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Original Research Article

Assessment of Analgesic Efficacy of *Ziziphus jujube* Hydroalcholic Fruit Extract

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Abstract: Pain is a term that refers to a spectrum of sensations of varying types and intensities, ranging from unpleasant to intolerable. The struggle to relieve pain began with the advent of mankind. Analgesics can be defined as drugs that reduce the sensation of pain without losing consciousness. Analgesics act in different ways on the peripheral and central nervous systems. They differ from anesthetics in that they reversibly eliminate sensation, acetaminophen [known in the US as acetaminophen, or simply APAP], non-steroidal anti-inflammatory drugs [NSAIDs] such as salicylates, morphine and opioids such as opiates. When choosing an analgesic, the severity and response to other drugs determine drug choice. World Health Organization [WHO] pain ladder. Herbal medicines have less side effects and less harm, so they have a higher market value. The nutritious jujube fruit (*Ziziphus jujube* Mill.) is a member of the Rhamnaceous family and grows mainly in inland areas of Europe, southern and eastern Asia, Australia and especially northern China. Jujubes have a long history as fruit and medicinal. The main bioactive components are vitamin C, phenols, flavonoids, triterpenoids and polysaccharides. Recent phytochemical studies of jujube fruit have highlighted the following biological effects: B. Anticancer, anti-inflammatory, anti-obesity, immunostimulatory, antioxidant, hepatoprotective and gastrointestinal protective activity in macrophages and inhibition of foam cell formation. Further focus on clinical trials and phytochemical definitions of jujube fruit will be essential for future research efforts. In this study, an attempt was made to evaluate the analgesic potential of *Ziziphus jujube* hydroalcoholic fruit extract.

Keywords: Hydroethanolic extract of *Ziziphus jujube* [HAJZ], Analgesic efficacy, Eddy Hot plate.

INTRODUCTION

Analgesics or analgesics are any of a group of drugs used to relieve pain [1]. Analgesics act in different ways on the peripheral and central nervous systems. They differ from anesthetics in that they reversibly eliminate sensation, acetaminophen [known in the US as acetaminophen, or simply APAP], non-steroidal anti-inflammatory drugs [NSAIDs] such as salicylates, morphine and opioids such as opiates. When choosing an analgesic, the severity and response to other drugs determine drug choice. The World Health Organization [WHO] [2] pain ladder suggests mild analgesics as a first step. Analgesia/pain is a disease-defined unpleasant sensation caused by an [external/internal] stimulus. This is the most important symptom that gives a warning signal and is primarily protective in nature. Analgesia by blocking pain nerve sensitization mechanisms induced by bradykinin, TNFα and ILs [3]. Analgesics are drugs that selectively relieve pain by acting on central nervous system or peripheral pain mechanisms without significantly altering consciousness. Pain is primarily a warning sign of a protective nature, but it also causes discomfort and distress. It can become unbearable and even helpless. Excessive pain can cause other effects such as feeling sick, anxiety, sweating, nausea, heart palpitations, increased or decreased blood pressure, and tachypnea. Analgesics relieve pain as a symptom without affecting the cause [3].

Mechanisms and Pathways of Pain Perception

Pain is a term that refers to a spectrum of sensations of varying types and intensities, ranging from unpleasant to intolerable. Painful stimuli are

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perceived by the morphologically least differentiated physiological receptors [sensors, nociceptors], namely free nerve endings. The bodies of primary bipolar afferent neurons are located in the dorsal root ganglia. Nociceptive impulses are conducted via myelinated [C fibers, conduction velocity 0.2–2.0 m/s] and myelinated axons [Aδ fibers, 5–30 m/s]. The free ends of Aδ fibers respond to intense pressure and heat, while the free ends of C fibers respond to chemical stimuli [H+, K+, histamine, bradykinin, etc.] due to tissue damage [4].

Pain sensation can be influenced or modified as follows [5]:

- Elimination of the cause of pain.
- Lowering of the sensitivity of nociceptors [antipyretic analgesics, local anesthetics].
- Interrupting nociceptive conduction in sensory nerves [local anesthetics].
- Suppression of transmission of nociceptive impulses in the spinal medulla [opioids].
- Inhibition of pain perception [opioids, general anesthetics].
- Altering emotional responses to pain, i.e., pain behavior.

Secondary metabolites form a variety of substances that are useful in treating certain human diseases. This may explain why most people in Africa today still rely on herbal medicines for treatment. According to the World Health Organization, more than 80% of the African population has access to primary health care traditional medicine and pharmacopoeia [6]. Among the various medicinal plants, some endemic and edible species can be used to produce raw materials or preparations containing phytochemicals with high levels of minerals with important antioxidant properties and health benefits, is of particular interest. Herbs are used in many fields, including pharmaceuticals, nutrition, fragrances, beverages, dyes, repellents, fragrances, and cosmetics [7]. *Ziziphus jujuba* Mill is a fruit tree of the *Rhamnaceae* family. It is mainly distributed in subtropical and tropical regions of Asia and America.

Ziziphus jujuba

This plant is rich in bioactive components such as vitamin C, flavonoids, triterpenoids, and polysaccharides [8]. It is used in traditional Chinese and Korean medicine as an antifungal, antibacterial, antiulcer, anti-inflammatory, and antioxidant remedy [9, 10]. Jujube is a blood purifier, hematopoietic promoter, viscous disposition promoter, expectorant, cough suppressant, anti-asthmatic, laxative, wound healing, aphrodisiac, semen suppressant, blood and bile coolant, itching. It has been introduced as a sedative for kidney and bladder pain.It also contributes to the treatment of rectal and intestinal ulcers/diseases and liver disease. Ripe jujube fruits have laxative properties, while unripe jujubes cure diarrhea. The plant is difficult to digest and can interfere with digestion in people with digestive problems. Bloating is also a side effect of jujube overdose. However, according to TPM, these side effects can be mitigated with the help of sugar and currants. Depending on the patient's physical condition, honey or libido-enhancing drugs are prescribed to avoid a decrease in libido after jujube consumption [11].

Vernacular Name		**Taxonomical description**	
Sanskrit	Rajabadari	**Kingdom**	*Plantae*
Punjab	Beri	**Division**	*Magnoliophyta*
Bengal	Ku	**Class**	*Magnoliopsida*
Assamese	Bogori	**Order**	*Rosales*
Uriya	Bodori	**Family**	*Rhamnaceae*
Gujarat	Bordi	**Genus**	*Ziziphus*
Hindi	Ber	**Species**	*Jujuba*

The present study was conducted to assess the antinociceptive potential of hydroethanolic extract of *Ziziphus jujube*.

Experimental Works

Preliminary work (Selection of Plant)

The plant was selected on the basis of their antioxidant and antimicrobial activities and wide medicinal uses in the traditional literature. The ease of availability of plant is also taken in to consideration during selection.

Gathering sufficient information from vivid articles and journals it was concluded that there is scope to explore some more pharmacological activities in the plant *Ziziphus jujube* hence, it was selected for further studies.

Collection of Plant

Ziziphus jujube fruits were collected from various places from Bhel area Govindpura Bhopal (M.P.) during the month of Aug 2018.

Authentication of Plant Material

The plant has been identified and authentication by, Head of the Department Botany at the Safia college of science, Bhopal (M.P.). The plant part specimens were submitted as herbarium (Voucher Specimen No: 105/ Safia College Bhopal, dated 07 Aug 2018).

Drying, Size Reduction and Storage of Plant Material

The plants parts were dried under shade. It was pulverized to coarse powder with the help of mixer grinder. The coarse powder was passed through sieve No. 20 to maintain uniformity and packed into airtight container and stored in cool and dry place. This material was used for the further study.

Preparation of *all Selected Plant Part* Extract

Extraction of *Ziziphus jujube* fruits was done by Soxhlet extraction method.

Acute Oral Toxicity Studies (OECD 423)

Acute oral toxicity study was evaluated as per OECD guidelines (423) on Wistar albino rats. Animals were provided by Sapience Bio Analytical Research Lab, Bhopal (M.P.) and experiment was done in the lab. Before experimentation rats were fasted overnight with water ad libitum. Three animals were selected which receives dose of 2000mg/kg. All three animals were received dose of 2000 mg/kg body weight of poly herbal pormolation (hydro- alcoholic extract of all plants extract+ 1% aqueous CMC) by gavage using oral cannula (limit test).Animals were observed individually for any toxicity sign of gross changes like convulsion, tremor, circling, depression, and mortality after dosing for 24 hours, with special attention given during the first 4 hours, and thereafter, 24 hours, Administered dose was found tolerable (as no death found) [12].

Analgesic Activity Models [13]

Animals: Adult Wistar rats of 150-200 g were used for the study. The rats were obtained from the Ravishankar College of pharmacy Bhopal for experimental purpose. The animals were maintained under controlled conditions of temperature (23 ± 2°C), humidity (50±5%) and 12 h light-dark cycles. All the animals were acclimatized for seven days before the study. The animals were randomized into experimental and control groups and housed individually in sanitized polypropylene cages containing sterile husk as bedding. They had free assessed to standard pellets as basal diet and water *ad libitum*. Animals were habituated to laboratory conditions for 48 h prior to experimental protocol to minimize if any of non-specific stress. All the studies conducted were approved by the Institutional Animal Ethical Committee (IAEC) of Ravishankar college of pharmacy Bhopal (M.P.) (Proposal no: RCOP/IAEC/MAY2018/03) according to prescribed guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animal, Govt. of India.

Experimental Protocols for Analgesic activity

Eddy's Hot Plate Test

The animals (Rats) were divided into respective groups of six animals each. Group I & II served as test control, Group III as standard treated orally with *Ziziphus jujube* extract of 350 mg/kg and 250 mg/kg p.o. body weight, Diclofenac as standard 50 mg/kg p.o. respectively. Group IV served as normal control. The animals were individually placed on the hot plate maintained at 55°C, one hour after their respective treatments. The response time was noted as the time at which animals reacted to the pain stimulus either by paw licking or jump response, whichever appeared first. The cut off time for the reaction was 15 seconds.

Table 1: *Ziziphus jujube* extract used in the estimation of analgesic activity by *Hot Plate Test*

Group	Treatment	Dose
GP-1 Test control / Extract group	*Ziziphus jujube hydroalcholic* extract	350 mg/kg p.o.
GP-2 Test control / Extract group	*Ziziphus jujube hydroalcholic* extract	250 mg/kg p.o.
GP-3 Standard control / Positive control	Diclofenac Na	50 mg/kg p.o.
GP-4 Normal control / Negative control	Normal saline	0.9 %

Acetic Acid-Induced Writhing Response in Mice

To evaluate the analgesic effects of the plant extract, the method described by Dharmasiri *et al.*, was followed with slight modifications. Different groups of six mice each received orally normal saline solution (2 ml/kg, p.o.) (i.e. control), Standard as Diclofenac (50 mg/kg) and HEZJ (350 mg/kg, p.o.) and (250 mg/kg, p.o.) respectively. 30 minutes later 0.7% acetic acid (10 ml/kg) solution was injected intraperitoneally to all the animals in different groups. The number of writhes (abdominal constrictions) occurring between 5and 20 min after acetic acid injection was counted. A significant reduction of writhes in tested animals compared to those in the control group was considered as an antinociceptic response [14].

Table 2: *Ziziphus jujube* extract used in the estimation of analgesic activity by acetic acid induced writhing technique

Group	Treatment	Dose
GP-1 Test control-1	*Ziziphus jujube* extract	350 mg/kg
GP-2 Test control-2	*Ziziphus jujube* extract	250 mg/kg
GP-3 Standard control	Diclofenac Na	50 mg/kg
GP-4 Normal control	Normal saline	0.9 %

RESULT AND DISCUSSION

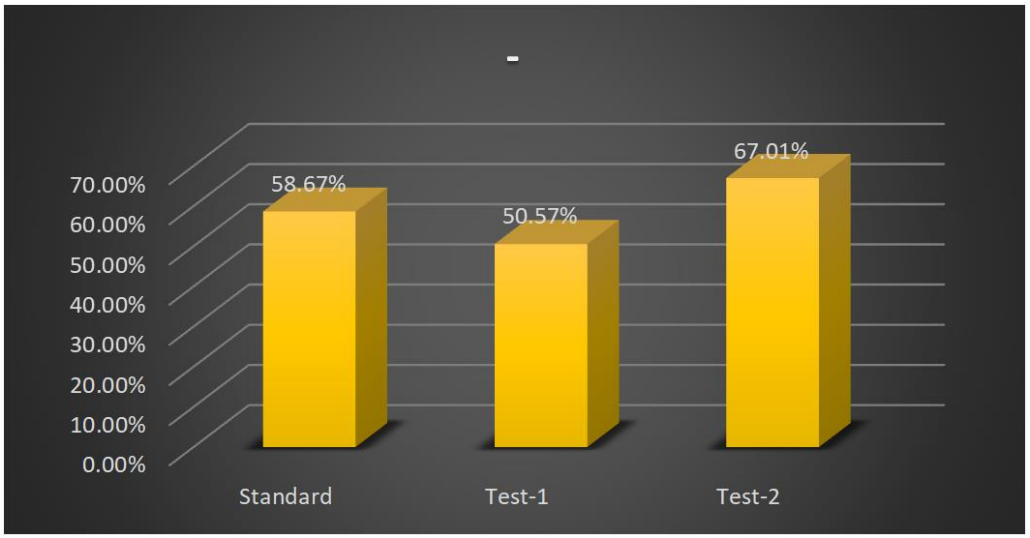
Jujube (*Ziziphus jujuba* Mill.), a highly nutritious and functional fruit, is reported to have various health benefits and has been extensively planted worldwide, especially in China. Many studies have shown that bioactive components derived from jujube fruit have significant nutritional and potential biological effects. The present study was conducted to assess the antinociceptive efficacy of hydroethanolic fruit extract of *Ziziphus jujube*. The methods selected were chemical nociception in the test model of acetic acid-induced writhing and thermal nociception hot plate. These methods were selected to evaluate both centrally and peripherally mediated effects of *Ziziphus jujube*. The hot-plate test is commonly used to assess narcotic analgesia. HEZJ showed antinociceptive effects in this test. The result of Eddy hot plate reaction revealed that the HEZJ at 250 mg/kg and 350 mg/kg p.o. showed significant outcome as compared with standard (table 4). Hence, it is assumed that *Ziziphus jujube* fruits had analgesic effect at the central nervous system. The abdominal constriction response induced by acetic acid is a sensitive procedure to establish peripherally acting analgesics. This response is thought to involve local peritoneal receptors. The writhing test is a very sensitive method for preliminary evaluation of anti-nociceptive activity and the ED50 values obtained in animals using this test can be correlated with the analgesic doses in humans, still it cannot indicate whether the effects result from central and/or peripheral actions. The analgesic potential of the extract was shown by acetic acid test to be significant but was not specific. The test did not indicate if the potential resulted from central and/or peripheral actions. The results of acetic acid writhing test in rats showed a significant decrease in number of writh in Poly-herbal formulation of all plants extracts suggesting peripheral analgesic effect. In the acetic acid induced writhing method the standard analgesic drug (Diclofenac 10mg/ kg, p.o.) as well as the test drugs *Ziziphus jujube* fruits extract +1% CMC**,** obtained in doses of (250 & 350 mg/kg, p.o.) showed a significant reduction in the number of writhing in rats as compared to the control rats. The result was tabulated in the table 3 which showed that HEZJ extract at 350 mg/kg p.o showed significant result having 67.01% of writhing reduction as compared with standard (diclofenac) 58.67%.

Table 3: Analgesic activity of the poly-herbal formulation (Acetic acid Induced model)

Group Name	Treatment	Dose	No. of writhes / 30 mins	% Reduction in Writhing
Disease Control	0.7 % acetic acid	0.7 % acetic acid in volume of 10 mg /kg, i.p.	86.90 ± 2.30	-
Standard	Diclofenac Na + 0.7 % acetic acid in volume of 10mg /kg, i.p.	50 mg/kg, p.o.	35.91 ± 2.21**	58.67 %
Test-1	*Ziziphus jujube* fruits extract + 0.7 % acetic acid in volume of 10mg /kg, i.p.	250 mg /kg, p.o.	42.95 ± 4.23**	50.57 %
Test-2	*Ziziphus jujube* fruits extract + 0.7 % acetic acid in volume of 10mg /kg, i.p.	350 mg/kg p.o.	28.66 ± 2.19**	67.01 %

Values are expressed as mean ± SEM. *P <0.01, **P < 0.001 (N= 6). Value are mean±SEM, of six animals in each group.

Following repeated measures ANOVA parametric methods, using Dunnett Test.



Graph 1: Analgesic activity of the poly-herbal formulation (Acetic acid Induced model)

Table 4: Analgesic activity by Eddy's hot plate model in rats

Reaction time in seconds (20 secs)							
Group Name	**Treatment**	**Dose**	**0 min**	**30 min**	**60 min**	**90 min**	**120 min**
Normal Control	Control	1% CMC,p.o.	3.44 ± 0.25	4.87 ± 0.09	5.20 ± 0.19	5.61 ± 0.56	4.89 ± 0.34
Standard	Diclofenac	50mg/kg, p.o.	6.85 ±0.55*	8.1 ± 0.06*	12.9 ±0.25*	14.9 ±0.36*	16.9 ±0.20*
Test-1	*Ziziphus jujube* fruitsExtract	250 mg/kg, p.o.	9.0 ± 0.20*	11.4 ± 0.58	12.9 ± 0.63*	13.21 ± 0.54*	14.6 ± 0.53*
Test-2	*Ziziphus jujube* fruitsExtract	350mg/kg p.o.	10.76 ±0.52	12.6 ±0.81*	14.2 ±0.34*	15.2 ±0.21*	15.4 ± 0.45*

Values are expressed as mean ± SEM. *P <0.01, **P < 0.001 (N= 6) Values are mean±SEM, of six animals in each group.

Following repeated measures ANOVA parametric methods, using Dunnett Test.

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