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Evaluation of wound healing activity of *Solanum nigrum* and *Periploca aphylla* in albino rats

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A B S T R A C T

Medicine of plant origin is based on the premises that plant contains natural substances, can promote health and alleviate illness. Two plants *Periploca aphylla* L (family: Asclepiadaceae) and *Solanum nigrum* L (family: Solanaceae) were used for the current studies to investigate the effects of methanolic extract against wound healing. For this purpose, two animal models i.e excision wound model and incision wound model in albino rats were used. Animals were divided into different groups and the treatment was employed for 20 days according to adopted protocol. The extracts of both plants were applied in the form of ointments prepared accordingly. At the end of the experiment of excision wound model the percentage wound contraction was found by measuring the healed area divided by total are and in incision wound model the tensile strength is calculated by measuring the tensile strength divided by the cross sectional area of the skin. Results of the study showed that the percentage wound contraction was markedly increased from 4th day to 20th day. Moreover, results revealed that the tensile strength was also increased gradually. Tissues of the incision wounded rats were preserved for histopathological analysis. Standard drug treated rats led to reduce polymorphonuclear leukocytes, oedema and necrosis whereas the plants extract treated rats were found to have mild vascular proliferation and reduction of accessory skin structures. Along with these, considerable increase in the dermal collagen content was evident from the histopathological observations. Thus, the wound healing potential of *Solanum nigrum* and *Peirploca aphylla* extracts could be justified. Preliminary phytochemical analysis confirmed the presence of alkaloids, tannins, flavonoids, saponins and glycosides in both plant extracts. Of which, flavonoids and tannins are already reported to possess wound healing activity so these constituents could possibly be responsible for the activity of *Solanum nigrum* and *Periploca aphylla.*

Keywords: Methanolic extracts; Wound healing; Tensile strength; Phytochemicals

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INTRODUCTION

The wounds are accidental events of life which occur due to physical, chemical and thermal injury. They cause pain, bleeding, disability and often possess problems in clinical practice (Mostafa et al., 2012). Usually wounds are physical injuries that result in an opening or break of the skin and this process that is fundamentally a connective tissue response. Initial stage of this process involves an acute inflammatory phase followed by synthesis of collagen and other extracellular macromolecules that help in the

formation of scar (Talekar, 2012). Proper healing of wound has been found essential for the restoration of disrupted anatomical continuity and disturbed functional status of the skin (Begum and Nath, 2000). Wound healing is basically composed of five interconnected and overlapping phases; homeostasis and inflammation, neovascularization, granulation, re-epithelization and remodeling (Suguna et al., 2002) The first phase of hemostasis begins immediately after wounding, with vascular constriction and fibrin clot formation. The clot and surrounding wound tissue release pro-inflammatory cytokines and growth factors such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF). Once bleeding is controlled, inflammatory cells migrate into the wound (chemotaxis).

The inflammatory phase, which is characterized by the sequential infiltration of neutrophils, macrophages and lymphocytes (Gosain and Dipietro, 2004; Broughton et al., 2006; Campos et al., 2008). A critical function of the neutrophils is the clearance of invading microbes and cellular debris in the wound area, although these cells also produce substances such as proteases and reactive oxygen species (ROS), which cause some additional bystander damage. The macrophages play multiple roles in wound healing. In the early wound, macrophages release cytokines that promote the inflammatory response by recruiting and activating additional leukocytes. Macrophages are also responsible for inducing and clearing apoptotic cells (including neutrophils), thus paving way for the resolution of inflammation. As macrophages clear these apoptotic cells, they undergo a phenotypic transition to a reparative state that 2 stimulates keratinocytes, fibroblasts, and angiogenesis to promote tissue regeneration (Meszaros et al., 2000; Mosser and Edwards, 2008). In this way, macrophages promote the transition to the proliferative phase of healing. T-lymphocytes migrate into wounds following the inflammatory cells and macrophages, and peak during the late-proliferative/earlyremodeling phase. The role of T-lymphocytes is not completely understood and is a current area of intensive investigation. Several studies suggest that delayed T-cell infiltration along with decreased T-cell concentration in the wound site is associated with impaired wound healing, while others have reported that CD 4+ cells (T-helper cells) have a positive role in wound healing and CD8+ cells (T-suppressor-cytotoxic cells) play an inhibitory role in wound healing (Swift et al., 2001; Park and Barbul, 2004). Interestingly, recent studies in mice deficient in both T- and B-cells have shown that scar formation is diminished in the absence of lymphocytes (Gawronska-Kozak et al., 2006). In addition, skin gamma-delta T-cells regulate many aspects of wound healing, including maintaining tissue integrity, defending against pathogens, and regulating inflammation. These cells have also been called dendritic epidermal T-cells (DETC), due to their unique dendritic morphology. DETC are activated by stressed, damaged, or transformed keratinocytes and produce fibroblast growth factor 7 (FGF-7), keratinocyte growth factors, and insulin-like growth factor-1, to support keratinocyte proliferation and cell survival. DETC also generate chemokines and cytokines that contribute to the initiation and regulation of the inflammatory response during wound healing. While cross-talk between skin gamma-delta T-cells and keratinocytes contributes to the maintenance of normal skin and wound healing, mice lacking or defective in skin gamma-delta T-cells show delay in wound closure and a decrease in the proliferation of keratinocytes at the wound site (Jameson and Havran, 2007; Mills et al., 2008). Re-epithelization The proliferative phase generally follows and overlaps with the inflammatory phase, and is characterized by epithelial proliferation and migration over the provisional matrix within the wound (re-epithelialization). In the reparative dermis, fibroblasts and endothelial cells are the most prominent cell types present and support capillary growth, collagen formation, and the formation of granulation tissue at the site of injury. Within the wound bed, fibroblasts produce collagen as well as glycosaminoglycan and proteoglycans, which are major components of the extracellular matrix (Jameson and Havran, 2007; Mills et al., 2008).Remodeling Following robust proliferation and ECM synthesis, wound healing enters the final remodeling phase, which can last for years. In this phase, regression of many of the newly formed capillaries occurs, so that vascular density of the wound returns to normal. One critical feature of the remodeling phase is ECM remodeling to an architecture that approaches that of the normal tissue. The wound also undergoes physical contraction throughout the entire wound-healing process, which is believed to be mediated by contractile fibroblasts (myofibroblasts) that appear in the wound (Gosain and DiPietro, 2004; Campos et al., 2008).

Material and methods

Plant material used

Fresh whole plants of *Periploca aphylla* was collected from semi-tribal area of Makerwal and Gulla Khel (lying between Khyber Pakhtunkhwa and Punjab provinces), Pakistan. The *Solanum nigrum* collected from district Kotli, Azad Jammu and Kashmir during the months of February and March. The

collected plants identified with morphological and taxonomic keys provided in various texts by Botanist in Department of Botany, University of Sargodha. Voucher specimen is stored thereof.

Chemicals and equipments used

Framycetin (Sanofi Aventis), Wool fat, Hard Paraffin, Cetostearyl alcohol, xylene and White Soft Paraffin. Hematoxylin and eosin stains. All chemicals will be provided by the Faculty of Pharmacy University of Sargodha, Sargodha. Rotary Evaporator (Stuart, Bibby Steriline Ltd. UK), Weighing balance (SHIMADZU Corporation, Japan) were also used during study.

Preparation of ointments by Fusion method

Preparation of 10% w/w ointment

Wool fat - 2grams, Hard paraffin – 2grams, Cetostearyl alcohol – 2grams, White soft paraffin – 34grams were used for preparation of test ointment. Each ingredient was mixed and heated gently with stirring then cooled. The base was then being packed in a wide mouth container. Methanol extract of *Periploca aphylla* – 4gram and methanol extract of *Solanum nigrum* – 4gram were were added slowly to the above melted ingredients and stirred thoroughly until the mass cools down and a homogeneous product was formed. The ointment was then being packed in a wide mouth container (Kodati., 2011).

Experimental animals used

Wister albino rats of either sex, weighing about 150-250 grams, procured from National Institute of Health, Islamabad, were housed in the metal cages in the animal house of Department of Pharmacy, University of Sargodha, Sargodha. After procurement, the rats were divided into different groups and left for seven days so that the animals can acclimatize to experimentation room where they were provided standard husbandry conditions; temperature was maintained at 25±2 ˚C, 12-h light: 12-h dark cycle and free access to laboratory feed and tap water was provided *ad libitum* throughout the experiment (Ibrahim *et al*., 2008).The experimental protocols employed were got approved from the institutional ethical committee of University of Sargodha, Sargodha.the test animals were divided as , **G-I**: served as vehicle control and applied simple ointment, **G-II**: 2% w/w Framycetin ointment applied, **G-III**: normal ointment base and **G-IV**: 10% w/w extract ointment is applied.

Experimental procedure

Preparation of extracts

Fresh whole plants collected from the fields. The collected plants rinsed with distilled water, cut into small pieces and shade dried at room temperature. Extraction from the whole plant is carried out following a maceration procedure. A total of 7.5kg of each plant were finally powdered with the help of a china herbal grinder and stored in air-tight containers in cellophane bags at a temperature of 4 °C (Akhtar *et al.*, 2009). 7.5Kg of powered plants were extracted successively ina methanol using 30 L solvent for cold maceration. The process of maceration continued for seven days at room temperature (25±2 ˚C) with occasional shaking for each solvent (Pattanayak *et al.*, 2011). The solvent from each extracted material was evaporated using rotary evaporator till complete evaporation and the residue was weighed. The final yield was found to be 435 g. The methanolic extract was tested for the presence of flavonoids with the help of chemical tests: few drops of 1% aluminium solution were added to a portion of each filtrate. A yellow colouration was observed indicating the presence of flavonoids (Edeoga *et al.*, 2005) and the presence of flavonoids was also confirmed with the help of Shibata's test (Potchoo *et al*., 2008).

Preliminary Phytochemical Test

The preliminary phytochemical test of the extracts for the presence of alkaloids, flavonoids, terpenoids, glycosides, saponins and tannins was performed by the standard methods (Plummer 1984 and Pollock and Stevense et al. 1965). Experimental Animals-Adult albino Wistar rats (150 - 200 gm) of either sex used in the experiment were allowed to acclimatize to the laboratory conditions for 7 days in cages prior to commencement of the experiment with 12hr day and night schedule at a temperature of 26±4 c. The animals were maintained with standard pellet diet and water ad libitum. The experimental protocol was approved by the Institutional Animal Ethics Committee and animals were maintained under standard conditions in the animal house approved by Committee for the Purpose of Control and Supervision on Experiments on Animals. A total of 40 rats were used for the estimation of wound healing activity of the selected plants, 20 animals for each plant. The animals were divided randomly into 4 groups of 5 animals each.

Induction of Wound

Two models of inducing wound were used for each plant.

Excision Wound Model

Hair was removed from the dorsal thoracic central region of anaesthetized rats using xylene. The rats were depilated on the back. One excision wound was inflicted by cutting away a 300mm full thickness of skin from a predetermined area; the wound left undressed to the open environment. Then the ointments were applied. Then calculated as percent reduction in wound area (Kodati., 2011).

$$\%\text{wound contraction} = \frac{\text{healed area}}{\text{total area}} \times 100$$

The progressive changes in wound area were monitored planimetrically by tracing the wound margin on graph paper every alternate day. Epithelization time was noted as a number of days after wounding required for the scar to fall off leaving no raw wound behind.

Incision Wound Model

Two 6cm long paravertebral incision were made through full thickness of skin on either side of the vertebral column of the rat. Wounds were closed with interrupted sutures, 1cm apart with the help of black silk surgical thread and a curved needle (no.11). The sutures were removed on the seventh day. Wound breaking strength was measured in anesthetized rats on the tenth day after wounding by continuous constant water supply technique (Das., 2013, Talker *et al*., 2012). Wound breaking strength was measured on 10^{th} post wounding day. The breaking strength was measured with a manually operated instrument in terms of weight (Lee 1968). The animals were treated with drugs as in excision wound model except that the treatment was given up to 9^{th} day (Pattanaik *et al*., 2014).

$$\text{Tensile strength} = \frac{\text{breaking strength (grams)}}{\text{cross sectional area of the skin (mm2)}}$$

Treatments of the Groups

Collection of Samples and Histological Examination

From the healed wound, a specimen sample of tissue is isolated from each group of rats for histopathological examination. (Kodati *et al.,* 2011). The tissue was processed in the routine way for histological evaluation. Five micrometer thick sections were stained with haematoxylin and eosin, the routine stain used in the histopathology, and recommended as a general survey stain. The tissue samples were evaluated for the following histological criteria; the extent of reepithelization, the maturation and organization of the epidermal squamous cells, the thickness of the granular cell layer, the degree of tissue formation. The different animal groups were assessed blindly by pathologist and results were compared with the control group.

Statistical Analysis

The data obtained were calculated as mean ± S.E.M. The significance of the difference of the mean value with respect to control group was analyzed by one-way ANOVA followed by Dunnet's t- test using Statistica 8.0. $p<0.05$ or above was considered to be significant (Talker *et al*., 2012, Das., 2013).

RESULTS AND DISCUSSION

Preliminary Phytochemical Test

The preliminary phytochemical analysis of the methanolic extracts of *Solanum nigrum* and *Periploca aphylla* showed the presence of the major phytoconstituents like tannins, saponins, flavonoids, alkaloids, cardiac glycosides, terpenoids and reducing sugars. Moreover, there are plenty of research studies proved the potent wound healing activities was due to the presence of flavonoids and terpenoids which serve as a defensive agent against any pathogen (Hostettmann and Marston, 1995). Table 1 shows the active substances in the various members of the *Solanum nigrum* plant whereas Table 2 shows phytochemical profile of Periploca *aphylla*.

Table 1. The results of the testing for the active substances in the various members of the *Solanum nigrum* plant.

Active substance	Leaves	Twigs	Flowers	Fruits	Roots
Alkaloids	+++	++	++	+++	+
Saponins	+++	+	+	++	+
Tannins	++	+	+	+++	-
Glycosides	+++	++	+	++	-
Coumarins	++	++	-	++	-
Terpenoids	-	+	-	++	+
Flavonoids	+++	++	+	++	-
Volatile oils	-	-	-	-	-

Wound Healing Effect

Table 3 and Figure 4 summaries the wound healing effects of test extracts. The studies on excision wound healing model reveals that all the 4 groups showed decreased wound area from day to day. However, on 20th post wounding day, Group-I animals showed 90.15±0.27% of healing, whereas Group-II and Group-III animals showed 98.50±0.44% and 99.70±0.11% of healing. Group IV animals showed 91.08±0.77% of wound healing (table 4). All readings are found to be statistically significant and comparable with control. The epithelization time i.e. times at which complete scar

formation occur, also suggest that all treated groups were found to be significant and comparable with control. On the basis of the results obtained in the present investigation, it is concluded that the methanolic extract of Solanum *nigrum* and *Periploca aphylla* has significant wound healing activity. Wound healing activity of both plant extracts were found to be better than the standard framycetin ointment treated group.

Table 2: Phytochemical profile of *Periploca aphylla.*

Chemical components	n-Hexane ext.	chloroform ext.	water ext	methanol ext.
Alkaloids	-	-	-	-
Saponins	-	-	-	-
Tannins	-	-	+	+
Glycosides	-	-	-	-
Coumarins	-	+	+	+
Terpenoids	-	+	+	+
Flavonoids	-	-	-	-

Table 3: Effect of *Solanum nigrum* and *Periploca aphylla* on healing of excision wound model.

	Percentage wound contraction on post wounding days					Epithelization in days
	4th	8th	12th	16th	20th	
Group I	17.31±0.26	34.42±0.27	58.66±0.28	81.06±0.26	90.15±0.27	22.5 ± 0.92
Group II	32.22±0.50	63.70±0.49	78.05±1.05	89.12±0.39	98.50±0.44	17.80 ± 0.56
Group III	33.52±0.49	67.81±0.52	82.55±0.68	93.40±0.55	99.70±0.11	16.55 ± 0.46
Group IV	18.20±0.47	35.97±0.36	61.50±0.50	82.25±0.51	91.02±0.77	21.52 ± 0.54

Values are Mean ± S.E.M. of five animals in each group. *p<0.001 as compared to control.

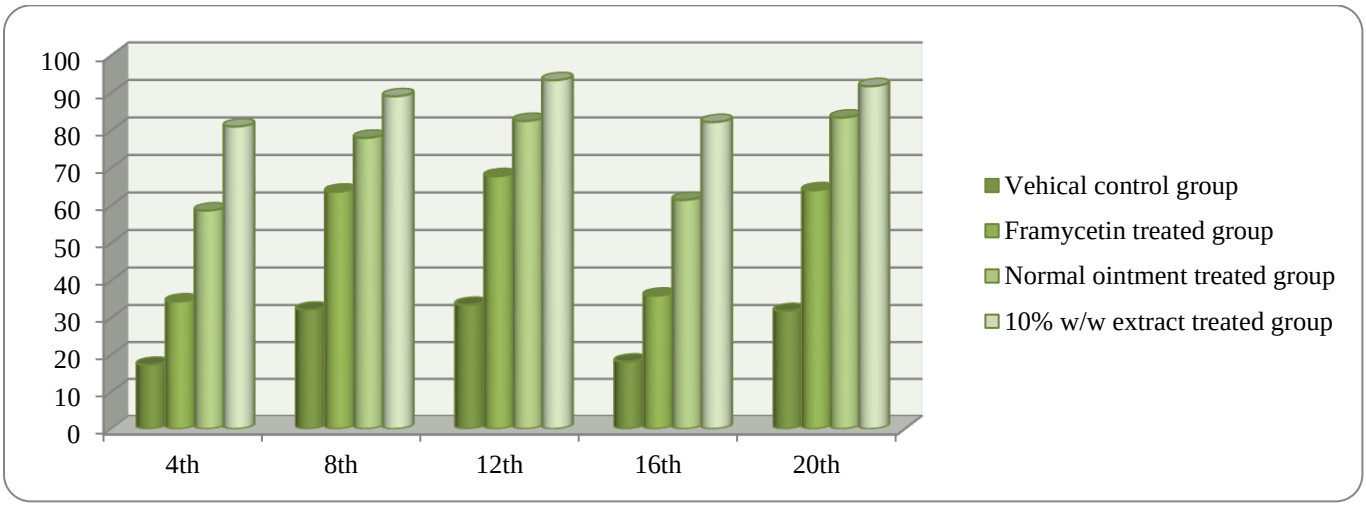

Figure 1: Effects of methanolic extracts of Solanum *nigrum* and *Periploca aphylla* and framycetin on excision wound model in mice.

Histopathological Observations

Treatment of rat wounds with plants extract of *Solanum nigrum* and *Periploca aphylla* and standard drug treated animals led to reduced polymorphonuclear leukocytes (PMNLs), congestion, oedema, mononuclear leukocyte infiltration and necrosis. *Solanum nigrum* and *Periploca aphylla* treated animals were

found to have mild vascular proliferation and reduction of accessory skin structures. Along with these, considerable increase in the dermal collagen content was evident from the histopathological observation. On the contrary, in disease control group focal dermal fibrosis, brownish pigments in macrophages were observed (Figure 5).

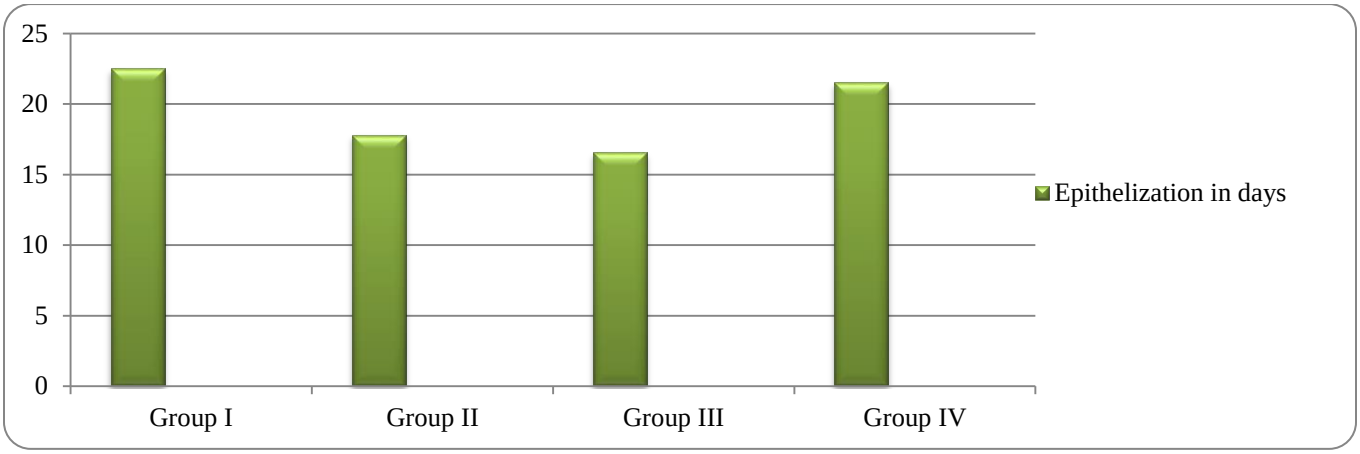

Figure 2 Epithelization in days.

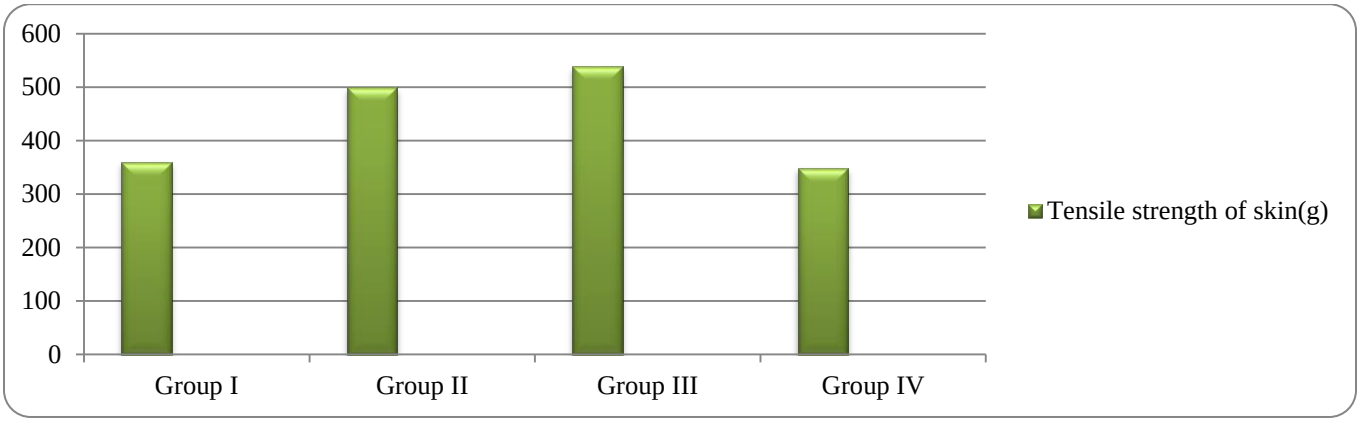

Figure 3: Tensile strength of skin in grams.

Table 4: Effect of *Solanum nigrum* and *Periploca aphylla* on healing of incision wound model.

Sr. no.	Groups	Tensile strength of skin(g)
1	Group I	359.60 ± 0.92
2	Group II	499.10 ± 1.27
3	Group III	538.10± 1.52
4	Group IV	348.30 ± 0.94

DISCUSSION

Wound healing is a complex process of restoring cellular structures and tissue layers in damaged tissue together to its normal state and commencing in the fibroblastic stage where the area of the wound undergoes shrinkage (Chitra *et al*., 2009). It's well known that wound-healing started instantly while the skin was subjected to injury or trauma (Singer and Clark, 1999). Wounds are referred to as disruption of normal anatomic structure and function. Skin wounds could happen through several causes like physical injuries resulting in opening and breaking of the skin (Gerald *et al*; 1994). The most common symptoms of wounds are bleeding, loss of feeling or function below the wound site, heat and redness around the wound, painful or throbbing sensation, swelling of tissue in the area and pus like drainage (Rashed *et al*; 2003). It comprises of different

phases such as contraction, granulation, epithelization and collagenation (Ayyanar & Ignacimuthu, 2009; Wild et al., 2010). Wound healing can be discussed in three phases viz. Inflammatory phase, proliferative phase and maturational or remodeling phase. The inflammatory phase is characterized by homeostasis and inflammation. Proliferative phase is followed by epithelialization, angiogenesis and collagen deposition. In the maturation phase, the wound undergoes contraction resulting in a smaller amount of apparent scar tissue (Phillips et al., 1991). Granulation tissue which is formed in the final part of the proliferative phase is primarily made up of fibroblasts, collagen, oedema and new small blood vessels. The increase in dry granulation tissue weight in the test treated animals suggests higher protein content (Devipriya & Shyamladevi, 1999). Wound healing is a very complex, multifactor sequence of events involving several cellular and biochemical processes. The aim in these processes is to regenerate and reconstruct the disrupted anatomical continuity and functional status of the skin. Healing process, a natural body reaction to injury, initiates immediately after wounding and occurs in four stages. The first phase is coagulation which controls excessive blood loss from the damaged vessels. The next stage of the healing process is inflammation and debridement of wound followed by re epitheliazation which includes proliferation, migration and differentiation of squamous epithelial cells of the epidermis. In the final stage of the healing process collagen deposition and remodeling occurs within the dermis (Phillips *et al*; 1991).

The results showed wound healing and repair, accelerated by applying methanolic extracts of *Solanum nigrum* and *Periploca aphylla*, which was highlighted by the full thickness coverage of the wound area by an organized epidermis. The enhanced capacity of wound healing with the plants could be explained on the basis of wound contraction effects of the plants that are well documented in the literature. Study on animal models showed enhanced rate of wound contraction and drastic reduction in healing time than control, which might be due to enhanced epitheliasation. The animals treated with standard and extract showed significant results when compared with different groups and control. The treated wound after 20^{th} day itself exhibit marked dryness of wound margins with tissue regeneration. However, histological evaluation showed that, increased cellular infiltration from haematoxylin and eosin staining in treated cases may be due to chemo tactic effect enhanced by the crude extract which might have attracted inflammatory cells towards the wound site (Hernandez *et al*; 2001). Increased cellular proliferation may be due to the mitogenic activity of the plant extract, which might have significantly contributed to healing process. Early dermal and epidermal regeneration in treated mice also confirmed that the extract had a positive effect towards cellular proliferation, granular tissue formation and epitheliazation.

Tannins and flavonoids are the major phytoconstituent present in both these plants which may be responsible for wound healing action. The plant *Solanum nigrum* containing the tannins possesses wound healing activity as that of the *Periploca aphylla* (Rashed; *et al* 2003). The methanolic extract of the *Solanum nigrum* and *Periploca aphylla* possess wound healing action by improving regeneration and organization of the new tissue due to the presence of tannins (Leite *et al*; 2002). A number of secondary metabolites/active compounds isolated from plants have been demonstrated in animal models (in vivo) as active principles responsible for facilitating healing of wounds. Some of the most important ones include tannins from *Terminalia arjuna*, (Chaudhari and Mengi; 2006), oleanolic acid from *Anredra diffusa* (Letts *et al*; 2006), polysaccharides from *Opuntia ficus-indica* (Trombetta *et al*; 2006), gentiopicroside, sweroside and swertiamarine from *Gentiana lutea* (Ozturk *et al*; 2006), shikonin derivatives (deoxyshikonin, acetyl shikonin, 3-hydroxy-isovaleryl shikonin and 5,8-*O*dimethyl acetyl shikonin) from *Onosma argentatum* (Ozgen *et al*; 2006), asiaticoside, asiatic acid, and madecassic acid from *Centalla asiatica* (Maquart *et al*; 1999, Shukla *et al*; 1999, Hong *et al*; 2005), quercetin, isorhamnetin and kaempferol from *Hippophae rhamnoides* (Fu SC *et al*; 2005), curcumin from *Curcuma longa* (Jagetia and Rajanikant; 2004).

CONCLUSION

It is convincible from the data presented that the flavonoid and tannins fractions of both the plants showed wound healing activity in rats. Histological evaluation shows there was a marked infiltration of the inflammatory cells, increased blood vessel formation and enhanced proliferation of cells as a result of treatment with methanolic extracts of *Solanum nigrum* and *Periploca aphylla.* This study thus demonstrates the wound healing activity of methanolic extracts of both plants, *Solanum nigrum* and *Periploca aphylla* found to be effective in the functional recovery of the healing of wounds and also in histopathological alterations. As infections being a major cause of morbidity and mortality in wound patients, these herbal extracts may prevent infection that leads to high risk of sepsis, and thereby prevents the prolongation of inflammatory phase.

Further study on the fractionation of active components and the mutual effect of these plant extract machinery on infecting microbial species may provide a better understanding of the infection management in the process of wound healing.

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