Traditionally, different parts of plants such as bark, stem, and leaves have been used in wound healing. Around 10% of the angiosperm plants produce a natural polymer from specialized laticiferous cells called latex. The major role played by the latex is in wound healing and defensive mechanism against infectious diseases in plants. In the past 20 y, with biochemical and pharmacological characterization of plant latex it has come to light that proteases are involved in wound healing. Some have been extensively studied with characterization while some are yet to be explored. This review conglomerates the reports of different families of laticiferous plants studied scientifically for wound care. The review also emphasizes on the methodology to be adopted in accessing the proteases studied for procoagulant and thrombolytic activities. Emphasis was given on the all possible reports on laticiferous plants in wound healing with thorough literature survey from sources viz, PubMed and Google Scholar. However, research on latex protease is still in budding stage. Adopting the proteases having promising applicability in wound care needs to be focussed.

Keywords: Wound healing, Plant latex, Proteases, Coagulation, Laticiferous plants.

INTRODUCTION

The physiological event associated with loss of functional capacity of a living cell or tissue due to trauma caused by physical, chemical, microbial or other factors is called a wound. This damage immediately attracts the attention of various cellular and non-cellular factors for its repair. This complex cascade of biochemical events that ultimately achieves restoration of an original structure, function and composition of cell/tissue is termed as "wound healing". Wound healing is a well-orchestrated mechanism that occurs within a defined period of time. It mainly involves four phases—hemostasis phase (within minutes), inflammatory phase (24 to 48 h may be up to 2 w), proliferative phase (2 d to 3 w) and remodeling phase (3 w to 2 y) [1]. When this normal mechanism fails, external aid becomes a necessity. Throughout the world, plant sources such as leaves, stem, bark, root, latex, and whole plant have been extensively used in order to achieve wound healing. This paper mainly concentrates upon summarizing the up-to-date scientific research in wound care carried out using plant latex and their proteases present in it.

Proteases (3.4.21) are the enzymes involved in the catabolism of protein into peptides and amino acids. Based on the catalytic residues, proteases are classified into aspartate proteases, cysteine proteases, glutamic acid proteases, serine proteases, threonine proteases, and metalloproteases. The major proteases that are involved in the blood coagulation cascade and thereby in wound healing are the serine proteases and metalloproteases (MMPs). [2] This paper mainly concentrates upon summarizing the up-to-date scientific research in wound care carried out using plant latex and their proteases present in it.

Regulation of the proteases is known to be an important factor in the wound healing mechanism. The wounded environment includes the active keratinocytes, fibroblasts and endothelial cell which are involved in the regulation of protease levels at the wounded site. This is the innate mechanism of wound healing and when this fails the external application of proteases becomes a must. The proteases involved in the wound healing also must be capable of breaking down the collagens, elastin, and proteoglycans [2]. The degradation of newly formed extracellular matrix is because of excessive wound proteases that disturb the balance between tissues break down and repairs [3]. Hence protease action can impair wound healing process.

The role of proteases can be assessed based on the chart mentioned in (fig 1). Both fibrinolytic and fibrinolytic property needs to be assessed thereby ascertaining the protease to be either procoagulant or antiocoagulant respectively. Procoagulant activity also called as hemostatic activity indicates that it aids in blood clot formation or in other words fibrin clot formation, which is essential to stop bleeding and enable the wound healing process. Otherwise, some proteases possess fibrinolytic activity also known as anticoagulant activity which indicates that they aid in degradation of the fibrin clot or thrombus formed in blood circulation. Thus it is established that proteases play as major pharmaceuticals in wound care.

Latex is a natural plant polymer secreted by highly specialized cells known as laticifers. Plant latex is a mixture of secondary metabolites, and bioactive components like acetogenins, alkaloids, resins, phytosterols tannins, terpenoids, and enzymes [4, 5]. Laticiferous plants belonging to families Althiagiacae, Amaranthaceae, Apocynaceae, Asclepiadaceae, Asteraeae, Caricaceae, Diptero-carpaeae, Euphorbiaceae, Lamiacae, Moraceae, Papavaceae, Plumbaginaceae, and Solanaceae have been traditionally used for various purposes including wound healing, some of which have been extensively studied.

Bioactives of plant latex possess anti-carcinogenic, anti-proliferative, anti-inflammatory, vasodialatory, antioxidant, antimicrobial, antiparasitic, insecticidal and wound healing properties [4]. Also provides the methodical approach towards studying the wound healing property of the protease. This paper mainly concentrates upon summarizing the up-to-date scientific research in wound care carried out using plant latex and their proteases present in it. Also we provide the methodical approach towards studying the wound healing property of the proteases.

Plants with latex proteases involved in wound healing

Argemone mexicana

Argemone mexicana also known as Mexican poppy, is a species of Poppy, found mainly in Mexico. It belongs to the family Papavaceae. It has bright yellow coloured latex. Though the latex is poisonous to grazing animals it is considered to be medically useful. Latex of Argemone mexicana is used to treat boils, as wound dressing agent and is also used to treat dermatitis. Latex of this plant is used externally to disinfect open wounds. The in vivo wound healing activity of the extract and latex of Argemone mexicana was compared to that of established drugs. The tensile strength of the extract-treated-group was found to be higher than the latex-treated-group of animals on 12th post-wounding day [6-8].

Asclepias curassavica

Asclepias curassavica is a tropical evergreen perennial subshrub. It is native to American tropics and belongs to the family of Apocynaceae. It is commonly known as tropical milkweed. The stem of this plant produces latex when subjected to superficial incisions. This latex produced, contains many proteins and exhibits proteolytic activity. It acts as an emetic and vermifuge and can be used against gonorrhea.
The study was conducted mainly to identify the clotting factors present in the latex and to analyse their thrombin like activity. Various assays like proteolytic assay, the thrombin time assay, fibrinogen polymerisation assay, inhibitor assay and concentration dependent coagulation assay were carried out. It was observed that the plasma clotting time reduced from 143 seconds to 56 seconds in the presence of crude latex extract. Further detailed studies like in-silico studies–docking studies showed that cysteine proteases interacted with the clotting factors. Thus it was concluded that cysteine proteases found in the latex of Asclepias curassavica were capable of accelerating the blood coagulation process and were also responsible for thrombin like activity [9].

**Artocarpus heterophyllus**

*Artocarpus heterophyllus* is a tree belonging to Moraceae family. It is popularly known as Jackfruit and its fruit is widely consumed. Though the origin of this species is yet unknown, it is believed to be indigenous to the rainforests of India and Southeast Asia. *Artocarpus heterophyllus* is a latex producing plant and research concerning this latex has led to the discovery of a serine protease with fibrinogenolytic and fibrinolytic properties. AMP48, a 48KDa antimicrobial protease, was isolated and purified from the latex and its human fibrinogenolytic and fibrinolytic activity were studied. The serine protease effectively hydrolysed the subunits of human fibrinogen as well as human fibrin clot. The extent of fibrin clot degradation by AMP48 enzyme was studied using attenuated total reflection Fourier transform infrared spectroscopy. These studies revealed that an incubation period of 60 min, at a temperature of 37 °C was required by the protease to effectively digest all three subunits of human fibrinogen. The hydrolysis of fibrin clot was brought about by the alteration of the secondary structure of β-sheet and α-helix resulting in the conversion of solid state of the clot to partial liquid state. Thus, considering these properties it was concluded that the serine protease enzyme, AMP48, can be used as an effective antithrombotic agent [10].

**Calotropis gigantea**

*Calotropis gigantea* also known as Crown flower is a laticiferous plant belonging to the family Apocynaceae, subfamily Asclepiadaceae and is known for its medical properties. It is native to India, Sri Lanka, China, Malaysia and tropical Himalayas. It is a large shrub sporting clusters of either white or lavender waxy flowers. Literature reveals that the latex from *Calotropis gigantea* is a potential source of proteolytic activity, activated partial thromboplastin time, prothrombin time, fibrinogen agarose plate assay, the fibrinogen polymerisation assay, fibrinogenolytic activity and human plasma clot hydrolysing activity. The results of these experiments were obtained by performing animal experiments involving Swiss mice maintained under monitored conditions. Sepsis was deliberately induced in these organisms to determine the platelet count and proteolytic activity whereas human blood samples were used for experimenting on different wound healing mechanisms. Finally, it was concluded that the cysteine proteases present in the latex of this plant possess various properties that aid clotting of blood in wounded regions. It was also deduced that, along with the clot forming property, the proteases in the latex possessed clot dissolving properties as well. This was exhibited by two of the isolated subfractions, LPP11 and LPP11, which demonstrated thrombin-like and plasmin-like properties. The effect was such that the clotting time was reduced by 50% by these fractions as observed in the APTT assay. Thus the therapeutic potential and the ability to maintain coagulation haemostasis of protein fractions derived from latex of *Calotropis procera* was determined.

**Calotropis procera**

*Calotropis procera* commonly known as milkweed or a small tree belonging to the laticiferous family Apocynaceae and subfamily Asclepiadaceae. It is native to Africa and Southern China. The latex of this plant has been used in the treatment of various diseases and is also known to possess anti-inflammatory properties [14].

A study was conducted on the inflammatory properties of the proteases present in the latex of *Calotropis procera* [14]. Study includes proteolytic activity, activated partial thromboplastin time, prothrombin time, fibrinogen agarose plate assay, the fibrinogen polymerisation assay, fibrinogenolytic activity and human plasma clot hydrolysing activity. The results of these experiments were obtained by performing animal experiments involving Swiss mice maintained under monitored conditions. Sepsis was deliberately induced in these organisms to determine the platelet count and proteolytic activity whereas human blood samples were used for experimenting on different wound healing mechanisms.

Finally, it was concluded that the cysteine proteases present in the latex of this plant possessed various properties that aided clotting of blood in wounded regions. It was also deduced that, along with the clot forming property, the proteases in the latex possessed clot dissolving properties as well. This was exhibited by two of the isolated subfractions, LPP11 and LPP11, which demonstrated thrombin-like and plasmin-like properties. The effect was such that the clotting time was reduced by 50% by these fractions as observed in the APTT assay. Thus the therapeutic potential and the ability to maintain coagulation haemostasis of protein fractions derived from latex of *Calotropis procera* was determined.

---

Swamy et al.  
Int J Pharm Pharm Sci, Vol 7, Supple 1, 44-49

"Drugs from Nature: Plants as an important source of pharmaceutically important metabolites"  
Guest Editor: Dr. Dhananjaya Bhadrupura Lakkappa
Table 1: Activities of different laticiferous plants

<table>
<thead>
<tr>
<th>Family</th>
<th>Plant Name</th>
<th>Common name</th>
<th>Role</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apocynaceae</td>
<td>Datura stramonium L.</td>
<td>Mexican poppy</td>
<td>Latex of the plant applied on wounds.</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Argemone Mexicana</td>
<td>Purging Nut</td>
<td>Applied to wounds to cure stubborn wounds.</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Ficus benghalensis</td>
<td>Groot's milk tree</td>
<td>Treats boils, as a wound dressing agent.</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Ficus carica</td>
<td>Mountain papaya</td>
<td>Latex is used in open wounds</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Ficus elaphanta</td>
<td>Deviled backbone</td>
<td>Heals wounds</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Euphorbia candicifolia</td>
<td>Devil's Backbone</td>
<td>Used as folk medicine for open wounds</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Euphorbia helioscopia</td>
<td>Sun spurge</td>
<td>Latex applied on skin eruptions</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Euphorbia hirta</td>
<td>Asthma weed or Pill-Bearing Spurge</td>
<td>Applied to snake bites and scorpion stings.</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Euphorbia neriifolia</td>
<td>Common Milk Hedge, Hedge Euphorbia, Oleander Spurge</td>
<td>Treatment of wounds in the form of topical application</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>Euphorbia pilosa</td>
<td>Downy spurge, Hairy spurge, Wf'smich</td>
<td>Applied to syphilitic sores.</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>Euphorbia primulifolia</td>
<td>-</td>
<td>Applied as an analgesic to tsetse fly bites.</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Hevea brasiliensis</td>
<td>Rubber tree</td>
<td>Enhanced vascular permeability and angiogenic activity</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td>Jatropha curcas</td>
<td>Purging Nut</td>
<td>Used in the treatment of ulcers, bleeding gums, tumours and wounds.</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>Jatropha gossypifolia</td>
<td>Cotton-leaf physic nut bush, Red physic nut</td>
<td>Whole plant latex applied on wounds.</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>Pedilanthus tithymaloides</td>
<td>Devil's Backbone, Japanese Poinsettia, Slipper Spurge, Redbird Cactus, Christmas Candle, African Coffee Tree, Slipper Spurge, Redbird Cactus, Christmas Candle</td>
<td>Latex of the plant applied on the wound.</td>
<td>[40]</td>
</tr>
<tr>
<td></td>
<td>Ricas communis L.</td>
<td>Castor bean, African coffee tree</td>
<td>Latex of the plant applied on the wound.</td>
<td>[40]</td>
</tr>
<tr>
<td></td>
<td>Arnica montana</td>
<td>-</td>
<td>Latex is applied on the navel</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>Artocarpus heterophyllus</td>
<td>Jackfruit</td>
<td>An effective anthrombic agent</td>
<td>[10]</td>
</tr>
<tr>
<td></td>
<td>Ficus bengalensis L.</td>
<td>Indian banyan, Cluster fig. Tree, Indian fig. Tree or Gular [Gular]</td>
<td>The latex is applied on the navels</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>Ficus glomerata</td>
<td>-</td>
<td>Treat boils, wounds.</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>Ficus hispida</td>
<td>-</td>
<td>Treatment of ulcers, haemorrhage, diabetes, wounds and boils</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>Argemone Mexicana</td>
<td>Mexican poppy</td>
<td>Treat boils, as wound dressing agent, treat dermatitis, disinfect open wounds</td>
<td>[8]</td>
</tr>
<tr>
<td></td>
<td>Plumbago zeylanica L.</td>
<td>Chitu, Teete, Fire plant</td>
<td>Milk latex is applied on affected parts of scabies</td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td>Jatropha curcas</td>
<td>-</td>
<td>Whole plant latex applied on wounds.</td>
<td>[38]</td>
</tr>
</tbody>
</table>

Table 2: Different classes of proteases found in various Laticiferous species

<table>
<thead>
<tr>
<th>Name</th>
<th>Species name</th>
<th>Class of protease</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artocarpin</td>
<td>Artocarpus heterophyllus</td>
<td>Serine protease</td>
<td>[10]</td>
</tr>
<tr>
<td>Asclepias c 1</td>
<td>Asclepias curassavica</td>
<td>Cysteine protease</td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td>Calotropis gigantean</td>
<td>Cysteine protease</td>
<td>[11]</td>
</tr>
</tbody>
</table>

"Drugs from Nature: Plants as an important source of pharmaceutically important metabolites"  
Guest Editor: Dr. Dhananjaya Badrapura Lakkappa
Carica pandamarcensis
Commonly known as mountain papaya, the papaya-like Carica pandamarcensis is a plant belonging to the Caricaceae family. It is native to the Andean range from Panama to Bolivia. The immature fruit of this species has latex which is found to contain large amounts of cysteine proteinase. A fraction, P1G10, containing these cysteine proteinase enzyme is toxic as well as an irritant. However, further investigations have revealed that the constituents of latex can be beneficial as well. A 34 kDa serine protease in the latex of Carica pandamarcensis was named Hirtin and was found to possess fibrinolytic and fibrinogenolytic activities. Thus the study was concluded saying that hirtin is a thrombin like serine protease and may have potential industrial and the therapeutic applications.

Euphorbia caducifolia
Euphorbia caducifolia is a cactus-like, indoor growing Euphorbia. It is an Euphorbiaceae specie that is native to Rajasthan of India, but is also found in rocky desert areas of Pakistan. Some of its common names are Leafless Milk Hedge and Leafless Euphorbia and is found to be very similar to Euphorbia nivalis. The latex of this plant is used by the local inhabitants for various medicinal purposes such as treatment of bleeding wounds, cutaneous eruptions and other skin diseases. In vitro tests, clotting of platelet-free plasma and angiogenesis in the chick chorioallantoic membrane, were carried out in order to determine the effect of Euphorbia caducifolia on the mechanism of wound healing. Excision and incision wound models were used and the effect of latex on clotting and angiogenesis was studied by observing the wound contraction, tensile strength and hydroxyproline and DNA content.

This study showed increased angiogenesis and favoured clotting mechanism. Thereby, it was concluded that Euphorbia caducifolia latex can be effectively used in wound healing.

Euphorbia hirta
Euphorbia hirta is a weed belonging to family Euphorbiaceae and is found distributed in the tropical regions of major continents such as Africa, Asia and America. It is possibly native to India and is commonly known by the names Ashwana weed or Pili-Bearing Spurge. Since the plant belongs to a laticiferous family, the sap of the plant contains latex that is toxic as well as an irritant. However, further investigations have revealed that the constituents of latex can be beneficial as well. A 34 kDa serine protease in the latex of Euphorbia hirta was named Hirtin and was found to possess fibrinolytic and fibrinogenolytic activities. Thus the study was concluded saying that hirtin is a thrombin like serine protease and may have potential industrial and the therapeutic applications.

Euphorbia neriifolia Linn
Euphorbia neriifolia is a succulent shrub native to India, Myanmar, Pakistan, New Guinea and the Malay Archipelago. It belongs to the laticiferous family of Euphorbiaceae and was first described by Carl Linnaeus. The common names provided for Euphorbia neriifolia are Common Milk Hedge, Hedge Euphorbia, Glender Spurge and so on. The latex of this plant has been widely used in the treatment of wounds in the form of topical application. This fact has been supported by a study where the aqueous extract of latex of this plant was evaluated for its wound healing activity. Surgically produced cutaneous wounds in guinea pigs were used for the study. The wounds were treated with 0.5% and 1% of euphorbia latex separately. Upon doing this, it was observed that 0.5% topical treatment had no significant effect, while 1% latex treatment decreased the wound area by 18% and 30% on day 4 and day 7 respectively and also increased the tensile strength by 80% on 7th day of application. Similarly, epithelial regeneration, increased DNA and hydroxyproline content were seen on the use of 1% latex. The increase in tensile strength, DNA content, epithelialisation and angiogenesis was observed and it was concluded that the latex of Euphorbia neriifolia has the significant positive effect over wound healing.

Euphorbia nivalis
Euphorbia nivalis is commonly known as Leafy milk hedge, a spiny, wild, deciduous plant that belongs to the family Euphorbiaceae. The production of latex is the characteristic feature of this plant. This latex is further characterised by the presence of proteolytic enzymes in abundance. It is native to Northern and Central India.

| Plant Name                  | Scientific Name                      | Related to the latex, its biochemical compounds and its applications has considerably broadened.
|----------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Carica pandamarcensis      | Carica pandamarcensis               | Euphorbia caducifolia is a cactus-like, indoor growing Euphorbia. It is an Euphorbiaceae specie that is native to Rajasthan of India, but is also found in rocky desert areas of Pakistan. Some of its common names are Leafless Milk Hedge and Leafless Euphorbia and is found to be very similar to Euphorbia nivalis. The latex of this plant is used by the local inhabitants for various medicinal purposes such as treatment of bleeding wounds, cutaneous eruptions and other skin diseases. In vitro tests, clotting of platelet-free plasma and angiogenesis in the chick chorioallantoic membrane, were carried out in order to determine the effect of Euphorbia caducifolia on the mechanism of wound healing. Excision and incision wound models were used and the effect of latex on clotting and angiogenesis was studied by observing the wound contraction, tensile strength and hydroxyproline and DNA content. This study showed increased angiogenesis and favoured clotting mechanism. Thereby, it was concluded that Euphorbia caducifolia latex can be effectively used in wound healing.
| Carica papaya               | Carica papaya                       | Euphorbia hirta is a weed belonging to family Euphorbiaceae and is found distributed in the tropical regions of major continents such as Africa, Asia and America. It is possibly native to India and is commonly known by the names Ashwana weed or Pili-Bearing Spurge. Since the plant belongs to a laticiferous family, the sap of the plant contains latex that is toxic as well as an irritant. However, further investigations have revealed that the constituents of latex can be beneficial as well. A 34 kDa serine protease in the latex of Euphorbia hirta was named Hirtin and was found to possess fibrinolytic and fibrinogenolytic activities. Thus the study was concluded saying that hirtin is a thrombin like serine protease and may have potential industrial and the therapeutic applications.
| Carica pandamarcensis      | Carica pandamarcensis               | Euphorbia neriifolia is a succulent shrub native to India, Myanmar, Pakistan, New Guinea and the Malay Archipelago. It belongs to the laticiferous family of Euphorbiaceae and was first described by Carl Linnaeus. The common names provided for Euphorbia neriifolia are Common Milk Hedge, Hedge Euphorbia, Glender Spurge and so on. The latex of this plant has been widely used in the treatment of wounds in the form of topical application. This fact has been supported by a study where the aqueous extract of latex of this plant was evaluated for its wound healing activity. Surgically produced cutaneous wounds in guinea pigs were used for the study. The wounds were treated with 0.5% and 1% of euphorbia latex separately. Upon doing this, it was observed that 0.5% topical treatment had no significant effect, while 1% latex treatment decreased the wound area by 18% and 30% on day 4 and day 7 respectively and also increased the tensile strength by 80% on 7th day of application. Similarly, epithelial regeneration, increased DNA and hydroxyproline content were seen on the use of 1% latex. The increase in tensile strength, DNA content, epithelialisation and angiogenesis was observed and it was concluded that the latex of Euphorbia neriifolia has the significant positive effect over wound healing.
| Carica papaya               | Carica papaya                       | Euphorbia hirta is a weed belonging to family Euphorbiaceae and is found distributed in the tropical regions of major continents such as Africa, Asia and America. It is possibly native to India and is commonly known by the names Ashwana weed or Pili-Bearing Spurge. Since the plant belongs to a laticiferous family, the sap of the plant contains latex that is toxic as well as an irritant. However, further investigations have revealed that the constituents of latex can be beneficial as well. A 34 kDa serine protease in the latex of Euphorbia hirta was named Hirtin and was found to possess fibrinolytic and fibrinogenolyic activities. Thus the study was concluded saying that hirtin is a thrombin like serine protease and may have potential industrial and the therapeutic applications.
| Carica pandamarcensis      | Carica pandamarcensis               | Euphorbia neriifolia is a succulent shrub native to India, Myanmar, Pakistan, New Guinea and the Malay Archipelago. It belongs to the laticiferous family of Euphorbiaceae and was first described by Carl Linnaeus. The common names provided for Euphorbia neriifolia are Common Milk Hedge, Hedge Euphorbia, Glender Spurge and so on. The latex of this plant has been widely used in the treatment of wounds in the form of topical application. This fact has been supported by a study where the aqueous extract of latex of this plant was evaluated for its wound healing activity. Surgically produced cutaneous wounds in guinea pigs were used for the study. The wounds were treated with 0.5% and 1% of euphorbia latex separately. Upon doing this, it was observed that 0.5% topical treatment had no significant effect, while 1% latex treatment decreased the wound area by 18% and 30% on day 4 and day 7 respectively and also increased the tensile strength by 80% on 7th day of application. Similarly, epithelial regeneration, increased DNA and hydroxyproline content were seen on the use of 1% latex. The increase in tensile strength, DNA content, epithelialisation and angiogenesis was observed and it was concluded that the latex of Euphorbia neriifolia has the significant positive effect over wound healing.

Guest Editor: Dr. Dhananjaya Bhadrapura Lakkappa
The protease in the latex was found to belong to the class of cysteine proteases. It was observed that they reduced bleeding/clotting time and whole blood coagulation time, thereby reducing the rate of bleeding from fresh wounds. The results obtained were as such—a reduction in clotting time from 57 and 60s to 8 and 14s, respectively on topical application of the latex and an increase in wound contraction by 99.29% on the 16th post wounding day. Thus it was concluded that the latex of Euphoria nivula is a promising haemostatic agent and wound healing promoter [22].

Ficus hispida

Ficus hispida belongs to the family Moronaceae. It is a moderate sized tree and is native to India and other tropical countries. It is considered to be traditionally valuable plant due to its pharmacological activities. Different parts of this plant are used for the treatment of ulcers, haemorrhage, diabetes, wounds and boils. The plant also produces milky and sticky latex which has a vital role in wound healing. A study concerning the effect of proteases on haematological value of mice, wound healing response and anti-inflammatory conditions revealed that the clotting time and an erythrocyte sedimentation rate increased when treated with various dosages of isolated proteases. In case of the effect of proteases on wound healing responses, it was observed that the ointment containing 1% (w/w) of proteases showed better healing quality. The proteases also showed mild anti-inflammatory activity [23].

Hevea brasiliensis

Most commonly known as the rubber tree, Hevea brasiliensis belongs to the family Euphorbiaceae. It is a native to Brazil and Guianas. It belongs to a laticiferous family and hence produces milky latex which is the major raw material for natural rubber.

Using Hevea brasiliensis as the source of latex [24], its effect on vascular permeability and angiogenesis, two critical events of wound healing were observed. The serum showed enhanced vascular permeability and angiogenic activity, thus facilitating wound healing. Animal models were used for the purpose of study and the effect of serum on blood vessels was found to be more prominent at a concentration of 7.5 μg, showing an increase in the growth of blood vessels by 50-60%. However, the rate of wound healing significantly reduced when serum treated with proteases was used. Thus, it was concluded that a protein present in the serum influenced wound healing and that the activity of proteases was detrimental to the process.

Jatropha curcas

Jatropha curcas is a small flowering species with soft bark and milky latex. It belongs to the family Euphorbiaceae and is commonly known as Purging Nut. It is native to an American tropic. Jatropha curcas is considered as a valuable plant as its seeds, leaves, flowers, nuts, bark, roots and latex have got various potential applications. The latex of this plant is used in the treatment of ulcers, bleeding gums, tumours and wounds [25].

When the latex of Jatropha curcas is applied directly on the wound, the bleeding soon stops. Studies showed that the latex of this plant has got coagulating activity. In the experiments carried out using the latex, it was noted that there was a significant reduction in the clotting time of human blood [26]. Another detailed study revealed that a proteolytic enzyme called curcin present in the latex of Jatropha curcas is associated with wound healing. The latex also exhibits anti-inflammatory property [27].

Pergularia extensa

Pergularia extensa is a hispid, perennial vine which belongs to the family Apocynaceae and is commonly known as Purging Nut. It is native to an American tropic. Jatropha curcas is considered as a valuable plant as its seeds, leaves, flowers, nuts, bark, roots and latex have got various potential applications. The latex of this plant is used in the treatment of ulcers, bleeding gums, tumours and wounds [25].

When the latex of Pergularia extensa is applied directly on the wound, the bleeding soon stops. Studies showed that the latex of this plant has got coagulating activity. In the experiments carried out using the latex, it was noted that there was a significant reduction in the clotting time of human blood [26]. Another detailed study revealed that a proteolytic enzyme called curcin present in the latex of Pergularia curcas is associated with wound healing. The latex also exhibits anti-inflammatory property [27].

Pugellaria rubra

Pugellaria rubra Linn commonly known as red jasmine is a laxative tree belonging to the family Apocynaceae. It is native to Mexico and is found throughout India [28]. The latex of this tree has proteolytic enzymes in abundance. The extent of involvement of these proteases in wound healing was studied by [28]. The aim of their study was to investigate the anti-inflammatory activities of the protease isolated from the latex of Pugellaria rubra Lin. The study involved the anti-inflammatory effects of the Pugellarin-R, a protease isolated from the latex of this plant by aceton precipitation method. On administering Pugellarin-R, either directly or in the form of ointments to rats with carrageenan-induced paw oedema, a significant increase in the rate of wound healing or decrease in the time taken for wound healing was observed. The results of the study showed that administration of 80 mg/kg of Pugellara-R reduced carrageenan induced paw oedema by 48.8% and application of 0.5% Pugellaria-R ointment showed an increase in wound healing in an excision wound model when compared with the effect of the standard drug. Thus the study was concluded stating that the protease, Pugellarin-R, extracted from latex of Pugellaria rubra Lin had significant anti-inflammatory and wound healing properties.

Synadenium grantii

Synadenium grantii, belonging to the Euphorbiaceae family, can be described as a succulent shrub with milky latex and is found to originate in eastern Africa. Hence the name African Milk Bush. The study on the latex of this plant has yielded contradictory results. While the latex is generally considered to be poisonous, some of its constituents, on the other hand, have proven to be beneficial. A 34kDa latex glycoprotein was observed to possess various properties that could influence wound healing. At an incubation period of 240 min and concentration of 1.5 μg, the latex glycoprotein shows maximum fibrinogenolytic activity. Also, while the latex glycoprotein falls to induce clot formation in purified fibrinogen, it acts effectively on citrated human plasma and significantly reduces the re-calcification time from 165s to 30s. Further, on performing an inhibitor assay, the latex glycoprotein was concluded to be a serine protease. The latex glycoprotein with protease activity exhibited heat-dependant fibrinogenolytic behaviour leading to the conclusion that the latex is a mixture of specific and non-specific proteases of which majority are heat labile. The study also suggested that, along with being involved in the blood coagulation cascade, the protease also exhibited clot dissolving property. These facts thus evidence the use of this latex in folk medicine for wound healing [29].

Wrightia tinctoria

Wrightia tinctoria also known as Ivory wood or Pala indigo plant is a small deciduous tree that belongs to the same laticiferous family Apocynaceae. It is native to India and Burma. It is popularly used folk medicinal plant. The latex of this plant has been used extensively in the treatment of psoriasis, blisters, and mouth ulcers and also for topical applications on fresh wounds. A comparative study was carried out between the effects of latex proteases of Wrightia tinctoria and Neosporin, a standard drug on wound healing revealed the presence of thermo stable serine proteases, which were inhibited by Phenylmethylsulfonyl Fluoride (PMSF) but were relatively more effective in wound healing. Thus the study supported the topical application of Wrightia tinctoria latex on fresh wounds for enhanced wound healing [30].

CONCLUSION

Wound healing is a natural process occurring in the human body. The process of wound healing mainly takes place as a result of four precisely and highly programmed phases namely haemostasis, inflammation, proliferation and remodeling. Various external agents can aid the natural process of wound healing. Plant kingdom is rich in chemical constituents that play a major role in the healing process. This review mainly concentrates on the role of latex of various plants that help in wound healing process. Most of the plants in this review are those with wound healing potential. The plants mentioned in this review can be
furthermore subjected to animal and human studies to determine their effectiveness. Intensive research related to protease will help in developing ointments or cosmetic creams containing the plant extracts which can be employed in wound healing.

ACKNOWLEDGEMENT


REFERENCES

2. McCarty SM, Cochrane CA, Ogg PD, Percival SL. The role of endogenous and exogenous enzymes in chronic wounds: a focus on the implications of aberrant levels of both host and bacterial proteases in wound healing. Wound Repair Regeneration 2012;20:125-36.