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Full Length Research Paper

Anti-inflammatory and wound healing activity of *Fagonia schweinfurthii* alcoholic extract herbal gel on albino rats

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Traditionally, a large number of plants are used for treatment of inflammation and wounds. In Asian and African countries *Fagonia schweinfurthii* (Hadidi) (F. Zygophyllaceae) and the closely related herb, such as *Fagonia arabica* are traditionally used for treatment of inflammation, open wounds, boils, skin eruptions, allergies, etc. Hence, the present study was conducted to investigate the anti-inflammatory and wound healing effects of 90% alcoholic extract of *F. schweinfurthii* formulated gel on carrageenan induced rats paw edema and excision wound model, respectively. The effects were compared with the anti-inflammatory diclofenac sodium ointment (Diclomax®) and the wound healing povidone-iodine (Betadine®) drugs. The herbal gels and diclofenac sodium ointment were topically applied (0.5 g) to the planter surface of the left hind paw and anti-inflammatory effect was observed within 3 h. The wound healing effect was investigated by application of 0.5 g/wound of the *F. schweinfurthii* gel and Betadine® once daily for 19 days to the excision wound of albino rats and was observed at 4 days intervals. It was observed that gel formulations have progressive anti-inflammatory effect and accelerate the wound closer time. This study suggests that *F. schweinfurthii* plant extract gel formulation could be developed as a therapeutic agent for anti-inflammatory and wound healing effects.

Key words: *Fagonia schweinfurthii*, herbal formulation, anti-inflammatory, wound healing.

INTRODUCTION

Fagonia schweinfurthii and its closely related species are widely distributed in deserts and dry areas of India to tropical Africa and Chile to South West U.S.A. They are traditionally well known for the treatment of hemorrhoids, inflammation, sores, leprosy, open wounds and fever in the form of internal and external conventional formulation (Miller et al., 1988). When the powder that is made up of the whole plant of *F. schweinfurthii* is dusted on boils and skin eruptions, it causes healing and when the whole plant is boiled in water, its bath is useful for allergies and other skin diseases and decoction is given orally as blood purifier (Qureshi et al., 2010). The other species like *Fagonia bruguieri* aqueous extract is claimed for anti-allergy (Abdulaziz and Hussein, 2007). *Fagonia cretica* methanol extract is claimed for good antimicrobial potential (Anjum et al., 2007) and it exhibited strong free radical scavenging properties against reactive oxygen and nitrogen species (Rawal et al., 2004). The other effects of *Fagonia* species include anti-inflammatory, analgesic, antipyretic and thrombolytic activity (Prasad et al., 2007; Satpute et al., 2009). Many chemical constituent's, such as triterpenoids, saponins, flavonoid glycosides, etc., have already been reported in different *Fagonia* spp. (Shaker et al., 1999; Abdel-Khalik et al., 2001; El-Wakil, 2007). Although, currently used anti-inflammatory and wound healings drugs are associated with some severe side effects, herbal products are often perceived as safe, because they are natural therefore, the development of potent anti-inflammatory and wound healer drugs with fewer side effects is necessary (Gesler, 1992). Inflammation is considered as a primary physiologic defense mechanism that helps body to

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protect itself against infection, burn, toxic chemicals, allergens or other noxious stimuli. An uncontrolled and persistent inflammation may act as an etiologic factor for many of the chronic illnesses (Kumar et al., 2004). Wound healing is the process of repairing injury of skin and other soft tissue. This dynamic process is classically divided into three overlapping phase "inflammation, proliferation and remodeling" (Harding et al., 2002). Initial stages of wound healing involve an acute inflammatory phase followed by synthesis of collagen and other extracellular matrix which are later remodeled to form scar (Bhagavathula et al., 2009). Thus, the present study aim to investigate wound healing and anti-inflammatory activities to justify the traditional claims of this plant gel form.

MATERIALS AND METHODS

Collection of plant and authentication

The plants of *F. schweinfurthii* was collected during December, 2009, from local area of Riyadh, Saudi Arabia and was kindly authenticated by Dr. Mohammad Atiqur Rahman, taxonomist of the Medicinal, Aromatic and Poisonous Plants Research Center (MAPPRC), College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. A voucher specimen is deposited at the herbarium of the College of Pharmacy, King Saud University.

Chemicals

Diclofenac sodium (1%) ointment (Diclomax®) and 10% povidone-iodine (Betadine®) were purchased from a local pharmacy. Triethanolamine and ethanol were obtained from Merck & Co. Inc (USA). Carrageenan and carbapol-934 gel were supplied by Sigma (USA).

Extraction of plant

The air dried powdered plant was extracted with 90% ethanol in a soxhlet apparatus at 60°C. The extract was concentrated to syrupy solution using rotary evaporator under reduced pressure at 40°C. The thick solution was lyophilized using freeze drying system. The yield (13. 5%) was used for the experimental studies**.**

Animals

Healthy Wister albino rats of either sex weighing ≈200 g, obtained from the Experimental Animal Care Center, College of Pharmacy, King Saud University, Riyadh were used. Rats were maintained under controlled condition at temperature (22 ± 20°C), humidity (55%) and light (12 h light/dark condition). The animals were provided with Purina chow and drinking water *ad libitum*. The experiments and procedure used in this study were approved by the Ethical Committee of the College of Pharmacy, King Saud University, Riyadh, KSA.

Acute toxicity study

The acute toxicity of *F. schweinfurthii* alcoholic extract was determined in rats according to the previous method (Adedapo et al., 2009) with slight modifications. Rats that fasted for 12 h were randomly divided into four groups (n = 5). Graded doses of the extract (300, 600, 1200 and 2400 mg/kg p.o.) were separately administered to the rats. All the animals were then observed over a period of 10 days for deaths and signs of acute toxicity.

Preparation of herbal gel

Herbal gels 10 and 20% were prepared separately according to the method (Dey et al., 2009) with slight modifications. Carbapol-934 (1.8%) and sufficient amount of distilled water were mixed in a separate beaker and soaked for 24 h at room temperature. Triethanolamine was added drop-wise with constant stirring using mechanical stirrer. After gel formulation, a weighed amount of (10 and 20 g) extract powder was incorporated in gelling agent separately and mixed using glass rod. A similar procedure was followed for control base gel without powdered extract.

Anti-inflammatory study

Carrageenan-induce rat paw edema model was used for anti-inflammatory study (Maswadeh et al., 2006). Twenty rats were divided into four groups and fasted overnight with free access to water before the experiment proceeds. Rats of the first, second and third groups were treated with the control base, 10 and 20% gel formulations. Rats of the forth group (standard) were treated with marketed gel formulation (Diclomax®). Each formulation (0.5 g) was applied to the planter surface of the left hind paw by gently rubbing 50 times with the index finger. After 1 h, inflammation was induced by subplanter injection of 0.1 ml of 1% carrageenan solution in normal saline into the treated paw of all rats. The paw volume of each rat was measured in milliliter using a plethysmometer (Aptex, France) at 0 and 3 h post carrageenan injections. The percentage anti-inflammatory activity was calculated using the following equation:

$$\text{Percentage anti-inflammatory activity} = (V_{3h} - V_{0h})/V_{0h} \times 100$$

where V_{3h} is the paw volume after 3 h carrageenan injection and V_{0h} is the initial paw volume.

Wound healing study

The excision wound model was used to study the wound contraction of *F. schweinfurthii* extract herbal formulations (Okoli et al., 2009). At the beginning of the experiment, twenty rats were anesthetized using diethyl ether and the dorsal skin of each rat was shaved with an electric clipper and put in separate cage. After 12 h, all animals were again anesthetized by diethyl ether and the shaved areas were sterilized with 70% alcoholic solution and sketch wound area (≈ 2.5 cm^2). A predetermined dorsal area was excised using toothed forceps, scalpel and pointed scissors. A fresh surgical blade was used for the perpendicular cut in each animal and the tension of the skin was kept constant during the procedure. Animals were divided into four groups (n = 5). Rats of the first, second and third groups were treated with the control base, 10 and 20% gel formulations. Rats of the forth group (standard) were treated with marketed formulation (Betadine®). The base gel, extract gels and standard drug (0.5 g, each) were applied topically on the wound surface once a day for 19 days. The wound areas were traced on graph paper (1 mm^2) immediately after the wound excision and every 4 days until healing was accomplished. The reduction in the wound size was calculated according to the following formula:

$$\text{Wound contraction (\%)} = [(W_0 - W_t)/W_0] \times 100$$

Table 1. Effect of *Fagonia* alcoholic extract gel formulations on Anti-inflammatory.

Treatment	Net increase in paw volume (ml)	Reduction of edema (%)
Control base	2.28 ± 0.06	-
10% gel	1.88 ± 0.08*	17.54
20% gel	1.10 ± 0.10***	51.75
Diclomax®	0.44 ± 0.06***	80.70

Each value is the mean ± SEM, n = 5. Values differ significantly (*P < 0.05 and ***P< 0.001) from control base gel.

where W_0 is the wound diameter on day zero and W_t is the wound diameter on day t.

The time taken for 50% of wound closure (WC_{50}) was calculated by a plot of percentage wound closure against days.

Statistical analysis

The results were expressed as mean ± SEM. The data were subjected to one-way ANOVA student t-test using graphPad Prism 5 software. P < 0.001 was considered as significant.

RESULTS AND DISCUSSION

Animal toxicity study

Oral administration of graded doses (300 to 2400 mg/kg p.o.) of the alcoholic extract of *F. schweinfurthii* to rats, did not produce any mortality and changes in behavior, breathing, cutaneous effects, sensory nervous system responses or gastrointestinal effects during the 10 days observation period. The obtained results signify that the use of the plant for treatment is safe. So the formulations (10 and 20% gel) were selected for anti-inflammatory and wound healing studies**.**

Anti-inflammatory study

The anti-inflammatory activity was expressed as "mean increase in paw volume ± SEM" in terms of milliliter and percentage inhibition in paw volume by different gel formulation and standard drug. The 20% herbal gel produced significant (P < 0.001) reduction of Carrageenan-induced paw edema (1.10 ± 0.10 ml) as compared to the control base gel group (2.28 ± 0.06 ml) after 3 h from carrageenan injection. The reference drug was found to be comparatively more potent as compared to formulated gel (0.44 ± 0.06 ml). The percentage inhibition of paw edema for 10 and 20% and Diclomax® was 17.54, 51.75 and 80.70%, respectively (Table 1). The probable mechanism of inflammation action is bi-phasic, the first phase is attributed to the release of histamine, serotonin, 5-HT and kinins in the first hour; while, the second accelerating phase of swelling is related to the release of prostaglandin, bradykinins and lysozymes-like substances in 2 to 3 h (Brooks and Day, 1991; Silva et al., 2005). Carrageenan-induced edema involves the synthesis or release of pain and fever mediators like prostaglandins (PGE), histamine, bradykinins, leucotrienes and serotonin. This model has a significant predictive test for anti-inflammatory agents acting by the mediators of acute inflammation (Adedapo et al., 2009). The results of this study indicated that *F. schweinfurthii* extract gel formulation can be effective in acute inflammatory disorders. The plant contains polyphenolic compounds, saponins and flavonoid glycosides that could be responsible for the anti-inflammatory activity either alone or may be due to inhibition of inflammatory mediators in combination with other constituents (Adamu et al., 2007).

Wound healing study

The percentage of wound contraction in the second, third and fourth groups were 6.93 ± 0.11, 8.40 ± 0.20 and 9.06 ± 0.11 on the 4th day and 90.53 ± 0.10, 93.93 ± 0.09 and 95.53 ± 0.10 on the 19th day, respectively. The percentage of wound contraction of the first group 6.13 ± 0.23 and 72.08 ± 0.16 on 4th and 19th days, respectively was comparatively lower than the other three groups (Table 2). The WC_{50} (time for 50% wound healing) of control base, 10 and 20% herbal gel and standard drug (Betadine®) was, 13.92, 11.06, 10.53 and 10.82%, respectively (Table 3). The wound size decreases after 4th (A) and 19th (B) day of 10 and 20% gel and Betadine® was clearly indicating the wound healing effects (Figures 1 to 3). Wound healing is an elementary response to tissue injury that it consequences in restoration of tissue integrity, is mainly achieved by the synthesis of the connective tissue matrix. It involves regeneration of specialized cells by proliferation of surviving cells characterized by the formation of granulation tissue and wound contraction, which is largely due to the action of myofibroblasts (Okoli et al., 2009). All groups show the wound healing, including control base gel, because of biological response regulating the body's own cellular defense mechanisms which contributes in

Table 2. Effect of *Fagonia* alcoholic extract gel formulations on wound healing.

Treatment	Percentage wound contraction (mean ± SEM)				
	4-days	8-day	12 days	16 days	19 days
Control base	6.13 ± 0.23	17.96 ± 0.03	48.93 ± 0.11	55.33 ± 0.11	72.08 ± 0.16
10% gel	6.93 ± 0.11	32.93 ± 0.16	61.33 ± 0.23	80.40 ± 0.20	90.53 ± 0.10
20% gel	8.40 ± 0.20	36.60 ± 0.17	64.66 ± 0.11	83.46 ± 0.11	93.93 ± 0.09
Betadine®	9.06 ± 0.11	24.46 ± 0.09	66.93 ± 0.11	85.86 ± 0.11	95.53 ± 0.10

Each value is the mean ± SEM, n = 5. Values of percentage wound reduction of each formulation differ when compared with control base gel.

Table 3. Effect of *Fagonia* alcoholic extract gel formulations on WC_{50}.

Treatment	WC_{50} (Days)
Control base	13.92
10% gel	11.06
20% gel	10.53
Betadine®	10.82

Each value is the time taken for 50% wound closure (WC_{50}). Values of WC_{50} of each formulation differ when compared with control base gel.

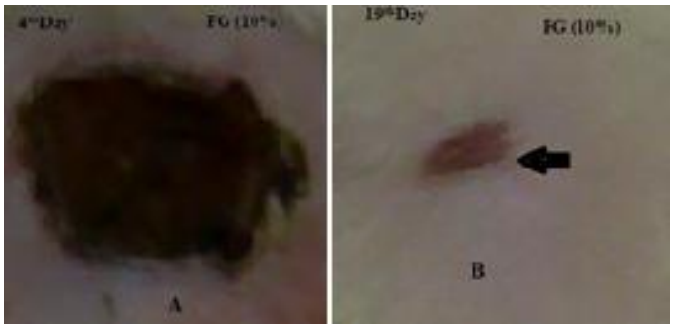

Figure 1. Excision wound healing of 10% *Fagonia* alcoholic extract gel formulation treated rat on 4th (A) and 19th (B) days observation.

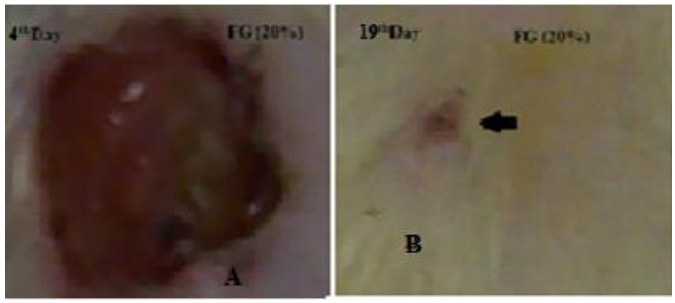

Figure 2. Excision wound healing of 20% *Fagonia* lcoholic extract gel formulation treated rat on 4th (A) and 19th (B) days observation.

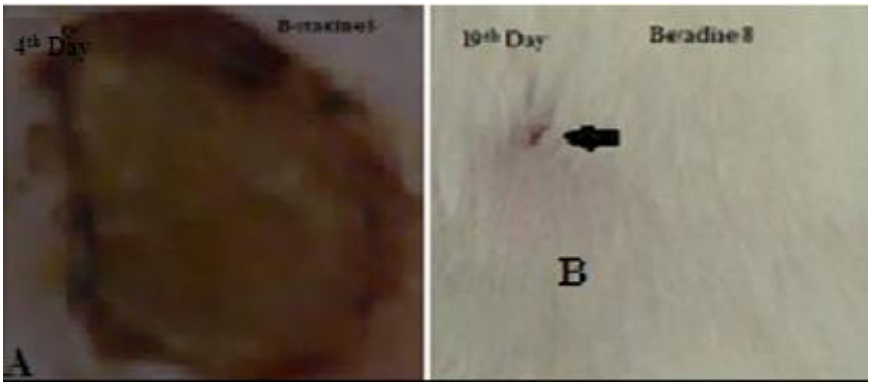

Figure 3. Excision wound healing effect of 10% povidone-iodine (Betadine®) treated rat on 4th (A) and 19th (B) days observation.

wound healing and its repair (Malviya and Jain, 2009). The formulated gel fasten the wound healing process may be due to enhancing the cellular defense mechanisms, proliferation, suppression of inflammation and contraction of the collagen tissue and could be delayed by reactive oxygen species or microbial infection (Marwah et al., 2007). The polyphenolic compounds have improved regeneration and organization of the new tissue and hasten the wound healing process (Leite et al., 2002) may be due to anti-inflammation, anti-oxidant and antimicrobial activities. The plant contains polyphenolic compounds including saponins, flavonoids, glycosides (Kumar et al., 2004; Abdel-Khalik et al., 2001; Gesler, 1992) and these compounds showed the antioxidant and anti-microbial (Anjum et al., 2007; Rawal et al., 2004) and anti-inflammatory (present study). The result of the present study revealed that the topical application of 10 and 20% extract gel on the experimentally excised wound accelerate the wound healing process.

Conclusion

In conclusion, the plant is safe for use as no mortality was recorded in the acute toxicity test. The two gel (10 and 20%) prepared with *F. schweinfurthii* reduced significantly the formation of edema induced by carrageenan and exhibited a good anti-inflammatory effect comparable to those of Diclomax® and exhibited a good wound healing effect comparable to those of Betadine®. The study has thus, provided some rationalization for the folkloric use of the plant in several communities for conditions, such as inflammation, boils, skin eruptions and other skin diseases.

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