

Evaluation of wound healing activity of *Hibiscus rosa sinensis* linn in albino rats

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ABSTRACT

Background: From debridement to the appearance of healthy granulation tissue is the maximum time during which the patient suffers more economically and psychologically. Due to high cost expenditure in hospitalisation, dressing material cost and loss of daily earnings during this period which puts a psychological pressure over patient and family especially in India where majority of the population is still below poverty line. Also access to quick treatment is yet not possible to majority of population living in rural with no access to basic healthcare.

Methods: It was an experimental study wherein Wistar rat models were used to check for the wound healing property of *Hibiscus Rosa Sinensis* (HRS) compared with one of the common standard drugs of treatment for available today, betadine. To observe the wound healing property of the HRS flower extract, the experiment was divided into 2 parts i.e. excision wound model and incision wound model. The groups were treated with respective medication along with a control group of rats.

Results: At the end of the experiment, it was observed that HRS flower extract increased the wound breaking strength as compared to control but not as effectively as compared to the betadine ointment.

Conclusions: HRS flower extract helps in early epithelization and helps in decreasing the wound size. Betadine is associated with adverse events like life threatening allergic reactions, water retention, etc.

Keywords: Animal, Betadine, Hibiscus, Skin, Flower, Wound healing, Wistar

INTRODUCTION

Wound and wound healing is a matter of great concern for all the medical practitioners ever since the dawn of civilization and rise of modern medicine.¹ Irrespective of the inciting injury, similar healing process takes place, i.e., the lost tissue is not regenerated but is replaced by a fibrous tissue.²

Knowledge of wound healing and various promoters of wound healing enable the doctors to manipulate the wound

to achieve an optimal result in a rapid period. Infinite literatures on solution of wound healing suggest that the problem is not so simple and straightforward to tackle.

During time of invent of asepsis and dawn of antibiotic era, wound care had achieved milestones, but the widespread development of antibiotic-resistant bacteria is a major roadblock.³

In India where majority of population is from poor economic background, it is difficult for many patients to

afford costly wound care modalities. For these patients being bedridden is a curse as majority of them earn livelihood on daily wages basis.⁴

Pharmaceutical companies are taking advantages of these complexities to introduce multiple remedies, staking high claims for commercial interest. Numerous remedies are available today to counter the various detrimental factors to the natural wound healing process.⁵ Considering these factors, it is necessary to incorporate a simple, cheap, easily available, effective modality that can also be used without any medical supervision to treat wound healing.⁴

Hibiscus rosa sinensis (HRS) extract was found to be such a great modality in better wound care as it is cheap, easily available, had no side effects and can be applied without any assistance.⁶

There are very few studies present in literature comparing the efficacy of HRS extracts with modern medicines. Due to this reason, present study aimed at studying the effectiveness of HRS flower extract as a wound healing agent as compared to betadine ointment.

The aim was to study the wound-healing activity of *Hibiscus rosa-sinensis* in albino rats. The objective was to evaluate natural wound healing process in (control) group of rats, to evaluate wound healing property of *Hibiscus rosa sinensis* flower on (test) group of rats, to evaluate wound healing property of betadine topical ointment on (standard) group of rats and to compare the wound healing property of *Hibiscus rosa sinensis* flower and betadine topical ointment.

METHODS

The present study was conducted in the Department of Pharmacology, Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha, Maharashtra, India. The study was carried out for a period of 24 months from November 2016 to November 2018.

The approval from Institutional Animal Ethical Committee of the research protocol was approved by the Institutional Animal Ethical Committee (no: DMIMSDU/IAEC/2016-17/12), Jawaharlal Nehru Medical College, Sawangi, Meghe, Wardha, Maharashtra, India.

Material

Hibiscus rosa sinensis (HRS) flower

Fresh HRS flower were collected from area near by JNMC, Sawangi, Wardha, Maharashtra, India.

Authentication of the plant

The plants were identified and authenticated by the taxonomist at Mahatma Gandhi Ayurveda College, Wardha, Maharashtra, India.

Purchase of chemicals

Betadine topical ointment (10%), ketamine, xylazine and petroleum jelly (ointment base) was obtained from Maharashtra Scientific Medical Store (Wardha, Maharashtra, India).

Animals

The study was conducted using 36 Wistar Albino rats, of either sex weighing 150-250 g from institutional animal house, Sawangi (Meghe), Wardha, Maharashtra, India.

Inclusion criteria

- Sex: male and female rats,
- Weight: 150-250 gm,
- Age: 02 months to 14 months.

Exclusion criteria

- Pregnant female rats,
- Age: more than 14 months,
- Unhealthy/diseased rats.

About 7 grams of reddish-brown semisolid extract was obtained from 50 grams of dried powder of flowers (Figure 1 and Figure 2).

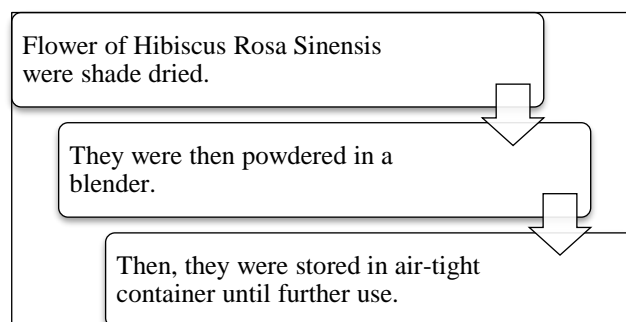


Figure 1: Preparation of plant material in powdered form.

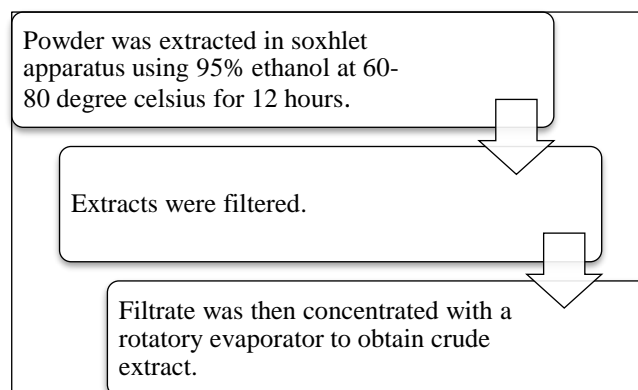


Figure 2: Preparation of crude ethanolic extract.

Ointment formulations

About 5% (w/w) of HRS extract was determined to be the optimum dose to promote wound healing according to Raduan S et al, and Meena AK et al.^{8,9} Ointment formulations was prepared from the extract 5% (w/w), where 5 gram of the extract was incorporated into 100 grams of petroleum jelly. Betadine topical ointment (10% w/w) was used as a standard drug for comparing the wound healing potential of the extract.

Acclimatization

Rats were only used after 7 day acclimatization period (12:12 hours, light:dark cycle) to the laboratory environment. They were housed under the standard nutritional and environmental conditions of light, temperature and humidity. They were fed with standard laboratory chow and provided water ad libitum. Post experimental study, the rats were returned to the animal house after rehabilitation.

Primary skin irritation test

The skin irritation test was done by a method based on the test described by Suraj et al.¹⁰ A 2 cm² dorsal area was trimmed and then shaved. After cleaning the area with surgical spirit, 5% w/w of extract was applied topically to observe any adverse reaction. Similarly, 10% w/w betadine ointment was applied topically to observe any adverse reaction. Animals did not show any adverse effects and thus the prepared extract was considered safe for topical application along with the standard drugs.

Preoperative preparation

Weight of the rats was taken. Pre-emptive analgesia was considered and ophthalmic ointment to the eye was administered following induction of anesthesia to prevent corneal drying. Body hair was removed from the surgical site and surgical scrub alternating between a disinfectant and alcohol was carried out. Warm fluid bag was used to prevent heat loss. Isotonic fluid was kept ready in case of excessive fluid loss.

Induction of anesthesia

Injection ketamine (50 mg): 0.4 ml and injection xylazine (2%): 0.4 ml was given intra-peritoneal.¹¹ Since, it is a dissociative anaesthetic, it interrupts the neuronal traffic between the cortex and thalamus. This effect is characterized by sustained reflex movements, stiff muscle, unconsciousness and open eyes. Absence of response to painful stimuli indicates complete induction of anaesthesia.

Post-operative management

Isotonic fluid was supplied along with warm fluid bag or gloves as required. Rats were frequently checked every 10-

15 mins during recovery from anesthesia. Food and water intake were observed and also analgesic were administered.

Excision wound⁷

Rats were inflicted with excision wound by cutting away a 500 mm² full thickness of skin on the back as described by Morton JJ et al, under anaesthesia.¹²

The wound was left undressed to open environment. The rats were divided into following groups and received the following treatment:

Table 1: Grouping for excision wound model.

Group	Total no. of rats	Treatment
I (Control)	6	Untreated, saline
II (Standard)	6	10% w/w betadine topical ointment
III (Test)	6	50 mg of ointment prepared from 5% of ethanolic extract of HRS

- The ointment was topically applied once a day, starting from the day of the operation, till complete epithelization. This model was used to monitor wound contraction and wound closure time.
- Wound contraction was calculated as percentage reduction in wound area. The progressive change in wound area was monitored by tracing the wound margin on graph paper every alternate day.

Percentage (%) wound closure= (Wound area on Day 0- Wound area on Day 'n')/ (Wound area on Day 0) * 100

Incision wound^{6,13}

After inducing anaesthesia, a 2 cm long paravertebral incision was made through the full thickness of the skin on left side (flank) of the vertebral column of the rats back as described by Ehrlich HP et al.¹⁴ The wound was closed with interrupted sutures (ethilion/nylon).

The rats were divided into following groups and received the following treatment:

Table 2: Grouping for incision wound model.

Group	Total no. of rats	Treatment
I (Control)	6	Untreated, saline
II (Standard)	6	10% w/w betadine topical ointment
III (Test)	6	50 mg of ointment prepared from 5% of ethanolic extract of HRS

- The ointment was topically applied once a day. The sutures were removed on the 7th day. Wound-breaking strength (wound healing) was measured in anesthetized rats on the 10th day after wounding using a tensiometer.

Measurement of wound breaking strength¹⁵

Tensile strength, the force required to open a healing skin wound, was used to measure healing. The instrument used for this measurement is tensiometer. It consisted of animal operation table serving as the base. On one side of the operation table, an IV stand was fixed. It served as a fix point to which one Kelly’s forceps was fixed at one end.

Another Kelly’s forceps were tied to a piece of fishing line (20-lb test monofilament) to which 500 ml polyethylene bottle was tied at the end. The grips of the Kelly’s forceps were then attached to the either side of the incised wound and was to adjust so that the polyethylene bottle was freely hanging in the air.

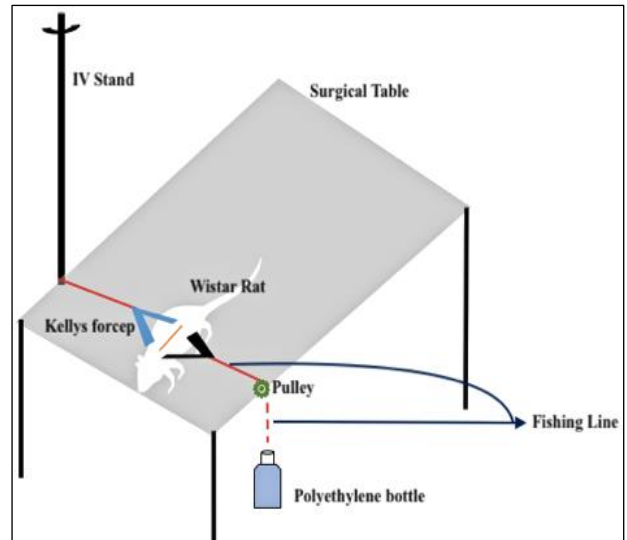


Figure 3: Tensiometer arrangement (self-made).

Table 3: Comparison of wound area (mm²) in three groups by applying descriptive statistics.

Group	N	Mean	SD	SE	95% confidence interval for mean		Minimum	Maximum	
					Lower bound	Upper bound			
Day 0	Control	06	508.66	11.57	4.72	496.52	520.80	490.00	520.00
	Standard	06	513.66	07.73	03.15	505.54	521.78	500.00	520.00
	Test	06	505.00	08.94	03.65	495.61	514.38	490.00	515.00
Day 2	Control	06	462.00	06.60	02.69	455.07	468.92	452.00	470.00
	Standard	06	423.16	08.40	03.42	414.35	431.98	417.00	440.00
	Test	06	460.50	09.37	03.82	450.66	470.33	446.00	470.00
Day 4	Control	06	398.33	09.89	04.03	387.95	408.71	384.00	414.00
	Standard	06	351.83	16.22	06.62	334.80	368.86	321.00	364.00
	Test	06	407.66	08.52	03.48	398.72	416.61	396.00	420.00
Day 6	Control	06	364.00	22.76	09.29	340.10	387.89	320.00	380.00
	Standard	06	263.16	17.64	07.20	244.64	281.68	231.00	280.00
	Test	06	364.50	10.34	04.22	353.63	375.36	348.00	375.00
Day 8	Control	06	310.83	08.01	03.27	302.42	319.23	297.00	320.00
	Standard	06	191.66	15.95	06.51	174.91	208.41	173.00	217.00
	Test	06	304.83	13.94	05.69	290.19	319.47	285.00	320.00
Day 10	Control	06	283.66	12.04	04.91	271.02	296.30	264.00	297.00
	Standard	06	138.66	16.76	06.84	121.07	156.26	120.00	164.00
	Test	06	248.66	14.94	06.10	232.97	264.35	224.00	270.00
Day 12	Control	06	254.33	11.75	04.80	241.99	266.67	240.00	264.00
	Standard	06	89.16	14.20	05.79	74.26	104.07	75.00	110.00
	Test	06	183.83	05.77	02.35	177.77	189.89	175.00	192.00
Day 14	Control	06	237.33	09.50	03.87	227.36	247.30	226.00	248.00
	Standard	06	44.50	12.38	05.05	31.49	57.50	32.00	60.00
	Test	06	143.00	08.48	03.46	134.09	151.90	130.00	150.00
Day 16	Control	06	214.16	11.17	04.56	202.43	225.89	198.00	228.00
	Standard	06	16.83	07.85	03.20	08.58	25.08	09.00	28.00
	Test	06	97.66	10.61	4.33	86.52	108.80	86.00	110.00
Day 18	Control	06	202.33	11.96	04.88	189.78	214.88	186.00	218.00
	Standard	06	01.66	01.96	00.80	-00.39	03.73	00.00	04.00
	Test	06	47.33	12.04	04.91	34.69	59.97	34.00	64.00

Water added to the polyethylene bottle was weighed and considered as the tensile strength of the wound (Figure 3).

The endpoint was achieved as soon as the wound gapping was seen. Tensile strength of the healed wound for an individual animal was calculated by the mean determination of the tensile strength of the 2 paravertebral incision.

Statistics

The data was subjected to statistical evaluation by applying the tests of significance as Paired t-test, One-way ANOVA and multiple comparison test: post hoc Tukey test. The software used in the analysis were SPSS 17.0 version and GraphPad Prism 5.0 and $p < 0.05$ is considered as level of significance.

RESULTS

Table 3 shows the increasing mean difference of wound area between rats treated with HRS flower extract (test), betadine ointment (standard) and saline treated (control).

On Day 0, the mean wound area of control, standard and test group were $508.66 \pm 11.57 \text{ mm}^2$, $513.66 \pm 07.73 \text{ mm}^2$ and $505.00 \pm 08.94 \text{ mm}^2$ respectively. On Day 18, the readings recorded were $202.33 \pm 11.96 \text{ mm}^2$, $01.66 \pm 01.96 \text{ mm}^2$ and $47.33 \pm 12.04 \text{ mm}^2$ respectively (Table 3).

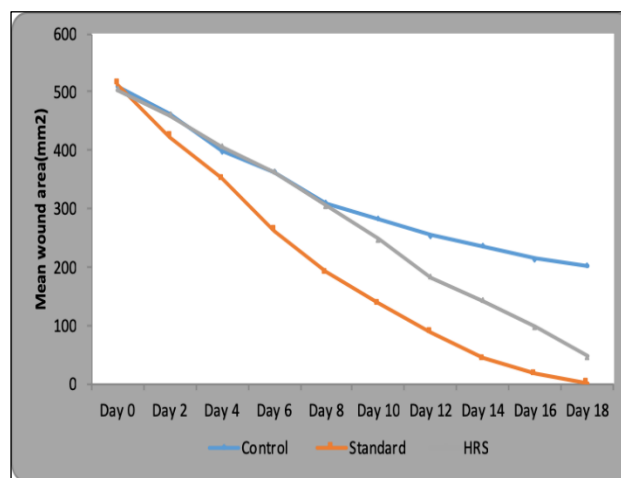


Figure 4: Comparison of wound area (mm2) in three groups.

Table 4: Comparison of wound area (mm²) in three groups by applying One Way ANOVA.

Source of variations	Sum of squares	df	Mean square	F	p-value	
Day 0	Between Groups	227.11	2	113.55	1.24	0.316
	Within Groups	1368.66	15	91.24		
	Total	1595.77	17			
Day 2	Between Groups	5808.11	2	2904.05	43.11	0.0001*
	Within Groups	1010.33	15	67.35		
	Total	6818.44	17			
Day 4	Between Groups	10733.44	2	5366.72	37.10	0.0001*
	Within Groups	2169.50	15	144.63		
	Total	12902.94	17			
Day 6	Between Groups	40872.11	2	20436.05	65.44	0.0001*
	Within Groups	4684.33	15	312.28		
	Total	45556.44	17			
Day 8	Between Groups	54086.77	2	27043.38	158.02	0.0001*
	Within Groups	2567.00	15	171.13		
	Total	56653.77	17			
Day 10	Between Groups	68700.00	2	34350.00	158.63	0.0001*
	Within Groups	3248.00	15	216.53		
	Total	71948.00	17			
Day 12	Between Groups	82424.11	2	41212.05	331.10	0.0001*
	Within Groups	1867.00	15	124.46		
	Total	84291.11	17			
Day 14	Between Groups	111571.44	2	55785.72	530.00	0.0001*
	Within Groups	1578.83	15	105.25		
	Total	113150.27	17			
Day 16	Between Groups	118093.44	2	59046.72	591.65	0.0001*
	Within Groups	1497.00	15	99.80		
	Total	119590.44	17			
Day 18	Between Groups	132755.11	2	66377.55	681.96	0.0001*

From Figure 4, it is evident that betadine had the most efficacious wound healing activity followed by the HRS flower extract (Figure 4). The difference in the wound healing property observed in comparing the 3 groups was statistically significant (p-value=0.0001) (Table 4 and Table 5).

Table 6 illustrates the wound area over a period of 18 days. While the standard group shows the most effective healing, the test group shows a slow but effective healing as well over a period of 18 days.

Table 5: Comparison of wound area (mm²) in three groups by applying multiple comparisons: post hoc Tukey test.

Time period	Group		Mean diff. (I-J)	Std. error	p-value	95% confidence interval	
						Lower bound	Upper bound
Day 0	Control	Standard	-5.00	5.51	0.645	-19.32	9.32
		Test	3.66	5.51	0.787	-10.65	17.99
Day 2	Control	Standard	8.66	5.51	0.288	-5.65	22.99
		Test	38.83	4.73	0.0001*	26.52	51.14
Day 2	Standard	Test	1.50	4.73	0.946	-10.80	13.80
		Test	-37.33	4.73	0.0001*	-49.64	-25.02
Day 4	Control	Standard	46.50	6.94	0.0001*	28.46	64.53
		Test	-9.33	6.94	0.394	-27.36	8.70
Day 4	Standard	Test	-55.83	6.94	0.0001*	-73.86	-37.79
		Test	100.83	10.20	0.0001*	74.33	127.33
Day 6	Control	Test	-0.50	10.20	0.999	-27.00	26.00
		Test	-101.33	10.20	0.0001*	-127.83	-74.8
Day 8	Control	Standard	119.16	7.55	0.0001*	99.54	138.78
		Test	6.00	7.55	0.712	-13.61	25.61
Day 8	Standard	Test	-113.16	7.55	0.0001*	-132.78	-93.54
		Test	145.00	8.49	0.0001*	122.93	167.06
Day 10	Control	Test	35.00	8.49	0.002*	12.93	57.06
		Test	-110.00	8.49	0.0001*	-132.06	-87.93
Day 12	Control	Standard	165.16	6.44	0.0001*	148.43	181.89
		Test	70.50	6.44	0.0001*	53.76	87.2308
Day 12	Standard	Test	-94.66	6.44	0.0001*	-111.39	-77.93
		Test	192.83	5.92	0.0001*	177.44	208.21
Day 14	Control	Test	94.33	5.92	0.0001*	78.94	109.71
		Test	-98.50	5.92	0.0001*	-113.8	-83.11
Day 16	Control	Standard	197.33	5.76	0.0001*	182.35	212.3
		Test	116.50	5.76	0.0001*	101.51	131.48
Day 16	Standard	Test	-80.83	5.76	0.0001*	-95.81	-65.85
		Test	200.66	5.69	0.0001*	185.87	215.46
Day 18	Control	Test	155.00	5.69	0.0001*	140.20	169.79
		Test	-45.66	5.69	0.0001*	-60.46	-30.87

Table 6: Percentage of wound healing.

Day (Duration)	Control	Standard	Test
Day 0	0%	0%	0%
Day 2	9%	18%	9%
Day 4	22%	32%	19%
Day 6	28%	49%	28%
Day 8	39%	63%	40%
Day 10	44%	73%	51%
Day 12	50%	83%	64%
Day 14	53%	91%	72%
Day 16	58%	97%	81%
Day 18	60%	100%	91%

Table 7: Comparison of skin breaking strength (g) in three groups by applying descriptive statistics.

Groups	N	Mean	SD	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Control	06	15.76	1.12	0.46	14.58	16.94	14.00	17.00
Standard	06	41.36	2.04	0.83	39.22	43.51	38.00	44.00
Test	06	26.50	2.16	0.88	24.22	28.77	24.00	30.00

Table 8: Comparison of skin breaking strength (g) in three groups by applying One-way ANOVA.

Source of variations	Sum of Squares	df	Mean Square	F	p-value
Between Groups	1983.16	2	991.58	292.98	0.0001*
Within Groups	50.76	15	3.38		
Total	2033.93	17			

Table 9: Comparison of skin breaking strength (g) in three groups by applying multiple comparisons: post hoc Tukey Test.

Groups		Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Control	Standard	-25.60	1.06	0.0001*	-28.35	-22.84
	Test	-10.73	1.06	0.0001*	-13.49	-7.97
Standard	Test	14.86	1.06	0.0001*	12.10	17.62

Percentage reduction in wound area recorded on Day 18 in control, standard and test were 60%, 100% and 91% respectively (Table 6).

Table 7 and Figure 5 shows the comparison of skin breaking strength observed in the three groups. The skin breaking strength of control, standard and test group were 15.76±1.12g, 41.36±2.04g and 26.50±2.16g respectively. The group of rats treated with betadine topical ointment showed the highest tensile strength followed by the HRS flower extract (Table 7) (Figure 5).

The difference in the skin breaking strength observed in comparing the 3 groups was statistically significant (p-value=0.0001) (Table 8 and Table 9).

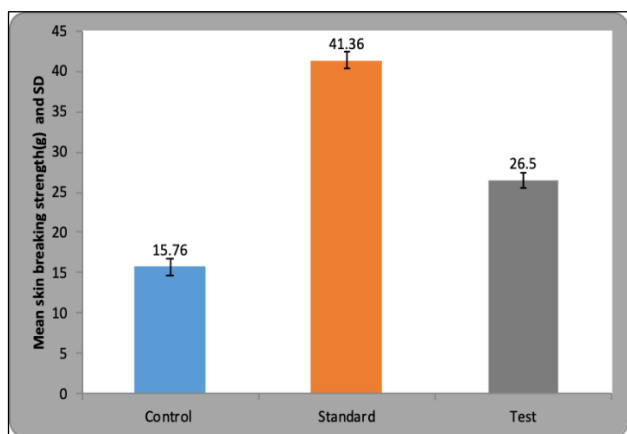


Figure 5: Comparison of skin breaking strength (g) in three groups.

DISCUSSION

The present study was undertaken to evaluate wound healing activity of *Hibiscus rosa sinensis linn* in albino rats and comparing it with standard treatment. This was considered as the aim of the study. The finding and results from this study is similar to several other studies that have included extracts of HRS flower.^{6,13,16}

Betadine is a formulation based on povidone-iodine. Povidone iodine is an effective antiseptic with bactericidal property against gram positive and gram-negative organism, that does not impede wound healing.¹⁷⁻²⁰ However, several studies have reported side effects such as life-threatening allergic reactions, visible water retention, boy temperature fluctuations etc.²¹

Bhaskar A et al, had reported similar findings regarding the skin breaking strength in their study by the 12th day.¹³

Shivananda NB et al, reported higher collagen content in HRS flower treated rats. They demonstrated an increase in hydroxyproline, an amino acid which is a major component of collagen.⁶

Although HRS flower as such has no specific antimicrobial activity of its own, the wound healing promoting effect can be attributed to its various hormonal activities which include hypoglycaemic, androgen like, antioxidant and anticonvulsant activities.⁶ The increased tensile strength, enhanced wound contraction and short epithelization period clearly indicate and support the wound healing promoting effect of HRS flower extract.

Shen H et al, demonstrated that N-butyl alcohol extract of HRS (NHRS) flower is far more potent than other forms of HRS extract. They also suggested that NHRS increases secretion of vascular endothelial growth factor (VEGF) which accelerates wound healing and accelerates the regeneration of epidermal layer by upregulation of transforming growth factor (TGF- β 1). They concluded that NHRS elevates levels of VEGF and TGF- β 1 which promotes faster wound repair via increased angiogenesis, collagen fibre deposition and as well as increasing the activity of macrophages.¹⁶

Bhaskar A et al, reported the presence of tannins, saponins, flavonoids and terpenoids in their phytochemical evaluation of HRS flower extract which highlighting flavonoids as the active substance in promoting wound healing. However, they have reported an increase in the hexosamine and uronic acid molecules which are responsible for the synthesis of extracellular matrix as the primary method of wound healing.¹³

Factors that delay the healing example diabetes, obesity, stress, and other are not taken purposefully to establish that HRS improves wound healing when no other deteriorating factors are present.

Recommendations

The experiment needs further evaluation in other animals such as dogs, monkeys etc. Clinical evaluation needs to be carried out. Cellular level and molecular level studies are required to conclude regarding mechanism of action.

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Ethical approval: The study was approved by the Institutional Animal Ethical Committee, Jawaharlal Nehru Medical College, Sawangi, Meghe, Wardha, Maharashtra, India (no: DMIMSDU/IAEC/2016-17/12)

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