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Evaluation of Herbal Ointments Formulated with Methanolic Extract of *Cajanus scarabaeoides*

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ABSTRACT

The plant *Cajanus scarabaeoides* (L.) possess wound healing, anti-diabetic, anti- inflammatory, hepatoprotective, anti-diarrhoeal, anthelmintic and anti-bacterial activities. The emulsifying ointment formulations containing extracts of the above mentioned herb were formulated, evaluated and their wound healing activity was studied on experimentally induced open wounds in albino rats. The extract (0.5 and 1.0. g) was incorporated into 10 g of a simple ointment base by melting and triturating to give two batches of each the both hydrophilic and hydrophobic ointment formulation. The pH, viscosity, spreadability, stability studies and skin irritation test were determined. The measurement of the wound areas were taken up-to 18th days and the percentages of wound closures were calculated. Blank ointment base and Gentamycin ointment (1% w/w) served as the control and standard treatments. The prepared ointments were passed all the physical evaluation parameters. There were no changes in pH, viscosity, spreadability, consistency, and phase separation when the ointments were kept at different temperatures for 90 days. These formulations did not produce any skin irritation. Topical application of the prepared ointment on the excision wound in rats caused a significantly ($p<0.05$) higher rate of wound healing and reduced the epithelialization period in a dose-related manner. Application of the hydrophilic ointment containing the highest concentrations of *Cajanus scarabaeoides* (L.) extract (1, 10 g ointment) showed the highest rate of wound closure. The formulated ointments were evaluated and effective in wound care and should be explored in harnessing the potentials of the plant in the treatment of topical diseases.

Key words: Herbal ointment, cajanus scarabaeoides, excision model, quality control, wound healing

INTRODUCTION

The delivery of drug through the skin has long been a promising concept because of the ease of access, large surface area, vast exposure to the circulatory and lymphatic networks and non-invasive nature of the treatment (Daniels and Knie, 2007). Along with other topical dosage forms, herbal drugs are also formulated in the form of ointment. Wound is a break in the normal tissue

continuum, resulting in a variety of cellular and molecular sequel. Wound may be created by physical, chemical, thermal, microbial or immunological abuse to the tissue (Patil *et al.*, 2009). The wound healing process consists of integrated cellular and biochemical events leading to reestablishment of structural and functional integrity with regain of strength of injured tissue (Panda *et al.*, 2010). Wound healing is an extreme complex phenomenon involving a number of well-orchestrated processes, including coagulation, inflammation, formation of granulation tissue, synthesis of extracellular matrix protein, remodeling of connective tissue parenchymal components, collagenization and acquisition of wound strength (Subramanian *et al.*, 2006). Cutaneous wound repair is accompanied by an ordered and definable sequence of biological events starting with wound closure and progressing to the repair and remodeling of damaged tissue (Norfarizan-Hanoon *et al.*, 2009). 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 (Esimone *et al.*, 2009).

The literature reveals that the plant *C. scarabaeoides* leaves are useful in treatment of dropsy, fever, pains, sores, anemia, cholera and dysentery. The leaves are mixed with honey and given to the women after child birth. The plant is reported useful in rheumatism and fever and poses proteinase inhibition activity and *in vitro* digestibility of seed protein. The essential oil obtained from it leaves possess fungicidal activity in different test pathogens (Pullaiah, 2006).

In our earlier study it was reported that medicinal plant *C. scarabaeoides* (Family: Fabaceae) commonly known as Rantur or Banna adhaki, shows the presence of alkaloids and glycosides in petroleum ether extract, glycosides and steroids in chloroform extract and glycosides and flavonoids in methanol extract. In pharmacological screening it was found that the methanolic extract of *C. scarabaeoides* exhibit significant antimicrobial, antidiabetic (Pattanayak *et al.*, 2009a) and antidiarrheal activity (Pattanayak *et al.*, 2010).

Hence, by correlating above consequence (presence of flavonoids, analgesic activity, antimicrobial activity and antidiabetic activity) an effort has been made to establish the scientific validity to investigate the possible wound healing activity of different ointments preparation made from the methanolic extract of *C. scarabaeoides* and perform possible evaluation tests for ointments.

MATERIALS AND METHODS

Plant materials: The whole plant of *C. scarabaeoides* was collected in August 2010 from Midnapur, West Bengal, India. The whole plant material was taxonomically identified by Dr. S.C. Majumdar, Taxonomist, Botanical Survey of India, Koregaon Road, Pune 411 001. The whole plant were dried under shade with occasional shifting and then powdered with a mechanical grinder and stored in an airtight container.

Preparation of methanolic extracts: The powder obtained was subjected to successive soxhlet extraction with the solvents with increasing order of polarity i.e., petroleum ether (50°C), chloroform (50°C) and methanol (60°C). The percentage yield of methanolic extracts was found 8.94% w/w.

Drugs and chemicals: The following drugs and chemicals were used with their sources: Petroleum ether (SD Fine, Mumbai), chloroform (SD Fine, Mumbai), methanol (SD Fine, Mumbai), anesthetic ether, Liquid paraffin, Triethanolamine, Sodium hydroxide (Reseach Lab, Pune), Proylene glycol, White petrolatum, PEG 6000 (Polyoxyethylene glycol), Petroleum jelly,

Methylparaben (Himedia Laboratories Private Ltd., Mumbai, India), Stearyl alcohol, Propylene glycol, Sodium lauryl sulphate (Loba Chemical Private Ltd., Mumbai).

Preparation of ointments: In preparation of hydrophilic ointments of *Cajanus scarabaeoides* (C.S.H.L.-I and C.S.H.L.-II) stearyl alcohol and white petrolatum were melted together at about 75°C. The other agents including extracts in different concentration were dissolved in purified water are added with stirring until the mixture congeals. Sodium lauryl sulphats were act as emulsifying agents with stearyl alcohols and white petrolatum comprising the oleaginous phase of emulsion and the other ingredients aqueous phase. At the last methyl and propyl paraben were added which is preservative.

In preparation of hydrophobic ointments of *Cajanus scarabaeoides* (C.S.H.H.-I and C.S.H.H.-II) the waxy bases were melted using water bath. Petroleum jelly which having high melting point were melted first. Then low melting substances cetostearyl alcohol, PEG 6000 and liquid paraffin were melted. After that different concentration of extracts were dissolved in small quantity of purified water and added it in large volume non-aqueous phase. At the last methyl paraben is added. Cooled under stirring and soft mass of ointment is obtained.

Animals: Thirty five Swiss Albino rats of either sex weighing 150-200g were used with the approval of the Institute Animal Ethics Committee (1197/C/08/CPCSEA). Animals were fed a standard pellet (Lipton India, Ltd.) and water ad libitum and maintained at 24-28°C temperature, 60-70% relative humidity and 12 h day and night cycle.

Physical evaluations: Preliminary evaluation of formulations at different concentrations was carried out as follows:

pH: The pH of various formulations was determined by using Digital pH meter (Digital pH meter 335, Systronics, Noroda, Ahmedabad). The 0.5 g of the weighed formulation was dispersed in 50 mL of distilled water and the pH was (Panigrahi *et al.*, 1997).

Homogeneity: All the developed ointments were tested for homogeneity by visual inspection. They were tested for their appearance with no lumps (Panigrahi *et al.*, 1997).

Viscosity: The measurement of viscosity of prepared ointments was carried out with Brookfield Viscometer (model LV-DV-II, Helipath spindle type S-96). The values of each formulation were done in triplicate and average values were depicted in Table 1. The viscosity values are expressed as Mean±Standard deviation (Kim *et al.*, 2003).

Spreadability: Spreadability of the formulation was determined by an apparatus suggested by Mutimer *et al.* (1956) which was suitably modified in the laboratory and used for the study. The experiment was performed as described by Wood *et al.* (1963). Spreadability was determined by using the formula. (S = M.L/T). Where S = spreadability, M = Weight tied to upper slide, L = Length of glass slides and T = Time taken to separate the slides completely from each other. In this present experiment, M = 80 g, L = 10 cm and T was recorded in the Table 1 (Ehrlich and Hunt, 1968).

Table 1: Preparation of medicated formulations with methanolic extract of *Cajanus scarabaeoides*

Formulations	Ingredients	Concentration (% w/w)
C.S.H.L.-I	Extract	5
	Sodium lauryl sulphate	1
	Proylene glycol	12.5
	Stearyl alcohol	25
	White petrolatum	25
	Methyl paraben	1 Drop
	Purified water	31.5
C.S.H.L.-II	Extract	10
	Sodium lauryl sulphate	1
	Proylene glycol	12.5
	Stearyl alcohol	25
	White petrolatum	25
	Methyl paraben	1 Drop
	Purified water	26.5
C.S.H.H.-I	Extract	5
	Cetostearyl alcohol	10
	Polyethylene glycol 6000	5
	Petroleum jelly	70
	Liquid paraffin	10
	Methyl paraben	1 Drop
C.S.H.H.-II	Extract	10
	Cetostearyl alcohol	10
	Polyethylene glycol 6000	5
	Petroleum jelly	65
	Liquid paraffin	10
	Methyl paraben	1 Drop

C.S.H.L.-I: Hydrophilic ointments of *Cajanus scarabaeoides* (5% w/w), C.S.H.L.-II: Hydrophilic ointments of *Cajanus scarabaeoides* (10% w/w), C.S.H.H.-I: Hydrophobic ointments of *Cajanus scarabaeoides* (5% w/w), C.S.H.H.-II: Hydrophobic ointments of *Cajanus scarabaeoides* (10% w/w)

Acute skin irritation study: This test was performed on albino rats and weighing between 150-200 g. The animals were given standard animal feed and had free access to water *ad libitum*. The total mass was separated into four groups, each batch containing five animals. Dorsal hairs at the back of the rats were removed one day prior to the commencement of the study and kept individually in cages to avoid contact with the other rats. Two groups of each were used for control and standard irritant. Other two groups were used as test. The 50 mg of the each formulation of different concentrations were applied over one square centimeter area of whole and abraded skin to different animals. Aqueous solution of 0.8% formalin was used as standard irritant. The animals were observed for seven days for any signs of oedema and erythema (Marzulli and Maibach, 1997).

Stability studies: The stability studies were carried out in all formulations at different temperature conditions (4, 25 and 37°C) for 3 months. All the evaluation parameters i.e., pH, viscosity, spreadability, consistency and phase separation studied at different time intervals i.e., 15, 30, 60 and 90th days (Shinde *et al*., 2005; Mohanta *et al*., 2007).

Evaluation of wound healing activity (Excision method): The animals were divided into 7 groups of 5 rats each.

- Group I served as control (Blank hydrophilic ointment base)
- Group II served as control (Blank hydrophobic ointment base)
- Group III served as standard (Gentamycin ointment 1%)
- Group IV served as test group treated with C.S.H.L.-I
- Group V served as test group treated with C.S.H.L.-II
- Group VI served as test group treated with C.S.H.H.-I
- Group VII served as test group treated with C.S.H.H.-II

Dorsal hairs at the back of the rats were removed by hair remover cream. Rats were anaesthetized by anesthetic ether prior to excision. A circular wound of about 2.5 cm diameter was made on depilated dorsal thoracic region of rats under aseptic conditions and was observed throughout the study. Area of the wounds were measured (in sq. mm) instantaneously by placing a transparent polythene graph paper over the wound and then tracing the area of the wound on it (Approx. area 500 sq. mm). All the samples e.g., control, standard and four formulated ointments, were applied once daily for 18 days, starting from the day of wounding. The observations of wound area and percentage wound closure were made on 3rd, 6, 9, 12, 15 and 18th post wounding days. The percentage of wound contraction was calculated by the formula (1-wound area at the studied day/wound area at initial day)×100. Reduction in the wound area was expressed as percentage of the initial wound diameter (Panda *et al.*, 2009; Mankani *et al.*, 2004).

Statistical analysis: The experimental results were expressed as the Mean±Standard Error of Mean (SEM) and the statistical significance was evaluated by One-way Analysis of Variance (ANOVA) followed by Dunnett's t-test. The Graphpad Prism version 4 software was used for analyzing the experimental results.

RESULTS AND DISCUSSION

The various physicochemical parameters utilized to evaluate the prepared ointment formulations are shown in Table 2.

The pH of the formulations lies in the normal pH range of the human skin (6.8±1). All the formulations did not produce any skin irritation, i.e., erythema and edema for about a week when applied over the skin. The rheological behaviors of the different formulations of ointments in Rotational Brookfield Viscometer indicated that the when speed of spindle increases viscosity decreases. A comparative study of viscosity and spreadability showed that the viscosity of the formulations increases, spreadability decreases and vice versa. These formulations did not produce any skin irritation for about a week when applied over the skin. From the stability studies, Ointments showed no changes in pH, viscosity, spreadability, consistency and phase separation after keeping at different temperatures for 90 days.

All the ointment formulations with methanolic extracts of *C. scarabaeoides* showed significant promotion of wound-healing activity with statistically significant (*$p<0.05$) in all the seven groups of animal which were depicted in the Table 3. The highest wound closer was observed by C.S.H.L-II followed by C.S.H.H-II, C.S.H.L-I and C.S.H.H-I. The mean percentage closure of wound area was calculated on the 3rd, 6th, 9th, 12th, 15th and finally 18th days. The wound healing activity was found to be comparable with that of the reference standards and control bases. The percentages closure of excision wound area in animals treated with C.S.H.L-I, C.S.H.L-II, C.S.H.H-I, C.S.H.H-II were compared with that of the commercial products of Gentamycin ointment. Out of the four formulations the C.S.H.L-II was shown (99.56%) maximum wound healing activity.

Table 2: Physicochemical evaluations and stability studies of different formulation of ointments

Time period (days)	Ointment formulation	Physical evaluation parameters			
		pH	Viscosity (cps) Mean±SD	Spreadability (sec)	Homogeneity
0	C.S.H.L-I	7.1±.18	16.520±0.06	27.5±1	Passes
	C.S.H.L-II	7.4±.23	16.680±0.08	26.8±1	Passes
	C.S.H.H-I	6.4±.09	16.340±0.03	22.3±1	Passes
	C.S.H.H-II	6.2±.74	16.130±0.09	21.5±1	Passes
15th	C.S.H.L-I	7.0±.53	16.830±0.02	28.1±1	Passes
	C.S.H.L-II	7.3±.64	17.030±0.05	27.5±1	Passes
	C.S.H.H-I	6.3±.28	16.720±0.04	23.4±1	Passes
	C.S.H.H-II	6.1±.69	16.560±0.01	22.6±1	Passes
30th	C.S.H.L-I	7.0±.25	17.120±0.05	28.6±1	Passes
	C.S.H.L-II	7.3±.37	17.630±0.07	28.5±1	Passes
	C.S.H.H-I	6.2±.21	16.980±0.08	24.1±1	Passes
	C.S.H.H-II	6.1±.38	16.610±0.02	23.2±1	Passes
60th	C.S.H.L-I	7.0±.08	17.560±0.09	29.3±1	Passes
	C.S.H.L-II	7.2±.97	17.930±0.04	29.6±1	Passes
	C.S.H.H-I	6.1±.59	17.110±0.06	25.7±1	Passes
	C.S.H.H-II	6.1±.42	16.930±0.07	24.3±1	Passes
90th	C.S.H.L-I	6.9±.32	17.670±0.02	30.1±1	Passes
	C.S.H.L-II	7.1±.48	18.060±0.08	30.9±1	Passes
	C.S.H.H-I	6.1±.07	17.230±0.03	28.7±1	Passes
	C.S.H.H-II	6.1±.34	17.210±0.04	26.4±1	Passes

Table 3: Topical application of ointments from extract of *C. scarabaeoides* on wound healing activity in rats. [% of wound healing = (1-wound area at the studied day/wound area at initial day) × 100]

Group	Wound area in mm^2 and (Percentage of wound healing)						
	0 day	3rd days	6th days	9th days	12th days	15th days	18th days
Control I	511.23±1.12	482.79±1.56	412.32±0.79	302.83±0.13	251.64±0.15	135.92±1.78	83.24±0.57
	(0.00)	(4.58)	(19.34)	(40.76)	(50.77)	(73.041)	(83.71)
Control II	506.35±0.15	474.79±0.54	432.56±1.62	308.68±0.28	248.56±0.47	137.19±0.59	88.53±0.12
	(0.00)	(6.23)	(14.57)	(39.03)	(50.91)	(72.90)	(82.51)
Standard	513.10±0.00	438.56±1.13	305.08±1.07	202.93±0.62	128.35±0.51	40.16±0.82	0±0.00
	(0.00)	(14.52)	(40.14)	(60.45)*	(74.98)*	(92.17)*	(100.00)*
C.S.H.L-I	521.17±2.34	472.36±0.35	365.14±0.72	238.58±0.93	152.17±0.42	53.04±0.54	7.72±0.11
	(0.00)	(9.36)	(29.93)	(54.22)*	(70.80)*	(89.83)*	(98.51)*
C.S.H.L-II	508.26±1.01	451.59±0.83	350.28±0.09	225.35±0.49	130.09±0.72	46.18±0.79	2.23±0.08
	(0.00)	(11.14)	(31.08)	(55.66)*	(74.40)*	(90.91)*	(99.56)*
C.S.H.H-I	518.32±1.38	466.82±1.22	345.17±1.56	259.23±0.83	165.18±0.33	57.36±0.42	11.08±0.24
	(0.00)	(9.93)	(33.40)	(49.98)*	(68.13)*	(88.93)*	(97.86)*
C.S.H.H-II	502.29±0.53	465.56±0.04	337.19±0.81	250.84±0.22	145.13±1.31	48.86±0.35	4.13±0.06
	(0.00)	(7.31)	(32.86)	(50.06)*	(71.10)*	(90.27)*	(99.17)*

Values are expressed Mean±SEM of six readings; Significance evaluated by one-way analysis of variance (ANOVA) followed by Dennett's t-test versus control group,*$p<0.05$, (n = 5). Values in parentheses indicate the percentage of wound healing

DISCUSSION

The both hydrophilic and hydrophobic ointments of methanolic extract of *Cajanus scarabaeoides* prepared by fusion method, by using different percipients and different concentration of extract. The mechanical evaluation parameters like pH, viscosity, spreadability, homogeneity are important

tests to evaluate pharmaceutical ointment formulations. The result of all the formulations near to pH 6.8±1 indicates better chemical compatibility of ointments with skin. The results of viscosity gives an idea about measurement of strength and the result of spreadability denote the extent of area to which the prepared formulations readily spreads on application to skin or affected part and homogeneity confirms no lumps. The results of stability study indicates the there is no change in results of evaluation parameters of prepared ointments up to 90th days. The absence of erythema and edema for about a week when the ointments are applied over the skin for skin irritation test indicates patient compliances and fewer side effects. The results of the physical evaluation of ointment preparation with methanolic extracts of *C. scarabaeoides* indicate the suitability of method for the production of ointments (Ansel *et al.*, 2005).

In wound healing process cellular structures and tissue layers in damaged tissue are restored as closely as possible to its normal state. It has three phases; inflammatory, proliferative and maturational. In the first stage of wound, an inflammatory response occurs, which is characterized by hemostasis and inflammation. Epithelization, angiogenesis and collagen deposition occurs in the proliferative phase. Then wound undergoes shrinkage and contraction resulting in a smaller amount of apparent wound tissue. The wound healing process depends upon the type and extent of damage, the general state of the host's health and the ability of the tissue to repair. The fibroblast, collagen, edema and small new blood vessel are found in granulation tissue of the wound. The undifferentiated mesenchymal cells of the wound margin modulate themselves into fibroblast. These fibroblasts start migrate into the wound gap along with the fibrin strands and closes the wound area (Singh *et al.*, 2005; Puratchikody and Nagalakshmi, 2007; Odimegwu *et al.*, 2008).

The wound healing activity of the ointments containing methanol extract of *Cajanus scarabaeoides* was evaluated for its wound healing potentials in excision wound model in rats. Both hydrophilic and hydrophobic ointments responded significantly in this wound models tested. The results of wound healing were also comparable to that of the standard drugs Gentamycin ointment used as standard drugs. The results were also comparable in terms of wound contracting ability, epithelization period at the wound area and percentage of wound closer (Nagori and Solanki, 2011).

In the preliminary phytochemical and pharmacological studies of methanol extract of *C. scarabaeoides* revealed the presence of glycosides and flavonoids and showed significant antimicrobial and antidiabetic activity (Pattanayak *et al.*, 2009b). Flavonoids reduce lipid per-oxidation by preventing or slowing the onset of cell necrosis and by improving vascularity. So, any drug that inhibits lipid per-oxidation may increases the viability of collagen fibrils by increasing the strength of collagen fibers, increasing the circulation, preventing the cell damage and by promoting the DNA synthesis (Getie *et al.*, 2002). It is also called that flavonoids promote the wound healing process mainly due to their astringent and antimicrobial property, which seems to be responsible for wound contraction (Tsuchiya *et al.*, 1996).

Further phytochemical studies are needed to isolate the active compound (s) responsible for wound healing activities. Further studies with purified constituents are needed to understand the complete mechanism of wound healing activity of *C. scarabaeoides*.

Thus, this investigation confirms the use of the both hydrophilic and hydrophobic ointments containing *C. scarabaeoides* extract as a wound-healing ointment preparation.

CONCLUSION

Topical route of application has a great potential as an effective and safe way to administer in the form of ointments. Ointments prepared from the methanolic extract of *C. scarabaeoides* passes

all physical evaluation parameters and it shows significant local wound healing activity in both hydrophilic and hydrophobic ointment bases. Preliminary tests of skin irritation in rats may indicate negligible systemic absorption and side effects. The prepared ointments pass other physical evaluation test parameters. Based on the results of these tests, trails may be performed on human beings.

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