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THERAPEUTIC POTENTIAL OF MADHUSARPI IN WOUND HEALING: A COMPREHENSIVE REVIEW

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ABSTRACT

Wound healing is a natural restorative response to tissue injury, and is complex process to achieve anatomical and functional integrity of disrupted tissue by various component like neutrophil, macrophages, lymphocytes, fibroblasts, collagen; in an organised staged pathway -Haemostasis →inflammation→ proliferation → matrix synthesis (collagen and proteoglycan ground (substance) maturation → remodelling → epithelialisation → wound contraction (by myofibroblasts).[1] *Acharya sushruta*, the father of surgery described in his text "*Shashti Upakramas*" for the management of wound (vrana) these are the 60 different regimens for the purpose of wound healing the cover all the aspect of wound healing. *Madhusarpi* is one of them which is indicating for *Sadyovrana*.[2] *Madhusarpi* is combination of Madhu (Honey) and Sarpi(Ghee) which is describe for sadyovrana mostly occurs due to trauma, surgical wound, accidental injuries etc.

KEYWORDS: *Madhusarpi*, *Sadhyovrana*, *vrana*, wound healing, Honey, Ghee.

INTRODUCTION

Acharya Sushruta has given superior position to *Vrana*. *Sushruta* defined *Vrana* as a complex phenomenon causing destruction or rupture of discontinuation of tissue in a particular part of the body with pain, swelling, discolouration, discomfort. Healing is the interaction of a complex cascade of cellular events that generates wound resurfacing, reconstitution and restoration of the tensile strength of injured skin. *Acharya Sushruta* recommended the application of the *Madhusarpi* (honey and ghee) combination in the management of *Sadyovrana* (Traumatic wound), post operation wound *(Su.chi.1/130). Acharya Sushruta* has elaborated various measures for wound management among them the *Madhusarpi* has been indicated for wound resulting abdominal surgeries [application of *Madhusarpi* over the intestines before repositioning them into the abdomen during surgery for intestinal obstruction, to enhance healing and prevent complication*(Su.chi.14/17).*[3] head injuries [If there is no CSF(Cerebrospinal fluid) discharge after the cranial bone fracture then apply honey and ghee and bandage it and make the patient drink ghee for a week*(Su.chi.3/46).*[4]*]* he emphasized its use in fresh wound due to its healing properties.

Honey contains a high amount of sugar, making it highly osmolar and show hygroscopic effect, due to these properties it draws moisture from the wound surface there by creating a barrier that prevent bacterial growth. This natural effect of honey help protect the wound from infection and promote healing. An addition honey have low pH, and producing hydrogen peroxide (H2O2), good nutrient source for the skin cells, all this help in controlling infection and promoting wound healing.

The different ingredient present in the ghee have role in the wound healing like Oleic acid, linoleic acid, lauric acid and capric acid are the major fatty acids found in the Ghee along with other fatty acids. Both Oleic acid, linoleic acid are important functional aspect of healing through the increasing wound healing tissue mass.[4] like antimicrobial activity, wound environment of healing, medium for carrying the other ingredient to the cell, help collagen synthesis and wound healing

AIM

To comprehensively review the therapeutic potential of *Madhusarpi* (honey and ghee combination) in wound healing based on *Ayurvedic* references and modern scientific evidence.

OBJECTIVE

To review available experimental (in-vivo and in-vitro) and clinical studies assessing the efficacy of *Madhusarpi* in wound healing.

METHODOLOGY

Literature review: The present review was compiling and analyzing on the basis of classical and contemporary literature related to *Madhusarpi* (honey and ghee). *Acharya Sushruta* describe properties of both *Madhu*(honey) and *Sarpi*(ghee) in detail, in these reivew our focus in wound healing properties of this combination. Also carried out research literature from standard index research articles (Pubmed, Scopus and AYUSH Research portal database).

REVIWE OF LITERATURE

Several clinical studies have evaluated wound healing outcomes in various types of wound including Malignant ulcers, Chronic Venous Ulcers, Diabetic ulcers, Infected mesh hernioplasties, post caesarean wound demonstrated significantly positive result found with the use of the honey and ghee combination.

1) In malignant ulcers:- five fungating breast tumors, three fungating inguinal/iliac nodes. In every case treated there was reduction/disappearance of the foul odor within 7 to 12 days greatly improving the quality of life, the dressing ensured the ulcers became cleaner with less odour, discharge, bleeding, especially in the breast lesion making adjuvant therapy more acceptable.

2) Chronic Venous Ulcers: Thirteen cases of large, painful venous ulcers were treated, with duration of ulcers ranging from one to nine years. Compression dressing, elevation as in all reported studies were the mainstay of treatment and were part of the treatment with ghee and honey dressing in all cases.

All were large, deep medial ulcers, with fibrotic margins, necrotic floor, weeping discharge, surrounded by deeply pigmented thickened skin not putting on pressure. All cases had undergone treatment, including multiple surgical procedures. The first effect of this dressing on venous ulcers seen in every case was a dramatic relief from pain. In three cases, there was no improvement in terms of ulcer healing over three weeks and treatment was discontinued.

The response was good in nine cases, ulcers were covered with healthy granulation and were skin grafted, but graft broke down on follow-up in four cases within 4–9 months. In one case

islands of epithelium appeared spontaneously on the granulation tissue and spread to cover the ulcer. Unsure what these small pale islands were, histology showed epithelialisation

3) Diabetic ulcers: 29 cases have been treated and evaluated. 14 of 29 cases were first seen after being treated elsewhere for 17 to 64 days. Dressing continued till the ulcer healed (10 cases) or the wound was healthy and ready for grafting (19 cases). Ulcers healed in 17 to 36 days (mean 21 days), healthy granulation was seen in 11 to 32 days (mean 16 days). Honey was not considered a factor compromising the patient's diabetes. Seven cases required amputation of one or more toes due to gangrene, three of part of the fore foot due to bone destruction, but in no case did the leg require amputation. One case was lost to follow up, in one case part of the skin graft broke down.

4) Infected mesh hernioplasties: Eleven such cases with mesh exposed were treated, five of ours and six referred for treatment. In three cases mesh was exposed for the entire extent of the incision, in eight for part of the incision. In every case the exposed mesh was gradually covered with healthy granulation tissue, and the wound healed over a period of three to five weeks with spontaneous apposition of the edges without need for secondary suturing. Serial photographs allay disbelief. In no case did the mesh require removal. The integrity of hernia repair was not compromised. No reference in literature is found to this clinical application of ghee and honey dressing, which could be of use in infected mesh hernioplasty at any site.

5) Post Cesarean, Post hysterectomy wound infection: Eleven cases, with infection deep to the sheath/muscle were treated. All healed with a thin scar without secondary suturing within two or three weeks.[5]

6) *Sadyovrana* (Non healing traumatic wound) how positive effect of *Madhusarpi* with assessment criteria like pain, burning, swelling, length of wound. In this study, on the 7th day a significant reduction in pain was observed as compared to control group, and burning, swelling in both the group same effect show while effect in length of wound is significantly reduce on 7th day as compared to control group.[6]

Dr Rajendra Haribhau Amilkanthwar in his study reported that using *Madhusarpi* combination for mound management show on the 15th day the difference in pain sensation was statistically significant. There was still some pain in patients of control group but in the patients of experimental group. On the seventh day, 21 patients in the experimental group and

5 in the control group showed 75–100% healing. The difference was statistically significant, indicating better results in the experimental group. On the 15th day the experimental group showed better result than the control group. On the 7th day no patient from experimental group showed discharge but 10 patients from control group showed mild discharge. This difference was highly significant statistically.

Most patients in both groups healed within 6–10 days, with a higher number in the experimental group. Delayed healing was more common in the control group, indicating faster recovery in the experimental group. The calculated t-value for the decrease in wound area from the first to the seventh day was statistically significant ($P < 0.05$), indicating better healing in the test group. The reduction in wound area was greater in the test group compared to the control group.[7]

DISCUSSION

Acharya Sushruta describe *Madhusarpi* combination for *Sadyovrana* (traumatic wound) for wound management in the *Shasthi Upkrama* (sixty types of wound management procedure). In traumatic wounds, there is provocation of pitta dosha, leading to an increase in local heat (*Ushma*). This elevated heat manifests as burning sensation and swelling (*Shopha*). Ghrita, having *sheet virya*, pacifies aggravating *pitta*, thereby reducing these symptoms. Simultaneously, due to tissue damage and loss of *dhatu*, *vata dosha* become vitiated, producing pain and discomfort. *Snigdha* and *mridu qualities* of *ghrita* helps in alleviating *vata*, bringing soothing and pain reliving effect. This *ghrita* being both *vata-pittashamak*, helps in early relief from pain and inflammation. Honey is *Madhur(sweet)* by *rasa*, *kshaya(astringent)* by *anurasa*, *ruksha(dry)*, *sheeta virya(cold)* and good for normal complexion, causes cleaning and healing of wound. It penetrates deep in tissue.

Ghee and honey dressing has anti-inflammatory.[8] bacteriostatic, anti-microbial even in presence of drug resistant organism property, desloughing, deodorant property. Provokes rapid proliferation of healthy granulation tissue, of special benefit when preparing large areas, as in burns, for skin grafting.

Honey and ghee combination maintains a moist, pliable wound, which heals with soft epithelization, reduces pain, reduce inflammation, swelling, fast healing reduces length of wound. This combination dressings are pain-free, require no anaesthesia, sedation.

Honey as a barrier effect against pathogen; When honey applied to wounds, the high osmolarity of honey, due to the high sugar content, causes a hygroscopic effect at the wound site, retracting water from colonizing bacteria. This effect, in addition to the intrinsic low pH of honey, and the presence of antimicrobial molecules, creates an unsuitable environment for the invasion and survival of bacteria.

Two different types of honey exist, depending on the species of flowers that the bees pollinate. The types can be distinguished based on their main antimicrobial mode of action: 'peroxide' versus 'non-peroxide'. The activity of the first type, the 'peroxide-based' honey group, is related to glucose oxidase, an enzyme secreted by the bee that, in the presence of water, converts the glucose in honey into gluconic acid and hydrogen peroxide (H2O2). The latter is bactericidal, even at the low concentrations generated in the honey, and is regarded as one of its main antimicrobial mechanism. The peroxide production is higher when the honey has a lower sugar concentration because of the higher enzyme activity of glucose oxidase in the presence of water. When honey is applied to the wound bed, retraction of water from the wound due to the high osmolarity of the honey automatically aids the process of hydrogen peroxide release. An important detail is that this release is spread in time, preventing accumulation and cytotoxic concentrations of hydrogen peroxide. The main antimicrobial action of the second type, the 'non-peroxide-based' honey group, is related to the antimicrobial molecule methylglyoxal (MGO).[9] Manuka honey is the best-known non-peroxide-based honey. The nectar of the flowers of the Manuka tree (Leptospermum scoparium) contains high amounts of dihydroxyacetone and so does the derived honey. The dihydroxyacetone is converted non-enzymatically by the Maillard reaction into MGO. It is believed that the presence of MGO in the honey inhibits the glucose peroxidase enzyme as no hydrogen peroxide is produced. Both honey types contain additional molecules that exert direct antimicrobial effects, including polyphenolic compounds (phenolic acids, flavonoids, and tannins) and antimicrobial peptides such as bee defensin-1.

Honey also has multiple physicochemical and molecular properties that enhance wound healing. Wound healing is a dynamic and a precisely coordinated process of sequential cellular, molecular, and biochemical events aimed to restore the integrity of the injured tissue as quickly as possible. The physicochemical properties of honey that stimulate wound healing include its osmotic activity and the creation of moist and an acidified wound microenvironment. This leads to an outflow of lymph fluid, promotes autolytic debridement,

enriches circulation with a better supply of oxygen and nutrients, and creates an optimized environment for regenerating tissue. Honey forms a good nutrient source for the skin cells, such as fibroblasts during cell proliferation and keratinocyte migration during re-epithelialization. It is also widely reported that the formation of new blood vessels, angiogenesis, is accelerated by honey. Phenolic constituents of honey act as antioxidants, scavenging free radicals created by activated neutrophils and macrophages, thus protecting the wound micro-environment. Clinical studies also demonstrate that honey can minimize scar formation, likely due to its anti-inflammatory, anti-oxidative, and remodeling properties.

It can also be applied subcutaneously, intra-abdominally, and orally to aid wound repair. Shown below is a compelling overview of the existing literature using honey in non-conventional applications in both humans and animals. Honey has beneficial molecular properties on wound repair that directly support the different processes illustrated in during the different wound healing phases. Honey can stimulate a pro-inflammatory response by activating TLR4 signaling, which is necessary during the inflammatory phase to attract leukocytes, including granulocytes and macrophages, subsequently eliminating the debris in the wound bed and protecting against pathogens. Honey drives immunomodulatory actions on the wound because of its cytokine releasing effect on cells within the wound area, such as monocytes/macrophages, neutrophils, fibroblasts, endothelial cells, and keratinocytes. In the inflammatory phase of wound healing, the production of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) enhances the first inflammatory reaction, critical to wound repair. Honey seems to first enhance this pro-inflammatory response before it subsequently suppresses the production of these pro-inflammatory cytokines by downregulating NF-κβ and MAPK pathways and promoting the resolution of inflammation. Honey also lowers the formation of reactive oxygen species (ROS) apart from reducing wound inflammation. Honey activates, as a feedback mechanism, NRF2-target genes, including heme oxygenase (HO-1), peroxiredoxin (PRDX1), SOD, glutathione reductase, and catalase mediating an anti-inflammatory and anti-oxidant response.

During the cell proliferation phase, honey stimulates the proliferation of new dermal cells, such as keratinocytes, fibroblasts, and endothelial cells, and the production of extracellular matrix (ECM) proteins to promote tissue regeneration. In the clinical setting, this can be observed by a decrease in the five cardinal signs of inflammation (i.e. rubor, tumor, calor, dolor, function loss). Interestingly, honey can thus both drive and attenuate inflammation.

This is likely dependent on the phase of wound healing, the microenvironment, and the composition of honey components. Honey consists of multiple different components, including carbohydrates, flavonoids, amino acids, vitamins, and minerals. Numerous compounds contribute to the marked antioxidant and anti-inflammatory activity, such as flavonoids, phenolic acids, tocopherols, ascorbic acid, and enzymes, including catalase (CAT) or superoxide dismutase (SOD) and Maillard reaction like products, such as MGO. Components of honey can act as a danger signal and activate the immune system via TLR4 signaling. Exposure of macrophages to honey promotes pro-inflammatory cytokines release, unrelated to possible LPS contamination. A 5.8 kDa molecule in honey was shown to be responsible for activation of TLR4, but not TLR2, in human monocytes, resulting in TNF-α production. Blocking TLR4 but not TLR2 significantly reduced honey-stimulated TNF-α production by human monocytes. As proof of principle, honey-stimulated cytokine production was evaluated in macrophages from wild type, TLR2, and TLR4 knockout (KO) mice. Honey-stimulated TNF-α production was observed in wild type and TLR2 KO macrophages but not in TLR4 KO cells. Keratinocytes showed increased mRNA levels of the pro-inflammatory cytokines TNF-α, IL-1β, TGF-β, and MMP-9 in the cytoplasm when treated with honey, which was followed by collagen IV matrix degradation, a step linked to the migration of keratinocytes over denuded epithelial surfaces .Antioxidant systems reduce the adverse effects of ROS(Reactive oxygen species) and reactive nitrogen species (RNS), inhibit the NADPH oxidases responsible for producing superoxide anions, act as metal chelators, and interfere with the chain reactions of free radicals. Flavonoids from honey, such as chrysin, apigenin, quercetin, inhibit pro-inflammatory enzymes like cyclooxygenases (COX), lipoxygenase, cytochrome P450, and consequently, the formation of pro-inflammatory cytokines. Additionally, flavonoids in honey also reduce pro-inflammatory gene expression by inhibiting the activation of NF-κβ and p38-MAPK in the cytosol. An important process during the proliferation phase is cell proliferation, migration, and wound contraction as these will help fill the gap in the wound. During the proliferative phase, α-smooth muscle actin-positive myofibroblasts excrete ECM (extracellular matrix) molecules, such as collagens, fibronectin, proteoglycans, and elastin, which are necessary for normal wound healing. However, a prolonged persistence of myofibroblasts, due to the presence of inflammatory and oxidative stress, leads to excessive scar formation due to the continued production of ECM molecules and contraction. Honey may facilitate apoptosis of myofibroblasts. By targeting the redox balance, honey can create a pro-healing microenvironment that optimizes scarless wound healing. Also, exposure of keratinocytes to

honey increases the production of matrix metalloproteinases (MMPs), such as MMP-9, and influences the degradation of collagen IV, which is important during the remodeling phase.[10]

SARPI (GHEE)

In *Ayurveda* there is description of four types of '*Sneha' Sarpi*, *Taila*, *Vasa*, *Majja*. According to *Samhitas- Sarpi* is considered as superior among all due to its property of "*Sanskaaranuvarti"*. It means that if it is processed with other drug, it accepts all qualities of that drug without changing its own. Also, among all types of ghee, Gau *Sarpi* is described as superior due to its properties.

Antimicrobial Activity of *Sarpi* (Ghee)

Oleic acid, linoeic acid, lauric acid and capric acid are the major fatty acids found in the Ghee along with other fatty acids. Oleic acid has been found to have strong inhibitory action on certain bacteria and viruses. It has been observed that linoleic acid is capable of inhibiting the growth of Staphylococcus aureus by altering its protein synthesis, cell wall, nucleic acids and cell membrane during division.

The other constituents of ghee include Vitamins A, D, E and K. Quantitatively Vit. A is more abundant than others. These are related with proper growth and tissue regeneration. Vitamin A interferes with wound healing causing lysis of lysosomal membranes, stimulation of fibroblasts and collagen deposition.

Moist Environment

An open wound which is directly exposed to air, will dehydrate and a scab or escar is formed. This forms a mechanical barrier to migrating epidermal cells and is then forced to move in a deeper level of tissue, which prolongs the healing process. Moist healing prevents the formation of scab as the dressing absorbs wound exudate secreted from the ulcer. The property of maintaining moist environment at wound site is well known for honey. Ghee by its lipid nature helps in retaining the moisture.

Triglyceride

The cell membrane is made up of lipid bi-layer. The lipophilic substances are better carried to the cells with lipid media. Here ghee acts as a vehicle for honey to reach to intracellular part. Ghee as mentioned in the literature contains 97% triglycerides i.e. fatty acids. Fatty acids belong to a class of compounds formed by a long hydrocarbon chain and a terminal

carboxylic group. They have three main functions: they are structural components of biological membranes, they act as precursors of intracellular messengers and they are oxidized producing ATP (adenosine triphosphate).

Linoleic acid as a pro inflammatory agent and growth factor Linoleic acid is a powerful pro-inflammatory mediator that causes migration of granulocytes and macrophages as well as important changes in granulation tissue. linoleic acid is essential for regulation of the biochemical events that precede the fibroblastic mitogenesis since it stimulates some factors of cellular growth. Linoleic acid has also been shown to participate in cell proliferation and inflammatory process, where in the latter it plays a role as a mediator of leukocyte function having chemotactic and stimulatory effects on neutrophils.[4,11]

The production of hydrogen peroxide(H2O2) is modulated by LNM (linoleic acid) in the first hour after injury. The increase in H2O2 content could activate activators protein -1(AP-1), triggering the expression of inflammatory cytokines and growth factors.AP-1 activation is also associated with proliferation of cells such as keratinocytes and fibroblasts, which are important for the closure of the wound.[12]

CONCLUSION

Being patient friendly, patient compliance is never an issue. No adverse reaction was seen in any case and successfully manage like chronic diabetic wound, traumatic wound, infected wound, burn *Madhusarpi* play a significant role in wound management. *Madhusarpi* can be considered an effective, safe, and affordable topical formulation for the management of various types of wound (*Vrana*), aligning with the classical principle described by *Acharya Sushruta* and supported by modern scientific evidence.

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