Research Article

Evaluation of wound healing potential of *Nerium indicum*, *Artocarpus heterophyllus, Murraya koenigii and Punica granatum* using incision wound model in rats

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Abstract

Objective: The objective of present work was to assess the wound healing potential of *Nerium indicum*, *Artocarpus heterophyllus, Murraya koenigii* and *Punica granatum* formulated as poly-herbal ointment and gel using Incision wound model in albino rats. These plants exhibit anti-diabetic, anti-inflammatory, anti-microbial, anti-leukemic, anti-mycobacterial, antioxidant, antitumor, antiulcer, antiviral, anticancer, antimalarial, cytotoxic, anti-protozoal and wound healing properties. **Materials and Methods:** Solvent extraction method was used for extraction of plant material for further processing into different formulations. Poly-herbal ointment and gel formulation were prepared by mixing the extract of *Nerium indicum*, *Artocarpus heterophyllus, Murraya koenigii* and *Punica granatum.* Incision wound model on albino rats was used for the assessment of wound healing potential. **Results and Conclusion:** The studies on incision wound healing model reveals that F2 poly-herbal ointment formulation show better wound healing potential in comparison to gel formulation as well as all extracts of the plants and there was no mortality observed in the course of study. These studies has indicated that ointment and gel poly-herbal formulation of *Nerium indicum, Artocarpus heterophyllus, Murraya koenigii* and *Punica granatum* has been utilized for wound healing and it is safer for topical application. No toxicity and mortality has been observed during the experimental tenure.

Keywords*:* Wound healing, *Nerium indicum, Artocarpus heterophyllus, Murraya koenigii, Punica granatum,* incision wound model

Introduction

The current life style and rising health concerns have led to an increase in the demand for food and food products, which provide health benefits beyond the basic nutrition. Natural antioxidants play an important role in human health care. Besides natural antioxidants, many artificial antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and propyl gallate may also be used but may produce toxic substances, which shall harm human health. Fruits & vegetables are important sources of natural antioxidants. Higher intake of fruits and vegetables has been proven to reduce the risk of chronic diseases. This positive characteristic can be attributed to phyto-chemicals such as carotenoids, alkaloids, vitamins, minerals and poly-phenols (Medoua et al., 2014). These beneficiary effects of antioxidant improved wound healing potential.

Wound infection is one of the most common diseases in developing countries because of poor hygienic conditions (Kumar et al., 2006). Wounds are the physical injuries that result in an opening or breaking of the skin and appropriate method for healing of wounds is essential for the restoration of disrupted anatomical continuity and disturbed functional status of the skin. Wound healing process holds several steps which involve coagulation, inflammation, formation of granulation tissue, matrix formation, remodeling of connective tissue, collagenization and aquisation of wound strength (Enoch et al., 2005; Guo et al., 2010; Shukla et al., 2019).

Nerium indicum mill, also known as Kaner (Figure 1). It is evergreen shrub or small tree that grows up to 5m in height (Nagargoje et al., 2013). Leaves and flowers are used to treat malaria and as traditional medicine it induces the termination of embryo. The root powder is an external remedy for hemorrhoids and ulcers around genitals. *Nerium indicum* Mill has gain many properties like bitter, acrid, astringent,

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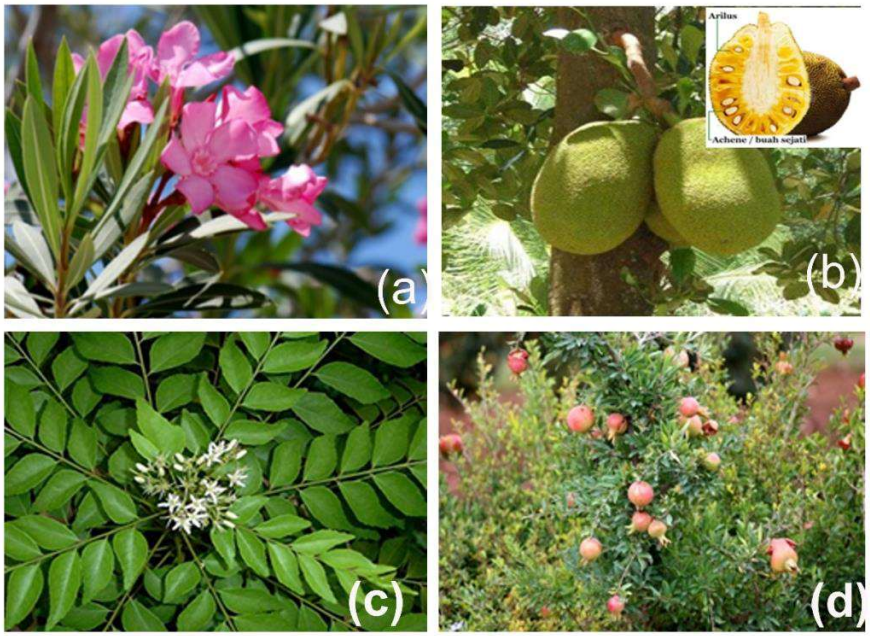

Figure 1. Leaves of *Nerium indicum* Mill (Kaner) (b) *Fruit of Artocarpus heterophyllus* Lam (Jackfruit, Kathal) (c) Leaf of *Murraya koenigii Linn* (curry leaf) (d) Fruit of *Punica granatum* Linn (Anardana)

anthelmentic, aphrodisiac, stomachic, febrifuge, It is also used as antimalarial (Sharma et al., 2005) anti-diuretic, emetic, expectorant, cardio tonic, anticancer and applied in the treatment of cardiac asthma, renal and vesicle calculi, chronic stomach, snake bites, joint pains, ulcers etc (Dey et al., 2014).

Artocarpus heterophyllus Lam is a species of tree of the mulberry family Moraceae. It is also known as jackfruit (Eng.), Kathal (Hindi), Kanthal (Beng.). It is native to Western Ghats of India, malaysia, central and eastern Africa and south-eastern Asia (Elevich et al., 2006). Jackfruit *(Artocarpus heterophyllus* Lam) was flakes of ripe fruits are high in nutritive value; every 100 gm of ripe flakes contains 287-323 mg potassium, 30.0-73.2 mg calcium and 11-19 gm carbohydrates. The *Artocarpus heterophyllus* (Figure 1) contains various chemical constituents as several flavones colouring matters, morin, dihydromorin, cynomacurin, artocarpin isoartocarpin, cyloartocarpin, artocarpesin, oxydihydro artocarpesin, artocarpetin, norartocarpetin, cycloartinone and artocarpanone (Akhilhari et al., 2014) .

The heart wood on analysis yields moisture 6.7%, glucosides 38.0%, lipids 0.7%, albumin 1.7% and cellulose 59.0% (Baliga et al., 2011). The plant also contains free sugar (sucrose), fatty acids, ellagic acid and some essential Amino acids like Arginine, cystine, histidine, leucine, lysine, metheonine, theonine, tryptophan (Baker et al., 2015). The leaves and stem show the presence of sapogenins, cycloartenone, cycloartenol, β-sitosterol and tannins, they show estrogenic activity. A root contains β-sitosterol, ursolic acid, betulinic acid and cycloartenone (Ojwang et al., 2018).

The leaves are useful in fever, boils, wounds and skin diseases. The young fruits are acrid, astringent, and carminative. The ripe fruits are sweet, cooling, laxative, aphrodisiac and also used as a brain tonic. The seeds are, diuretic, and constipating. The wood is nervine, antidiabetic, sedative and is useful in convulsions (Mohammed et al., 2018). The latex is useful in dysopia, ophthalmic disorders and pharyngitis and also used as antibacterial agent. The ash of Jackfruit leaves is used in case of ulcers. The dried latex yields artostenone, convertible to artosterone, and a compound with marked androgenic action. The root is a remedy for skin diseases and asthma. An extract of the root is taken in cases of fever and diarrhea. The bark is made into poultices. Heated leaves are placed on wounds. The wood has a sedative property and its pith is said to be abortifacient. Latex is used as an antiinflammatory agent (Burci et al., 2018).

Murraya koenigii Linn, called curry leaf, is a small, tropical to sub-tropical tree or shrub that typically grows to 6-15' tall and is noted for its pungent, aromatic, curry leaves which are an important flavoring used in Indian/Asian cuisine. This tree is native to moist forests in India and Sri Lanka. Fragrant white flowers (each to 5/16" across) in many flowered panicles (terminal cymes) bloom irregularly throughout the year. They are best used fresh in cooking (dried leaves may be used but have significantly diminished flavor). Aroma/flavor of the fresh leaves is enhanced when the leaves are fried in oil or butter (Singh et al., 2014). Curry leaves are often added to vegetable dishes. They add subtle

flavors to many other dishes, including meat, seafood, chutneys, coconut sauces, relishes, marinades and omelets.

It is a warming, strongly aromatic herb that improves appetite and digestion. The leaves, roots and bark can all be used internally in the treatment of digestive problems. The oil obtained from the leaves used as antioxidant, anthelmintic (Sharma et al., 2010) and antibacterial properties (Rajendran et al., 2014). It has been shown that the leaves increase digestive secretions; relieve nausea, indigestion and vomiting. The leaves can be used internally in treating constipation, colic, antimicrobial (Salomi et al., 2010) and diarrhea. The leaves are used in the treatment of diarrhea and dysentery. The leaves can be applied externally as a poultice to treat burns and wounds (Jadhav et al., 2017). The roots and bark are harvested as required and can be used fresh or dried. A paste made from the bark is applied to the bites of poisonous insects and other animals.

Punica granatum Linn is a deep-rooted but slow-growing, spiny, deciduous shrub or small multipurpose tree, it is particularly valued for its edible fruit, but also has medicinal properties, is a good source of tannins and has many agro-forestry applications. Fruit–raw, Juicy and refreshing with a sub-acid flavor (Nayak et al., 2013). The fruit is 5-13 cm in diameter; it has a hard, tough case that contains lots of seeds, each surrounded by a delicious juicy red flesh (Shirote et al., 2018). The fruit juice can be used in soups, sauces, jellies, ice cream, cakes etc. The fruit contains about 1.5% protein, 1.6% fat, 16.8% carbohydrate, 0.6% ash (Sangeetha et al., 2015).

All parts of the plant contain unusual alkaloids, known as 'pelletierines', which paralyse tapeworms so that they are easily expelled from the body by using a laxative. The plant is also rich in tannin, which makes it an effective astringent. It is used externally in the treatment of vaginal discharges, mouth sores and throat infections. The whole plant, but in particular the bark, is having antibacterial, antifungal (Mansourian et al., 2014), antiviral, anticancer (Li et al., 2016) and astringent properties. The flowers are used in the treatment of dysentery, stomach ache and cough. The juice of the flowers is used to treat nose bleeds. The seeds are demulcent and stomachic. It is also used as anti-diabetic (Redha et al., 2018) and having antioxidant, anti-inflammatory (Amer et al., 2015), and anti-proliferation properties (Bekir et al., 2013). A decoction of the seed is used to treat syphilis. The fruit is a mild astringent and refrigerant in some fevers and especially in biliousness. It is also cardiac and stomachic. The juice of the fruit is used to treat jaundice and diarrhea. It is a specific remedy for tapeworm infestation. The rind of the fruit is ground in water and drunk every morning by diabetics.

The objective of present work is to evaluate the wound healing potential of some Indian plant including *Nerium indicum* Mill, *Artocarpus heterophyllus* Lam, *Murraya koenigii* Linn and *Punica granatum* Linn. Two ointment (F1 & F2) and Gel (F3 & F4) formulation is prepared for topical application and compare with extract of individual plants.

Materials and methods

Plant material collection and authentication

The leaves of *Nerium indicum* Mill (NI) were collected at in the month of June, 2016 from local area of Shubham Nursery Bhopal M.P., Pulp of *Artocarpus jeterophyllus* Lam (AH) and Whole plant of *Murraya koenigii* Linn (MK) from local market of Barkheda and Bark of *Punica granatum* Linn (PG) from Vidisha district, Madhya Pradesh. The specimens were submitted and identified as *leaves* of *Nerium indicum* Mill, pulp of *Atrocarpus heterophyllus* Linn, bark of *Punica granatum* Linn, Whole plant of *Murraya koenigii* Linn and authenticated by Dr. Zia ul Hassan, Department of Botany, Saifia Science College, Bhopal. The oppression no. for the specimen is 498/BS/saifia/NI_MK_PG_AH /04/16/07 has been preserved for future identification. The samples were shade dried so as to protect its chemical constituents not to get degrade at high temp.

Extraction of plant materials

The leaves of NI, pulp of AH, bark of PG and leaves of MK were collected fresh and dried on filter paper sheets under shade at room temperature until with changing of color of filter papers. The shade-dried, coarsely powdered materials (500g) were defatted by petroleum ether (45°C). The defatted marc was then subjected to Soxhlet extraction with 70% ethanol to obtain hydro-alcoholic extract. The hydro-alcoholic extracts were evaporated under reduced pressure at low temperature (30°C) to dryness to yield different extracts, stored in an airtight container in refrigerator for further experimental studies.

Preparation of ointment and gel formulations

Poly-herbal formulation of all four plants has been prepared after completion of extraction and phyto-chemical studies. In this regards water soluble base is first choice for the formulation development of poly-herbal ointment and gel formulations. Water soluble base was used by their ease of preparation and cleaning after application.

Formulation of ointment

Poly-herbal ointment formulation was prepared by the fusion method (Shubhangi et al., 2016). Polyethylene glycol (PEG) Ointment base, a mixture of PEG 4000 and PEG 600 (Asija et al., 2015) found to have sufficient consistency in ratio 3:7 respectively, thus suitable for ointment preparation with concentration of 10 % & 15%

w/w of all plants extracts. Two formulations F1 and F2 were prepared by Fusion method e.g. one containing all four extracts of above mentioned plants parts in equal ratio i.e. 2.5% w/w of each extract for the preparation of 10 % w/w ointment in PEG ointment base (treated as poly-herbal-I or test-I) and the other one containing all four extracts of above mentioned plants parts in equal ratios i.e. containing 3.75% w/w of each extract, equal to total 15% w/w in PEG ointment base (treated as poly-herbal-II or test-II). The prepared formulations was then evaluated by various parameters e.g. consistency, stability (Sawant et al., 2016). The Quantity used for the ointment formulation was depicted in table 1.

Formulation of topical gel

Topical gel formulations of different concentration using carbopol base were formulated. The various ingredients used for the two different formulations are mentioned in **Table 2**. All formulations were having carbopol gel base. Formulations I was 2.5% (w/w) of each extract for the preparation of 10% (w/w) gel and formulation II was 3.75% concentration of each extract for the preparation of 15% (w/w) gel, mixed properly with stirrer (Mishram et al., 2018; Shahtalebi et al., 2018; Aslani et al., 2018).

Table 1. Formulation of Ointment

S. No.	Ingredients	Quantity (%)	
		F1	F2
1.	*Nerium indicum* Linn. (Leaves extract)	2.5	3.75
2.	*Murraya koenigii* (whole plant extract)	2.5	3.75
3.	*Punica granatum* (bark extract)	2.5	3.75
4.	*Artocarpus heterophyllus* (Pulp extract)	2.5	3.75
5.	Ointment base	Q.S.	Q.S.

Table 2. Formulation of topical gel

S. No.	Ingredients	Quantity (For 100 ml)	
		F3 (10%w/w)	F4 (15%w/w)
1	*Nerium indicum* Linn. (Leaves extract)	2.5	3.75
2	*Murraya koenigii* (Whole plant extract)	2.5	3.75
3	*Punica granatum* (Bark extract)	2.5	3.75
4	*Atrocarpus heterophyllus* (Pulp extract)	2.5	3.75
5	Carbopol 940	1	1
6	Glycerin	5 ml	5 ml
7	Tri-ethanolamine	Q.S.	Q.S.
8	Propyl paraben	Q.S.	Q.S.
9	Distilled water	Q.S.	Q.S.

Wound healing activity

Incision model, using Albino rats was selected for assessing the wound healing activity. This model was employed to study tensile strength measurement and histological assessment. These parameters were selected in albino rats because of easy availability and simplicity in handling them.

Selection and procurement of animals

Institutional animal ethics committee (IAEC) permitted for the animal studies (Reg. No.: CPCSEA/1413/PO/ES/07). Albino rats of either sex were procured and weighing 150-200 gm was selected. All were maintained at 24-28^{0}C, housed individually with free access to food and water. They were fed with standard diet and kept in well-ventilated animal house with alternate dark-light cycle of 12h throughout the studies.

Oral toxicity studies

Albino rats of weight 150-200gm were selected for acute oral toxicity study and it was conducted according to the Organization for Economic Co-operation and Development (OECD) (OECD: Guidelines 420; Fixed Dose Method) for oral administration of extracts. Eighteen hour overnight fasted animals were subjected to oral administration of extracts at a dose of 2000 mg/kg body weight. All the animals were kept under observation for first 3h for any changes or toxic effects like neurological, gross behavioral and lethality. The animals were observed and confirmed the absence of any toxic effects, hence two dose of combination 10% and 15% ointment were prepared with simple ointment base for topical application and 10mg/ml oral dose taken for study.

Incision wound model

In the incision wound model, albino rats depilated by removing hairs at the dorsal thoracic region before wounding. Rats were anaesthetized by diethyl ether prior to incision. Six centimeter long para-vertebral incisions were made through full thickness of skin on either side of vertebral column of the rat. The wounds were closed with interrupted sutures of one centimeter apart. The rats are categorized into fifteen groups (n=6). The animal of **group I** treated as control-I and only ointment base applied topically. The animal of group II was treated as standard group which received the povidone iodine applied topically. Group III- XIV were treated as TEST I- X and where F1 and F2 (ointment formulations), NIL5, NIL10, MKL5, MKL10, PGB5, PGB10, AHP5, AHP10, F3 and F4 (gel formulations) applied topically, respectively. The animal of group XV treated as control-II and only gel base applied topically. All the samples were applied once daily for 10

days, starting from the day of wounding. The sutures were removed on 8th post wounding day. The tensile strength of wounds was measured on 10th day following continuous water flow technique (Rashed et al., 2003).

Tensile strength measurement

The tensile strength was calculated in incision wound model. On 10th day the rats were again anesthetized and each rat is placed on a stack of paper towel on the middle of the board. The amount of the towel could be adjusted in such a way so that the wound is on the same level of tips of the arms. The clamps are then carefully clamped on the skin of the opposite side of the skin of wound at a distance of 0.5 cm away from the wound. The longer pieces of the fishing line are placed on the pulley and finally to the polyethylene bottle and the position of the board is adjusted so that the bottle receive a rapid and constant rate of water from the large reservoir, until the wound began to open. The amount of water in polyethylene bag is weighed and consider as tensile strength of the wound (Shukla et al., 2018).

Histopathological studies

The skin specimens were collected in 10% buffered formalin from rats of the twelve groups. Then, 5µm thick sections were sliced and stained with haematoxylin and eosin. The light microscope was used to evaluate the sliced sections in terms of collagen formation, fibroblast proliferation, keratinisation, and epithelisation (Shukla et al., 2019).

Statistical analysis

Statistical analysis was performed using Graph Pad Prism version 7 for Windows (Graph Pad Software, San Diego, CA, USA) and Microsoft Excel 2013. Raw data obtained from different wound models are expressed as mean±SEM. Values less than 0.05 were considered to be statistically significant. The data were analyzed using Graph Pad Prism version 7 for Windows and differences among groups were compared by one-way ANOVA followed by Dunnett's test.

Results and discussion

Extraction

The extraction was done by continuous hot percolation method i.e. Soxhlet apparatus. The dried and pulverized drug was defatted with petroleum ether. The obtained marc was then extracted with 70% Hydro-alcoholic solution. The drying of extract containing solvent (70% hydro alcoholic solution) was done by rota vacuum evaporator. The data depicted in the table 3.

Wound healing activity

The results of the incision wound healing activity of extract and formulations are represented in table 4. The results were expressed as mean breaking strength (tensile strength) of incision wound. The studies on incision wound healing model reveal that the test group (F1 and F2) showed high breaking strength of wound from 1st day to 10th day e.g. 508.17±7.23 and 537.48±3.71 gm. The other test groups of individual drug ointments at different concentrations has shown different breaking strength results e.g. NIL5 and NIL10 shown 498.31±2.34 and 502.45±2.88, MKL5 and MKL10 shown 457.98±3.61 and 469.73±5.29, PGB5 and PGB10 shown 477.5±3.88 and 489.28±5.67, AHP5 and AHP10 shown 488.35±6.26 and 496.29±2.58 respectively. Ointment formulations F1 and F2 have shown significant wound healing activity, which was comparable to that of standard marketed preparation. The F2 formulation was found more active than the F1, F3 and F4. The tensile strength is more when compared to standard. On 10th day complete healing of wound was observed with standard marketed ointment, and ointment of formulations produced 508.17±7.23 (F1) and 537.48±2.11 (F1), 504.27±4.22 (F3) and 506.91±3.75 (F4) healing of wound as compared to control. The control (ointment base) has shown 339.58±6.52g healing. Wound healing potential of F2 has shown in figure 2.

Table 3. Percentage yield of hydro-alcoholic extracts from different plant

S. No.	Parts	Extract color	Yield (in gm)	% Yield (w/w)
1.	NIL	Greenish brown	20.43	26.28
2.	AHP	Yellowish	8.24	10.05
3.	PGB	Dark brown	8.97	11.34
4.	MKL	Greenish brown	20.76	26.11

Initially 80 g of crude drug was taken. **Where NIL-** Hydroalcoholic Extract of *Neium indicum* leaves**, AHP-**Hydroalcoholic Extract of *Artrocarpus heterophyllus* pulp**, PGB-** Hydroalcoholic Extract of *Punica granatum* Linn.Barkand **MKL-** Hydroalcoholic Extract of *Murraya koenigi* Linn.whole plant.

Table 4. Effect of Poly-herbal formulation and extracts on incision wound model

S. No.	Groups (n)	Tensile strength (gm)
I	Control	306.58±6.52
II	Standard	476.80±4.80
III	F1	508.17±7.23**
IV	F2	537.48±2.11***
V	NIL5	498.31±2.34**
VI	NIL10	502.45±2.88**
VII	MKL5	457.98±3.61*
VIII	MKL10	469.73±529*
IX	PGB5	477.54±3.88*
X	PGB10	489.28±5.67*
XI	AHP5	488.35±6.26*
XII	AHP10	496.29±2.58**
XIII	F3	504.27±4.22**
XIV	F4	506.91±3.75**
XV	Control 2	342.44±5.27

Note: n =6 animals in each group, values are expressed as Mean ±SEM, If *=p<0.05, **=p<0.01, ***=p<0.001 when compare to control.

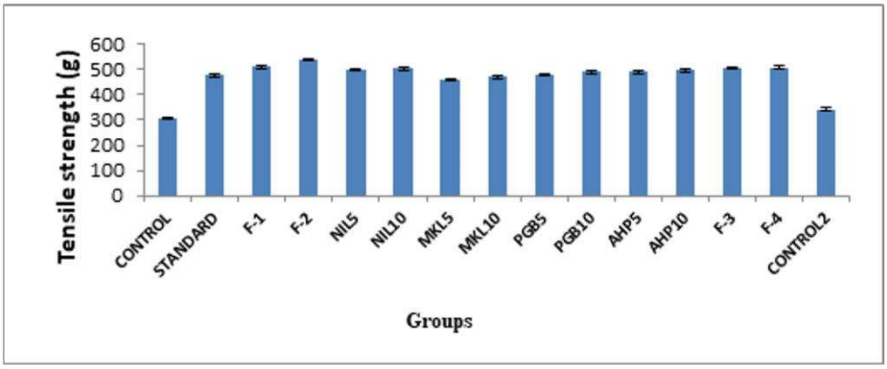

Figure 2. Tensile strength of wound in different groups of incision wound model

Figure 3. Incision wound healing activity of best group (F-2)

Histopathology profile

The Histopathological studies for the incision model revealed **figure 4(a to o)** that the wounds treated with different herbal ointment and gel formulations (GIV< GIII< GXIV< GXIII) (F2< F1< F4< F3) has showed intermittent epidermis. Vacuoles are observed in various sections but with at moderate level. The collagen formation was also less in those groups. The inflammatory cells were also not present. Necrosis was observed larger in spatial extend, also the collagenation with disquieted epidermis was observed.

The necrosis was found in reduced manner in the following order of groups: control < control2 < MKL5 < MKL10 < PGB5 < PGB10 < AHP5 < AHP10 < NIL5 < F-3 < F-4 < NIL10 < F-1 < F-2 < Standard. The order of healing can be arranged as follows: control < MKL5 < MKL10 < PGB5 < PGB10 < AHP5 < AHP10 < NIL5 < F-3 < F-4 < NIL10 < F-1 < F-2 < Standard. In standard treated animal's hyper-granulation and inflammatory cells were apparent. The adnexa were restored in the dermis. The degree of fibrosis was high and collagen tissues were observed. Normal histopathological characteristics were observed in the control group. In the maturation and remodeling phase during the wound healing the cell population was decreased. The scar formation was observed with the increase in collagen deposition in the granulation tissues.

In the present research work ointment and gel formulations with extract of four herbal drugs was prepared and evaluated for the wound healing activity by Incision wound model in animals (albino rat). The hydro-alcoholic extracts prepared by using soxhletion method were incorporated in the ointment base for formulation. After completion of formulation they were evaluated for its physicochemical parameters like colour, odour, pH, spreadability, extrudability, consistency, diffusion study, solubility, washability. Also the formulations were evaluated for its stability at various temperature conditions which shows no change in the irritancy, spreadability and diffusion study. The four individual drugs extracts e.g. *Nerium indicum* leaves, *Murraya koenigii* whole plant, *Punica granatum* bark and *Artocarpus heterophyllus* pulp has shown wound healing properties but the formulation F2 has shown better and improved results in wound healing. Thus it could become a medium to use the medicinal properties of extracts effectively and easily as a simple dosage form. The topical use of herbal ointment formulation accelerates the re-epithelialization of burn wound with proper healing process as compared with the marketed product. The experiment confirmed the therapeutic action of the NIL, PGB, AHP and MKL extracts and was supported by the *in vivo* data. The results obtained also provide rational pharmacological evidence for the use of the NIL, PGB, AHP and MKL extract in the treatment of various types of wounds. Results from this study deliver reasonable pharmacological proof for the use of herbal ointment formulation (F2) for the treatment of wounds. All the results indicated the effectiveness of herbal ointment F2 in enhancing wound

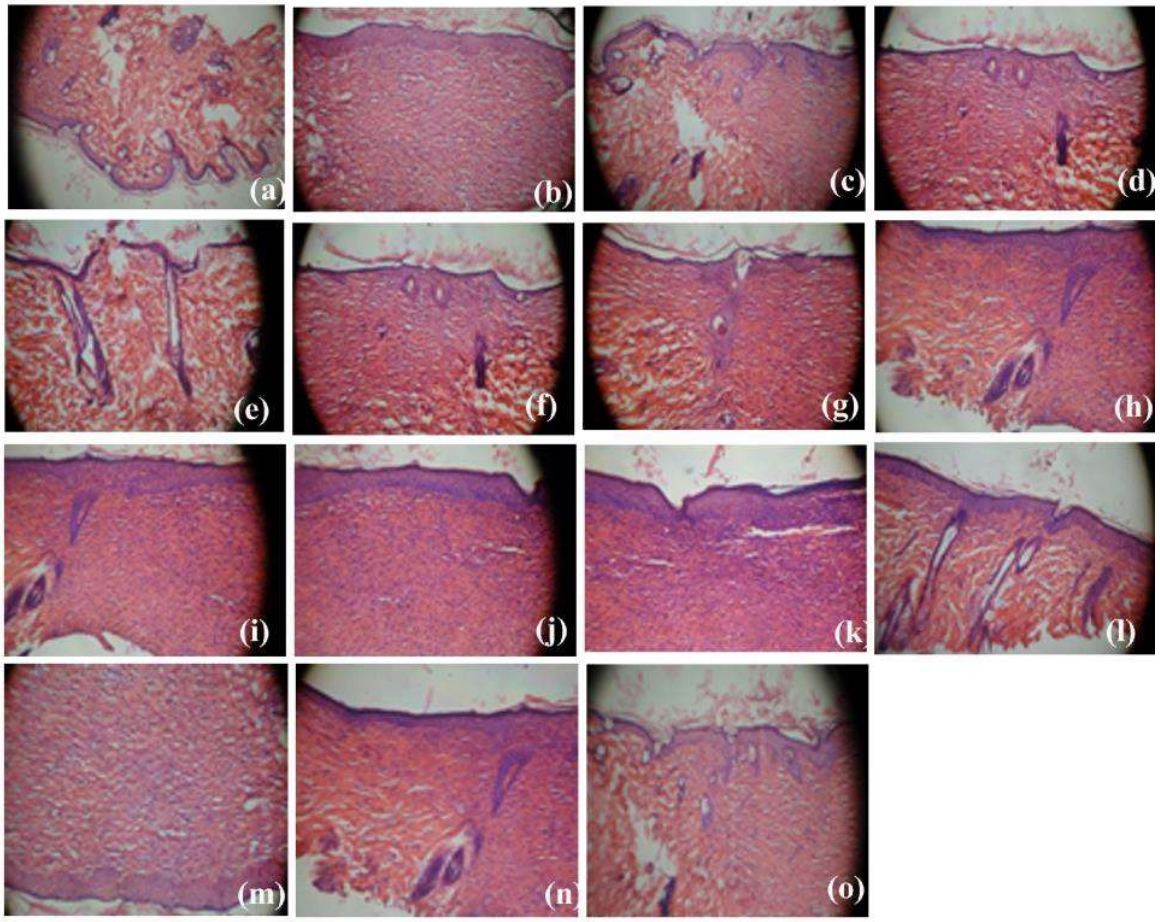

Figure 4. Histopathology of skin at day 10 stained with H&E (100X): (a) Group-I, (b) Group-II, (c) Group-III, (d) Group-IV, (e) Group-V, (f) Group-VI, (g) Group-VII, (h) Group-VIII, IX, (j) Group-X, (k) Group-XI, (l) Group-XII,(m) Group-XIII, (n) Group-XIV, (o) Group-XV

healing activities. The herbal ointment prepared from hydralcoholic extract of *Nerium indicum* leaves, *Murraya koenigii* whole plant, *Punica granatum* bark and *Artocarpus heterophyllus* pulp showed marked reduction in wound tensile strength in comparison to control group when examined for wound healing activity by topical application in albino rats. The formulation will be helpful in wound healing with no side effects and will be beneficial for society and industry with standardization approaches.

Conclusion

Incision wound model suggested that the four individual plant extract have shown the wound healing potential although the prepared ointment and gel formulations have better and synergistic action than individual. The ointment formulations were more effective than gel formulations and especially the formulation F2 has more wound healing potential among others. The poly-herbal formulations containing plant extracts in 15% amount has better wound healing potential.

Conflicts of interest

The author declares no conflicts of interest.

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