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WOUND HEALING ACTIVITY OF *GUETTARDA SPECIOSA* LINN.

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Abstract:

Traditionally the plant diversity was conserved through the temple premises based on their medicinal values. Medicinal activities of many temple plants are scientifically unexplored. The present research was focused to evaluate the wound healing activity of the sacred tree Guettarda speciosa commonly known as Indian lavender which is conserved in many temples and also promoted to grown as ornamental. The plant leaf is enriched with alkaloids, flavonoids, phenols, tannins, terpenoids, etc. Traditionally the leaf is used in cuts and wounds. Hence, the present research carried out to find the wound healing activity of ethanolic leaf extract of G. speciosa by excision wound model on Wistar albino female rats. 5% and 10% (w/w) leaf extract ointments were used for studying the wound healing activity. Lyramycin was used as a standard reference drug. The result showed that animals treated with 10% (w/w) leaf extract ointment possesses significant wound healing activity. The result confirmed and concluded that the activity of the extract is based on a dose-dependent manner.

Keywords: *Wound healing, Guettarda speciosa, excision wound model, ointment, Lyramycin.*

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INTRODUCTION:

A vast number of plants are possessed different medicinal properties. One of the unavoidable important utility is healing of diseases. There is an increase in usage of herbal therapy and also increase of new diseases. There is no way for people to divert from herbal medicine. Traditional medicaments, chiefly obtained from plants have played a vital role in sustaining disease free human existence on this planet [1, 2]. In recent years most of the people depend upon plants for their disease curing. In this way one of the dangerous diseases is wound. If the wound is not taking care it may leads to cancer. The process of tissue repair after an insult to the tissue (wound) is called 'wound healing' [3]. A wound is a breaking in continuity of tissue from violence or trauma. Healing of wound is a restoration of the wounded or inflamed tissue to normal condition [4] by multifactorial physiological process of repairing injured tissues that involves several cell types that result into restoration of a physical barrier [5]. Wound healing involves various phases which include granulation, collagenation, collagen maturation and scar maturation [6].

Wound healing involves continuous cell-cell and cell-matrix interactions that allow the process to proceed in three overlapping phase's *viz*. inflammation, cellular proliferation and remodeling. Phase 1 is a coagulation and inflammatory phase (0-3 days) and this involves migration of neutrophils at margin of incision, moving towards the fibrin clot. Phase 2 is a proliferative phase (3-12 days) in which the neutrophils are largely replaced by the macrophages. Granulation tissue progressively invades the incision space and the incisional space is filled with granulation tissue. Collagen fibrils become more abundant and begin to bridge the incision. Phase 3 is a remodeling phase (3-6 months), involving continuous accumulation of collagen and proliferation of fibroblasts. There is marked reduction in leukocyte infiltration and edema. The phase involves synthesis of collagen fibers, leading to increase in tensile strength of the skin [7].

The reports about medicinal plants affecting various phases of the wound healing process, such as coagulation, inflammation, fibroplasia, collagenation, epithelization and wound contraction are abundant in the scientific literature [8-11]. Many researchers worked in various parts of plants for wound healing activities. But still there are no pharmacological reports available on *Guettarda speciosa* Linn leaves. Hence, the present research was carried out to evaluate wound healing activity by excision wound model in ethanolic leaf extract of *G. speciosa*.

G. speciosa is a sacred tree, conserved in temple premises and also promoted to grown as ornamental tree. Traditionally Tamil Nadu people believed that leaf of *Guettarda speciosa* is used to cure the various ailments. There are reports of the use of this genus in traditional medicine for the most diverse purposes, especially for the treatment of wounds and inflammations [12-14]. But in some other countries the stem, bark, latex, flowers, fruits and even whole plants are used. Traditionally in Fiji the stem is used in a preparation utilized to promote menstruation. In Tahiti, the plant has antidiarrhoetic, febrifugal and anticholinergic applications. In Tonga, a tea made from the inner bark is used to treat epilepsy. The inner bark is used in the treatment for conjunctivitis. In New Guinea, a preparation of the bark is drunk to cure dysentery. The leaf decoction is used to treat cough, cold and sore throats. In Tuvalu, the leaves are used for poultices [15-17]. Infusion of the bark is used in treating postpartum discharges. A decoction of the bark or an infusion of the leaves is drunk daily to treat secondary amenorrhoea. In Micronesia, itchy skin rashes are treated with fluid from the leaves. The shoots are washed in oil and used in treating ulcerated sores of the anus. Liquid from the bark is drunk to treat edema. In India, the inner bark of this plant is being traditionally used in ulcer, wounds, sores, diarrhoea, febrifugal, epilepsy and anticholinergic applications [16, 17].

In the previous study, phytochemical analysis of various extracts of *Guettarda speciosa* leaves revealed that the presence alkaloids, flavonoids, phytosterol, saponin, phenols, tannins, fixed oil, glycerine, cardiac glycosides, glycosides, terpenoids and coumarin. These secondary metabolites may be reason for wound healing activities.

MATERIALS AND METHOD:

Plant extraction

Guettarda speciosa Linn. plant twigs were collected from Perundurai, Erode (District), Tamil Nadu, India. The plant was authenticated by Dr. G.V.S. Murthy, Scientist and Head, Botanical Survey of India, Southern Regional Circle, Coimbatore (Tamil Nadu), India. Coarse powder from the shade dried leaves of *G. speciosa* (500g) was exhaustively extracted with 80% ethanol using Soxhlet apparatus. The extract was dried (free of solvent) using a vacuum evaporator. The extract thus obtained was stored in a refrigerator and used for *in vivo* wound healing activity [18].

WOUND HEALING ACTIVITY

Experimental animals

24 healthy Wistar albino female rats, weighing 180 –

200gm were used for studying the wound healing activity. The animals were procured from the Small Animals Breeding Station, Mannuthy, Kerala, India. Animal experiment was done in compliance with the Institutional Ethical Committee-CPCSEA (Reg. No. 1454/PO/C/11/CPCSEA; Approval no. ML-EA-CPCSEA/01-2013/07). The animals were housed in polypropylene cages (38 x 23 x 10 cm) with not more than six animals per cage and maintained under standard environmental conditions (14h of dark/ 10h light cycles; temperature 25±2ºC; 35-60% humidity, air ventilation) and were fed with standard pellet diet (M/s. Hindustan Lever Ltd., Mumbai, India) and fresh water *ad libitum.* The animals were acclimatized to the environment for two weeks prior to experimental use. Animals were starved overnight before the experimental schedule, but had free access for water *ad libitum.*

Preparation of Ointment

To 10 gm of Petroleum jelly 0.5 gm of ethanolic extract of leaf of *G. speciosa* was added and stirred to produce the 5% low dose extract. The 10% high dose extract was prepared by stirring 10 gm of Petroleum jelly with 1.0 gm of ethanolic extract. This 5% and 10% ointments were used for topical application [19].

Excision Wound Model

Wistar albino female rats, (180 - 200gm) were divided into four groups of 6 animals each (n=6). Wounds were created at the back of each animal of groups I to IV. An area of about 1.0 sq. cm was marked out. The marked area was excised with sharp knife and scissors under ether anesthesia [20]. Group I served as induced and group II treated with standard which was topically applied with lyramycin for 21 days after the wound excision. Groups III and IV were topically applied with 5% and 10% (w/w) ointments, respectively prepared using the ethanolic extract and petroleum jelly for 21 days. The length and breadth of the wounds were measured for 21 days using a vernier caliper and the results are expressed in terms of percentage reduction in the wound size. On days 0, 6, 12 and 18 and 21 the wound area was photographed. Wound healing was calculated as percentage of reduction in wound area [21].

$$\% \text{ of WR} = \frac{\text{Initial WA} - n^{th} \text{ day WA}}{\text{Initial WA}} \times 100$$

WR =Wound Reduction
WA= Wound Area
n^{th} = specific day

Statistical Analysis

For *in vivo* wound healing activity the values are expressed as mean (n = 6) ± Standard Deviation (SD). Statistical significance of differences between the groups was performed by two tailed Student's t test for unpaired observations using Graphpad InStat demo version 3.10 (Graphpad Software Inc. CA, USA). P <0.05 are considered as significantly different.

RESULT:

The *in vivo* wound healing activity of ethanolic leaf extract of *G. speciosa* was demonstrated by excision wound model. The prepared leaf extract ointments (5% and 10% w/w) were used for topical application in the experimental rats. The drug lyramycin was used as standard. The leaf extract ointment treated groups showed significant wound healing (P<0.05) from the third day onwards, which was comparable to that of the standard drug, lyramycin treated group of animals. Especially, high dose of leaf extract ointment (10% w/w) treated group of animals showed significant wound contraction from the 9^{th} day onwards and achieved 100% healed wound on 18^{th} day of post wounding which was similar to the effect of standard drug. But the low dose of leaf extract ointment (5% w/w) was healed the wound on 21^{st} day of post wounding whereas in induced group of animals on 21^{st} day showed 90.65% wound reduction. From the result it confirmed that all the ointment extracts showed the significant effects of wound healing but are a dose-dependent manner. Table 1 shows wound size of animals for 0^{th}, 3^{rd}, 6^{th}, 9^{th}, 12^{th}, 15^{th}, 18^{th} and 21^{st} days of post wounding. Fig. 2 shows the percentage wound reduction on 0^{th}, 6^{th}, 12^{th}, 18^{th} and 21^{st} days of post wounding. The percentage of wound reduction was much more with the 10% w/w leaf extract ointment treated group at 18^{th} days for 100% reduction which was almost similar to that of the lyramycin treated group.

Table No. 1 Effect of ethanolic extract of leaf of G. speciosa on excision wound model

Groups	Wound size (mm) on various days							
	0th day	3rd day	6th day	9th day	12th day	15th day	18th day	21st day
Induced (G-I)	10.52±0.10	10.37±0.09	9.67±0.06	8.54±0.11	6.52±0.14	4.33±0.11	2.84±0.08	0.98±0.09
Standard (G-II)	10.44±0.13ns	8.19±0.09*	6.08±0.03*	4.19±0.05*	2.13±0.05*	0.86±0.03*	0	-
GSE LD (G-III)	14.46±0.18*	13.39±0.21*	12.24±0.15*	9.42±0.19*	7.11±0.10*	4.02±0.09*	1.18±0.10*	0
GSE HD (G-IV)	14.54±0.17*	12.91±0.42 *	10.59±0.22 *	6.46±0.17*	3.26±0.13 *	1.23±0.07*	0	-

*- Significant at 5% level ($p<0.05$); ns-non significant
Values are mean ± SD of six observations
Groups compared: G-II; G-III; G-IV vs G-I

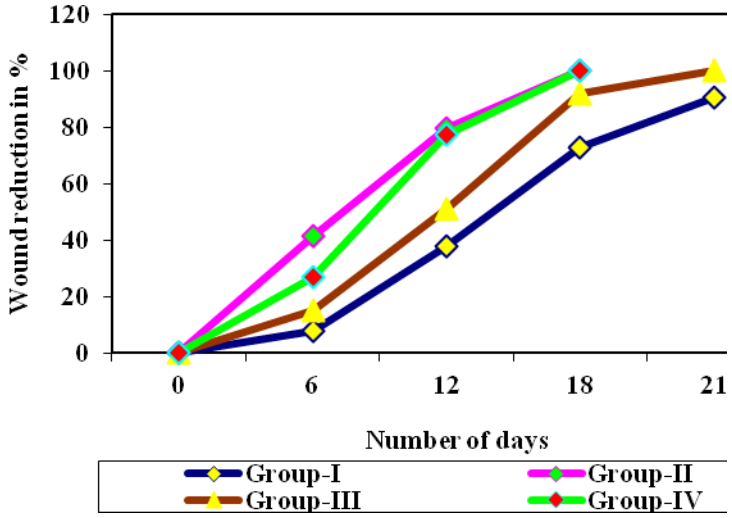

Fig. No.1 Percentage reduction of wound size in *G.speciosa* against excision wound model

Values are expressed as mean ± SD of six observations
Induced (G-I): Induced; Standard (G-II): Lyramycin; GSE LD (G-III): Low dose (5% leaf extract of *G. speciosa*) ointment; GSE HD (G-IV): High dose (10% leaf extract of *G. speciosa*) ointment

DISCUSSION:

Plants are known as eminent healer due to it possesses variety of healing power. Therefore, the herbal medicines have received much attention as sources of lead compounds since they are considered as time tested and relatively safe for both human use and environment friendly [22]. In a century back herbal medicine are cheap and easily available, but today plants are in a position to conserve in any ways. There are lots of diseases in the world; among them wound is a severe but curable ailment. Wounds are the foremost case of physical disabilities for human beings [23]. The objectives of wound management are to heal the wound in the shortest time possible, with minimal pain to the patient. But, healing the wound is based upon the condition of damaged tissues. According to [24] the wound healing is a complex and dynamic process by which cellular structures and tissue layers in a damaged tissue restores itself as closely as possible to its original state. Wound contraction begins a week post wounding at the fibroblastic stage with the wound area undergoing shrinkage [24, 25].

Despite of large number of researches, the wound healing is still challenging to the investigators [26-29]. More than 70% of wound healing pharma products are plant based [30]. In recent times, focus

on plant researchers has increased all over the world and large body of evidence has collected to show immense potential of medicinal plants used in various traditional systems [31]. Several medicinal plants have been used since time immemorial for the treatment of cuts, wounds and burns and showed promising effects. Some very common plants like *Aloe vera*, *Azadirachta indica*, *Carica papaya*, *Celosia argentea*, *Centella asiatica*, *Cinnamomum zeylanicum*, *Curcuma longa*, *Nelumbo nucifera*, *Ocimum sanctum*, *Phyllanthus emblica*, *Plumbago zeylanica*, *Pterocarpus santalinus*, *Terminalia arjuna* and *Terminalia chebula* have been extensively reported in Ayurveda, Siddha and Unani systems of medicines for their wound healing potential [30]. Moreover, the *in vivo* wound healing activity was also reported on many plants like *Merremia tridentata* [32], *Diospyros cordifolia*, [33], *Bryophyllum pinnatum* [34], *Butea monosperma* [35], *Lantana camara* [36], *Wattakaka volubilis* [37], *Acacia suma* [38], *Houttuynia cordata* [39] etc.

In the present study, the wound healing activity of ethanolic leaf extract of *G. speciosa* was demonstrated using excision model. Two different doses (5% and 10% w/w) of ointment leaf extract were used. From the result, it confirmed that the high dose 10% (w/w) ointment extract was significantly healed ($p< 0.05$) the wounds as similar to standard drug lyramycin. On the 18th day of post wounding the high dose leaf extract ointment and standard drug healed the wounds 100%. While low dose 5% (w/w) ointment extract takes 21 days for complete healing. All these treatments are compared with the induced group. Hence, the healing activity was a dose-dependent manner. The healing activity may be due to the presence of phytochemicals present in the leaf extract. In the previous study, it confirmed that the leaf contained alkaloids, flavonoids, phenols, tannins, terpenoids etc. Many previous reports support the present research. The phytoconstituents present in extract enhanced wound healing which could be a function of either individual or synergistic effects of bioactive molecules. Indeed, terpenes, alkaloids, tannins, saponins and flavonoids promote wound healing due to their astringent, antioxidant and antimicrobial properties [40, 41].

Several studies demonstrated that the phytochemical constituents present in medicinal plants promote the wound healing process [42-44]. The *Rafflesia hasseltii* extract exert their wound healing activity through the tannins [45]. The gel of ethanolic extract of the plant *Vernonia scorpioides* possess wound healing action by improving regeneration and organization of the new tissue due to the presence of tannins [46]. Some of the most important phytochemicals obtained from plant origin viz., tannins from *Portulaca oleracea* [47] and *Terminalia arjuna* [48], oleanolic acid from *Anredra diffusa* [49], polysaccharides from *Opuntia ficus-indica* [50], gentiopicroside, sweroside and swertiamarine from *Gentiana lutea* [51], shikonin derivatives (deoxyshikonin, acetyl shikonin, 3-hydroxy-isovaleryl shikonin and 5,8-Odimethyl acetyl shikonin) from *Onosma argentatum* [52], asiaticoside, asiatic acid and madecassic acid from *Centalla asiatica* [53, 54], quercetin, isorhamnetin and kaempferol from *Hippophae rhamnoides* [55] and curcumin from *Curcuma longa* [56] are played an important role in wound healing process. Mechanisms of wound healing may be contributed to stimulate the production of antioxidants in wound site and provides a favorable environment for tissue healing [57]. All these earlier studies are in accordance with the present study.

CONCLUSIONS:

In conclusion, the current research has proved that, 10% (w/w) ethanolic leaf extract of *G. speciosa* significantly increased the rate of wound contraction. Further study need to find out the bioactive compounds which are reason for wound healing.

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