EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 7
72-77
Year: 2019

# EVALUATION OF ACUTE PANCREATITIS AND CANNABIS ABUSE ASSOCIATION AND OUTCOMES: A CROSS SECTIONAL STUDY USING LARGE INPATIENT DATA

**Muhammad Talal Sarmini MD*[1], Mohammad Maysara Asfari MD[1,2*], Yasser Al-Khadra MD[1], Mohammad Alomari MD[1], Sara Kousha PharmD[2], Arthur J McCullough MD[3,4]**

[1]Department of Internal Medicine, Cleveland Clinic, Cleveland Ohio, United States.
[2]Department of Gastroenterology, Medical College of Georgia/Augusta University, Augusta, Georgia.
[3]Department of Inflammation and Immunity Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Cleveland Ohio, United States.
[4]Department of Gastroenterology, Cleveland Clinic, Cleveland Ohio, United States.
*(both authors contributed equally to the study).

***Corresponding Author: Dr. Muhammad Talal Sarmini MD**
Department of Internal Medicine, Cleveland Clinic, Cleveland Ohio, United States.

**Article Received on 07/05/2019** **Article Revised on 28/05/2019** **Article Accepted on 19/06/2019**

## ABSTRACT
Cannabis is the most commonly used illicit drug in the United States and worldwide. The association between cannabis abuse (CA) and acute pancreatitis (AP) is still controversial. We conducted this study to clarify this association. Methods: We queried the National Inpatient Sample (NIS) database between 2002 and 2014 and identified patients who were diagnosed with CA. The association between CA and AP was assessed using multivariate logistic regression. We used propensity score matching to assess outcomes of patients with AP and CA compared to AP patients without CA. Outcomes of interest included: mortality, acute kidney injury (AKI), acute respiratory failure (ARF), hypocalcemia and length of stay (LOS). Results: Out of 101,020,258 total patients, 836,960 (0.828%) were diagnosed with CA. CA patients were younger (34.7 vs 48.1), less likely to be female (39.2% vs 58.6%) and more likely to be African American (30.5% vs 14.1%) ($P < 0.001$). They also had a higher rate of smoking and alcohol use. CA group had lower rate of AP (OR: 0.74, 95% CI 0.73-0.76, $P < 0.001$). Using propensity score matching, we identified two groups with AP with and without CA. CA group had lower mortality (0.4% vs 1.2%), less ARF (1.7% vs 4.8%), less AKI (7% vs 9.4%) and shorter LOS (4.29 vs 5.92), (P 0.01 < all). Conclusion: Patients with CA had lower rate of AP and had better inpatient morbidity and mortality. This finding is likely due to the anti-inflammatory effects of cannabinoids. Additional studies are needed to clarify this association.

**KEYWORDS:** Acute pancreatitis, marijuana abuse, cannabinoids, anti-inflammatory.

## INTRODUCTION
Acute pancreatitis (AP) is a serious inflammatory disorder of the pancreas and is one of the most common gastrointestinal disorders that require hospital admission worldwide and in the United Sates (US) with average of 270,000 hospital admissions in the US annualy.[1,2] The inflammation in the pancreas may resolve spontaneously or lead to necrosis in the pancreas or the surrounding fat tissues.[2,3] Furthermore, AP can lead to a systemic inflammatory process which might affect one or more organs.[4] Alcohol abuse and biliary stones are considered the leading factors for AP.[5] Additionally, drugs, lipoprotein lipase deficiency, hypertriglyceridemia, hypercalcemia, pancreas divisum, endoscopic retrograde cholangiopancreatography (ERCP) and some viral infections are less frequent causes of AP.[3,5]

Cannabis is the most common illicit drug in the US and it is more common among young people[6] and has a long history as an affective analgesic.[7] Due to the concern of its psychotropic effects, cannabis was removed from the medical use in the United States in 1941.[8] In the last two decades, the medical and recreational use of cannabis has increased, and there has been a significant interest to study the different aspects of cannabis and investigate its safety and efficacy in treating medical conditions.[9] Cannabinoids use has been studied in palliative care for cancer patients given its antiemetic and analgesic properties.[7] It has also been studied in epilepsy, multiple sclerosis, colitis and multiple other disorders.[10,11] Although cannabinoids have a known strong anti-inflammatory effect, the relation between AP and cannabis abuse (CA) is still controversial in the literature.

Therefore, we conducted our study to investigate the association between AP and CA using one of the largest inpatient data sets in the United States. We also compared the outcomes of AP in patients who used cannabis versus those who did not.

## METHOD

***Patient population:*** Using the National Inpatient Sample (NIS) data from 2002 to 2014, a cross-sectional study was performed. The NIS is the largest all-payer inpatient database in the USA and contains a sample of over than eight million inpatient stays each year, which represent an approximately 20% sample of discharges from all community hospitals participating in the Healthcare Cost and Utilization Project (HCUP). It excludes rehabilitation and long-term acute care hospitals. Each record of the NIS data includes primary and secondary diagnoses up to 25 and primary and secondary procedures up to 15. It also contains the patient demographics, discharge status, length of stay, disease severity, and comorbidity measures.

**Study population, inclusion, and exclusion criteria:** All adult patients (≥18 years old) were included from the NIS years 2002-2014. Using International Classification of Diseases 9th version (ICD-9) code, we identified all records with CA and AP using the following codes: (304.30, 304.31, 304.32) and (577.0) respectively. Patient demographics and comorbidities were identified using the Clinical Classification Software codes provided by the HCUP, Elixhauser comorbidities and appropriate ICD-9 codes. Supplementary table shows comorbidities ICD-9 codes and Elixhauser comorbidities used for CA, AP and other comorbidities of interest as well as the outcomes. Since NIS is a publicly available database, Institutional board review approval was not required.

***Outcomes:*** We evaluated the association between CA and AP by comparing patients with CA to those who had no CA. Furthermore, we compared the outcomes between AP patients who had CA versus the AP patients without CA. The primary outcome was in-hospital mortality. Secondary outcomes included: acute respiratory failure (ARF), acute kidney injury (AKI), hypocalcemia and length of stay (LOS).

## STATISTICAL ANALYSIS

The data were expressed as mean values ± standard deviation, and frequencies were reported in percentages. Independent t-tests were used for the comparison of continuous variables measurements, while chi-square test for categorical variables. Multiple logistic regression was used to assess the association between AP and CA. The regression model was adjusted for: patient demographics, other relevant comorbidities (alcohol abuse, dyslipidemia, biliary disease, hypercalcemia and smoking), hospital characteristics, patients' insurance and socioeconomic status. Propensity score-matched analysis was computed using logistic regression. Nearest number matching without replacement with a 1:1 ratio method was used to compute propensity matching. The propensity score model included patient's demographics, other relevant comorbidities (alcohol abuse, dyslipidemia, biliary disease, hypercalcemia and smoking), hospital characteristics, patients' insurance and socioeconomic status. Individuals in both groups had comparable baseline characteristics (including age, race and gender) (P> 0.05 to all). P-value less than 0.05 was considered statistically significant. SPSS version 25 software (IBM Corp, Armonk, NY) was used for all statistical analyses.

## RESULTS

Our nationwide cohort evaluated total of 101,020,258 hospitalizations of which 836,960 (0.828%) had CA. As shown in table 1, patients with CA were younger (34.7 vs 48.1), less likely to be females (39.2% vs 58.6%), and more likely to be African American (30.5% vs 14.2%) compared to patients without CA (P < 0.001 for all). Patients in the CA group had higher prevalence of alcohol abuse (27.5% vs 3.2%) and smoking (45.1% vs 9.3%) compared to the non-CA group. However, patients in the CA group had lower prevalence of dyslipidemia (7.8% vs 17.7%), biliary disease (1.2% vs 2.3%) and hypercalcemia (0.2% vs 0.3%) (P <0.001 for all) compared to the control group.

Using multivariate logistic regression was conducted for the association between AP and CA. As shown in Figure 2, after adjusting for patient's demographics, hospital characteristics, patients' insurance and socioeconomic status and other relevant comorbidities (biliary disease, hypercalcemia, alcohol abuse and smoking), patients with CA had lower odds of AP compared to the non-CA group (Odds Ratio [OR], 0.74, 95% confidence interval [CI], 0.73-076, P < 0.001)

**Outcomes:** To assess outcomes of CA patients, propensity score matching analysis was used for AP patients with and without CA. We identified 12,137 AP patients with CA and compared with 12,137 AP patients without CA. As shown in Figure 3, interestingly, AP patients with CA had significantly lower in-hospital mortality (0.4% vs 1.2%, P <0.01) compared to those who had AP without CA. In addition, AP patients with CA had less AKI (7% vs 9.1%) and less ARF (1.7% vs 4.8%), (P<0.01 for all). Further, Patient with AP and CA had statistically significant shorter LOS (4.29 ± 4.11 vs 5.92 ± 8.77, P<0.01) compared to the control group. Although AP patients with CA had also less rates of hypocalcemia (1.5% vs 1.7%) compared to the AP patients without CA, but it was not statistically significant (P > 0.1).

**Table 1: Baseline Characteristics of Cannabis Abuse and Non-Cannabis Abuse Patients.**

| Variable | CA | Non-CA | P-Value |
|---|---|---|---|
| Age (mean±SD) | 34.77 ± 13.42 | 48.10 ± 27.98 | <0.001 |
| Sex | | | |
| Female % | 39.2 | 58.6 | <0.001 |
| Race % | | | <0.001 |
| White | 55.0 | 66.3 | |
| Black | 30.5 | 14.2 | |
| Hispanic | 9.7 | 12.8 | |
| Asian or Pacific Islander | 0.8 | 2.7 | |
| Native American | 1.0 | 0.6 | |
| Other | 3.0 | 3.4 | |
| Primary expected payer % | | | <0.001 |
| Medicare | 13.8 | 37.9 | |
| Medicaid | 36.9 | 19.7 | |
| Private Insurance | 23.1 | 33.9 | |
| Self-Pay | 18.2 | 4.9 | |
| No Charge | 1.8 | 0.5 | |
| Other | 6.2 | 3.2 | |
| Median Household Income % | | | <0.001 |
| 0 to 25 percentiles | 26.9 | 27.1 | |
| 26 to 50 percentiles | 25.3 | 25.6 | |
| 51 to 75 percentiles | 23.8 | 24.0 | |
| 76 to 100 percentiles | 23.2 | 23.3 | |
| Bed Size % | | | <0.001 |
| Small | 11.2 | 13.3 | |
| Medium | 25.2 | 25.4 | |
| Large | 63.6 | 61.2 | |
| Location/Teaching Status % | | | <0.001 |
| Rural | 9.3 | 12.4 | |
| Urban Nonteaching | 35.5 | 40.6 | |
| Urban Teaching | 55.2 | 47.0 | |
| Hospital Region % | | | <0.001 |
| Northeast | 19.9 | 19.0 | |
| Midwest | 26.4 | 22.4 | |
| South | 34.6 | 39.0 | |
| West | 19.1 | 19.6 | |
| Alcohol abuse % | 37.5 | 3.2 | <0.001 |
| Biliary disease % | 1.2 | 2.3 | <0.001 |
| Dyslipidemia % | 7.8 | 27.7 | <0.001 |
| Smoking % | 45.1 | 9.3 | <0.001 |
| Hypercalcemia % | 0.2 | 0.3 | <0.001 |
| | | | |
| Abbreviations: CA: cannabis abuse; SD: standard deviation | | | |

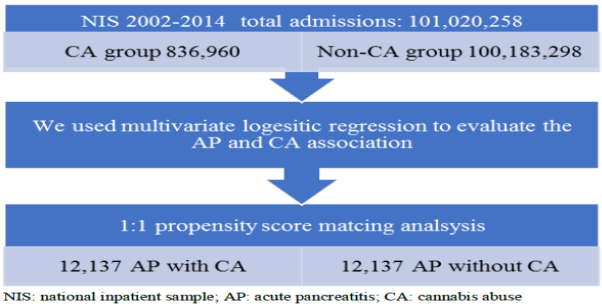



**Figure. 1. Identification of study population and design using the National Inpatient Sampling database.**

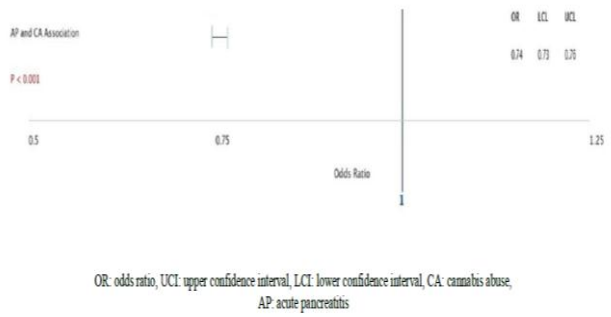
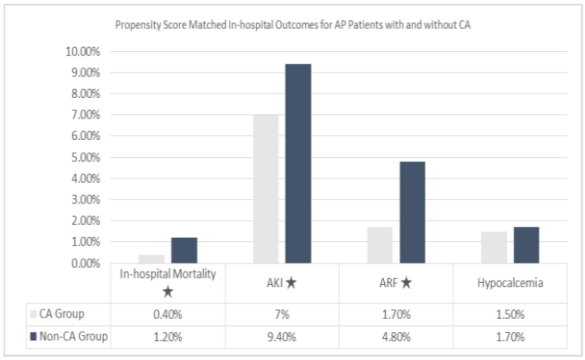



**Figure. 2. The Association between cannabis abuse and acute pancreatitis.**




CA: cannabis abuse, AP: acute pancreatitis, AKI: acute kidney injury, ARF: acute respiratory failure
★ P<0.01

**Figure. 3. Propensity score matched outcomes for acute pancreatitis patients with and without cannabis abuse**.

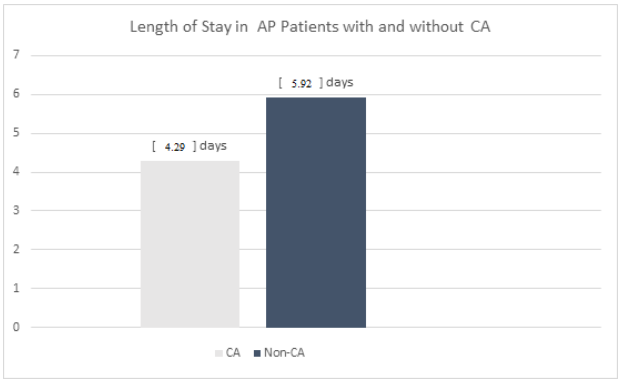



**Figure. 4. Length of stay comparison in acute pancreatitis with and without cannabis abuse.**

## DISCUSSION

Using a large national database, we found that patients with CA were less likely to develop AP regardless of the etiology. Furthermore, patients with CA who developed AP had lower in-hospital mortality, and less complications such as ARF and AKI compared to AP patients without CA. In addition, patient with AP and CA had shorter LOS. There was no statistical difference in the rate of hypocalcemia incidence between the two groups, though it was less in the CA group. To our knowledge, this is the largest study that assessed the association between AP and CA. It is also the first study to evaluate the outcomes of AP patients with CA compared to those without CA.

The mechanism of AP, regardless of the etiology, is believed to be premature activation of the intracellular digestive enzymes within the acinar cells which leads to auto-digestion of the local tissues.[12] The activated pancreatic enzymes are potent stimulators of macrophages which produce interleukins and proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), and promotes the inflammation cascade.[13] The local inflammation in the pancreatic tissues can affect the local circulation and oxygenation which in turn cause necrosis and subsequently possible infection.[14] After the initial injury to the local tissues, circulating inflammatory cells are attracted to the pancreas via adhesion molecules which may lead to severe AP.[15] In addition, the acinar cells are thought to secrete cytokines and chemokines which promotes the local inflammation and triggers a cascade of factors that can lead to severe inflammatory response and can affect distant organs.[14,15] Despite the amount of knowledge present regarding the pathology of AP, there is no known treatment which can alter the inflammatory cascade and our current approach is supportive in major.[12]

By definition a cannabinoid compound is a molecule that can affect the cannabinoid receptors and it can be either endogenous or exogenous in origin.[16] There are three types of cannabinoid compounds; phytocannabinoids which are naturally found in the cannabis plant, endocannabinoids which are metabolites of arachidonic acid and synthetics cannabinoids.[17,18] The cannabis plant contains more than 60 types of cannabinoid compounds, but the main compound is the delta-9-tetrahydrocannabinol (THC),which is mainly responsible for the psychoactive effects.[19,20] The second most available compound is cannabidiol (CBD) and it has minimal psychoactive effects.[19] Cannabinoid receptors are divided into two groups, CB1 and CB2.[21] CB1 receptors are mainly expressed in the brain and various peripheral tissues whereas CB2 receptors are expressed mostly in the immune and hematopoietic systems.[22] CB1 and CB2 are subtypes of G proteins and are connected with complex signaling systems called the endocannabinoid system.[21,22] The endocannabinoid system is not just the cannabinoids receptors and the endocannabinoids but also includes the enzymes which regulate the synthesis and degradation of these ligands that comprise a complicated system.[17]

CB1 activation will mainly affect the brain, and it is thought to inhibit excessive neuronal excitation and suppress many neural transmitters.[21] CB2 activation, on the other hand, mainly affects the immune system controlling cytokine production and immune cell migration.[23] The fact that CB2 receptors are expressed mainly in the immune system explains the potent anti-inflammatory role for cannabinoids which can explain the findings of our study. Cannabinoids are thought to affect the immune system in multiple pathways. It causes induction of apoptosis, inhibits cell proliferation, suppresses of cytokine production and induces T-regulatory cells.[24]

There are limited and contradictory data in the literature regarding the role of cannabinoids in AP. Li et al[25] found that CB1 and CB2 agonists improved pathological changes associated with AP in mice as they decreased the Interleukin 6 (IL-6), tumor necrosis factor (TNF) levels and the myeloperoxidase (MPO) activity. Another similar study by Bergmann et al[26] demonstrated that synthetic CB1 and CB2 agonists resolved abdominal pain associated with AP in mice and decreased inflammation and tissue pathology. Interestingly, another study found that synthetic CB1 and CB2 agonist

improved pancreatic edema, inflammation and pancreatic morphology when given before AP induction in rats, but it worsened the inflammation and edema when injected after inducing AP.[27] The dual effect of CB1 and CB2 agonist suggested that the cannabinoid receptor system effect in the body might differ according to local inflammation. A study by Michler et al[28] showed that CB1 and CB2 are both expressed on pancreatic acini and during AP, CB2 expression is up regulated especially on apoptotic cells. It was noted in this study also that selective CB2 activation decreased inflammation in AP by decreasing intra-acinar proinflammatory factors which downgraded the inflammation cascade. To the contrary, one study showed that selective CB1 activation worsened the induced AP in rats[29] while another one showed that using selective CB1 antagonist improved inflammation as well as survival in rats with induced AP.[30]

Long term CA has been linked to side effects including erectile dysfunction, infertility, visual and auditory disorders.[31] However, it is unclear whether CA is associated with acute pancreatitis. Grant el al[32] reported one of the first case reports linking AP to CA in 2004. These authors proposed that exogenous cannabinoids might interfere with pancreatic secretions given the distribution of cannabinoids receptors in the pancreas, or might affect the smooth muscles of the pancreatic ducts and sphincters. Since then, multiple case reports attempted to link AP to CA, but no clear mechanism in human or animal studies was found to explain this relation.[33–35] Our findings propose a protective effect of cannabinoids for AP development explained by its anti-inflammatory features.

Our study had multiple strengths. The data were obtained from one of the largest publicly available data sets that represents a large segment of the United States population. It is so far, to the best of our knowledge, the first observational and epidemiological study in humans that evaluated the outcomes of AP in patients with cannabis abuse.

It is worth noting that our study is a retrospective observational study, which poses a possible selection bias and unmeasured confounding factors. Further, data regarding the AP severity and the length and quantity of cannabis use could not obtained due to the nature of the data. In addition, exclusion of academic hospitals by the database could potentially exclude patients with more complex disease. Despite all these limitations, our findings highlight the importance of the need for further studies to better understand the role of cannabinoids and the endocannabinoid system in AP and if it can be used to alter the morbidity and mortality in humans.

In conclusion, the endocannabinoid system appears to play an important role in AP which is still not fully understood. Our study adds additional data to aid in the discussion of the medical use of cannabinoids and strengthens the need for additional clinical studies to investigate this association between AP and CA and assess whether cannabinoids, especially selective CB2 agonists, can alter the course and improve the outcomes in AP.

**ACKNOWLEDGEMENTS**

I would like to thank all authors their contribution to this article. There was no funding or grant provided for this article.

**REFERENCES**

1. Peery AF, Dellon ES, Lund J, et al. (Burden of gastrointestinal disease in the United States 2012 update). Gastroenterology, 2012; 143(5): 1179–1187.e3.
2. Lankisch PG, Apte M, Banks PA. (Acute pancreatitis. Lancet). 2015;386(9988):85–96.
3. Johnson CD, Besselink MG, Carter R. (Acute pancreatitis). Bmj., 2014; 349(aug12 4): g4859–g4859.
4. Zerem E. (Treatment of severe acute pancreatitis and its complications). World J Gastroenterol, 2014; 20(38): 13879–13892.
5. Spanier BWM. (Epidemiology , aetiology and outcome of acute and chronic pancreatitis : An update), 2008; 22(1): 45–63.
6. Agosti V, Nunes E, Levin F. (RATES OF PSYCHIATRIC COMORBIDITY AMONG U . S . RESIDENTS WITH LIFETIME CANNABIS DEPENDENCE), 2002; 28(4): 643–652.
7. Jensen B, Chen J, Furnish T, Wallace M, Wallace M. (Medical Marijuana and Chronic Pain : a Review of Basic Science and Clinical Evidence), 2015: 1–9. doi:10.1007/s11916-015-0524-x.
8. Russo EB. Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential, 2013: 478 pages.
9. Kong S, Application F, Data P. ( 12 ) United States Patent, 2011; 2(12): 12–15.
10. Marzo V Di, Bifulco M, Petrocellis L De, Melillo D. (The endocannabinoid system and its therapeutic exploitation). 2004; 3(September).
11. Couch DG, Maudslay H, Doleman B, Lund JN, O'Sullivan SE. (The Use of Cannabinoids in Colitis: A Systematic Review and Meta-Analysis). Inflamm Bowel Dis., 2018; 24(4): 680–697.
12. Kambhampati S, Park W, Habtezion A. (Pharmacologic therapy for acute pancreatitis). World J Gastroenterol, 2014; 20(45): 16868–16880.
13. Raraty MGT, Connor S, Criddle DN, Sutton R, Neoptolemos JP. (Acute Pancreatitis and Organ Failure : Pathophysiology, Natural History , and Management Strategies), 2004.
14. Pandol SJ, Saluja AK, Imrie CW, Banks PA. (Acute Pancreatitis : Bench to the Bedside), 2007: 1127–1151..
15. Hospital D, Road D. (Cytokine storm in acute pancreatitis), 2002: 401–410.
16. Brown AJ. (Novel cannabinoid receptors. Br J

Pharmacol), 2007; 152(5): 567–575.
17. Marzo V Di, Piscitelli F. (The Endocannabinoid System and its Modulation by Phytocannabinoids), 2015: 692–698.
18. Fride E. (HU-308 : A specific agonist for CB 2 , a peripheral cannabinoid receptor), 1999: 2–7.
19. Mechoulam R. (Plant cannabinoids : a neglected pharmacological treasure trove HO OH), 2005: 913–915.
20. Morrison PD, Zois V, Mckeown DA, et al. (The acute effects of synthetic intravenous D 9 - tetrahydrocannabinol on psychosis, mood and cognitive functioning), 2009: 1607–1616. doi:10.1017/S0033291709005522.
21. Pertwee RG. (Pharmacology of Cannabinoid CB1 and CB2 Receptors), 1997; 74(2): 129–180.
22. Aminski NOEK. (Cannabinoid Receptors CB1 and CB2 : A Characterization of Expression and Adenylate Cyclase Modulation within the Immune System 1), 1997; 287(142): 278–287.
23. Huffman JW, Mackie K, Pacher P, Rajesh M, Mukhopadhyay P, Hasko G. (CB 2 cannabinoid receptor agonists attenuate TNF- a -induced human vascular smooth muscle cell proliferation and migration), 2008; (November 2007): 347–357.
24. Nagarkatti P, Rieder SA, Hegde VL. (Cannabinoids as novel anti-inflammatory drugs). 1333–1349.
25. Li K, Feng J, Li Y, Yuece B, Lin ÞX. (Anti-Inflammatory Role of Cannabidiol and O-1602 in Cerulein-Induced Acute Pancreatitis in Mice), 2013; 42(1): 123–129.
26. Bergmann F, Agarwal N, Su YUN, et al. NIH Public Access, 2008; 132(5): 1968–1978.
27. Petrella C, Agostini S, Casolini P, et al. (Cannabinoid agonist WIN55 , 212 in vitro inhibits protein-1 ( MCP-1 ) release by rat pancreatic acini and in vivo induces dual effects on the course of acute pancreatitis), 2010; 6: 1248–1257.
28. Michler T, Storr M, Kramer J, et al. (Activation of cannabinoid receptor 2 reduces inflammation in acute experimental pancreatitis via intra-acinar activation of p38 and MK2-dependent mechanisms), 2018: 181–192.
29. Ceranowicz P. (Cannabinoids in acute gastric damage and pancreatitis). 2006;(December).
30. Exp TJ. (The Cannabinoid 1 Receptor Antagonist , AM251 , Prolongs the Survival of Rats with Severe Acute Pancreatitis), 2005: 99–107.
31. Weiss SRB, Ph D. (Adverse Health Effects of Marijuana Use). 2014.
32. Grant P, Gandhi P. (A case of cannabis-induced pancreatitis). JOP, 2004; 5(1): 41–43.
33. Barkin JA, Nemeth Z, Saluja AK, Barkin JS. (Cannabis-Induced Acute Pancreatitis A Systematic Review), 2017; 46(8): 1035–1038.
34. Herrero LN, Chaucer B, Singh S, Deshpande V, Patel SH. (Acute Pancreatitis Secondary to Marijuana Consumption), 2016; 17(3): 322–323.
35. Kayar Y, Eroılu H, Pamukçu Ö, Çetin H, Koçaş O, Atçi M. (Cannabinoid-induced acute pancreatitis). Turkish J Gastroenterol, 2014; 25(3): 335–336.