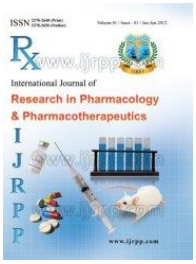
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.7 | Issue 4 | Oct - Dec - 2018***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Research article ***Open Access***

Demonstration of analgesic activity of *ferula asafoetida* in an animal model

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ABSTRACT

Background

Pain is a very unpleasant sensory and emotional experience due to tissue damage. There are many effective analgesics available, which are widely used to reduce pain, but they are associated with many side effects which limit their clinical use. Therefore, in this study we aim to demonstrate the analgesic activity of *Ferula Asafoetida* at three different doses in animal model.

Materials and Methods

The animals were divided into their respective groups of 6 mice each. Central Analgesic activity of *Ferula Asafoetida* aqueous extract at three different dose (5mg/kg, 10mg/kg, 20mg/kg) was assessed by hot plate method in mice. Difference in mean change in reaction time was calculated for each group and was compared with tramadol. Peripheral analgesic activity was assessed by acetic acid induced writhing in mice. Mean number of wriths was calculated and it was compared with diclofenac. Statistical analysis was done by ANOVA followed by Dunnett's t-test and $p < 0.05$ was considered significant.

Results

In the hot plate method, central analgesic activity of *Ferula Asafoetida* at a dose of 20mg/kg was statistically comparable to Tramadol at different time points (20min, 60 min, 90 min). Though there was a significant increase in reaction time of *Ferula asafetida* group at a dose of 10mg/kg when compared to control but was not statistically comparable to tramadol. In acetic acid induced writhing method, peripheral analgesic activity of *Ferula asafetida* at a dose of 20mg/kg was significantly comparable to diclofenac.

Conclusion

In this study it was concluded that *Ferula Asafoetida* has significant central as well as peripheral analgesic activity as compared to standard treatments i.e; Tramadol and Diclofenac respectively.

Keywords: Ferula Asafoetida, Hot Plate, Acetic acid induced writhing, Cyclo-oxygenase.

INTRODUCTION

Pain defined by the International Association for Study of Pain (IASP), as an "unpleasant sensory and emotional experience because of actual damage or potential tissue damage.'' [1]

Clifford J Woolf suggests that there are three classes of pain: nociceptive pain, inflammatory pain associated with tissue damage and immune cells infilteration, and pathological pain which is characterised as a state of disease caused by nervous system damage or nervous system dysfunction (for example fibromyalgia, peripheral neuropathy, tension type headache, etc.) [2]

Inflammation can be the cause of pain. Till now it has been seen that many endogenous substances such as prostaglandins and peptides play an important role in the process of inflammation. Nonsteroidal anti-inflammatory Drugs (NSAIDs) which have anti-inflammatory activity also have analgesic activity. [3]

Treatment of pain as well as inflammation is one of the major challenges. Management of many patients, who suffer from chronic and subacute pain, is quite challenging. So there is a need of an integrative approach. Increment in pain threshold sensation and improvement in the quality of life are the main components of effective pain control.

Despite that there are many effective analgesics available today which are widely used to reduce pain, most of the analgesics has lots of side effects which limit their clinical use [4]. Gastric pain, mucosal ulceration and loss of blood are produced by almost all NSAIDs to varying extents. Gastric toxicity is a major consideration regarding NSAIDs. NSAIDs causes Inhibition of cyclo-oxygenase (COX-1) mediated synthesis of PGs (PGE2, PGI2) which are gastroprotective. The deficiency of PGs causes reduction of mucus and secrection of bicarbonate ions, this leads to increased secretion of gastric acid and causes ulceration. Thus, NSAIDs enhance aggressive factors and reduce defensive factors in gastric mucosa which are ulcerogenic. This causes Peptic ulcer which significantly affects the quality of life.

Nowadays, there is increase in the use of many cultivated or wild plants which has various medicinal properties to cure or to prevent the disease [5] Pharmacologists as well as pharmaceutical industries are searching for new compounds having analgesic activity. Due to many side effects related to the use of NSAIDs, it is logical to search for a plant based medicine having analgesic activity, which could be used as pain killers with almost same efficacy and potency and reduced side effects. [6]

Ferula assafoetida is a synoicous, herbal, continual plant. [7] Oleo-gum-resin is obtained from the rhizome and root of the plant of Ferula asafoetida. [8] It is commonly known as "*Hing".*

Many pharmacological activities of Ferula Asafoetida have been studied, such as antioxidant, antispasmodic and hypotensive, antibacterial, antiviral, antifungal, cancer protective, anti-diabetic, anticancer, antispasmodic, relaxant effect, and neuroprotective role. [9] Various other pharmacological activities have been studied like anti inferitility, antinociceptive, analgesic, hepatoprotectant, anti haemolytic, anti hyperlipidemic effects, aphrodisiac, antiulcerogenic, nephroprotective, anti obesity, etc. [10]

As there are many limitations associated with the current analgesic treatment, therefore, we evaluated the analgesic activity of *Ferula Asafoetida* at different doses centrally as well as peripherally.

MATERIALS AND METHODS

A total of 36 Swiss Albino Mice of either sex, (weight 25-30gm) were taken. The animals were maintained in cages, under a temperature of 25 ± 2°Cand 45-55% relative humidity, with a 12-hour light/dark cycle. They were allowed food and water ad libitum.

All experiments were performed after approval from Institutional Animal Ethics Committee of Eras' Lucknow Medical College and as per the guidelines of Animal Care by CPCSEA.

Approval No: ELMC/PHARMA/2018/ (IAEC)-02-IMP/2018-1

Ferula Asafoetida powder was procured from the local market in Lucknow, Uttar Pradesh, INDIA and authenticated by a botanist in Lucknow.

Method of preparation of *Ferula Asafoetida* Extract [11]

10gm *Ferula Asafetida* powder was dissolved in distilled water (100ml) overnight at room temperature and the suspension which was obtained was administered intraperitoneally at three doses (5mg/kg, 10mg/kg, 20mg/kg) to the animals.

Drugs and extract administration

Tramadol at a dose of 22.8mg/kg [13] and sodium diclofenac at a dose of 30 mg/kg [15] were used as standard drugs as central analgesic and peripheral analgesic respectively and were administered intraperitoneally (i.p).

Ferula asafoetida was administered at 3 doses- 5mg/kg, 10mg/kg and 20mg/kg i.p.

Experiment Protocol

Total of 36 mice were taken.

Analgesic activity was measured by 2 methods.

Hot Plate Method [13]

This method was used for evaluating the effects of centrally acting analgesics. [3]

Animals were divided into groups having 6 mice each.

Group 1: Control– Distilled water 1ml/kg i.p.

Group 2: Standard: Tramadol 22.8mg/kg i.p.

Group 3: *Ferula Asafoetida* Group (Test Group)

- ***3A-*** *Ferula Asafoetida* extract i.p. at a dose of 5mg/kg
- ***3B-*** *Ferula Asafoetida* extract i.p at a dose of 10mg/kg
- ***3C-*** *Ferula Asafoetida* extract i.p at a dose of 20mg/kg

Before starting the experiment, animals were accommodated to the hot plate instrument for 5 minutes. The hot-plate apparatus, consists of a electrically heated surface. The temperature is controlled at 55° to 56°C. Before the drug adminstration, each animal was placed into an acrylic cylinder on the heated surface, and the time between placement and licking of their hind paws or jumping (whichever occurred first), was recorded in seconds as the response latency which is the reaction time. It was taken as the control latency for each mice. To prevent the burning of tail or paw a cut off time of 45 seconds was taken.

Each animal was given with its respective drug. The reaction time of each mouse was again evaluated at 20, 60 and 90 minutes [3] after the administration of the drug to record the test latencies until either licking or jumping occurs. Control and test latencies for each group was recorded and was then compared.

Acetic acid-induced writhing test [14]

This method has been used for evaluating the effects of peripherally acting analgesics. [3]

Animals were divided into groups having 6 rats each.

Group 1: Control– Distilled water 1ml/kg i.p.

Group 2: Standard: Diclofenac (30mg/kg i.p)

Group 3: *Ferula Asafoetida* Group (Test Group)

- ***3A-*** *Ferula Asafoetida* extract i.p. at a dose of 5mg/kg
- ***3B-*** *Ferula Asafoetida* extract i.p at a dose of 10mg/kg
- ***3C-*** *Ferula Asafoetida* extract i.p at a dose of 20mg/kg

Abdominal constriction test as decribed earlier is used to measure the analgesic activity. We used the same method for evaluating the peripheral analgesic activity of Ferula Asafoetida.

Mice were given ferula asafoetida extract at dose of 5, 10 and 20 mg/kg i.p, diclofenac sodium at a dose of 30 mg/kg i.p. After 15 minutes of administration of the respective drugs i.p. injection of 0.6% acetic acid at a dose of 10 ml/kg i.p was adminitered.

Animals were kept in different transparent cages. After 5 minutes of acetic acid administration, mice were observed for typical writhing response which is induced by acetic acid and the number of writhes such as hind limb stretching activity and abdominal muscle contraction of each animal was counted for a duration of 30 minutes. Mean number of writhes was calculated in each group which is the measure of analgesic effect.

The percentage of writhing inhibition was also calculated by the formula

$$\%\text{Inhibition} = \frac{\text{Mean number of writhes (control)} - \text{Mean number of writhes (test)} \times 100}{\text{Mean number of writhes (control)}}$$

STATISTICAL ANALYSIS

The data was tabulated using Microsoft Office Word and Microsoft Office Excel. The different groups were compared using Analysis Of Variance (ANOVA), followed by Dunnett's t test. Graph pad Prism software (version 6.02) was used, p value < 0.05 was considered as significant.

RESULTS

Hot plate method

Table 1: Effect of Ferula Asafoetida using Hot Plate followed by the administration of drugs in terms of Reaction Time.

Groups	0 min Mean ± SD in sec	20 min Mean ± SD in sec	60 min Mean ±SD in sec	90 min Mean ± SD in sec	P value F value
CONTROL	5.100±0.7483	5.333±0.5317	5.033±0.5241	4.883±0.6047	P=0.6428 F= 0.5675
TRAMADOL	5.317± 0.4262	9.750±0.7396*+	16.10±1.198*+	9.300±0.7211*+	p< 0.0001 F=177.7
FA 5 mg/kg	5.500±0.4382	5.350±0.5541#	4.967±0.5046#	5.017±0.6306#	P=0.2744 F= 1.392
FA 10 mg/kg	5.067±0.4676	8.017±0.3061*#+	9.933±0.5750*+#	7.783±0.2787*+#	p< 0.0001 F= 133.5
FA 20 mg/kg	5.050±0.3728	9.183±0.5154*+	14.85±1.326*+	8.450±0.9711*+	p< 0.0001 F= 127.7
ANOVA	P=0.4830 F=0.8925	p< 0.0001 F= 87.62	p< 0.0001 F= 204.5	p< 0.0001 F=53.33	

***When compared with baseline (p<0.05)**
 # When compared with standard; (p<0.05)
+ When compared with control; (p<0.05)

Data analyzed using one way analysis of variance (ANOVA) followed by Dunnet's test. Values are expressed as mean ± SD (n = 6 in each group) Where, min = minutes; SD = Standard Deviation FA = Ferula Asafoetida. All drugs were administered i.p (intraperitoneally)

Table 1 shows that there is no significant difference in the baseline values (0min) in any of the groups and there was no significant difference at 0min, 20, 60, 90 mins within the control group. There is significant increase in the reaction time at 20mins, 60mins, and 90 mins in the tramadol group when compared with the baseline values (0min) and control group. There was no significant difference in Ferula asafaoetida 5mg/kg group when compared to the control group. There is significant increase in the reaction time at 20mins, 60mins, and 90 mins in the Ferula Asafoetida (10mg/kg and 20mg/kg) groups when compared with the baseline values (0min) and the control group.

Though there was increase in reaction time in FA 10mg/kg group when compared to the control group but it was not statistically similar when compared to tramadol group.

There was no statistically significant difference between FA 20mg/kg group when compared with Tramadol Group.

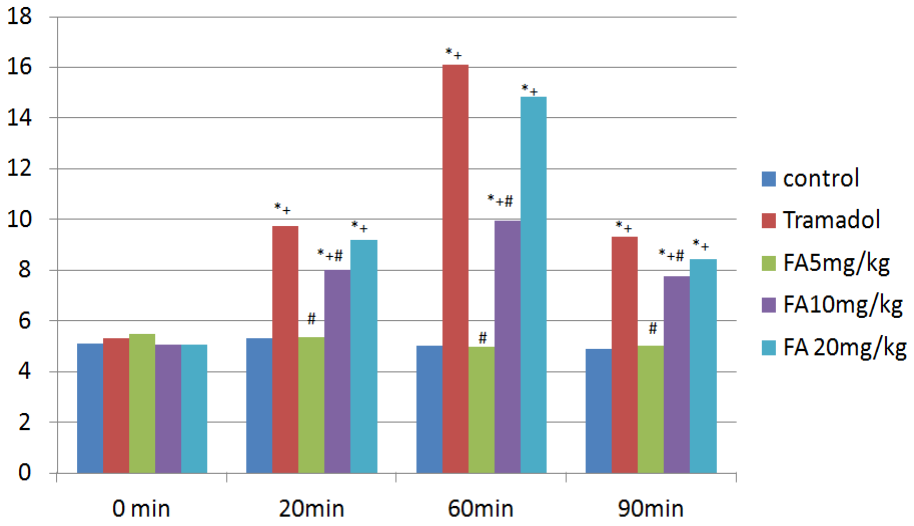

Fig. 1. The difference in mean change in reaction time at 0, 20, 60 and 90 minutes using hot plate test. (n=6).

*When compared with baseline ($p<0.05$)
When compared with standard; ($p<0.05$)
+ When compared with control; ($p<0.05$)

Fig.1. shows that there is significant increase in reaction time in tramadol group, ferula asafoetida group 10mg/kg and ferula asafoetida group 20 mg/kg at 20min, 60min and 60 min when compared to the control group. There is significant increase in tramadol group, ferula asafoetida group 10mg/kg and ferula asafoetida group 20 mg/kg groups at 20min, 60min and 60 min when compared to the baseline values. There is no significant difference in ferula asafoetida 5mg/kg group at any different time points when compared to the control group. There is no statistically significant difference between FA 20mg/kg group when compared with Tramadol Group.

Acetic Acid induced Writhing

Table 2. Demonstration of the effect of ferula asafoetida on acetic acid-induced writhing in mice.

Groups	*Number of Wriths Mean±SD*	*Percentage Inhibition*
Control	105.8±5.076	–
Diclofenac	29.50±3.564*	71.7%
FA 5mg/kg	92.00±4.604*#	13.24%
FA 10mg/kg	62.00±6.693*#	41.50%
FA 20mg/kg	33.83±2.927*	68.11%

P Value <0.0001. F Value= 307.6
Data analyzed using one way analysis of variance (ANOVA) followed by Dunnet's test. Values are expressed as mean ± SD (n = 6 in each group) Where, SD = Standard Deviation FA = Ferula Asafoetida. All drugs were administered i.p (intraperitoneally)

- *When compared to control ($p<0.05$)
- # when compared to standard ($p<0.05$)

Table 2 and Figure 2 shows the peripheral analgesic effect of ferula Asafoetida using acetic acid induced writhing model. There is a significant decrease in number of wriths in all the groups as compared to the control group. The percentage of inhibition of writhing in all the groups was significantly more as compared to control group. Maximum percentage inhibition of writhes was observed by FA 20 mg/kg group i.e; 68.11%, which had no significant difference diclofenac group which was taken as standard indicating that FA 20mg/kg group had comparable peripheral analgesic activity.

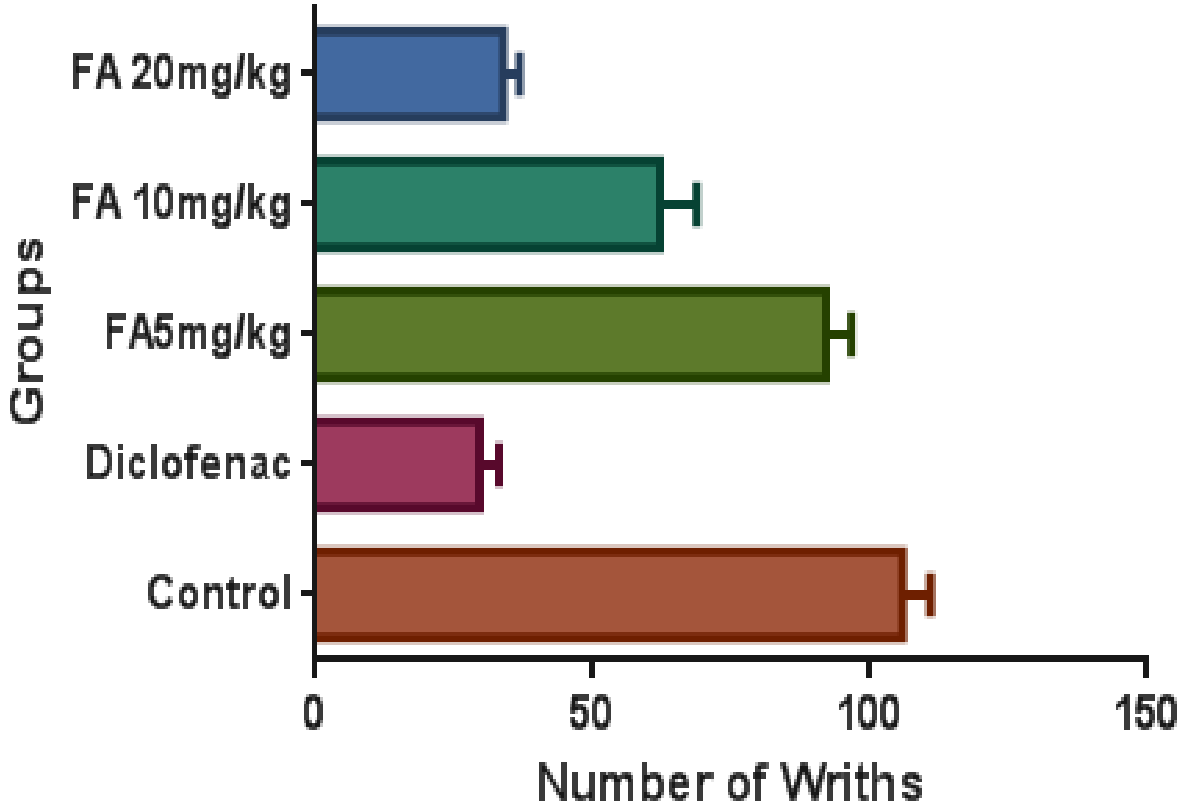

Figure 2: Effect of drugs on acetic acid induced writhing.

DISCUSSION

Pain refers to ill-defined sensations, leading to disabling conditions and is associated with many illnesses. Analgesics are the cornerstone in the management of pain but they are associated with many limitations. Consuming herbal drugs could be the promising agents for the management of pain. Therefore, we evaluated the central and peripheral analgesic activity of *Ferula asafetida*.

In this study, we investigated the analgesic activity of *Ferula Asafoetida* at three different doses (5mg/kg, 10mg/kg and 20mg/kg). Both central and peripheral analgesic activity of ferula asafoetida were investigated and compared with the standard treatment, Tramadol and Diclofenac respectively. In hot plate method, it was observed that there is a significant increase in the reaction time at all time points in the tramadol group when compared with the baseline values (0min) and when compared to the control group. There was significant increase in the reaction time at all time points in the *Ferula Asafoetida* (10mg/kg and 20mg/kg) groups when compared with the baseline values (0min) and when compared with the control group. The results of *Ferula asafoetida* 20mg/kg group was comparable to the standard Tramadol group. Therefore, it was found that Ferula Asafoetida 20mg/kg has a central analgesic activity.

In acetic acid induced writhing model, the peripheral analgesic effect of *Ferula Asafoetida* was also observed. There was a significant decrease in number of wriths in all the groups as compared to the

control group. The percentage inhibition of writhing in all the groups was significantly higher as compared to control group but the maximum percentage inhibition of writhes was observed in ferula asafetida 20 mg/kg group i.e; 68.11%, which had no significant difference when compared to Diclofenac group which was taken as standard. Therefore, this study showed that *Ferula Asafoetida* 20mg/kg has a peripheral analgesic activity also.

Peripheral pain is caused by release of various endogenous substances such as histamine, bradykinins and substance P. The Local peritoneal receptors are thought to be involved in peripheral pain. [15] It can also be caused by increased release of arachadonic acid which activates Cyclo-oxygenase (COX) pathway resulting in increased synthesis of prostaglandins [16] which sensitizes the nerve endings by acting on prostaglandin E2 receptor and transmit pain and to the brain leading to writhing response. [17] Therefore, we propose that ferula asafetida inhibits the release of arachadonic acid which further inhibits the production of prostaglandins leading to reduction in pain and increment in pain threshold, therefore, it has peripheral analgesic activity.

Central pain involves higher brain Functions mediated by supraspinal reflex to stimulate pain. [18] Thermal noxious stimuli is important for centrally mediated pain and is believed to be associated with activation of pain pathways. Opioid receptors are present in many regions of the nervous system that are involved in pain transmission and control, including primary afferent neurons, spinal cord, midbrain and thalamus. The opioids produce analgesia by actions at several levels of the nervous system, in particular, inhibition of neurotransmitter release from the primary afferent terminals in the spinal cord and activation of descending inhibitory controls in the midbrain. [11] Therefore, the central analgesic effect of ferula asafoetida might be associated with opioid pain inhibitory pathways.

K.Abo-EL-Sooud et al., [19] suggested that *Ferula asafoetida* extract exerted a good analgesic effect on chemically induced writhing and on tail flick model. He observed that the central analgesic activity of *ferula asafoetida* extract is more prominent than the peripheral analgesic activity. The extract exerted a significant increase in the latency in tail flicking by tail flick method. He suggested that the inhibition of prostaglandin synthesis mechanism seems to have peripheral analgesic effect. [20] The extract also seems to have morphine like effects, which explains its central analgesic effect. In our our study it was observed that *Ferula asafoetida* is equally effective in reducing central as well as peripheral pain.

Seyyed Majid Bagheri. et al., [5] evaluated the antinociceptive and anti-inflammatory effects of ferula asafetida. The results demonstrated that *ferula asafoetida* at a dose of 10mg/kg has the highest antinociceptive activity. He suggested the possible mechanism for *Ferula asafoetida* could be due to lipoxygenase and/or cyclooxygenase pathway inhibition in the arachidonic acid cascade, peripherally. They also examined anti-inflammatory activity of asafetida using the carrageenan induced paw edema in mice [21] this could be due to the monoterpenes, present in the plant. [22]. Umbelliprenin, which is one of the sesquiterpene coumarins of asafetida, has the potential to inhibit the 5-lipoxygenase activity and shows the anti-inflammatory action. [23] In our study we observed that ferula asafetida has a dose dependant effect in reducing pain and maximum efficacy was observed at 20mg/kg.

Appendino et al., [24] demonstrated that sesquiterpene dienones which has fetidones A and B and sesquiterpene coumarin ethers such as 8-acetoxy-5- hydroxyumbelliprenin are potent nuclear factor-kB–inhibitors.

S.M. Bagheri et al., [11] investigated antinociceptive activity of asafoetida on neurogenic and chronic pain in mice. The results demonstrated that *Ferula asafoetida* decreased acetic acid induced writhing in an inverse dose dependent manner, in which the lowest dose, 25 mg/kg and moderate dose 50 mg/kg produced significant analgesic effect which was comparable to sodium diclofenac. He suggested that the analgesic activity of *Ferula asafoetida* might be because of blocking of visceral receptors or due to the inhibition of prostaglandin synthesis. The results also demonstrated the central analgesic activity on hot-plate test and is thought to involve opioid pain inhibitory pathways. The results of this study was in concordance with our study.

Most of the Published articles are based on the evaluation in anti- inflammatory, anti oxidant and antinociception effects. Therefore, further studies are still needed to confirm the probable mechanism of

analgesic action. Clinical Trials are also required to further establish the clinical efficacy.

CONCLUSION

The present study demonstrated that *Ferula Asafoetida* extract 20mg/kg has a potent analgesic activity. The central analgesic activity may be associated with opioid pain inhibitory pathways and the peripheral analgesic activity may be associated with inhibition of prostaglandin synthesis. It is therefore needed to improvise the available commercial bulk of *Ferula asafoetida* so as to meet the natural requirement of this valuable product. Improved varieties with enhanced drug yields may hold a great promise.

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