

# Cordycepin prevents postoperative formation of intra-abdominal adhesion in a rat model: An experimental study

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## ABSTRACT

**BACKGROUND:** The aim of the present study was to investigate whether cordycepin prevented adhesion formation in a rat model.

**METHODS:** Rats were randomly assigned to 3 groups of 10 rats. Control group: The absence of adhesion was confirmed via laparotomy. Adhesion group: The cecum was removed from the abdomen and scraped with a dry gauze bandage until petechial hemorrhagic foci developed. Cordycepin group: The same surgical procedure was performed as in the adhesion group, and 10 mg/kg cordycepin was administered intraperitoneally. After 15 days, the rats were sacrificed humanely via cardiac blood withdrawal under anesthesia. The rats were then analyzed morphologically and histopathologically, and hydroxyproline (OH-p) and malondialdehyde (MDA) levels were measured.

**RESULTS:** Macroscopic analysis revealed significantly less adhesion in the cordycepin group than in the adhesion group ( $p<0.01$ ). Furthermore, significant histopathological improvement was also evident in the cordycepin group compared to the adhesion group ( $p<0.05$ ). The levels of OH-p and MDA in blood and tissue were higher in the adhesion group than in the control group, and lower in the cordycepin group than the adhesion group. Interestingly, MDA level was significantly lower (blood:  $p<0.05$ ; tissue:  $p<0.01$ ) in the cordycepin group than in the adhesion group, whereas only tissue OH-p was significantly lower in the cordycepin group compared with the adhesion group ( $p<0.05$ ). One rat in both adhesion group and cordycepin group died postoperatively.

**CONCLUSION:** Results indicated that cordycepin effectively reduced adhesion in a rat abrasion model. Thus, this agent may be valuable to prevent postoperative adhesion.

**Keywords:** Abdominal; adhesion; cordycepin, experimental; rat; study.

## INTRODUCTION

Postoperative adhesion is a major complication observed after abdominopelvic surgery. Adhesion may cause infertility,

abdominal or pelvic pain, or obstruction.<sup>[1,2]</sup> Recently, new surgical techniques, mucosal barriers, and many therapeutic agents, including progesterone, curcumin, methylene blue, vitamin E, surfactants, and hyperbaric oxygen, have been developed in efforts to prevent adhesion, but the work continues.<sup>[1,3-6]</sup> Cordycepin, an adenosine analogue initially isolated in China in 1964, has been demonstrated to have a variety of biological functions, and is used to treat various medical conditions. Cordycepin has fibrinolytic, anti-apoptotic, antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, nephroprotective, and hepatoprotective effects. It has been used as an herbal tonic in traditional Chinese medicine.<sup>[7-9]</sup>

Adhesion is an important problem for surgeons and has been the subject of many experimental and clinical studies using various parameters. Malondialdehyde (MDA) is a by-product

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**Table 1.** Grading of adhesion in rats according to the criteria of Nair et al.<sup>[10]</sup>

Grade		
0	Complete absence of adhesion	Insubstantial adhesion
1	Single band of adhesions between the viscera or from 1 viscus to the abdominal wall	Insubstantial adhesion
2	Two bands, either between the viscera or from the viscera to the abdominal wall	Substantial adhesion
3	More than 2 bands between the viscera or from the viscera to the abdominal wall, or whole of intestines forming a mass, without being adherent to the abdominal wall	Substantial adhesion
4	The viscera directly adherent to the abdominal wall, regardless of number or extent of adhesive bands	Substantial adhesion

formed when oxygen radicals produced by cells break down lipid-containing structures, such as plasma and cell membranes, in the inflammatory response.<sup>[10,11,12]</sup>

Tissue damage is used to assess the severity of inflammation and adhesion. Another parameter used to evaluate adhesion is hydroxyproline (OH-p), a hydroxylated derivative of the amino acid proline, which is abundant in collagen. OH-p is useful for assessing adhesion and wound healing.<sup>[11]</sup>

The aim of the present study was to investigate whether cordycepin would prevent adhesion formation in a rat model.

## MATERIALS AND METHODS

This study was conducted in the experimental animal and research laboratory of the Faculty of Medicine of Dicle University. Thirty female Wistar Albino rats weighing 220 to 260 g each were used. They received standard food and water ad libitum, and were housed with a 12-hour light/dark cycle for 1 week prior to commencement of the study. Twelve hours prior to administration of anesthesia, food was restricted but water was not. Each rat was anesthetized via intramuscular injection of 5 mg/kg xylazine (Rompun; Bayer AG, Leverkusen, Germany) and 50 mg/kg ketamine hydrochloride (Ketalar; Pfizer, Inc., NY, NY, USA). The anesthetized rats were placed in the supine position. The anterior abdominal wall was shaved and antisepsis was performed using povidone-iodine. The rats were randomly assigned to 3 groups (control, adhesion, and cordycepin groups; 10 rats per group).

**Control group.** A 3-cm midline incision was created in the anterior abdominal wall under sterile conditions and the ab-

sence of adhesion was confirmed by laparotomy. The abdominal wall was closed using a running suture (3/0 vicryl and 3/0 atraumatic silk).

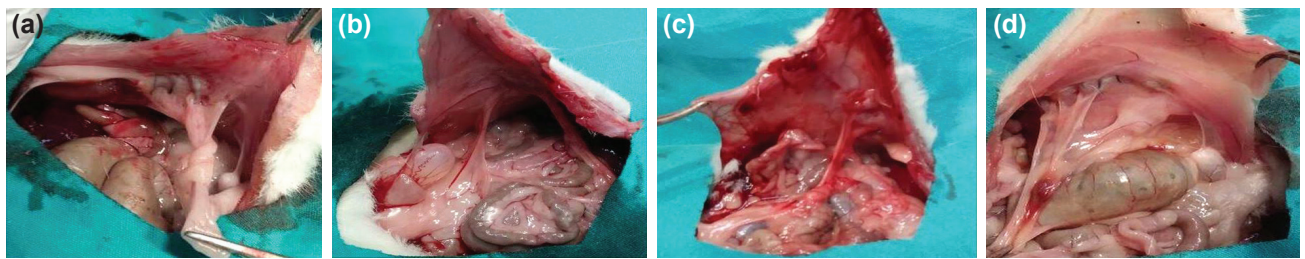
**Adhesion group.** A 3-cm midline incision was created in the anterior abdominal wall under sterile conditions. The cecum was removed from the abdomen and scraped with a dry gauze bandage until petechial hemorrhagic foci developed. Standard abrasion model was used.<sup>[13,14]</sup> The abdominal wall was closed with a continuous suture (3/0 vicryl) and the skin was closed using a 3/0 silk suture.

**Cordycepin group.** The procedures described above for the adhesion group were repeated and 10 mg/kg cordycepin (product number C 3394; Sigma-Aldrich Corp., St. Louis, MO, USA) single dose diluted with 0.9% sodium chloride to 1 mL was administered intraperitoneally.<sup>[15,16]</sup> After 15 days, all animals were humanely sacrificed via cardiac blood withdrawal under anesthesia. Next, a U-shaped incision was created in each abdomen. The abdominal walls were retracted upward to afford maximal field of vision. Adhesion was quantitatively assessed using the classification of Nair et al.<sup>[17]</sup> (Table 1).

The cecum and adherent abdominal wall were then sent for histopathological evaluation and measurement of tissue hydroxyproline level. All tissues were fixed in 10% (v/v) buffered formalin, embedded, processed, and sectioned using conventional laboratory methods. The tissue sections were stained with hematoxylin-eosin and examined under a light microscope.<sup>[11]</sup> The histopathological evaluations were performed by 2 pathologists blinded to the treatment using Zühlke method (Table 2).<sup>[18]</sup>

**Table 2.** Histological classification of adhesion according to Zühlke et al.<sup>[11]</sup>

Grade	
1	Loose connective tissue, cell-rich, old and new fibrin, fine reticulin fibers
2	Connective tissue with cells and capillaries, few collagen fibers
3	Connective tissue firmer, fewer cells, more vessels, few elastic and smooth muscle fibers
4	Old firm granulation tissue, cell-poor, serosal layers hardly distinguishable



**Figure 1.** (a) Single band of adhesion between the viscera or from one viscus to the abdominal wall. (b) Two bands, either between the viscera or from the viscera to the abdominal wall. (c) More than 2 bands between the viscera or from the viscera to the abdominal wall, or whole of intestines forming a mass, without being adherent to the abdominal wall. (d) The viscera directly adherent to the abdominal wall, regardless of number or extent of adhesive bands.

### Biochemical Evaluation

MDA level was measured spectrophotometrically as previously described.<sup>[12]</sup> A Shimadzu UV-1201 spectrophotometer (Shimadzu Corp., Kyoto, Japan) was used to measure color change upon reaction of thiobarbituric acid (TBA) with MDA. TBA concentration ( $\mu\text{moles/L}$ ) was calculated based on absorbance coefficient of the MDA-TBA complex. A dimethyl acetal-TBA complex served as a standard.<sup>[19]</sup>

Serum level of OH-p (catalog no: 201-11-0512; Shanghai Sunred Biological Technology Co., Shanghai, China) was measured using an enzyme-linked immunosorbent assay kit according to the manufacturer’s instructions. Briefly, samples were transferred to pre-coated wells, and then biotin-labeled antibodies were added. Initially, streptavidin-horseradish peroxidase was added to the wells. After incubation, the wells were washed to remove unbound antibodies. Next, chromogen solutions A and B were added and absorbance at 450 nm was measured.

All data were recorded as previously described. In short, tissue particles (0.12–0.25 g) were washed several times with physiological saline, dried on blotting paper, placed into Eppendorf tubes, and stored at  $-85^{\circ}\text{C}$ . After all sampling procedures had been concluded, tissue samples were removed from the freezer and homogenized using an automated tissue homogenizer. The MDA and OH-p levels in tissue particles were measured and normalized to the total protein level of homogenized tissue.

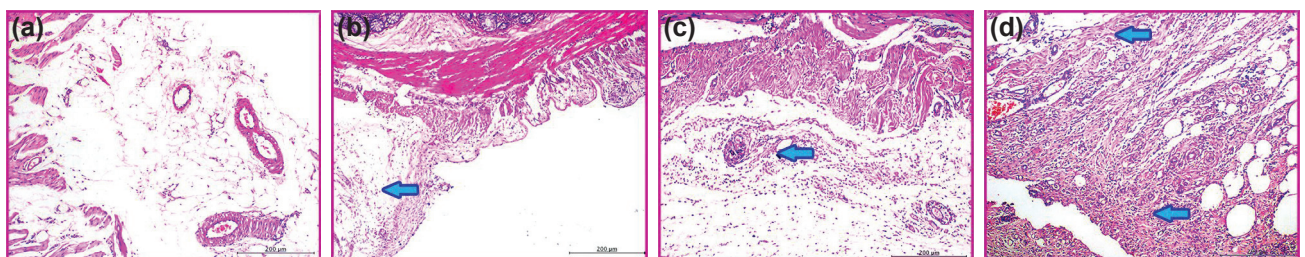
### Statistical Analysis

All data were analyzed using SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA). Kruskal-Wallis test was used to compare multiple independent samples. When a significant difference was evident, Mann-Whitney U test was employed for paired in-group comparisons. P value  $\leq 0.05$  was considered statistically significant.

### RESULTS

The levels of OH-p and MDA in blood and tissue were higher in the adhesion group than in the control group. Interestingly, the MDA level was significantly lower (blood:  $p < 0.05$ ; tissue:  $p < 0.01$ ) in the cordycepin group than in the adhesion group, whereas only tissue OH-p was significantly lower in the cordycepin group compared with the adhesion group ( $p < 0.05$ ).

Macroscopic analysis revealed significantly less adhesion in the cordycepin group than in the adhesion group in terms of grade assigned using the Nair system ( $p < 0.01$ ) (Fig. 1). Furthermore, significant histopathological improvement was also evident in the cordycepin group compared with the adhesion group in terms of Zühlke histopathological grading ( $p < 0.05$ ) (Figs. 2, 3). One rat in both the cordycepin group and the adhesion group died immediately after surgery, probably due to an anesthetic complication. The detailed findings are provided in Table 3.



**Figure 2.** (a) The control group was nonspecific. Hematoxylin-eosin (HE);  $\times 100$ . (b) Loose connective tissue (arrow), rich in cells, rare vascular formations. HE;  $\times 100$ . (c) Loose connective tissue, including cells and capillaries, rare collagen fibers (arrow). HE;  $\times 100$ . (d) Dense connective tissue, decreased inflammatory cells, significantly increased vascular formations (thin arrow), rare smooth muscle fibers. HE;  $\times 100$ .

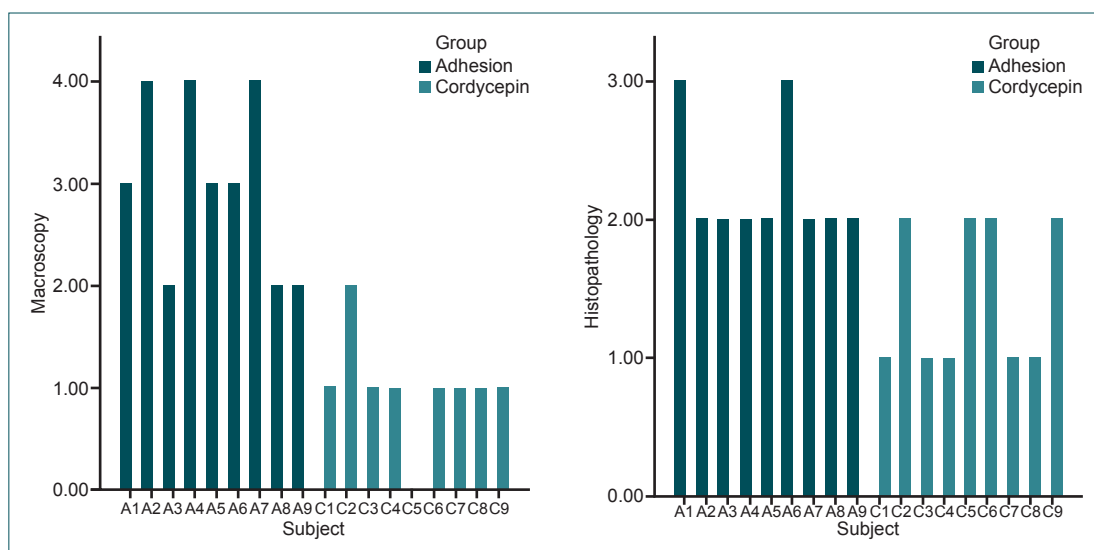


Figure 3. Macroscopic and histopathological evaluation results of rats in adhesion and cordycepin group.

## DISCUSSION

Adhesion is the most common complication to develop after an intra-abdominal procedure.<sup>[5]</sup> Adhesion increases vascular permeability and triggers fibrin release.<sup>[20]</sup> Adhesion formation is stimulated by plasminogen and increased level of inflammatory cytokines in postoperative tissue. Inadequate fibrinolytic capacity of tissue facilitates adhesion formation.<sup>[3]</sup> Inflammation develops early after surgery, and fibroblasts appear later. Then, collagen synthesis increases. Although several promising methods are used to prevent adhesion, no standard treatment is yet available.<sup>[2]</sup> Therefore, several different agents remain under evaluation.<sup>[20]</sup> Cordycepin was first isolated in 1950. It was made in vivo, and later in in vitro studies.<sup>[21]</sup> It is known to suppress inflammation, reduce inflammatory cytokine level, and inhibit fibrin release.<sup>[8,9]</sup> Recently, use of cordycepin has been examined in experimental studies of diabetes mellitus, osteoporosis, and hepatocellular carcinoma, but not adhesion.<sup>[22–26]</sup> Cordycepin metabolites appear in the blood and liver 2 hours after it is administered. To overcome the problem of rapid elimination, a large dose

must be administered.<sup>[26,27]</sup> Experimental studies have used intravenous cordycepin doses of 5, 10, 20 and 40 mg/kg/day.<sup>[15,16]</sup> We chose a single dose of 10 mg/kg, but further studies on dosage are required.

Various experimental models of adhesion have been reported, including abrasion, local peritoneal excision, ischemic injury, placement of a foreign body in the peritoneal cavity, thermal injury, deliberate bacterial contamination, and others.<sup>[28–33]</sup> In this study, the standard abrasion model was adopted, since it simulates mechanical trauma caused by laparotomy, which is the most common cause of adhesion. Adhesion was created in the standard manner of abrasion until petechial hemorrhage occurred.

To assess the development of adhesion, MDA and OH-p levels, known biochemical markers of adhesion, were measured.<sup>[10–12]</sup> The OH-p level reflects the level of collagen, and is recognized to be a good indicator of wound healing. Ozoğul et al.<sup>[10]</sup> tested aprotinin in an adhesion model and found that

Table 3. Detailed analysis of all groups

	Group 1 (Control, n=10)	Group 2 (Adhesion, n=9)	Group 3 (Cordycepin, n=9)	p(2,3)
	Mean±SD, Range (Min-Max)	Mean±SD, Range (Min-Max)	Mean±SD Range (Min-Max)	
Blood OH-p (ng/mL)	848±218 (616–1261)	928±164 (630–1092)	853±131 (667–1085)	>0.05
Blood MDA (µM)	5.6±4 (4–18)	18±8 (8–28)	7.2±5 (4–20)	<0.05
Tissue OH-p (Ng/g protein)	629±375 (109–1207)	1141±485 (351–1955)	665±233 (250–972)	<0.05
Tissue MDA (µM/g protein)	14±7 (7–27)	23±3 (19–27)	18±4 (9–21)	<0.01
Macroscopy	0	3±0.7 (2–4)	1±0.6 (0–2)	<0.01
Histopathology	0	2.4±0.4 (2–3)	1.4±0.5 (1–2)	<0.05

MDA: Malondialdehyde; OH-p: Hydroxyproline; SD: Standard deviation; Min: Minimum; Max: Maximum.

the OH-p level fell compared with the control group. Baykal et al.<sup>[11]</sup> tested polyglycolic acid in an adhesion model and found a significant association between adhesional grade and OH-p level. Okur et al.<sup>[12]</sup> tested an extract of Ecballium elaterium in an adhesion model and found that the OH-p level was higher in the adhesion group. In this study, the OH-p level in tissue and blood decreased in the cordycepin group compared with the adhesion group, but the difference was significant only in tissue ( $p < 0.05$ ). We attributed the increase in OH-p level observed in the adhesion group to collagen accumulation. OH-p is an essential amino acid found in all types of collagen in the body. Ninety percent of OH-p is metabolized in the liver and 10% is metabolized in the kidneys. The OH-p level in the blood changes for various reasons.<sup>[34]</sup> In this study, the tissue OH-p level was significantly lower in the cordycepin group compared with the adhesion group, while the decline seen in the blood was not significant, perhaps because OH-p in the blood takes 15 days to be metabolized.

MDA, an end-product of lipid peroxidation, is a marker of oxidative stress. Tissue damage can elevate MDA level.<sup>[35]</sup> Physiological changes associated with the development of adhesion can increase oxidative stress. Ten Raa et al.<sup>[36]</sup> found a positive correlation between severity of adhesion and oxidative grade. Furthermore, Ara et al.<sup>[37]</sup> demonstrated that MDA level was elevated in a peritoneal adhesion group and reduced in a test group. Similarly, Özler et al.<sup>[38]</sup> found that MDA level decreased in a treatment group but increased in an untreated adhesion group. We found that MDA levels in both blood and tissue were significantly lower in the cordycepin group than in the adhesion group ( $p < 0.05$ ,  $p < 0.01$ , respectively).

Various scoring systems are used to macroscopically evaluate adhesion.<sup>[17]</sup> We found that the cordycepin group had significantly less adhesion formation than the adhesion group ( $p < 0.01$ ). Histopathological evaluation revealed a significant decrease in the number of collagen fibers in the cordycepin group compared to the adhesion group ( $p < 0.05$ ).

This study had several limitations, including the dosage of cordycepin, time interval, administration method, and bio-availability. Therefore, further studies should be conducted in small or large animal models before proceeding to clinical studies in humans.

## Conclusions

We found that cordycepin effectively reduced adhesion in a rat abrasion model. Thus, this agent may be valuable to prevent postoperative adhesion. However, further studies on its clinical indications, safety, and dosage are required.

## Ethical approval

The article was approved by the animal ethics committee of the Medical Faculty of Dicle University.

## Sources of support

This study was supported by the Scientific Research and Project Coordinator (DUBAP, I4-TF-44) of Dicle University.

## Laboratory

Research was performed at the experimental animal laboratory, Dicle University, Diyarbakır, Turkey.

## Conflict of interest

None declared.

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## DENEYSSEL ÇALIŞMA - ÖZET

### Cordycepin'in sıçan modelinde karınıçi adezyonun ameliyat sonrası önleyici etkisi: Deneysel çalışma

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**AMAÇ:** Cordycepin'in sıçan modelinde adezyonu önleyip önlemediğini araştırmayı amaçladık.

**GEREÇ VE YÖNTEM:** Her biri 10'ar adet olmak üzere sıçanlar rastgele üç gruba ayrıldı. Kontrol grubu: Laparotomi ile adezyonun olmadığını doğruladık. Adezyon grubu: Çekum abdomenden çıkarıldı ve kuru spanç ile peteşial hemoraji odakları oluşana kadar scraping yapıldı. Cordycepin grubu: Aynı cerrahi prosedür adezyon grubunda tanımlandığı gibi yapıldı, ancak 10 mg/kg cordycepin intraperitoneal olarak uygulandı. On beş gün sonra sıçanlar anestezisi altında kardiyak kan çekme yoluyla sakrifiye edildi. Daha sonra sıçanlar morfolojik ve histopatolojik olarak analiz edildi ve hidroxyproline (OH-p) ve malondialdehyde (MDA) düzeyleri ölçüldü.

**BULGULAR:** Makroskobik olarak adezyonun Cordycepin grubunda adezyon grubuna göre anlamlı derecede azaldığı görüldü ( $p<0.01$ ). Bununla birlikte histopatolojik düzelmede Cordycepin grubunda adezyon grubuna göre anlamlı derecede düzelleme görüldü ( $p<0.05$ ). Kan ve doku OH-p ve MDA düzeyleri kontrol grubuna göre adezyon grubunda daha yüksekti. Bu değerler Cordycepin grubunda adezyon grubuna göre daha düşüktü. Malondialdehit seviyesi Cordycepin grubunda adezyon grubuna göre istatistiksel olarak anlamlı derecede düşüktü (kan  $p<0.05$ , doku  $p<0.01$ ). Buna karşılık yalnızca doku OH-p düzeyi adezyon grubuna göre Cordycepin grubunda istatistiksel olarak anlamlı derecede düşüktü ( $p<0.05$ ). Adezyon ve Cordycepin grubunda birer sıçan ameliyat sonrası kaybedildi.

**TARTIŞMA:** Cordycepin sıçan abrazyon modelinde adezyonu etkili olarak azalttığını tespit ettik. Bu yüzden bu ajan ameliyat sonrası adezyonu önlemek için değerli olabilir.

**Anahtar sözcükler:** Abdominal; adezyon; Cordycepin; çalışma; deneysel; sıçan.

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