoxide dismutase catalyzes the dismutation of superoxide anions which are produced by macrophages. It is an antioxidant enzyme, which protect tissues from oxygen free radicals. An increase in SOD activity at peritonitis and its correlation with the severity of the illness was reported before.[26,27] It was concluded that, SOD itself was a stress protein and elevation of SOD in inflammation might result from higher oxygen radical levels.[27] In this study, AV significantly decreased the elevated level of Cu, Zn-SOD in peritonitis group in comparison to control group.

Malondialdehyde is one of the most used biomarker of lipid peroxidation and oxidative stress and believed to increase in inflammatory process like peritonitis.[3,27] Peroxidation of cell membrane lipids can result in severe cell damage.[3] Several studies have shown decreased levels of MDA in diabetic rats with AV treatment.[11,28] In this study, AV significantly reduced the peritoneal MDA levels which were increased in peritonitis group in comparison to control group and seem to have an antioxidant effect.

Appropriate levels of NO are protective against inflammatory damage however sustained levels result in tissue toxicity. Previous studies have shown increased NO levels in dialysate during acute peritonitis.[29,30] In this study, peritoneal NO levels were significantly high in peritonitis group in accordance with previous studies. AV gel extract decreased the NO levels as well as antibiotheraphy. This antioxidant effect may be due to biologically active compounds of the gel.[4-6]

There wasn't any significant change or confluent necrosis in renal and liver histology of groups. Peritoneal thickness was also similar between groups. This study was an acute model and a longer time period would be needed to observe to histological change, cell infiltration to the tissue.

Conclusion

No toxic effect of the AV gel extract was reported in our study. The gel also seems to have an antioxidant and anti-inflammatory effects in rat peritonitis models. Results were suggestive for the use of AV in peritonitis; nevertheless, further studies are needed to examine the usage of the gel as an adjunction treatment choice in human beings.

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