

# Hypoglycemic, Antitussive and Analgesic Effects of Nanoparticles of *Cordia myxa* Fruits Extract

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## ABSTRACT

**Background:** *Cordia myxa* is a plant from Boraginaceae family and has many useful therapeutic properties. Aim of the study is to compare the pharmacological efficacy of *Cordia myxa* hydro-alcoholic extract (Bulk Extract (BE)) and nanoparticles of hydro-alcoholic extract (NPE) including hypoglycemic, antitussive, anti-inflammatory and analgesic activity. **Methods:** Hydro-alcoholic maceration extract of dry fruits was powdered to nanoparticle size by ball-milling technique. Hyperglycemia and cough were induced in mice by alloxan (120 mg/kg, i.p.) and ammonia, respectively. Inflammatory and analgesic evaluations of extracts were carried out with the formalin-induced edema in the mice paw and acetic acid tests. NPE and BE were administrated at single dose (750 mg/kg, i.p.). Positive control group was received dextromethorphan (10 mg/kg, orally) in cough and indomethacin (25 mg/kg, orally) for analgesic models. Blood glucose level, the number of coughs and writhes and duration of foot lickings were calculated. **Results:** The blood glucose did not statistically reduce by extracts. Both extracts could significantly inhibit the frequency of cough and

dramatically reduce the duration of paw licking. NPE could significantly reduce writhes. **Conclusion:** We concluded that extracts had no hypoglycemic activity. Both extracts created therapeutic activities better than dextromethorphan. NPE exerted better anti-inflammatory and analgesic activity compared to BE.

**Key words:** Anti-inflammatory, Analgesic, Antitussive effects, *Cordia myxa*, Nanoparticles.

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## INTRODUCTION

*Cordia myxa* (*C. myxa*) fruit is used in folk medicine as a calmativ rheumatic pain, an anthelmintic and antihelminthic. Mucilage of *C. myxa* has anti-leishmanial effects<sup>1,2</sup> and antiradical capacity.<sup>3,4</sup> In some studies, for *C. myxa* it was suggested that its mucilage could decrease rabbit blood pressure and stimulated the respiratory rate.<sup>5</sup> The aqueous *C. myxa* extract stimulated cell mediated and immune responses in mice.<sup>6</sup> The ethanolic extract of *C. myxa* fruits reduced lympho-proliferation and inhibited (without cytotoxicity) the percentage of PMNLs forming Formazan granules *in vitro* immune-modulating test.<sup>7</sup> Recent pharmacological studies have demonstrated that different extracts of *C. myxa* also have some properties like protective effect against doxorubicin-induced cardiotoxicity<sup>8</sup> and liver fibrosis<sup>9</sup> and hepatoprotective effect.<sup>10</sup> Also, antimicrobial effects of *C. myxa* were studied.<sup>11,12</sup>

The *C. myxa* has bronchodilator property probably affects via nitric oxide process.<sup>13</sup> In a study on hydro-alcoholic extract of *C. myxa* fruit it was shown that the extract has analgesic and anti-inflammatory properties in formalin test and acetic acid tests.<sup>14</sup> The *C. myxa* extract have been show nociceptive effect in hot plate test and increased the reactive time to the thermal stimuli.<sup>15</sup> The anti-inflammatory effects of *C. myxa* fruit was demonstrated in acetic acid induced colitis in rats.<sup>16</sup>

Nanotechnology is a branch of technology that attracted much attention today and can be used for improving methods of treatments and diagnosis related to the human and even animal's health.<sup>17,18</sup> Nanoparticles have a high surface to size.<sup>19</sup> Because of small size of nanoparticles, they can cross easily through barriers.<sup>20</sup> Nanoparticles have a conjugating

surface. They can be used for medical purposes, drug delivery, tumor detection and diagnostic imaging.<sup>20-23</sup> Thus, the aim of this study was to validate and making a comparison between efficacy of nanoparticle and bulk hydro-alcoholic extract of *C. myxa* fruits in pharmacological tests; hypoglycemic, antitussive, anti-inflammatory and analgesic activities in experimental and animal modeling.

## MATERIALS AND METHODS

### Animals

For the present study, we used male and female albino mice weighing 18–22 g were obtained from the animal research center of Jundishapur University of Ahvaz. Animal experimentation protocols conformed to the institutional animal ethics committee's guidelines (EE/97.24.3.49684/scu.ac.ir). This experimental study was conducted in veterinary medicine faculty, Shahid Chamran University of Ahvaz, Iran. Animals were housed in cages under 12 hr light-dark cycle conditions at room temperature and were fed with standard pellet die and had free access to water and food. Mice were divided into groups randomly.

### Preparation of Extract and Administration

The powder of fruits was extracted using maceration with ethanol. The powdered fruits were macerated in 70% (v/v) ethanol (5:10 w/v) at room temperature for 72 hr. Then, it was shaken for 4 hr. The mixture was filtered with Buchner funnel and Whatman filter paper No.1. The resulting extract concentrated under pressure using a rotary evaporator in 40°C.

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Next, the extract was powdered with freeze dryer.<sup>24</sup> The yield (w/w) of extract was 34.7%. The extract was stored at refrigerator for future studies. The hydro-alcoholic extract (bulk extract) and nanoparticles of powdered hydro-alcoholic extract were administrated at single dose (750 mg/kg, i.p.). For tests the extracts were suspended with normal saline. There were not any toxicity properties for this dose based on a preliminary experiment (data not showed). Normal saline was taken as control.

### Preparation of Nano Particle Size of Extract

The hydro-alcoholic extract powders were cryomilled in the liquid nitrogen using the zirconia balls at -50°C using a home-made attritor. The ball to powder ratio was 25:1 and the attrition speed was 250 rpm. The resulting mixture has been dried in an oven at 50°C for 12 hr.<sup>25</sup> In this paper, for determination nanoparticles size, the Scanning Electron Micrographs (SEM) of the Nano extract (Figure 1), was prepared in Isfahan University of Technology, Isfahan, Iran.

### Hypoglycemic study

Diabetes mellitus was induced by alloxan (Sigma Aldrich) 120 mg/kg body weight.<sup>26</sup> Thirty minutes prior to injection of alloxan, mice were treated with extracts. Blood glucose levels of mice were measured with glucometer (On Call Plus blood glucose meter, Germany) before treatment and subsequently at 1, 2 and 3 hr after treatment with extracts. Mice with blood glucose level more than 250 mg/dl were considered as diabetic. Three groups of mice were used. Control received normal saline (orally). Group two and three received Nanoparticle of Extract (NPE) and bulk extract (BE) (750 mg/kg, i.p.),<sup>27</sup> respectively.

### Antitussive study

Antitussive effects of extracts were measured by Murine method of ammonia induced cough as described before. Mice were numbered and divided into 4 groups. Twenty minutes after administration of extracts (750 mg/kg, i.p.),<sup>27</sup> mice were individually placed into a 500 ml wide mouth clear glass chamber, exposed to 1 ml 5% NH<sub>3</sub> (loaded in cotton) and the number of cough was counted during 2 min and then 5 min out of the chamber. For scoring purposes, a typical cough is indicated by contraction of abdominal cavity and subsequently opening of the mouth accompanying with sound of cough. Control groups treated with normal saline (orally) and dextromethorphan (Alhavi Pharmaceutical Company) (10 mg/kg, orally) as reference drug.<sup>28</sup>

### Anti-inflammatory and analgesic study

**Formalin test:** Groups of 8 mice were used. The inflammation was produced by subcutaneous injection of 0.04 ml 2.5% formalin in the plantar surface of right hind paw.<sup>29</sup> The extracts (750 mg/kg) were administrated intraperitoneally and after 20 min formalin was injected.<sup>27</sup> The duration of paw licking was measured by chronometer in 5 (acute phase) and 15-25 (chronic phase) min after formalin administration as acute and chronic phase, respectively. Control group received normal saline (orally). Indomethacin (25 mg/kg, orally) was used as reference drug.<sup>16</sup>

**Acetic Acid Test:** Mice were divided into groups of 8 mice for control and test. The extracts (750 mg/kg) were administrated 20 min prior to the acetic acid solution 1% v/v (0.3 ml, i.p.) injection.<sup>27</sup> The mice were individually placed into a stainless steel lab tray dish. The number of writhes produced in mice was counted in first and third 10 min after acetic acid injection. Stretching of the abdomen and at least one of the hind paws was considered as a writhe. Control received normal saline (orally) and indomethacin (25 mg/kg, orally)<sup>16</sup> was administrated as reference drug.<sup>29</sup>

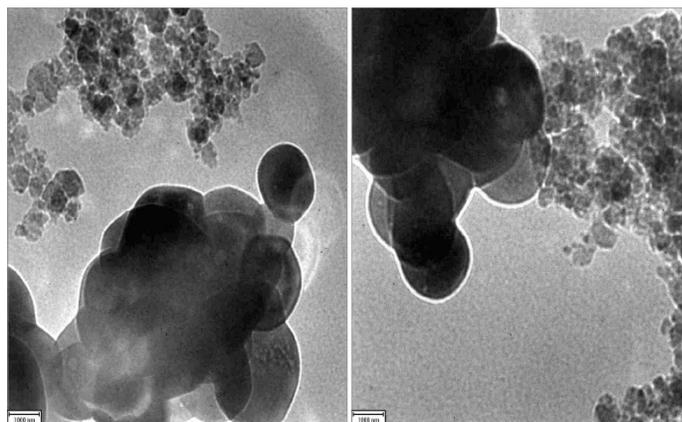
### Statistical analysis

The obtained data were analyzed using SPSS Statistic software (version 17, USA) by *t* test, ANOVA and LSD tests or repeat measure. Results are expressed as mean ± standard error (S.E.M). *P* value was considered significant when *P* < 0.05.

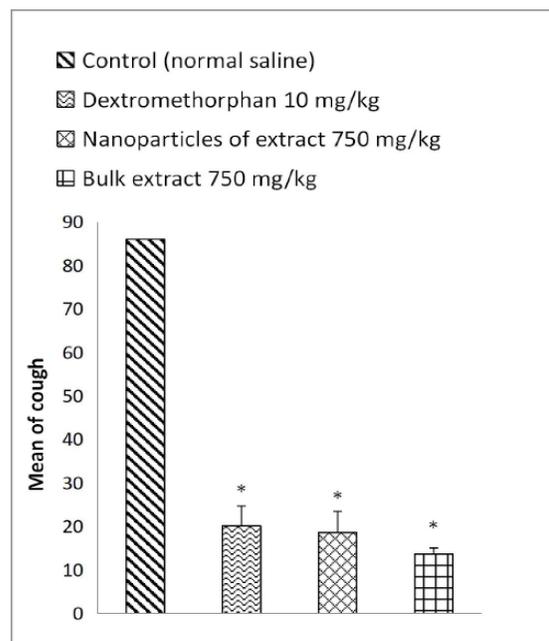
## RESULTS

The mean of blood glucose level were calculated (Table 1). There was no significant difference between groups and times. Only it was seen unexpected fluctuations in bulk group.

In order to evaluate the antitussive activity of NPE and BE mice cough model induced by ammonia are used. The effect of extracts on ammonia induced cough is shown in Figure 2. The mean of cough number was



**Figure 1:** Scanning electron microscope (SEM) images of the nanoparticles of *Cordia myxa* fruits extract.



**Figure 2:** Effect of intraperitoneally injected *Cordia myxa* nano particle and bulk hydroalcoholic extracts on ammonia-induced cough test in mice. The cough was produced by putting the mice into a glass chamber exposed to 1 ml 5% NH<sub>3</sub> (loaded in cotton). The number of cough was counted 2 and 5 min in and out of the chamber, respectively. Values are mean ± S.E.M of cough number. \**P* < 0.0001, compared to control.

measured 86 in control. The mean of cough was significantly decreased to  $18.67 \pm 4.807$  and  $13.67 \pm 1.358$  by NPE and BE in group 3 and 4, respectively. There was a significant difference between group 3 and 4 compared to control ( $P < 0.0001$ ). But there was any significant difference between NPE group compared to BE administrated group ( $P = 0.377$ ). Extracts are nearly more effective than that of dextromethorphan. But there were no significant difference between their effects. Dextromethorphan decreased the frequency of cough to  $20.17 \pm 4.52$  and it was significant compared to control ( $P < 0.0001$ ).

The mean of paw licking time (s) in the acute phase (0-5 min) after formalin injection in the group 1 to 4 were 65.6, 58.5, 28.67 and 50.33 sec, respectively on formalin test (Figure 3). The NPE exhibit significant anti-inflammatory activity compared to control ( $P = 0.021$ ). The mean of paw licking time (s) in chronic phase (15-25 min) after formalin injection in group 1 to 4 were 74.4, 4.33, 0 and 6.17 sec, respectively. Indomethacin as well as the NPE and the BE showed significant anti-inflammatory activ-

ity ( $P < 0.0001$ ). NPE and BE administrated groups did not demonstrated significant difference ( $P = 0.061$ ) (Figure 4).

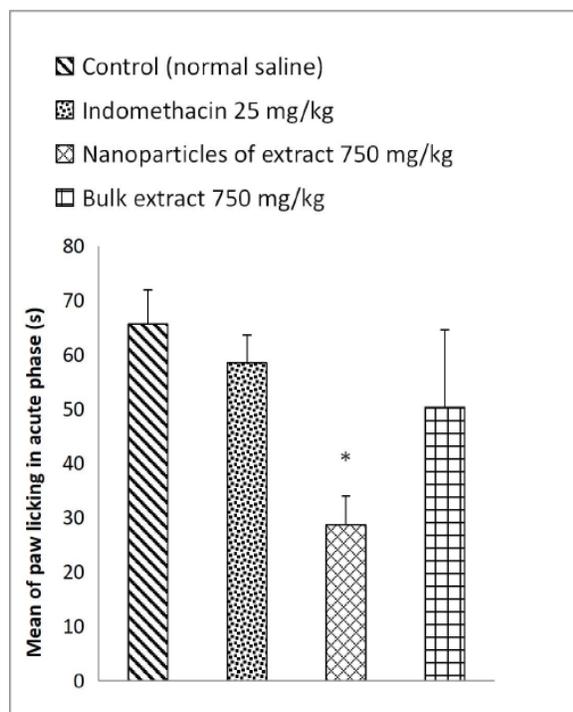
The bulk and nano particle of extract of *C. myxa* fruits significantly reduced the number of writhes induced by a 1% acetic acid solution. The mean of writhing numbers in the acetic acid test in the first 10 min after acetic acid injection was 38.4, 22, 26.33 and 47.0 writhes/10 min in the groups, respectively. The NPE significantly reduced the number of mice abdominal constrictions compared to control ( $P = 0.048$ ) and BE ( $P = 0.002$ ) (Figure 5).

The mean of writhing numbers in mice in third 10 min after acetic acid injection was 20.4, 0.7, 20.33 and 32.8 writhes/10 min, respectively. The bulk extract of fruits showed significant differences but no significant anti-inflammatory activity compared to control ( $P = 0.026$ ). The NPE showed no significant anti-inflammatory activity compared to control in the third min after intraperitoneally acetic acid injection ( $P = 0.989$ ) but it exhibit a significant reduce in the number of abdominal stretching rather than BE ( $P = 0.021$ ) (Figure 6).

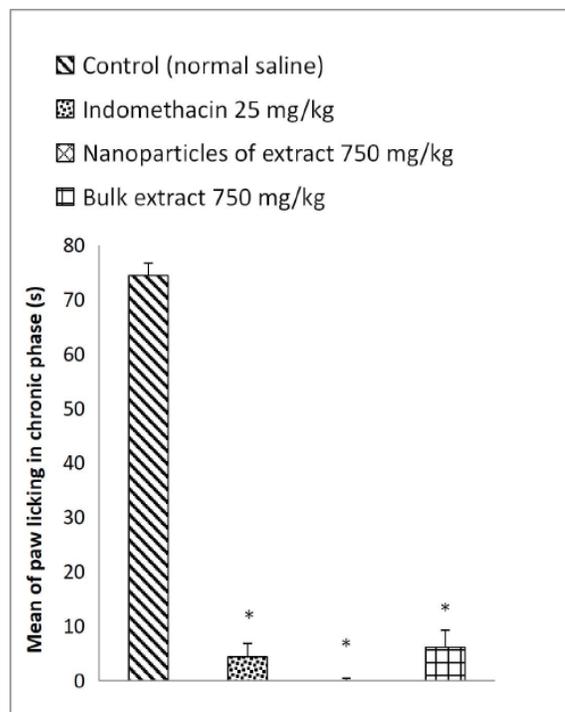
**Table 1: Effect of the intraperitoneal doses of nano and bulk extracts of *Cordia myxa* fruits on alloxan-induced diabetes in mice.**

Group	Treatment	Average of blood glucose level (mg/dl)			
		0 <sup>th</sup> hour	1 <sup>st</sup> hour	2 <sup>nd</sup> hour	3 <sup>rd</sup> hour
I	Normal saline	600	$561.6 \pm 13.46$	$526.6 \pm 34.26$	$525.4 \pm 55.47$
II	Nanoparticle of extract	$533 \pm 41.98$	$561.6 \pm 13.46$	$551.4 \pm 34.08$	$525.4 \pm 55.47$
III	Bulk extract	$379 \pm 64.00$	$501 \pm 17.62$	$381.33 \pm 69.90$	$422.5 \pm 50.50$

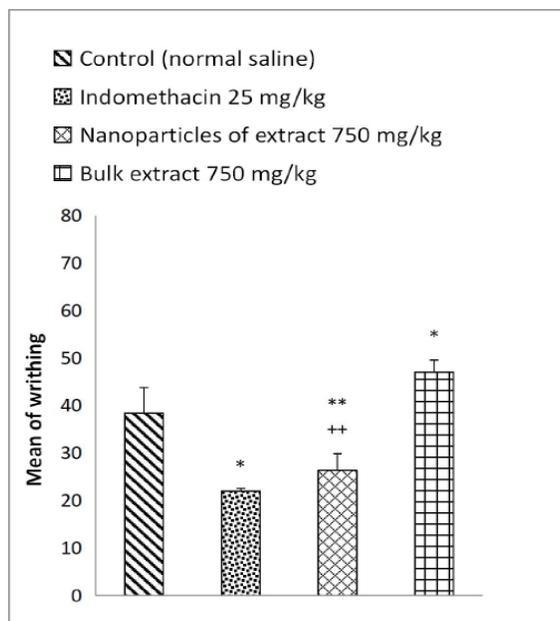
Values are the mean  $\pm$  S.E.M of blood glucose in diabetic mice, compared to control (normal saline).



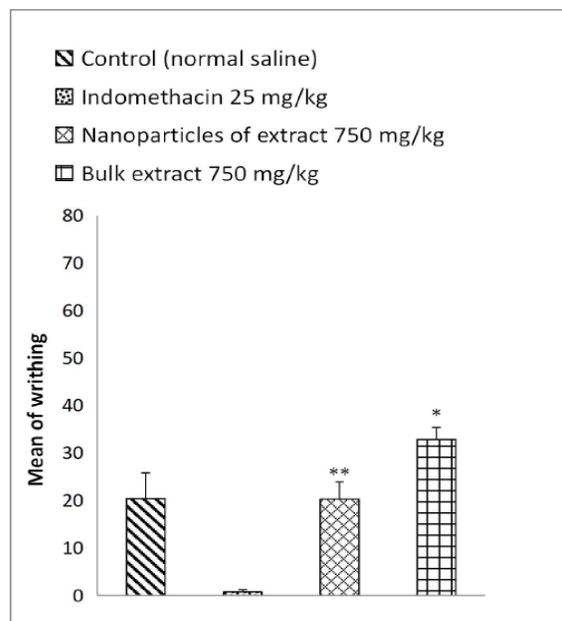
**Figure 3:** Effect of fruit *Cordia myxa* nano and bulk hydro-alcoholic extracts on formalin induced inflammation in hind paw of mice. The inflammation was produced by subcutaneous injection of 0.04 ml of 2.5% formalin in the right hind paw of the mice. Values represent the mean  $\pm$  S.E.M of duration of paw licking in 5 min after treatments as acute phase of inflammation, \* $P < 0.021$ , compared to control.



**Figure 4:** Effect of fruit *Cordia myxa* nano and bulk hydro alcoholic extracts on formalin induced inflammation in hind paw of mice. The inflammation was produced by subcutaneous injection of 0.04 ml of 2.5% formalin in the right hind paw of the mice. Values represent the mean  $\pm$  S.E.M duration of paw licking in 15-25 min after treatments as chronic phase of inflammation, \* $P < 0.0001$  compared to control.



**Figure 5:** Effect of intraperitoneally administrated *Cordia myxa* fruits nano and bulk hydroalcoholic extracts on acetic acid-induced writhing in mice. The number of writhes was counted in second 10 min after intraperitoneally injection of 0.1 ml of 1% v/v acetic acid. Values are mean  $\pm$  S.E.M of writhes in mice in second 10 min post acetic acid injection, \*  $P=0.0001$ , \*\*  $P=0.048$ , compared to control (normal saline); ++ $P=0.002$  compared to BE.



**Figure 6:** Effect of intraperitoneally administrated *Cordia myxa* fruits nano and bulk hydroalcoholic extracts on acetic acid-induced writhing in mice. The number of writhes was counted in third 10 min after intraperitoneally injection of 0.1 ml of 1% v/v acetic acid. Values are mean  $\pm$  S.E.M of writhes in mice in the third 10 min post acetic acid injection, \* $P=0.026$ , compared to control (normal saline); \*\* $P=0.021$ , compared to BE.

## DISCUSSION

In the present study hydro-alcoholic extract of *Cordia myxa* fruit was prepared. The nano particles of extract were produced by ball-milling technique. SEM figures of extract showed the formation of nanoparticle size of extract. The ball milling technique that used in this test is a simple method that doesn't need a high temperature for process.<sup>30-34</sup> So extract probably remains with at least changes in its constituents.

According to a study on phytochemical screening of *C. myxa* fruit extract it was concluded that the extract contains oil, glycosides, flavonoids, sterols, saponins, terpenoids, alkaloids, phenolic acids, coumarins, tannins, resins, gums and mucilage.<sup>35</sup> Thus, it could be suggested that the anti-inflammatory, analgesic and antitussive effects of the extracts may be due to their bioactive constituents specially flavonoids. The polyphenols and flavonoids in fruits may be modulated in anti-inflammatory and nociception effects.

Diabetes was induced by alloxan. Alloxan is a glucose analogue agent that uptake into the beta cells of pancreas by GLUT2 transmembrane carrier protein and accumulated in the cells. In the beta cells, alloxan can result in insulin-dependent diabetes and also by inhibition of glucokinase as glucose sensor could inhibit insulin secretion induced by glucose.<sup>36</sup> Thereby it could be explained that hypoglycemic activity of extracts is act via another mechanisms inducing diabetes not those involved in alloxan-induced diabetes. In our study, the NPE or BE did not have effective therapeutic hypoglycemic activity. This finding is not similar other studies. In a study it was reported that the *C. myxa* fruit aqueous extract caused a significant reduction in blood glucose and glycated hemoglobin of diabetic rats.<sup>37</sup> They used this extract at 500mg/kg of rats and for 30 days. This difference may be related to kind of our extract and dosage of treatment or design of study. However, more detailed researches can judge about it.

*C. myxa* is an effective traditional folk medicine for the treatment of cough. Dextromethorphan is a central acting antitussive drug.<sup>38</sup> Thus

it could be concluded that antitussive activity of extracts is by affecting cough center in brain. The extracts had suitable antitussive effect even better than dextromethorphan. But, NPE was not better than BE. It may be speculated that the size of particle for this extract was not to its delivery to lungs or brain for its antitussive effects. In some studies, Different extracts of *C. myxa* also have some properties like broncho-relaxant effect.<sup>15</sup> This effect may be related nitric oxide modulation.

For evaluation of anti-inflammatory and analgesic activity of extracts, 2.5% formalin was injected subcutaneously in palmar surface of right hind paw in mice. In this study, Indomethacin, a non-steroidal anti-inflammatory drug, produced an inhibitory effect on the inflammation in the formalin and acetic acid tests. Indomethacin is acting as inhibitor agent of cyclooxygenase (COX) 1 and 2. COX-2 is increased by inflammatory agents like cytokines to produce elements associated with pain and inflammation like prostaglandins.<sup>39</sup> Based on a study by Hunskaar and Hole, indomethacin and other NSAIDs affect second phase in this test.<sup>40</sup> As indomethacin can inhibit COX-2 as a NSAID, extracts may act as analgesic and anti-inflammatory agents via COX-2 mechanisms.

In the acute phase of the formalin test, both extracts were reduced paw licking but treatment with nano formulation showed a better effect than bulk extract and Indomethacin. In the chronic phase, both extracts and Indomethacin had significant difference compared the control group, but NPE could obviously reduce the number of paw licking in mice.

In the first 10 min of the acetic acid test, it was demonstrated that NPE had a better effect than BE in reducing writhings. But indomethacin showed better effect than NPE. In the third 10 min of this test, both extracts have no effect on decrease writhing induced by acetic acid. In our previous study, we demonstrated the hydro-alcoholic extract of this fruits possess analgesic and anti-inflammatory effects in formalin and acetic acid tests in mice.<sup>16</sup> Also this finding was reported by Ficarra *et al.* They demonstrated that the analgesic and anti-inflammatory effects of hydro-alcoholic extract of *Cordia myxa* fruits is comparable with indomethacin and tramadol.<sup>41</sup> At present our study we demonstrated the

nano particles of *C. myxa* has better analgesic and anti-inflammatory effects. This may be related to better absorption or distribution and higher blood concentration.

## CONCLUSION

Based on the results obtained from this study it is concluded that hydro-alcoholic maceration extracts have antitussive, analgesic, acute and chronic anti-inflammatory effects in experimental mice models. However, the chemical constituents and mechanism(s) involved in pharmacological effects including measurement of active compound concentration in blood remain to be investigated. We propose the active compounds of *C. myxa* are isolated and each of compounds distinctively evaluated on pharmacological properties.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

## ABBREVIATIONS

**ANOVA:** One way variance analysis ; **BE:** Bulk extract; **C. myxa:** *Cordia myxa*; **COX:** Cyclooxygenase 1 and 2; **i.p:** Intraperitoneally; **LSD:** Least statistical differences; **NH<sub>3</sub>:** Ammonium; **NPE:** Hydro-alcoholic extract; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **PMNLs:** Polymorph nuclear lymphocytes; **S.E.M:** Mean ± Standard error; **SEM:** The scanning electron micrographs.

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