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# PRECLINICAL STUDY OF *CELTIS OCCIDENTALIS* LEAVES EXTRACT ON PANCREATIC INJURY AND INFLAMMATION AGAINST ACETAMINOPHEN-INDUCED ACUTE PANCREATITIS IN RATS

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## ABSTRACT

Acetaminophen is used as a painkiller and to alleviate fever. With or without a prescription, overdoses of acetaminophen lead to acute inflammation of the pancreas, cause degeneration of pancreatic tissues, and elevate the blood pancreatic enzyme level. This research aims to investigate the protective and anti-inflammatory potential of the methanolic extract of *Celtis occidentalis* leaves against acetaminophen-instigated acute pancreatitis. Thirty adult male Swiss albino rats were divided into five groups; each group has six individuals ($n = 6$). Group I is considered a control group without any treatment. Group II was given a single dose of acetaminophen (1000 mg/kg/b.w.) for fourteen days consecutively. Group III was given a dose of acetaminophen (1000 mg/kg/b.w.) before Imipenem (500 mg/kg/b.w.) administration. Groups IV and V were also given a single dose of acetaminophen (1000 mg/kg/b.w.) before the administration of methanolic extracts of low dose (150 mg/kg/b.w.) and high dose (300 mg/kg/b.w.). Results clearly indicate that the pancreatic enzymes (serum amylase and serum lipase) significantly increased in the acetaminophen treated group, which shows the induction of acute pancreatitis. Animals treated with methanolic extracts of low dose (150 mg/kg) and high dose (300 mg/kg) significantly ($P<0.01$ and $P<0.001$) reduced the serum pancreatic enzyme level. Histopathological assessment of the pancreatic tissues of different treatment groups also revealed that acetaminophen severely altered the pancreas morphology, but treatment with methanolic extract (150 mg/kg and 300 mg/kg) vigorously recovered the alterations as compared to the Imipenem (500 mg/kg) treated group. It should be concluded that the methanolic extract of *C. occidentalis* has bioactive compounds with strong antioxidant and anti-inflammatory properties that potently regenerate histological alterations induced by acetaminophen in the pancreas.

## 1. INTRODUCTION

The pancreas is a vital organ of vertebrate animals and is associated with the digestive and endocrine systems. In the human body, it is located back to the stomach in the abdominal cavity and functions as a gland both endocrine and exocrine, used is combine term as heterocrine or mixed gland. The major portion of the pancreas is the exocrine region which is made up of acinar cells (99%) and produces exocrine secretions or digestive enzymes (proteases, lipases, amylases, etc.) and sodium bicarbonate ($NaHCO_3$) (Leung and Leung 2010). These exocrine secretions are important in the digestion, metabolism and assimilation of foodstuffs that we're daily consuming. The endocrine part of the pancreas is made up of different types of secretory cells (α-cells, β-cells, delta/Ɗ-cells, and pancreatic polypeptide/PP-cells, etc.) which respectively secrete glucagon, insulin, somatostatin, and pancreatic polypeptides. All these endocrine secretions are responsible for glucose metabolism and regulate the storage and release of glucose. For secretions of the aforementioned exocrine and

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endocrine chemicals, regulatory machinery is involved that releases neurocrine, endocrine, paracrine, and also some intracrine that regulates the secretion of all pancreatic juice and pancreatic hormones. If alterations occur in the regulatory pathway by activating or inhibiting any mechanism, it leads to considerable changes or diseases (Leung and Leung 2010).

Inflammation is the most common illness in the pancreas also termed pancreatitis. The leading causes of pancreatitis include chronic alcohol abuse, stones in the gall bladder and, to some extent, the prescribed drug usage. Due to the mentioned leading causes, over secretion of digestive enzymes occurs, but still in the pancreas due to blockage in the ducts and ductules and a lack of regulatory mechanisms, irritations caused in pancreatic cells, and finally inflammation (Uchendu, Agu et al. 2017). One of the most prevalent types of inflammation is acute inflammation, or acute pancreatitis, which is clinically characterized by abdominal discomfort, severe pain in the stomach region, and an elevated level of serum pancreatic enzymes. Acute pancreatitis is recognized to be caused by a number of risk factors, mainly chronic alcohol consumption and gallstones. Although drug-induced pancreatitis accounts for less than 2% of cases, due to less background knowledge and complex mechanisms of interrelationship with other illnesses, this has not have been clearly confirmed (Chen, Lin et al. 2015, Uchendu, Agu et al. 2017). In a previous report between 1966 and 2009, the number of cases of first attack acute pancreatitis varied from 4 to 45 per 100,000 people per year. Although it has declined recently, the fatality rate is still in the range of 3.3% to 6% (Yadav and Lowenfels 2006, Shen, Lu et al. 2012).

Paracetamol (acetaminophen), a widely prescribed and unprescribed drug, is mostly used as painkiller and to alleviate fever. Because of its wide availability, it is used to relieve different illnesses and as a leading medication for intentional and unintentional overdoses (Chen, Lin et al. 2015). Overdoses of paracetamol lead to hepatotoxicity, which is ultimately associated with nephrotoxicity (Thanacoody 2023), because the paracetamol-degraded metabolites (sulphation and glucuronidation) that might be produced in the liver and removed from the body via the kidney during waste excretion induce kidney failure (Hussein, Kandeil et al. 2022). Acute pancreatitis is more common in cases of acetaminophen intoxication. Among others, less frequent extrahepatic signs of acetaminophen intoxication for which there are few reports include acute pancreatitis (Chen, Lin et al. 2015). For the diagnosis of acute pancreatitis or when someone has symptoms of pancreatitis or other pancreatic disorders, amylase and lipase tests are used. A test used to monitor the concentration of these enzymes in blood while they are circulating (Ismail and Bhayana 2017).

Different treatment measures were used to cure various types of illnesses. For this purpose, different scientists worked on exploring novel compounds that have numerous therapeutic potentials (Chakraborty, Uddin et al. 2022, Sarwar, Hossain et al. 2022). Almost 80% of people primarily rely on natural products from medicinal plants for the recovery of different health issues (Riaz, Rasool et al. 2012, Atanasov, Zotchev et al. 2021). Medicinal plants, contain antimalarial compounds like quinine and digitoxin act as cardioactive medications, narcotic painkillers such as morphine; and anti-neoplastic treatments such as vincristine and vinblastine (Newman and Cragg 2020). One of the possible sources of therapeutic substances with promising ethnopharmacological characteristics is the genus Celtis. Nearly all of these plant parts (leaves, barks, roots, saps, etc.) have been used as traditional medicine to treat variety of illnesses, including diabetes, gastrointestinal, venereal, amenorrhea, pain, headaches, and fever (Krief, Hladik et al. 2005, Koduru, Grierson et al. 2007, Moffett 2010, Filali-Ansari, El Abbouyi et al. 2015).

Preliminary biological and medicinal studies of the extracts and other byproducts of the Celtis genus have uncovered a wide spectrum of biochemical activity. These include antioxidant, antidiabetic, analgesic, antifungal, anticancer, and anti-inflammatory as well as antibacterial features (Nchabeleng 2017, Ota, Višnjevec et al. 2017, Laryea and Sheringham Borquaye 2021, Baran, Keskin et al. 2022). The genus Celtis is commonly known as nettle trees or hackberries, placed in Cannabeceae family widely spread in Asia, Africa, northern Australia, and south and north America (Sattarian 2006, Bonner and Karrfalt 2008). The genus Celtis plants were formerly classified into two families; Ulmaceae and the newly formed Celtidaceae (Kozlowski 2021). This genus is particularly unique and can be distinguished from other genera in its family primarily by the features of its leaves, which are deciduous, alternating, and distinct with more than one vein. The flowers are small, greenish with single or both sexes. The ripened ovaries have one seed with a juicy nature (Duncan and Duncan 2000).

From the previously reported data, only 14 species from the genus Celtis have been assessed for

thorough studies considering the medicinal and phytochemical aspects of various bioactive compounds of those species. The previously reported species have different medicinal values and are used to treat a wide range of illnesses (Samadd, Hossain et al. 2024). The current study aims to evaluate the protective and ameliorative effects of *Celtis occidentalis* L. in male Wistar rats against acetaminophen instigated pancreatitis. This study offers a low-cost and natural therapy to prevent the pancreas from being toxic from an acetaminophen overdose.

## 2. MATERIALS AND METHODS

***Chemical reagents used and preparation of methanolic extract***

Methanol used as a solvent was purchased from Rahman Chemicals Lab in Barikot, Swat, KP Pakistan. Paracetamol and Imipenem (choice drug used against acute pancreatitis) were purchased from Sami Pharmaceutical Lab (Pvt.) Ltd. Lahore, Pakistan. For the detection of amylase and lipase enzymes, kits were acquired from Chughtais Lab (Pvt.) Ltd., Lahore. Leaves of the *Celtis occidentalis* plant were collected from Lal Qila Maidan Dir lower, KP Pakistan. The leaves were shade-dried for 20 days and then chopped by an electric rotor blender at the Department of Zoology, University of Malakand. The 200 grams powder were obtained and then soaked in 95% methanol for 10 days in shaker at room temperature. The obtained extracts were filtered through Whattman filter paper, and rotary evaporator was used for solvent evaporation under reduced pressure, and the obtained crude extract was kept in water bath at 40°C for 1 day to become dried.

***Animals Model and Experimental design***

Thirty adult male Swiss albino rats were obtained from the National Institute of Health (NIH) in Islamabad, weighing 150 grams. The animals were kept under standard conditions at 25±2°C temperature and 12 h light and 12 h dark cycles and were monitored for acclimation approximately ten days before to the start of the experiment. The animals handling and experimental protocol were approved by the ethical committee of the Department of Zoology, University of Malakand (E-SA-11-2009) and in accordance with the guidelines established by the American Physiological Society for Human and Animal Research (Association 2001). Thirty animals were divided into five groups with each group has six individuals (*n* = *6***)**. The study was about the induction of acute pancreatitis or acute inflammation, and treatment was lasted for 14 days trail with some modifications (Ifeyinwa, Victor et al., 2023).

**Group-I:** (Control group): No treatment was given to this group.

**Group-II:** (Acetaminophen treated group): This group was treated with a single dose of acetaminophen (1000 mg/kg/b.w.) via oral route (o.r.) for 14 days.

**Group-III:** (Imipenem treated group): This group was treated with a single dose of acetaminophen (1000 mg/kg/b.w.) before treatment with daily administration of Imipenem (500 mg/kg/b.w, o.r.).

**Group-IV:** (Extract-150 treated group): This group was treated with a single dose of acetaminophen (1000 mg/kg/b.w.) before treatment with daily administration of methanolic extract (150 mg/kg/b.w.).

**Group-V:** (Extract-300 treated group): This group was also treated with a single dose of acetaminophen (1000 mg/kg/b.w.) before treatment with daily administration of methanolic extract (300 mg/kg/b.w.).

***Induction of Acute Pancreatitis***

For the induction of acute pancreatitis, the required dosage of 120 mg was calculated and thoroughly mixed in 0.9 ml of distilled water. A single dose of 0.9 ml of solution was given to each individual rat (i.e., 1000 mg/kg/b.w.) of the four experimental groups. The calculated dosage was continuously administered for 14 days.

***Dissection of Animals and Sample Collection***

On day 15th, all group animals were anesthetized with chloroform (inhalation of fumes from soaked cotton wool with chloroform) in a closed container. A blood sample (5 ml) was collected from each group of individuals through a cardiac puncture and centrifuged. Serum was separated and stored at 4°C in eppendorf tube. Pancreas was taken from each group stored in 10% formalin for further histopathological assessment.

***Biochemical and Histopathological Analysis***

Different tests were performed for the determination of serum amylase and serum lipase levels. For assessment of serum amylase and serum lipase using the standard method of colorimetric detection (Kumar, Gromski et al. 2021). For histopathology, the pancreas of each group was embedded in paraffin wax, and sections were made via the HC-202 laboratory rotary manual microtome at a thickness of 5 microns. Hematoxylin and eosin (H & E) dyes were used for staining purpose (Koivukoski, Khan et al. 2023). Slides were studied under Olympus research microscope, CH20i (Binocular version).

***Statistical Analysis***

Data on biochemical parameters were statistically analyzed using SPSS version 27.0. Results were reported as mean ± SD (standard deviation), and one-way analysis of variance (ANOVA) was used to test the level of significance, followed by Tukey post hoc analysis. The levels of significance were considered below 0.05 ($p<0.05$).

## 3. RESULTS AND DISCUSSION

***Biochemical Data***

Blood levels of biochemical markers (i.e. serum amylase and serum lipase) were evaluated for an assessment of pancreatic functioning. Figure 1 represents statistical data on serum amylase and serum lipase. Significant ($p<0.001$ and $p<0.01$) changes were observed in biochemical markers among different groups of animals. Results indicate that a single dose of paracetamol (1000 mg/kg) potently induced acute pancreatitis compared to the normal control group. However, daily administrations of high dose methanolic extract of (300 mg/kg) mitigate acute pancreatitis, demonstrating that the methanolic extract of *C. occidentalis* has potent anti-pancreatitic potential compared to the Imipenem (500 mg/kg).

***Histopathological Results***

Figure 2 represents the pancreas sections of different experimental groups. Histology of control group pancreas (A) shows normal architecture with clearly visible zymogen granules, capillaries, lobular ducts, and interlobular septum. The pancreas section of acetaminophen treated group (B) shows histological alterations in pancreatic hepatocytes, dilation of interlobular septum, degeneration of zymogen granules, and collapsed capillaries. The Imipenem administered group (C) shows normal histology with rare alterations in pancreatic hepatocytes and a sparely dilated interlobular septum as compared to the acetaminophen-treated group. Histological architecture of pancreas treated with methanolic extract (150 mg/kg) (D) shows rare alteration in pancreatic hepatocytes, rarely found capillary collapse with little dilation. Other regions have no alterations to be found. Histology of pancreas treated with a methanolic extract (300 mg/kg) of *C. occidentalis* (E) shows morphologically normal, functionally active, and clearly visible pancreatic tissues, as compared to the control group pancreas. These pancreatic tissue sections clearly demonstrate that *C. occidentalis* has strong anti-inflammatory effects as compared to the Imipenem drug.

## 4. CONCLUSION

This research work revealed that administration of the *C. occidentalis* extract potentially reduced the deleterious effects induced by acetaminophen. The *C. occidentalis* provided defense against acute pancreatitis, prompting acetaminophen. The protection efficacy of the *C.* occidentalis extract was higher than when Imipenem was administered, which had a minimal effect. This study demonstrates how the *C. occidentalis* extract protects the pancreas from acute inflammation triggered by acetaminophen. Further research trials should be recommended to isolate compounds that actively decline serum lipase and serum amylase levels and regenerate histological alterations.

## 5. ACKNOWLEDGEMENTS

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## 6. CONFLICT OF INTEREST

All authors have declared that there is no conflict of interests regarding the publication of this article.

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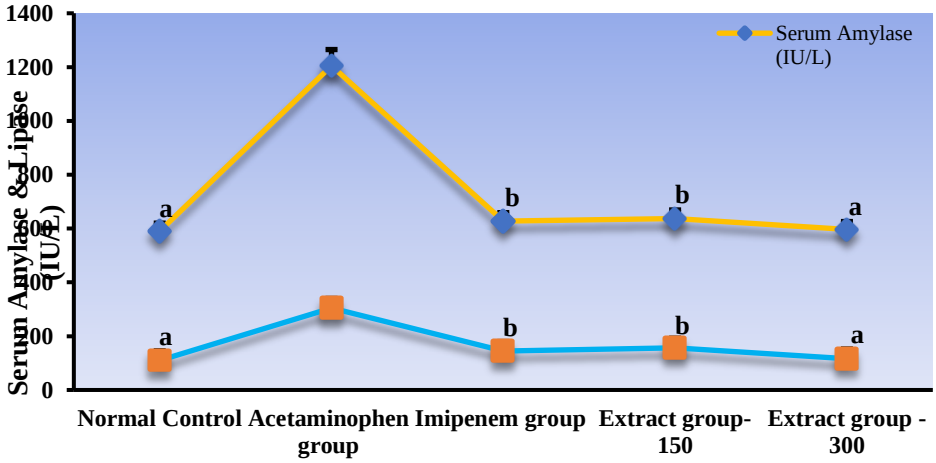


Figure 1: Represent the pancreatic enzymes (serum amylase and serum lipase) of different experimental groups. Data are presented in Mean ± SEMs (standard error means). ap < 0.001 and bp < 0.01 is considered level of significance.

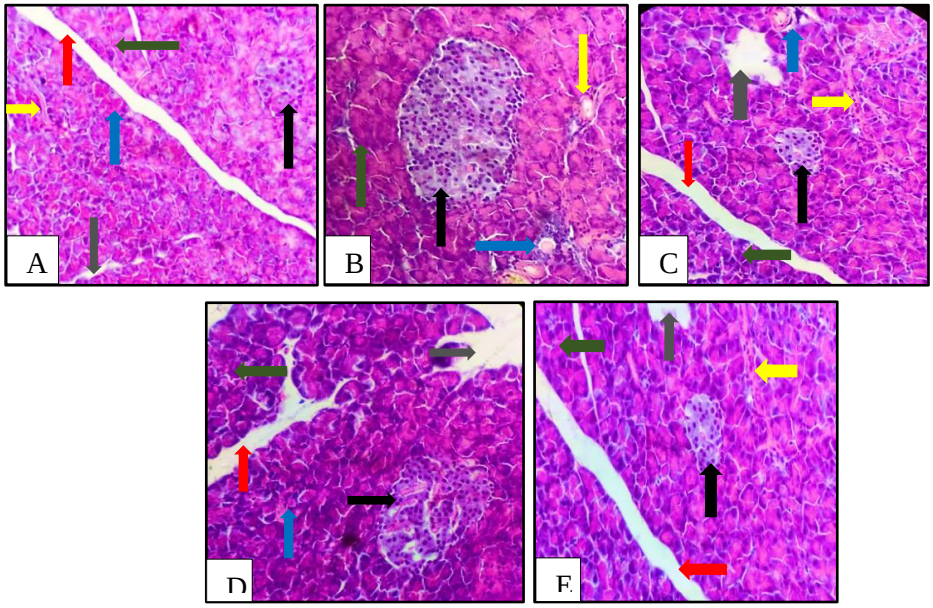


Figure 2. Represent pancreatic sections of different experimental groups. Photograph (A), pancreas section of the control group having normal histology. Photograph (B), pancreatic section of the acetaminophen group with altered histology. Photograph (C), pancreatic section of the imipenem group with rare alterations. Photograph (D), pancreas histology of the extract-150 group with rare alterations. Photograph (E), pancreatic section of the extract-300 group has normal histological architecture, same as the control group.

**Keys:** Islets of Langerhans-, Zymogen granules-, pancreatic duct- Capillary- pancreatic lobule- Interlobular septum-