

## Influence of *Tinospora cordifolia* on wound healing in wistar rats

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### ABSTRACT

**Background:** *T.cordifolia* is widely used in veterinary folk medicine ayurvedic system of medicine. It is known to possess various properties. In a study *T.cordifolia* promoted wound healing in diabetic patients. However, one study showed that octacosanol content in *T.cordifolia* possessed anti-angiogenic activity which can hinder wound healing. Therefore, effect of *T.cordifolia* on wound healing appears to be controversial and there is scarcity of information regarding its effect on wound healing in animal models.

**Methods:** Excision wound, resutured incision wound and dead space wounds were inflicted under light thiopentone anesthesia in male wistar rats (n=6 in each group). Methanol extract of *T.cordifolia* stem in the dose of 250 mg/kg was administered orally once a day for 10 days in resutured incision (assessed by wound breaking strength), dead space (granuloma dry weight and histopathology of granulation tissue) excision wounds was monitored by planimetry. Data was expressed as mean±SEM and analyzed by student's t-test. p <0.05 was considered as significant.

**Results:** The results of the present study revealed that *T.cordifolia* significantly promotes wound healing in all the three models viz. enhanced wound contraction and decreased days for complete epithelization in excision wound; increased breaking strength in resutured incision wound; increased granuloma dry weight and cellular infiltration in granulation tissue.

**Conclusions:** *T.cordifolia* significantly (p<0.05) promoted wound healing in all the three models of wound in male wistar rats.

**Keywords:** Excision wound, Dead space wound, Resutured incision wound, *Tinospora Cordifolia*

### INTRODUCTION

Wound healing is the restoration of tissue architecture and function following an injury.<sup>1</sup> The intrinsic proliferative capacity of individual tissue influences its ability to repair.<sup>1</sup> The term healing includes repair and regeneration. While repair describes healing by deposition of connective (fibrous) tissue leading to scar formation, regeneration refers to healing by proliferation of parenchyma cells.<sup>2</sup> The process of wound healing

involves an initial phase of inflammation followed by organization of fibrin rich exudate, re-epithelization and granulation tissue formation.<sup>3</sup> The proliferation of the cells in the process of wound healing can be triggered by various chemical mediators.<sup>1</sup> One of the most important mediators being a number of growth factors like epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), transforming growth factor-  $\alpha$  (TGF-  $\alpha$ ), platelet derived growth factor (PDGF) etc. These are produced by the leukocytes recruited to the site

of injury as a part of inflammatory process.<sup>1</sup> They are chemotactic for polymorphonuclear cells, macrophages and activate them for initial inflammatory process of healing. This immunomodulatory effect of growth factors is known to promote healing, by stimulating the formation of granulation tissue, promoting angiogenesis, enhancing proliferation of endothelial cells, epithelial cells, fibroblasts etc.<sup>1</sup> The healing process proceeds at an optimal rate that varies from species to species and from tissue to tissue in the same species.<sup>4</sup> However, the presence of certain pathological conditions like infections, nutritional deficiencies and metabolic disorders like diabetes mellitus can interfere with the process of wound healing.<sup>5</sup>

Diabetes mellitus (DM) is a secondary immunodeficiency disorder that is characterized by altered microvasculature, nerve function and immunity.<sup>5</sup> One of the complications seen with uncontrolled DM is non-healing ulcers. Various factors have been attributed to the pathogenesis of non-healing diabetic ulcer. Hyperglycemia is associated with reduced granulation tissue formation and accumulation of abnormal fibroblasts with impaired migration and proliferation leading to malformed extracellular matrix.<sup>6,7</sup> It has been reported that DM induces oxidative stress that increases the release of pro-inflammatory cytokines like TNF- $\alpha$  (tumor necrosis factor) leading to tissue destruction and decreased wound strength.<sup>8</sup> VEGF along with other growth factors like PDGF, TGF, FGF (fibroblast growth factor) etc. is well known to affect angiogenesis, a vital process in healing. Diabetic hyperglycemia has been reported to disturb the role of VEGF and its receptors thereby disrupting the endothelial proliferation and migration.<sup>6</sup> Defective release of PDGF in DM is known to induce aberrant response of inflammatory cells at the site of injury.<sup>7</sup> In addition, other growth factors like  $\beta$ -FGF, TGF- $\beta$ , GM-CSF (Granulocyte-macrophage colony-stimulating factor), EGF that are vital in wound healing have been reported to be defective in DM.<sup>9</sup> All these factors hindering the process of healing make the management of wounds difficult in diabetic individuals. Therefore, it could be expected that addition of these growth factors to the conventional therapy in diabetic individuals promote the healing process. Accordingly, a clinical study reported that EGF dressing produced healthy granulation tissue and decreased soakage as compared to control groups.<sup>10</sup> Similarly, an experimental study reported that PDGF improved neovascularization and wound closure in diabetic mice.<sup>11</sup> Likewise recombinant PDGF has shown to enhance healing of non-infective neuropathic foot ulcers in diabetic individuals.<sup>12</sup> However, such a treatment is very expensive and compels to search for an affordable alternative.<sup>13</sup> Literature survey reveals various products of *Tinospora cordifolia* possess immunomodulatory and anti-diabetic properties and therefore could be a cost-effective alternative to manage diabetic wounds.

*Tinospora cordifolia* (Wild) Hook F and Thoms is a deciduous climbing shrub of the family *Menispermaceae*. It is distributed throughout the Indian subcontinent and China.<sup>14</sup> In hindi, it is known as Giloya, a Hindu mythological term that refers to the heavenly elixir that has kept celestial beings eternally young.<sup>14</sup> In vernacular, it is known by various names like guduchi, amrita, shindilkodi etc.<sup>15</sup> The plant is widely used in veterinary folk medicine as general tonic, antiperiodic, antispasmodic, anti-inflammatory, anti-allergic, anti-arthritic, antipyretic, anti-oxidant, anti-neoplastic, hepatoprotective, immune modulatory etc.<sup>16,17</sup> The immune modulatory effect is attributed to its capacity to increase GM-CSF which in turn enhances the expression and activity of platelet and neutrophil derived PDGF.<sup>13,17</sup> Various actions of PDGF such as activation of polymorphonuclear cells, macrophages, fibroblasts, endothelial cells, stimulation of angiogenesis etc. contribute for its pro-healing activity.<sup>1</sup> *T.cordifolia* used as an adjuvant in a clinical study, has been reported to improve the healing of diabetic foot ulcer.<sup>13</sup> Clinically observed pro-healing effect of *T.cordifolia* bark could also be attributed to its effect on blood glucose, since it has been reported to possess anti diabetic activity in streptozotocin induced diabetic rats.<sup>18</sup> However, in contrast *T.cordifolia* is reported to possess anti-angiogenic activity through down regulation of vascular endothelial growth factor (VEGF) and by increasing the level of anti-angiogenic IL-2.<sup>17,19</sup> Dichloromethane extract of *T.cordifolia* has been reported to possess cytotoxic effect on cultured HeLa cells and to decrease proliferation of tumor cells.<sup>12,20</sup> Thus, the effect of *T.cordifolia* on wound healing appears to be controversial, since cytotoxic agents interfere with the healing process.<sup>21</sup> These controversy suggestive reports *T.cordifolia* and scanty information about its effect on wound healing prompted the present study. In the present study, methanol extract of *T.cordifolia* has been explored for its influence on healing of various cutaneous wound models, viz excision, resutured incision and dead space wounds in male wistar rats.

## METHODS

### *Plant extract*

In the present study the bark of *Tinospora cordifolia* was used, since it is approved by the ayurvedic pharmacopoeia of India due to its higher content of alkaloids.<sup>17</sup> The matured bark of *T.cordifolia* was freshly collected during summer from Belgaum, and was authenticated by qualified taxonomist Dr. Harsha Hegade, from Regional Medical Centre (RMRC), ICMR-Belgaum bearing the authentication voucher number RMRC-493. The bark was chopped, shade dried and coarsely powered. The powder was defatted with petroleum ether (60-80°C). The soxhlet extraction method was used with methanol as the solvent. After pouring methanol into the bottom extractor flask, the thimble containing the sample was placed inside the extraction

chamber and the condenser was fixed. When methanol in the flask was heated, its vapors condensed in the condenser. This condensed extractant dripped into the thimble containing the crude product holding the product. The process was continued until a drop of solvent did not leave any residue when evaporated. The extract thus obtained was dried using a vacuum evaporator and was stored in the refrigerator till further use. Methanol extract was considered since it has been reported that the major constituents of *T.cordifolia* (like alkaloids, tannins, flavonoids, etc.) are present in the methanol extract as compared to that of other solvents.<sup>22</sup>

The dose of 250 mg/kg body weight of rat was used as this dose had shown to possess the hypoglycemic activity.<sup>18</sup> The extract was dissolved in 0.3% carboxy methyl cellulose (CMC) and was administered orally. The duration of treatment was 10 days for animals inflicted with incision and dead space wounds, while it was continued in animals bearing excision wounds till the complete closure of the wounds. The control group was treated with CMC alone.

### Animals

Healthy male, adult wistar rats weighing 150-250 gm, procured from the central animal house of the institute were housed individually and maintained on standard pellet diet and tap water ad libitum for a week to acclimatize. The study was approved by institutional animal ethics committee. The animals were starved overnight prior to the day of experimentation and divided into control and treatment groups (n=6) for each wound model. All the wounding procedures were carried out under thiopentone anaesthesia with aseptic precautions.

### Wound models

- Excision wounds were made as described by Morton and Malone.<sup>23</sup> A circular impression using a seal of 2.5 cms diameter was made on dorsal, excised (approximate area of 500 mm<sup>2</sup>) and the animals were placed in individual cages. Wound healing was assessed by tracing the raw wound margin on polythene paper to determine the area on 0, 4<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup> and 16<sup>th</sup> day; and subsequently on alternate days till complete closure of the wound (falling of the scab without any raw area). The wound healing was expressed as percentage closure of the original wound area (on day 0).
- Resutured incision wounds were inflicted by placing silk sutures 1 cm apart on two 6 cm long paravertebral full thickness incisions.<sup>24</sup> Sutures were removed on 8th day and breaking strength of the wounds was measured on 11<sup>th</sup> day by using continuous water flow technique.<sup>25</sup> The breaking strength was expressed as the minimum weight of water necessary to bring about gaping of the wound. Three readings taken on each wound were used to

calculate the mean and the group mean was calculated using individual means. Subsequently the animals were sacrificed by overdose of an aesthesia.

- Dead space wounds were inflicted by implanting sterile cotton pellets weighing 10 mg and grass piths measuring 25 cm X 3 mm subcutaneously in the groin and axilla randomly.<sup>26</sup> On 11<sup>th</sup> day after sacrificing the animals the granulation tissue were obtained. The cotton pellets were dried at 60<sup>o</sup>C overnight and the dry weight was recorded to express as mg/100gm body weight.<sup>27</sup> The granulation tissues over the grass piths were preserved in 10% formalin for histopathological studies. The sections were stained with haematoxylin and eosin, and Von Gieson stain, respectively and the same was assessed for assessment under light microscope.

### Statistical analysis

Data were expressed as mean±SEM and were analysed by unpaired t-test. p<0.05 was considered to be significant.

## RESULTS

### Excision wound

The rate of wound closure expressed as mean percentage closure of the excision wound in *T.cordifolia* treated group was not significantly different from that of control group on days 4, 8 and 12 post wound. The mean percentage of wound closure in *T.cordifolia* group on 16<sup>th</sup> day (94.60±0.40) and 18<sup>th</sup> day (99.40±0.40) were significantly (p<0.05) more as compared to that of control group (88.90±1.99 and 93.60±1.74) (Table1).

The falling of the scab without any raw area was considered as complete epithelization. The mean time for complete epithelization in *T.cordifolia* group (18.40±0.25) was reduced significantly (p<0.001) as compared to that of control group (20.60±0.40) (Table 2). The scars were stellate shaped in *Tinospora cordifolia* treated group while they were oval shaped in control group.

**Table 1: Effect of *T.cordifolia* on mean percentage closure of excision wounds on various days after wounding.**

Days	Control group (Mean±SEM)	<i>T.cordifolia</i> group (mean±SEM)
4	18.04±1.78	11.00±2.50
8	52.26±3.38	38.40±6.78
12	81.74±3.58	87.00±1.30
16	88.90±1.99	94.60±0.40*
18	93.60±1.74	99.40±0.40**

\*p=0.02; \*\*p=0.01



### Resutured incision wound

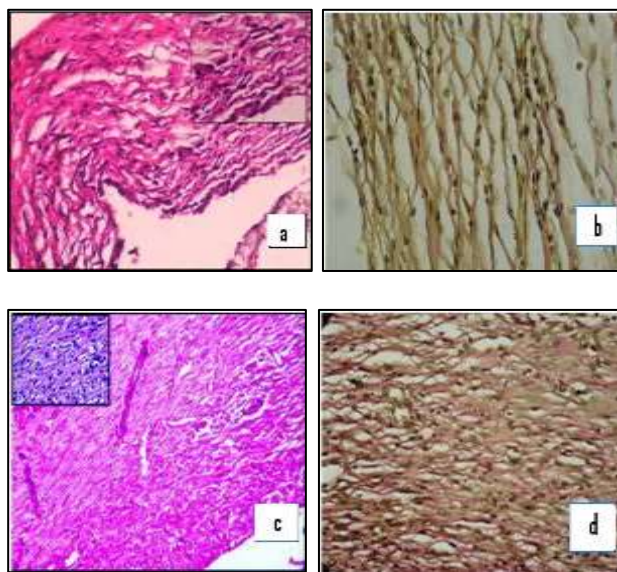
The breaking strength of 10 day old resutured incision wound in *T.cordifolia* treated group was significantly ( $p<0.0001$ ) more ( $543.0 \pm 34.63$  gm) as compared to that of control group ( $245.0 \pm 26.80$  gm) (Table 2).

**Table 2: Effect of *T.cordifolia* on wound healing of excision, resutured incision and dead space wound models.**

Wound model	Control group (mean $\pm$ SEM)	<i>Tinospora cordifolia</i> group
Days for complete closure	20.60 $\pm$ 0.40	18.40 $\pm$ 0.25*
Breaking strength of resutured incision wound (gm)	245.0 $\pm$ 26.80	543.0 $\pm$ 34.63 **
Granuloma dry weight (mg)	32.00 $\pm$ 1.23	69.40 $\pm$ 11.37***

\* $p=0.001$ ; \*\* $p<0.0001$ ; \*\*\*  $p=0.01$

### Dead space wound



**Figure 1: (a) to (d): Microphotographs of granulation tissue stained with H and E, and Van Geisons stains (H and E 20X); (a) and (b): Control group shows scanty granulation tissue; sparsely arranged fibroblasts with scanty collagen formation (a-Inset-40X-sparse infiltration with lymphocytes and macrophages); (c) and (d) - drug treated group shows granulation tissue with plenty of fibroblasts with abundant collagen. (c – inset- 40 X- dense infiltrations with lymphocytes and macrophages).**

The 10 day old cotton pellet induced granuloma was weighed after overnight drying in an incubator at 60°C and dry weight were noted. The mean dry weight of the cotton pellet granuloma in *Tinospora cordifolia* group

( $69.40 \pm 11.37$ ) was significantly ( $p=0.0114$ ) increased in the treatment group as compared to control ( $32.00 \pm 1.23$ ) (Table 2). The microscopic study was carried out arbitrarily quantifying the amount of granulation tissue and collagen in both the groups. The H and E stain revealed marked increase in the granulation tissue, with increased cell infiltration with lymphocytes, macrophages; while VonGeison stain showed marked increase in collagen content in the *T.cordifolia* treated group as compared to control group (Figure 1-a, b, c, d).

### DISCUSSION

The findings of the present study clearly indicate that *T.cordifolia* significantly ( $p < 0.05$ ) enhanced wound healing in all the three cutaneous wound models. There is paucity of information regarding similar studies about *T.cordifolia*. However, the present study agrees with a single clinical study which reported the pro-healing activity of *T.cordifolia*.<sup>13</sup> The mean percentage closure of the excision wound in the treated group was comparable to that of control group up to 12<sup>th</sup> day, but, then onwards wound closure rate was significantly ( $p < 0.05$ ) increased in the treatment group as observed on 16<sup>th</sup> and 18<sup>th</sup> day. It is difficult to explain why the healing process in excision wounds failed to accelerate up to 12 days after wounding. It is likely that in the initial phase of healing, down regulating effect on VEGF (through IL-2) by *T.cordifolia* dominates over its effect on other cytokines that promote angiogenesis and healing.<sup>19</sup> Mean time for complete closure of the wounds in control group ( $20.60 \pm 0.40$ ) was comparable to that ( $20.0 \pm 0.45$ ) of the earlier studies.<sup>28</sup> Enhanced closure rate in treated group could be explained on the basis of increased wound contraction as denoted by stellate shaped scars compared to oval shaped scars in control groups. It is also possible that enhanced granulation tissue formation (as observed in dead space wounds) and thereby epithelization contributes to earlier wound closure.

Breaking strength of re-sutured incision wounds of the control group in the present study was comparable to that of a previous studies ( $288.6 \pm 8.449$ g), while it was significantly ( $p < 0.0001$ ) increased in treated group, indicating *T.cordifolia* enhanced healing of incision wounds also.<sup>28</sup> It is well known that healing of incision wound depends upon both the quantity and quality of collagen and the extract appears to improve both the aspects of collagen, as evidenced by significantly increased amount of granulation tissue (granuloma dry weight) in dead space wounds of treated rats. Microscopic studies of granulation tissue confirm that the extract of *T.cordifolia* enhanced healing of dead space wounds; since there was marked increase in the granulation tissue and collagen content in the treated group as compared to controls (Figure 1).

In summary, the present study proves that the bark extract of *T.cordifolia* promotes healing of all the three types of wounds studied. Observed pro-healing activity of

*T.cordifolia* is enigmatic to explain, since it is reported to be cytotoxic.<sup>29</sup> The bark of the plant is reported to contain alkaloids, glycosides, lactones, flavonoids, saponins and steroids and it would be interesting to explore the phytoconstituent/s of the plant responsible for promotion of wound healing.<sup>30</sup>

Though, the aim of the present study was not to explore the mechanism of pro-healing activity of methanol extract of *T. cordifolia* on wounds; based on the earlier reports it could be hypothesized that pro-healing activity of *T. cordifolia* could be due to its immune modulatory activity, leading to enhanced activity of GM-CSF.<sup>13</sup> GM-CSF is known to increase the levels of PDGF that in turn plays a very important role in healing by increasing the activities of neutrophils, macrophages and pro-inflammatory cytokines like interleukin-6 and monocyte chemo-attractant protein-1; thereby enhancing revascularization and healing.<sup>1,13,31,32</sup>

The findings of the present study and an earlier experimental study together seem to corroborate the earlier clinical report that, the plant preparation promotes healing of diabetic wounds.<sup>13,18</sup>

## CONCLUSION

The results of the present study reveal that *T.cordifolia* promotes wound healing. This property of *T.cordifolia* could be attributed to its immunomodulatory effects. However, further studies are required to establish the role of particular constituents of *T.cordifolia* in promoting wound healing. Further, restoration of deranged glucose metabolism in diabetes mellitus by *T.cordifolia* could add to its pro-healing effect on diabetic ulcers that often challenge clinicians. However, experimental studies on diabetic animals followed by clinical studies involving larger number of patients are needed to validate the conjectural claim that the plant promotes healing of diabetic wounds.

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