



Anti- Oral Ulcer Activity of *Ficus deltoidea* Leaves Extract on Animal Model

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ABSTRACT

The purpose of this study is to investigate the effectiveness of *Ficus deltoidea* (*F. deltoidea*) as an anti-oral ulcer on animal models. Adult male Sprague Dawley rats were sedated with Nembutal through intraperitoneal route; oral ulcer models were made by applying 99.5% of glacial acetic acid moistened paper disc on rat buccal mucosa. Four groups of these rats were treated respectively with: no treatment (group 1: negative control); Triamcinolone acetonide (group 2: positive control); 250 mg kg⁻¹ *F. deltoidea* extract (group 3: experimental); 500 mg kg⁻¹ *F. deltoidea* extract (group 4: experimental) for 10 consecutive days, respectively. On days 2, 4, 6, 8 and 10, the ulcers size was assessed. Data was analysed statistically by using SPSS. The negative control rats exhibited buccal mucosa injury whereas treatment with *F. deltoidea* and Triamcinolone acetonide resulted in significantly reduced size of oral ulcer. The percentage of inhibitory area of oral ulcer was more prominent in 500 mg kg⁻¹ *F. deltoidea* extract than 250 mg kg⁻¹. Meanwhile, in vivo study showed that *F. deltoidea* extract not toxic up to 1000 mg kg⁻¹. The present findings suggest that *F. deltoidea* extract effectively accelerates oral ulcer healing process, and could therefore be developed as a therapeutic agent for healing oral ulcer.

Keywords: *Ficus deltoidea*, Mas Cotek, oral health, oral hygiene, oral ulcer

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INTRODUCTION

Oral health is essential to general health and the quality of life. It is a state of being free from mouth pain, diseases and disorders. In current clinical practice, oral ulcer has become one of the most common oral pathological conditions found in oral cavity. Oral ulcer occurs on the mucous membrane of the oral cavity and it is a sore lesion in the mouth (Sukhitashvili et al., 2012). There are several

types of oral ulcerations which are recurrent aphthous stomatitis (RAS), primary herpetic gingivo-stomatitis traumatic ulcer and vesiculobullous disorders. RAS is one of the most common painful oral mucosal conditions observed in patients. It is a common condition, restricted to the mouth, that typically starts in childhood or adolescence as multiple, small, round, or ovoid ulcers, with circumscribed margins, yellow or grey floors surrounded by erythematous haloes (Halim et al., 2014).

Treatment of oral ulcers depend on the aetiology and aimed primarily at symptom management, that is, suppressing inflammatory responses and reducing frequency of recurrences or avoiding occurrence altogether (Preeti et al., 2011; Srinivas-Rao, 2010). Treatment can be non-therapeutic and therapeutic management. Non-therapeutic treatment includes supportive measures with attention to immaculate oral hygiene, prevention of trauma and avoiding certain foods (Novianty et al., 2011). Therapeutic treatment options are including anti-inflammatory agents, immuno-modulatory agents and antibiotics (Srinivas-Rao, 2010). Herbal medicine is considered as a therapeutic agents (Osemene et al., 2011).

According to the World Health Organization (WHO), approximately 80% of people in developing countries depend on herbal medicines for primary health care, of which major portion involves the use of plants extracts or active principles originating from parts of plants. In most parts of the world, plant extracts are still used in their crude forms. These extracts are generally administered orally (Salleh & Ahmad, 2013). Today there is a worldwide resurgence in herbal medicine for medicinal purpose (Salleh & Ahmad, 2013) as can be seen in the fact that more than 40% of commonly prescribed medicine originate directly or indirectly in plants (Schulz & Tyler, 2001; Farnsworth & Soejarto, 1991). In Malaysia, herbal medicines have gained popularity as an alternative to modern medicine particularly with the establishment of Traditional and Complementary Medicine Division under the Ministry of Health, Malaysia, and also the presence of NKEA EPP#1 Research Grant Scheme (NRGS) under Ministry of Agriculture, Malaysia.

Ficus deltoidea (*F. deltoidea*) is a herbal plant popular with Malay people. It is traditionally used in treating ulcer and other diseases. *F. deltoidea* is a small perennial herb which rarely exceeds 2 meters in height and is domestically cultivated. It is known by various names such as Mas Cotek in Malaysia, Tabat Barito in Indonesia, Agoluran in the Philippines and Kangkalibang in Africa (Salleh & Ahmad, 2013). In Malaysia, most of *F. deltoidea* species are mostly y found in the eastern states of Terengganu and Kelantan. *F. deltoidea* is known as Mas Cotek in Malay language, with the word 'Mas' means gold and 'Cotek' means spot. Thus, the Malays called this plant *Mas Cotek* to refer to the golden spots found on the surface of the leaf (Ahmad et al., 2016).

Each part of the plant is known to have medicinal properties. The fruits are chewed to relieve headache, toothache and cold; powdered root and leaves of the plant has been applied externally to wounds and sores and around the joints for relief of rheumatism (Abkhan, 2009). It is also traditionally consumed as herbal drink for women after childbirth to help in strengthening the uterus (Salleh & Ahmad, 2013) and acts as a libido booster for both men and women (Bodeker, 2009).

Some studies have demonstrated the antioxidant role of *F. deltoidea* extracts (Hakiman & Maziah, 2009; Aris et al., 2009), antinociceptive, photocytotoxic (Hasham et al., 2013),

antidiabetic activities (Adam et al., 2012), antihypertensive activity (Razali et al., 2013), wound healing on neck skin of rats (Abdulla et al., 2010), and uterine contraction activities via multiple binding receptor (Salleh & Ahmad, 2013). Zahra et al. (2009) meanwhile reported that *F. deltoidea* water extract can significantly reduce peptic ulcer- induced by ethanol. In addition, preliminary acute toxicity studies reveal that *F. deltoidea* is not toxic based on brine shrimp toxicity test (Aminudin et al., 2007). In spite of these evidences the effect of *F. deltoidea* on oral ulceration has not been no scientifically documented.

METHOD

Preparation of *F. deltoidea* aqueous extract

Aqueous extract preparation was made based on Salleh and Ahmad (2013). The leaves of *F. deltoidea* from female sub-species used in this study were purchased from Herbal Plantation, Kuala Selangor, Malaysia. The leaves were air-dried, cut into small pieces and grounded into powder form. Each of the pulverized parts was weighed (100 g) and boiled twice in 1 L distilled water for 4 hours. The aqueous extract was then concentrated by heating at 60°C and was later subjected to freeze- drying (yield 7.36% and 11.61% w/w, dry weight basis for leaf) and was stored in a container until further use. Stock solution was obtained by dissolving small aliquots of this extract in distilled water based on desired concentration (Salleh & Ahmad, 2013).

Preparation of Triamcinolone acetonide dental, 0.1%

Triamcinolone acetonide dental is known as a medium-strength corticosteroid. In this study, Triamcinolone was used as a positive control and it was obtained from the Green Pharmacy, Puncak Alam. The drug was administered orally to the experimental models (Halim et al., 2014).

Animals preparation and experimental procedures

Adult male Sprague Dawley (SD) rats weighing 180 – 200 g were purchased from the animal house, Faculty of Pharmacy, Universiti Teknologi MARA. The rats were housed under controlled environment with temperature kept at 27°C, relative humidity between 30 - 70%, 12 hours' dark and 12 hours' light cycle and had free access to rodent food pellet and water ad libitum. The cleanliness of housing environment was maintained daily. Each group of rats to be studied consists of six animals (n = 6). All experimental procedures were approved by the Universiti Teknologi MARA Animal Ethics Committee.

An oral ulcer model was made by modification based on Slomiany et al. (1999) and Fujisawa et al. (2003). The rats were sedated with dose of 50 mg kg⁻¹ of Nembutal through intraperitoneal route. The anaesthetic effect was confirmed by monitoring the reduced respiratory rate and no response to gentle pinching of foot pad. The rats were placed under heat pad to maintain its core body temperature, while rectal temperature is continuously observed (Salleh et al., 2011). 4 mm filter paper disc (Whatman No. 1) soaked in glacial acetic acid (99.5%) was applied to the left buccal mucosa of the rats for 30 seconds. This technique generated an immediate tissue necrosis, which then produced a single crateriform ulcer in each of the

experimental rats 2 days later. The ulcer normally remains for 14 days (Novianty et al., 2011; Fujisawa et al., 2003), normally.

On the day of the experiment, the rats were randomly divided into 4 groups of 6 rats each as shown in Table 1. The groups were numbered 1- 4. In this study, the extract powder was dissolved in distilled water based on the concentration before being administered on the animal models. The animals were treated with application of medicament for 2 - 3 minutes, twice a day for 10 consecutive days. On day 2, 4, 6, 8 and 10, the ulcer size was assessed.

Table 1
The groups of sample based on type of treatments

Group 1:	rats were negative controls
Group 2:	treated with Triamcinolone acetonide, 0.1% as positive control (referred study done by Daddy et al. 2014 on oral ulcer)
Group 3:	treated with 250 mg kg ⁻¹ <i>F. deltoidea</i> leaves aqueous extract
Group 4:	treated with 500 mg kg ⁻¹ <i>F. deltoidea</i> leaves aqueous extract

Gross lesion and oral ulcer size evaluation

The evaluation procedure was made by modification based on Zahra et al. (2009). Each oral ulcer at buccal mucosa was examined. The length (mm) and width (mm) of the ulcer was measured by a sliding calliper and ruler. Ulcer size was taken on day 2, day 4, day 6, day 8 and day 10. The inhibition percentage (I%) was calculated by the following formula (based on Kauffman & Grossman, 1987 with modification):

$$I\% = \frac{UA_{\text{control}} - UA_{\text{treated}}}{UA_{\text{control}}} \times 100\% \quad (1)$$

UA: The sum of the areas of all lesions for each buccal mucosa

In vivo acute toxicity study

LD₅₀ is defined as the dose required to kill half the members of a tested population in the specified duration. LD₅₀ figures are frequently used as a general indicator of a substance's acute toxicity. In this part of the study, six rats were used for each dose. They were weighed and marked with a coloured marker pen. *F. deltoidea* leaves aqueous extract at doses 50, 150, 250, 500 and 1000 mg kg⁻¹ were administered orally. The time of administration was noted. The numbers of death in each dose within 48 hours were recorded. The probit units were obtained from the percentage of death occurring by referring to the simplified statistical table (Finney, 1971). The probit units were plotted against log-dose-concentration. The LD₅₀ was obtained using the following formula, with n= the total number of rats in each group:

$$SD = \frac{\text{dose of probit 6} - \text{dose of probit 4}}{2 \times 2n} \quad (2)$$

For gross behaviour study, each rat was observed for any abnormal signs and behaviours within 30 minutes after oral administration of varying concentrations of *F. deltoidea* aqueous extract. Animal surviving the observation period of 45 minutes were examined at interval of 2 hours for another 8 hours. Each rat was graded according to whether there were any changes in behaviour (spontaneous or induced) from the control rats:

- 0 = no change
- + = increased activity; subdivided into +1 (moderate) and +2 (significant)
- - = decreased activity; subdivided into -1 (moderate) and -2 (significant).

Statistical analysis

The collected data were analysed by SPSS version 21.0 for Windows. The data were analysed statistically by Independent t-test with significant p values of <0.05.

RESULTS AND DISCUSSION

Table 2 shows the comparison of oral ulcer size and inhibition percentage area between group 1 (negative control) and group 2 (positive control, treated with Triamcinolone acetonide dental, 0.1%). From day 2 until day 10, the oral ulcer size for group 1 (negative control) was = 15.90 ± 1.1 mm², with no occurrence of inhibition percentage. Thus, no healing process occurred for the oral ulcer. Meanwhile, for group 2 the effect of Triamcinolone on oral ulcer significantly reduced its size starting on day 6 with percentage of inhibition of 66.48% (*P<0.05) and full healing on day 10.

Triamcinolone acetonide dental is commonly used for the temporary relief of symptoms of mouth sores resulting from injury (Halim et al., 2014). This drug comes in the form of a dental paste which is applied to affected area on the inside of the mouth. It works by reducing the swelling and pain that can occur with mouth sores. However, there are side effects which include burning, irritation, dryness, or redness of the treated area (Fani et al., 2012; Khandwala et al., 1997).

Table 2

Comparison of oral ulcer size difference and inhibition percentage between group 1 (negative control) and group 2 (positive control/ treated with Triamcinolone acetonide)

Variable	Observed oral ulcer size and inhibition % in rats					
	Group 1 (negative control)	Group 2: treated with Triamcinolone acetonide, 0.1% (positive control)				
		Day 2	Day 4	Day 6	Day 8	Day 10
Mean \pm SEM (ulcer size, mm ²)	15.90 \pm 1.1	15.90 \pm 1.1	10.90 \pm 1.30	5.33 \pm 0.50	2.22 \pm 0.30	0.00
Inhibition (%)	0.00	0.00	31.45	66.48	86.04	100
p- values	-	-	-	*	**	***

All values are expressed as mean \pm standard error mean. Value with different superscripts are significantly different, *p<0.05; **p<0.01; ***p<0.001

Arguably, this study is the first to display the anti-oral ulcer effect of *F. deltoidea*, and role in healing oral cavity caused by oral ulcer. Table 3 shows the presence of 250 mg kg⁻¹ *F. deltoidea* aqueous extract can significantly reduce the size of oral ulcer and increase the percentage of inhibition area of oral ulcer. The size of oral ulcer started to reduce on day 6 with percentage inhibition area of 52.64% (*P<0.05). On day 8, the effect of *F. deltoidea* with the dose of 250 mg kg⁻¹ vigorously reduced the size of ulcer with percentage inhibition area of 92% (P<0.001). By day 10, the percentage inhibition area was 100% showing full recovery.

Table 3
Comparison of oral ulcer size difference and inhibition percentage between group 1 (negative control) and group 3 (treated with 250 mg kg⁻¹ of *F. deltoidea* extract)

Variable	Observed oral ulcer size and inhibition % in rats					
	Group 1 (negative control)	Group 3: treated with 250 mg kg ⁻¹ of <i>F. deltoidea</i> extract				
		Day 2	Day 4	Day 6	Day 8	Day 10
Mean ± SEM (ulcer size, mm ²)	15.90±1.1	15.60±0.8	12.20±0.40	7.53±0.50	1.22±0.90	0.6±0.30
Inhibition (%)	0.00	1.89	23.27	52.64	92.33	96.22
p- values	-	-	-	*	***	***

All values are expressed as mean ± standard error mean. Value with different superscripts are significantly different, *p<0.05; **p<0.01; ***p<0.001

Similarly, 500 mg kg⁻¹ of *F. deltoidea* aqueous extract also significantly reduced the size of the ulcer and increased the percentage of inhibitory area (Table 4). The size of oral ulcer significantly started to reduce from day 4 with percentage of inhibition area of 59.69%. By day 6, the percentage area increased to 92.33%, with full recovery on day 10.

Table 4
Comparison of oral ulcer size difference and inhibition percentage between group 1 (negative control) and group 4 (treated with 500 mg kg⁻¹ of *F. deltoidea* extract)

Variable	Observed oral ulcer size and inhibition % in rats					
	Group 1 (negative control)	Group 4: treated with 500 mg kg ⁻¹ of <i>F. deltoidea</i> extract				
		Day 2	Day 4	Day 6	Day 8	Day 10
Mean ± SEM (ulcer size, mm ²)	15.90±1.1	14.60±0.5	6.41±0.40	1.33±0.20	0.22±0.10	0.00
Inhibition (%)	0.00	8.18	59.69	91.64.64	98.62	100
p- values	-	-	*	**	***	***

All values are expressed as mean ± standard error mean. Value with different superscripts are significantly different, *p<0.05; **p<0.01; ***p<0.001

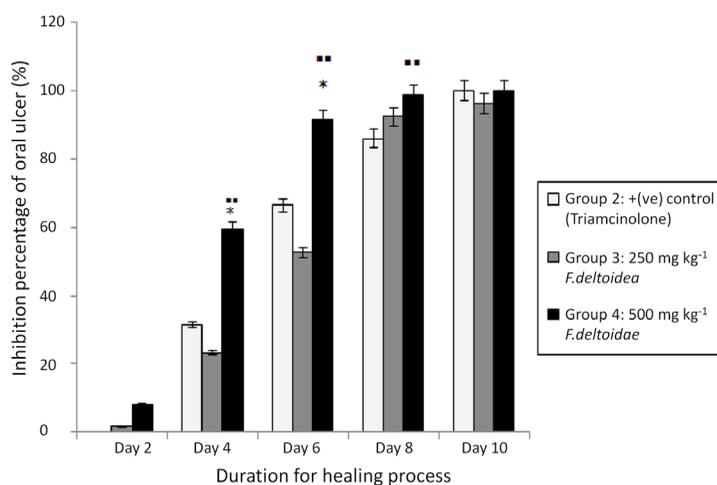


Figure 1. Inhibition percentage area of oral ulcer with different treatments. *Group 4 was significant as compared to positive control $p < 0.05$ (triamcinolone); ** Group 4 was significant as compared to group 3, $p < 0.01$

Figure 1 shows the percentage inhibitory area of oral ulcer increased rapidly in group 4 (treated with 500 mg kg^{-1} of *F. deltoidea* extract), and starting as early as day 4 compared with group 2 (treated with Triamcinolone) and group 3 (250 mg kg^{-1} *F. deltoidea*). Moreover, in day 6 the treatment with 500 mg kg^{-1} of *F. deltoidea* has vigorously increased the inhibition percentage area of oral ulcer to achieve full recovery on day 10. Thus, our findings suggest that 500 mg kg^{-1} of *F. deltoidea* leaves aqueous extract is more effective for the treatment of oral ulcer than 250 mg kg^{-1} and o Triamcinolone acetamide.

Apart from its effect on oral ulcer, *F. deltoidea* whole plant aqueous extract is also reported to reduce the size of peptic ulcer in rats (Zahra et al., 2009). In another study, Novianty et al. (2011) found that allicin from garlic extract significantly reduced the size of oral ulcer resembling the effect of Triamcinolone acetamide and that of *F. deltoidea* leaves aqueous extract. It is speculated that the effect of *F. deltoidea* leaves aqueous extract must work the same way as reported by Novianty et al. (2011) and Zahra et al. (2009).

F. deltoidea extract contain flavonoids with a high anti-oxidant (Hakiman & Maziah, 2009) content. Flavonoids are thought to provide health benefits through cell signalling pathways and antioxidant effects. They have been reported to possess anti- inflammatory and high antioxidant activities (Chua et al., 2015; Omar et al., 2011). Other phytochemical components in *F. deltoidea* such as tannins too possess significant anti-inflammatory activity (Sulaiman et al., 2008; Abdullah et al., 2009). Therefore, we predict that the effect of *F. deltoidea* aqueous extract on oral ulcer may increase cellular antioxidant enzyme and restore the impaired antioxidant defence system in patients with aphthous ulcer and their recurrences. Based on anti- inflammatory action of *F. deltoidea*, we also suggest that it may accelerate the healing process via re-epithelization at buccal mucosa.

In toxicological studies, five dose: 50, 150, 250, 500, 1000 mg kg^{-1} of *F. deltoidea* extract were administered orally to rats. Results indicated absence of lethal effects on rats as in the case

of each tested dose there were no acute toxicity symptoms and spontaneous activities and other physiological behaviours were unchanged (Table 5). According to the study done by Fazliana et al. (2008), *F. deltoidea* had no toxic effects to the bone marrow, liver and renal functions. Based on the haematological and biochemical results, their study also suggested that when *F. deltoidea* aqueous extract is administered to rats daily for 90 days no toxic effect were noted thereby suggesting it might be safe for humans too. According to the study done by Aminudin et al. (2007), non-toxicity of *F. deltoidea* leaves aqueous extract was also established by brine shrimp toxicity test. Farsi et al. (2013) too, showed no significant increase in urea and creatinine levels were observed, suggesting that this extract does not have an effect on renal functions. Thus, our study shows that *F. deltoidea* leaves aqueous extract is safe for consumption.

Table 5
Gross behavioural effects of the *F. deltoidea* leaves aqueous extract on rats ($n = 6$)

Activity	Doses (mg kg ⁻¹)				
	50	150	250	500	1000
Spontaneous activity	50	150	250	500	1000
Aggressiveness	0	0	0	0	0
Convulsion	0	0	0	0	0
Corneal reflex	0	0	0	0	0
Cyanosis	0	0	0	0	0
Exophthalmos	0	0	0	0	0
Gaspings	0	0	0	0	0
Hind limb placing	0	0	0	0	0
Piloerection	0	0	0	0	0
Positional	0	0	0	0	0
Straub tail	0	0	0	0	0
Stretching	0	0	0	0	0
Tail pinch	0	0	0	0	0
Tremors	0	0	0	0	0
Visual placing	0	0	0	0	0

Keys:

- 2 Significantly decrease in activity/ response
- 1 Moderate decrease in activity/ response
- 0 No change compared to the control
- +1 Moderate increase in activity/ response
- +2 Significant increase in activity/ response

CONCLUSION

F. deltoidea had significantly reduced the size of the oral ulcer and increased the percentage of inhibition area. *F. deltoidea* can be an alternative for the treatment of oral ulcer. The present study provides preliminary scientific evidences on the anti- oral ulcer potential of *F. deltoidea* leaves extract which has been found to have no significant toxic effect on rats. The findings thus justify the traditional use of *F. deltoidea* to heal oral ulcer.

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