American Journal of Pharmacology and Toxicology 6 (2): 68-75, 2011
ISSN 1557-4962

Reversal of Dexamethasone Depressant Action in Wound Healing by *Ficus Benghalensis* L. Roots

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Abstract: Problem statement: *Ficus benghalensis* is widely used plant world wide traditionally as well as scientifically. It has a wide uses in various medical ailments. As a part of pharmacological evaluations, we have carried out wound healing activity specially in dexamethasone depressed healing conditions. **Approach:** Wound healing activity was established by two medels namely incision and excision. **Results:** The roots of *Ficus benghalensis* clearly reverted the antihealing in presence of dexamethasone treated animals. It happened through increase in breaking strength in incision model and increase in percentage wound contraction and reduction in period of epithelialization. **Conclusion:** Presence of various chemical constituents in the roots of *Ficus benghalensis* specially saponins, flavanoids, taannins and alkaloids were responsible for antagonizing the antihealing effect of dexamethasone treated animals.

Key words: Ficus benghalensis, wound healing, dexamethasone treated, incision wound, excision wounds, wound models, drug administration, Analysis Of Variance (ANOVA), wistar rats

INTRODUCTION

Wound is a breach in the normal tissue continuum, resulting in a variety of cellular and molecular sequelae. The basic principles of optimal wound healing which include minimizing tissue damage, debriding nonviable tissue, maximizing tissue perfusion and oxygenation, proper nutrition and moist wound healing environment have been recognized for many years (Pierce and Mustoe, 1995). A number of drugs ranging from simple non-expensive analgesics to complex and expensive chemotherapeutic agents administered in the management of wound affect healing either positively or negatively (Prasad and Rao, 1995). Aspirin, indomethacin, cytotoxic agents and immunosuppressant have been proved experimentally to affect healing negatively (Lee, 1968; Rao *et al*., 1991; Raju and Kulkarni, 1986).

Ficus benghalensis (Moraceae, Mulberry family) is commonly known as Banyan tree or Vata or Vada tree in Ayurveda. There are more than 800 species and 2000 varieties of Ficus species, most of which are native to the old World tropics. *Ficus benghalensis* a remarkable tree of India sends down its branches and great number of shoots, which take root and become new trunk. This tree is considered to be sacred in many places in India. Earlier glucoside, 20-tetratriaconthene-2-one, 6-heptatriacontene-10-one, pentatriacontan-5-one, beta sitostirol-alpha-D-glucose and meso-inositol have been isolated from the bark of *Ficus benghalensis* (Subramanian and Misra, 1978; CSIR, 1952). Leaves contain crude protein 9.63%, crude fibres-26.84, CaO-2.53 and Phosphorus-0.4%. It yields latex containing Caoytchoue (2.4%), Resin, Albumin, Cerin, Sugar and Malic acid. It is used in Ayurveda for the treatment of Diarrhea, Dysentery and piles, (Mukherjee *et al*., 1998; Husain *et al*., 1992) teeth disorders, (Aiyer, 1960) Rheumatism, skin disorders like sores, (Warrier *et al*., 1996) to boost immune system, (Gabhe *et al*., 2006) as a hypoglycemic (Shrotri and Aiman, 1960; Deshmukh *et al*., 1960; Augusti, 1975; Augusti *et al*., 1994). The extracts of *Ficus benghalensis* were also reported to inhibit insulinase activity from liver and kidney (Achrekar *et al*., 1991). Fruit extracts exhibited anti-tumor activity in the potato disc bioassay (Mousa *et al*., 1994). Two flavonoid compounds, viz. 5, 7-dimethyl ether of leucopelargonidin 3-0-alpha-L rhamnoside and 5, 3,-dimethyl ether of leucocyanidin 3-0-alpha-D galactosyl cellobioside were obtained from the bark of *F. benghalensis* evaluated for anti-oxidant activity in hyperlipidemic rats Daniel *et al*., 1998). It was also found to inhibit the lipid peroxidation. (Shukla *et al*., 2004). Various extracts of *Ficus benghalensis* was screened for its anti-allergic and anti-stress potential in asthma by milk induced leucocytosis and milk induced eosinophilia (Taur *et al*., 2007). Other species of Ficus

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viz. *Ficus inspida* (Amorin *et al*., 1999). *Ficus carica*, (Iqbal *et al*., 2001).

Till today, there are not many agents which are able to successfully overcome the antihealing effect of corticosteroids. Dexamethasone is a very potent anti-inflammatory Glucocorticoids used in organ transplantation and skin allograft (Tripathi, 2004). Glucocorticoids are known to suppress wound healing (Paul and Thomas, 1968). Dexamethasone treatments strongly interfere with both the synthesis and degradation of type I and type III collagen (Oishi *et al*., 2002). It is also a potent transcriptional inhibitor of human type VII collagen promoter activity in dermal fibroblasts, which leads to decreased anchoring of fibril formation (Gras *et al*., 2001). Significant inhibition of growth of pathogenic microorganisms was observed in vitro by traditional drugs like Ficus benghalensis, Azardicta indica and Annona squamosa. No scientific evidence was available for the wound healing activity on the roots of *Ficus benghalensis*; therefore the present research was undertaken.

MATERIALS AND METHODS

Collection and Authentification of plant: Roots of *Ficus benghalensis* was collected from the adjoining areas of Modasa (Gujarat, India). The collection was done in the month of August, 2010. It has been authenticated by Dr. M.K. Jangid, Associate Professor, Department of Botany, Hemchandra North Gujarat University, Gujarat, India by carrying out microscopic and macroscopic characteristics and voucher specimen was deposited in the institute for future reference.

Preparation of the root extract: Dried and coarsely 500 g powdered roots of *Ficus benghalensis L.* were extracted with 90% (v/v) ethanol in soxhlet apparatus for 36 hrs and aqueous extract was prepared by using maceration technique of extraction. Filter the filtrate. The filtrate was concentrated on water bath using petridish. The temperature was maintained at 50 ^{0}C. The semisolid extract was dried and weighed. The semisolid mass (brown colour) was obtained and used for further phytochemical study and animal activity.

Acute toxicity study

Acute toxicity study was done in rats weighing between 150-200 g. Rats were fasted overnight. They were divided into 5 groups of two animals each. The ethanolic extract of *Ficus benghalensis* was administered orally through the feeding tube to the pair of rats of each group in ascending and widely spaced doses viz. 10, 30, 100, 300, 1000 mg kg^{-1}. The animals were observed continuously for 2 h and then occasionally for further 4 h and finally overnight mortality was recorded. No signs of toxicity were observed even with 1000 mg kg^{-1} of *Ficus benghalensis*. So the dose of the extract chosen for the study was 100 mg kg^{-1} which is corresponding to the 1/10th of the maximum tolerated dose (1000 mg kg^{-1}) (Ghosh, 1971).

Drugs and their administration: Ketamine injection was obtained from Neon Laboratories Limited (Mumbai, India), Dexamethasone was obtained from Zydus Alidac (Ahmedabad, India). For oral administration, a suspension of aqueous and ethanol extract (8%) was prepared using 2% gum acacia. The drugs were administered once a day from day 1 and continued till the completion of the models.

Wound Healing Models: Animals and grouping: Wistar albino rats of either sex weighing between 180 and 200 g were obtained from Jay Research Foundation, Vapi. The study was approved by the Institutional Ethics Committee for animal experimentation VBTCP (VBTCP/IEAC/10/12/31), Umrakh and all the procedures on animals were carried out as per CPCSEA guidelines, India. The animals were acclimatized to standard laboratory conditions of temperature (22±3°C) and maintained on 12:12 h light: dark cycle. They were provided with regular rat chow (VRK laboratory animal feed) and distilled water *ad libitum.*

Group 1: Control group treated with simple saline orally (*p.o*)
Group 2: Dexamethasone treated group intraperitoneally (*i.p*)
Group 3: Aqueous extract of *Ficus benghalensis* L. + Dexamethasone (*p.o + i.p*)
Group 4: Ethanolic extract of *Ficus benghalensis* L. + Dexamethasone (*p.o + i.p*)

Incision wound model: All animals were anaesthetized before wound creation and two paravertebral long incisions were made through the skin at the distance of about 1.5 cm from midline on each side of the depilated back of rat. The both edges kept together and stitched with black silk surgical thread (no. 000) and a curved needle (no. 11). The continuous threads on both wound edges were tightened for good closure of the wound. After stitching, extract ointment and standard ointment were applied daily up to 9 days; when wounds were cured thoroughly the sutures were removed on the day

9 and tensile strength of cured wound skin was measured using tensiometer.

Excision wound model: Excision wounds were created by excising a circular piece (500 mm^3 in area) of full thickness skin from the dorsal interscapular region. Wound contraction was monitored by measuring wound area, planimetrically, on alternate days till the wounds were completely healed. This was expressed as percentage of wound contraction. Time taken for complete epithelialization was noted by recording the days required for fall of scab leaving no raw wound behind.

Drug administration: Animals bearing a given wound were divided into 4 groups of 6 animals each. First group of animals received distilled water and served as control, Second group received dexamethasone (0.17 mg kg^{-1}im), third group received 100 mg kg^{-1}, orally of aqueous extract of *Ficus benghalensis and dexamethasone* (0.17 mg kg^{-1} im) *and* the fourth group received ethanolic extract of *Ficus benghalensis* (100 mg/kg, orally) and dexamethasone (0.17 mg kg^{-1} im). The *Ficus benghalensis(aqueous and ethanolic)* extract was given daily, dexamethasone on alternate days from day 0 to the day of complete healing or the 10th post-operative day, according to the wound healing model.

Statistical analysis: Results were Analysed by one Way Analysis Of Variance (ANOVA) using post hoc dunnet's test and p-value < 0.05 was considered significant.

RESULTS

Phytochemical analysis: On preliminary phytochemical screening the extract showed that the roots of *Ficus benghalensis* L. contain saponins, tannins, alkaloids and flavanoids while other constituents like amino acids, carbohydrate was absent (Table 1). Further the presence of these chemical constituents was confirmed by HPTLC analysis as R_f values for standard, aqueous and ethanolic extract respectively are shown in Plates and tables. The 3 D images contains First with Standard, secondly with aqueous and lastly with ethanolic extract peaks. (Fig. 1-4 and Table 1-5).

Incision wound model: A significant decrease in wound breaking strength in dexamethasone alone treated group was observed as compared to control group.

Table 1: Phytochemical analysis of extract of f*icus benghalensis*

Phytochemical	Confirmation
Amino acids	-
Carbohydrates	-
Tannins	+
Alkaloids	+
Flavonoids	+
Saponins	+

Table 2: Tannins

	Gallic acid		Ficus bengalensis (Alcoholic)		Ficus bengalensis (Aqueous)	
Peak	R_f	AREA	R_f	AREA	R_f	AREA
1	0.34	1571.7	0.17	1581.2	0.30	1864.0
2	0.42	12246.8	0.42	18372.5	0.38	32540.9
3	0.55	13677.0				

Table 3: Alkaloids

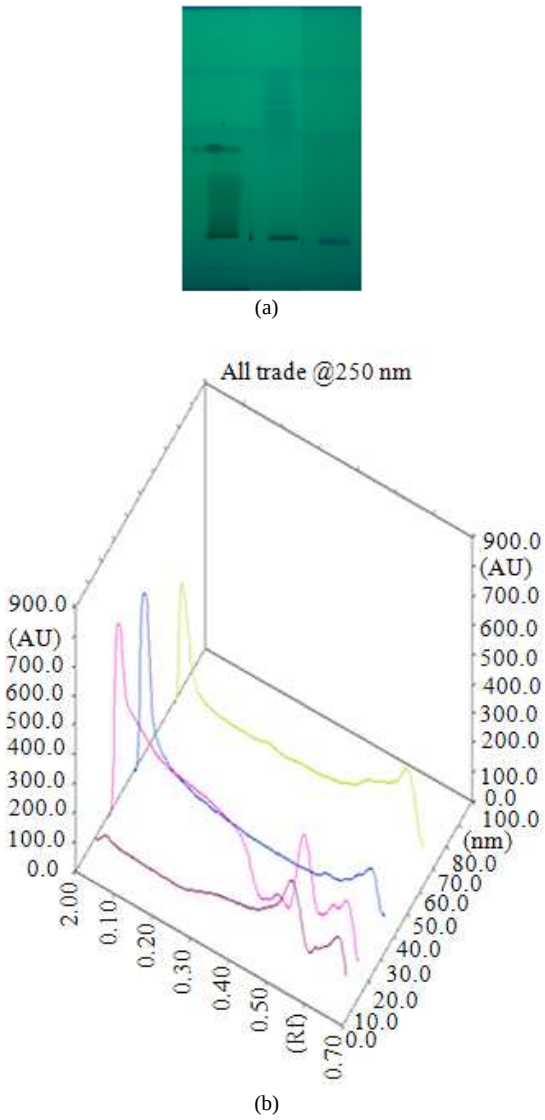
	Ficus bengalensis (Alcoholic)		*Ficus bengalensis* (Aqueous)	
Peak	R_f	AREA	R_f	AREA
1	0.04	22219.1	0.05	11863.3
2	0.13	4283.0	0.17	220.8
3	0.18	6652.7	0.30	1091.1
4	0.30	2595.6	0.36	728.2
5	0.41	171.4	0.41	168.5
6	0.44	1814.3	0.45	266.9
7	0.58	493.4	0.49	350.2
8	0.62	914.3	0.61	1224.9
9	0.67	652.4	0.67	807.5
10	0.72	3582.2	0.75	250.8
11	0.81	4417.8	0.81	425.0

Table 4: Flavanoids

	Rutin		*Ficus bengalensis* (Alcoholic)		*Ficus bengalensis* (Aqueous)	
Peak	R_f	AREA	R_f	AREA	R_f	AREA
1	0.01	2231.6	0.02	7848.1	0.05	7553.9
2	0.07	4429.9	0.06	13485.6	0.20	415.0
3	0.18	3762.5	0.32	7998.6	0.25	1373.7
4	0.23	6077.3	0.46	2067.4	0.60	173.5
5	0.28	62162.2	0.58	644.6	0.65	200.0
6	0.47	7114.3	0.66	164.7	0.77	1009.5
7	0.55	8088.2	0.79	1798.3	0.84	807.7
8	0.94	6217.7			0.94	5399.7

Table 5: Saponins

	Ficus bengalensis (Alcoholic)		*Ficus bengalensis* (Aqueous)	
Peak	R_f	AREA	R_f	AREA
1	0.19	1160.3	0.09	4408.3
2	0.29	4748.5	0.24	1821.6
3	0.59	393.3	0.30	1835.2
4	0.68	409.5	0.33	1372.7
5	0.89	351.0	0.54	3569.3
6	0.94	2483.4	0.63	4390.3
7			0.80	5144.3
8			0.88	376.3
9			0.96	638.7



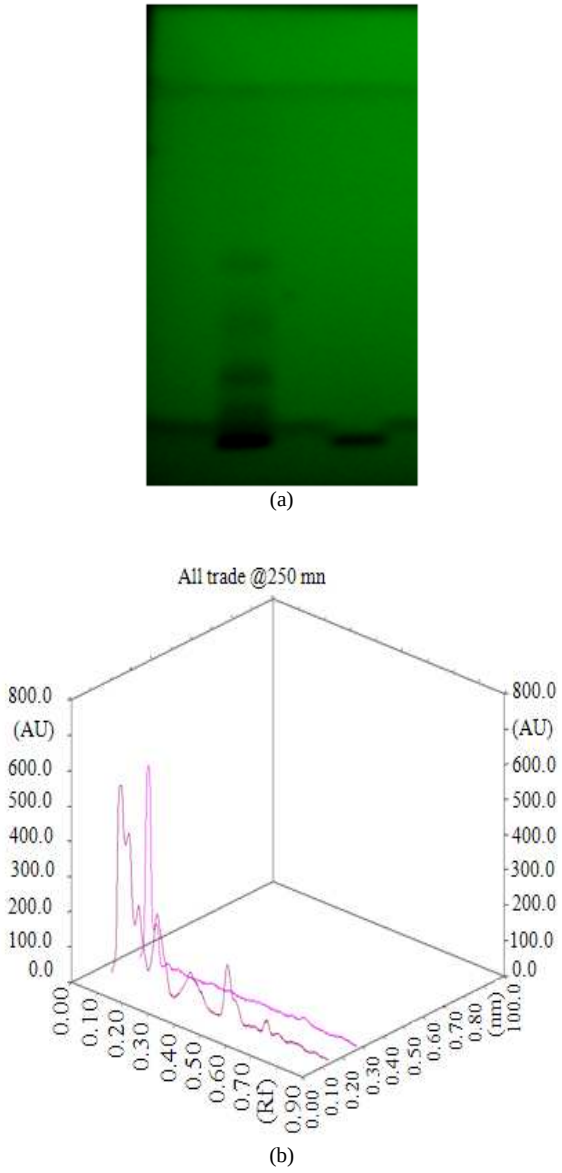
(a)

(b)

Fig. 1: HPTLC plate of Gallic Acid and extracts of *Ficus benghalensis* 3 D-image

Suppression of wound breaking strength by dexamethasone was effectively reversed (p-value< 0.05) when treated along with aqueous and ethanolic extract of *Ficus benghalensis* 100mg kg^{-1} extract as shown in Table 1 (Table 6 and Fig. 5).

Excision wound model: In excision wound model reversal effect was observed with the extract treated animals which showed significant decrease (p-value <0.05) in epithelization period (Table 2) and significant increase in percentage wound contraction as compared to dexamethasone alone.



(a)

(b)

Fig. 2: HPTLC plate of extracts of *Ficus benghalensis* 3 D- image

Table 6: Breaking Strength in 10 day old Incision Model

Groups	Breaking strength (skin)
Control (Simple Saline)	261.5 ±4.808
Dexamethasone	178.0±5.373
F.B. AQ + Dexamethasone	252.0±4.211***
F.B. ETH + Dexamethasone	205.5±4.985***

***: (p<0.05), values are in mean ± SE compared with dexamethasone group

In dexamethasone alone treated group significant increase (p-value <0.05) in epithelisation period and decrease in percentage wound contraction were observed when compared to control (Table 7, Fig. 6a and b).

Table 7: Percentage of wound contraction and epithelialization period in excision model

Groups	% Wound contraction in days					Period of Epithelialization (Days)
	Day 2	Day 4	Day 8	Day 12	Day 16	
Control (Simple Saline)	5.0 ± 0.87	20.5 ± 0.24	50.0 ± 0.23	60.2 ± 0.54	70.8± 0.32	21.0± 0.6146
Dexamethasone	2.0 ± 1.23	10 ± 1.54	30.5 ± 1.67	40.2 ±1.23	50.0 ± 0.23	22.83 ± 0.2582
FB.AQ.Extract+ Dexamethasone	10.0 ± 0.12	30.0± 0.21***	60.0 ± 0.65***	73.0 ± 0.13***	90.0 ± 0.00***	19.16 ± 0.4216***
FB. Eth. Extract +Dexamethasone	8.0 ± 0.12	25.5 ± 2.21***	55.5 ± 1.26***	70.0 ± 2.32***	80.0 ± 1.32***	20.0 ± 0.4773***

***: ($p<0.05$), values are in mean ± SE compared with Dexamethasone group

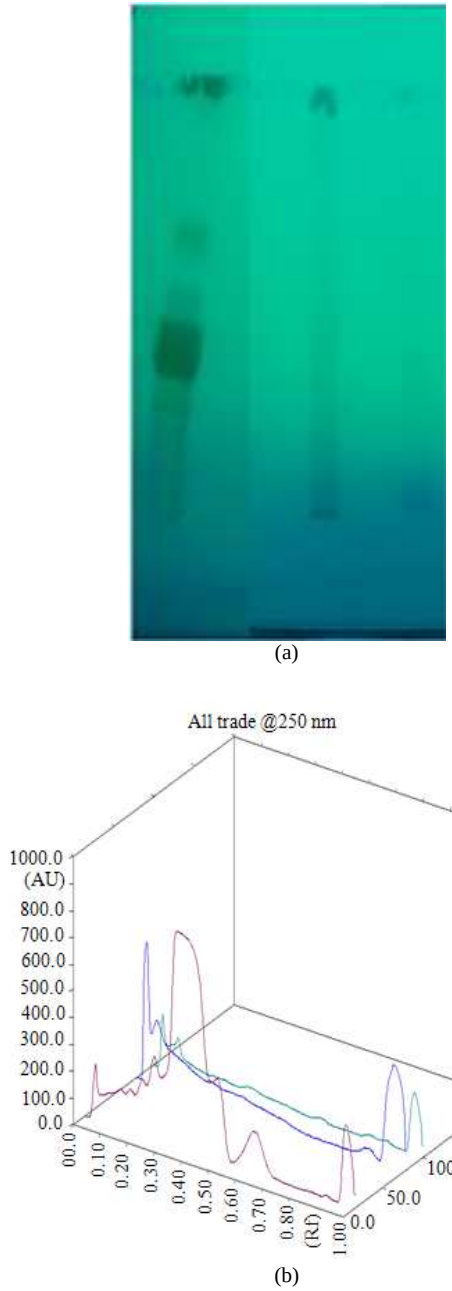


Fig. 3: HPTLC plate of extracts of *Ficus benghalensis* 3 D- image

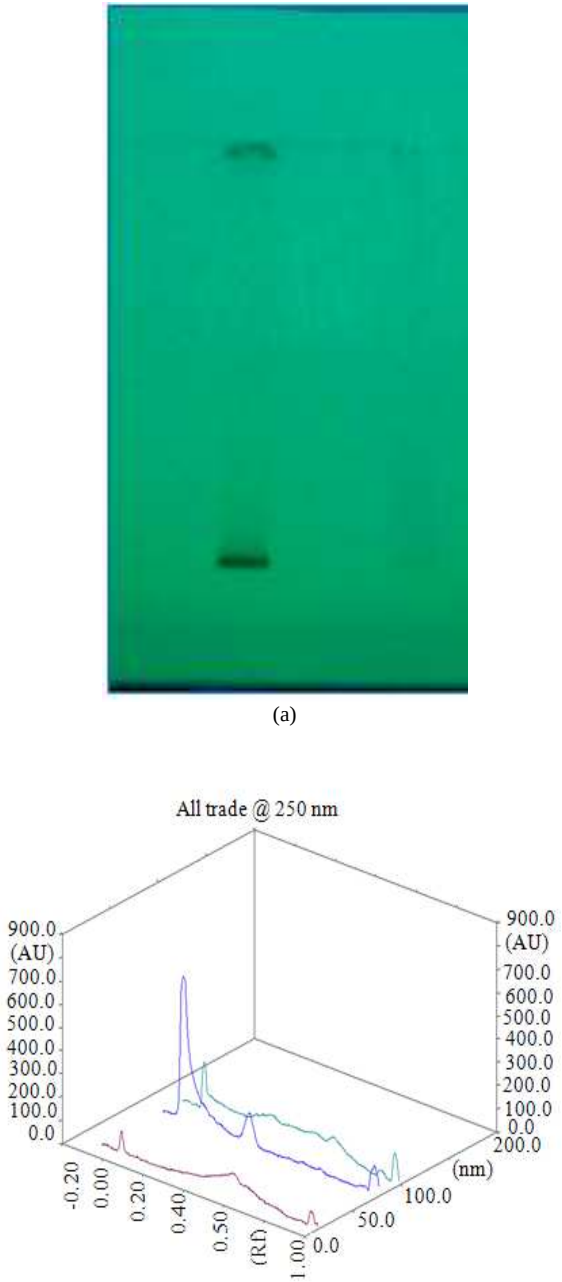


Fig. 4: HPTLC plate of extracts of *Ficus benghalensis* 3 D- image

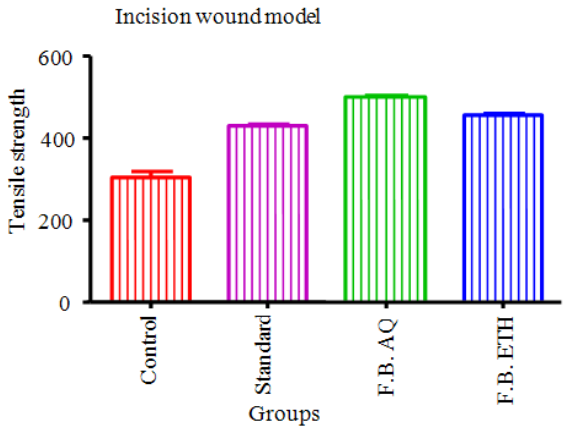
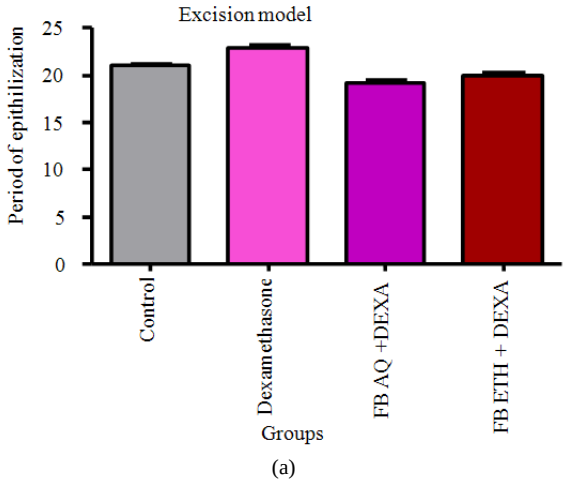


Fig. 5: Incision wound model



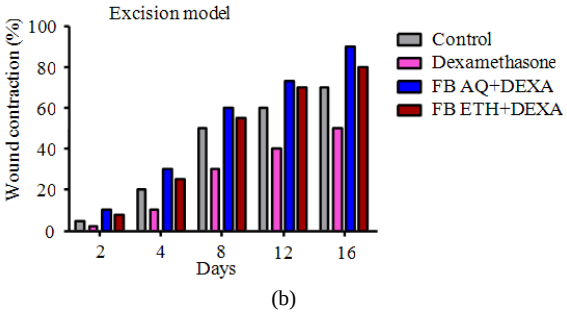


Fig. 6: Excision wound Model (a) Period of epithelialization in days (b) Percentage wound contraction in days

DISCUSSION

The complex process of healing involves various phenomena like wound contraction, granuloma formation, collagen maturation etc. The contribution for healing of such processes depends on the type of wound. Wound contraction plays a significant role in healing of excision wound while granuloma formation plays a role in healing of sutured incision. The results of the present study clearly demonstrate that the aqueous and ethanolic extract of *Ficus benghalensis* possess a definite reversal action in the steroid depressed wound healing. An increase in wound breaking strength of treated wounds may be due to increase in collagen concentration and stabilization of collagen fibres. In recent years oxidative stress has been implicated in a variety of degenerative process and disease. These include acute and chronic inflammatory conditions such as wound healing17. Recent studies with other plant extracts have shown that phytochemical constituents like flavanoids (Tsuchiya *et al*., 1996), alkaloids (Ansel *et al*., 1999), saponins (Mukherjee, 2002) and tannins (Rane and Mengi, 2003) are known to promote the wound-healing process. The study reveals that both aqueous and ethanolic extracts treated groups possesses good wound healing properties which may be attributed to the individual or combined action of phytoconstituents like, flavanoids, alkaloids, saponins and tannins present in it. However, from the study it was evident that aqueous extract was having more potential to antagonize the dexamethasone suppressant action. Ethanolic extract was also effective comparable to that of control group. Hence there is need to do research in detail for formulation and development.

CONCLUSION

In conclusion, the results of this study indicated that roots of *Ficus benghalensis* reverses dexamethasone depressed wound healing in both the wound models.

ACKNOWLEDGMENT

This study was supported by Vidyabharti Trust College of Pharmacy, Surat. The authors are thankful to the Managing Trustee for providing the necessary infrastructure to carry out the work successfully.

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