Application of the Animal Products Mucin and Honey in Wound Healing: A Pathophysiology, Therapeutics and Pharmaceutical Review

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ABSTRACT

Only few animal products such as insulin and growth hormones are widely used in therapeutics. In recent times animal products such as honey and mucin have been evaluated for use in medical practice. This paper focuses on the use of honey and mucin as wound healing agents. The use of two animal products singly and in combination is reviewed.

KEYWORDS: Animal products, mucin, honey, wound, healing
INTRODUCTION

Wound is an interruption in the continuity of the external surface of the body. Wound healing involves a well-orchestrated, complex process leading to repair of injured tissues. Wound healing can be delayed and this is more when an acute wound turns to chronic wound due to infection, non-ideal topical wound dressing preparation or underlying medical problems. Such chronic wound does not follow the normal pattern of repair due to physiological problems which lead to non-restoration of healthy granulation tissue in the wound bed associated with the loss of some physiological function (1). The final physiological strength of re-generated epidermis in the wound healing process is about 80% of the original strength (2). Rusczak (3) reported that human collagen matrices treated dermal wound had 75% tensile strength after healing. The myofibroblast mediates collagen deposition on wound and when this deposition is prevented the weaker the tensile strength of the wound surface (4). Myofibroblasts can contract by using smooth muscle type actomyosin complex, rich in a form of actin, called alpha-smooth muscle actin. These cells are then capable of speeding wound repair by contracting the edges of the wound. White et al (5) reported that wound exposed to 100% hyperbaric oxygen had increased tensile strength in 8 days while Diegelmann et al (6) have reported that 30% collagen in wound strengthened the tissue repair. The composition of wound fluid can be used to determine the rate of wound healing (1).

The knowledge of wound healing is important in formulating an ideal dressing preparation as suggested by Falcone and co-worker (7). An ideal wound medicament can ameliorate or prevent some complications of wound healing such as contracture, keloids, scar formation that could lead to various other surgical operations (8, 9). Many acute wounds turn into chronic wounds due to unavailability of ideal topical pharmaceutical formulations for wound dressing. This should be able to facilitate the formation of healthy granulation tissue and optimize the efficiency of such wound medicaments which should ultimately reduce the time for wound healing. Mackool et al (10) suggested that such medicament should be able to reduce scar and keloid formation. Mucin and honey have been shown in various reports to have wound healing effects.

Adikwu and co-workers (11, 12, 13) have reported that upon topical application of snail mucin to wounds, superficial healing is accelerated. Subrahmanyam (14), showed that wounds dressed with honey showed shorter healing time than silver sulphadiazine. Molan (15) reported that at concentrations of 58%, various samples of honey studied from 26 different floral sources showed antibacterial activity against Staphylococcus aureus as compared with phenol. Seven strains of bacteria found in wound have been reported to have their growth halted completely by gamma irradiated honey diluted to 5-10% (16). Ghaderi et al (17) reported that ten-fold diluted honeys still completely halt the growth of all the major wound-infecting bacteria, while Bergman et al (18) reported that topical application of undiluted honey is able to accelerate infected-wound healing. Efem et al (19), reported that 20 infected-wound cases treated with topical application of undiluted honey showed no pathogen after 1 week of treatment. Ali (20) reported that orally administered honey, 312 mg/kg, administered twice daily was comparable to sucralfate in accelerating the healing of indomethacin-induced gastric ulcers in rats. Deinzer et al (21) also stated that honey contains pyrrolizidine alkaloids which have antibacterial activity, while Gupta et al (22) reported that undiluted honey was efficacious in infected wounds of buffalo. Ndayisaba et al (23), reported that in 53 Burundian patients with wounds diverse in origin treated by daily topical
honey applications, healing was successful in 29 patients within 5 weeks. This study evaluated the topical formulations of mucin and honey using standard pharmaceutical bases, wound healing effects, tissue re-epitheliazation and efficacy in reducing bioload in wounds as compared to the effects produced by silver sulphadiazine cream (SSD).

**WOUND**

**Classification of wound**

Ramasastry (8) and Nwome et al (9) reported that wounds can be classified by the duration of the wound repair. Short-term wound healing is regarded as acute wound; while long-term wound healing (lasting more than 3 months) is classified as chronic wound. Wound can also be classified based on type of wound closure, as primary, secondary, or tertiary. Primary wound closes with minimal intervention, while secondary wound closes by contraction and re-epithelialization. In tertiary wound, there is delayed primary closure, and it only closes when there is initial debridement and suture or other surgical procedure.

**Stages of wound healing**

Wound healing is the body’s natural process of regenerating dermal and epidermal tissue. A set of events take place in a predictable fashion to repair the damaged tissue, and these events overlap with time. Although some authors (1, 9) consider healing to take place in four phases, wound healing is generally grouped into three phases - inflammatory, proliferative, maturation/remodeling.

**INFLAMMATORY PHASE**

The inflammatory phase includes the initial reaction to the injury in which a number of cells, including neutrophils, platelets and macrophages, migrate to the site. In the inflammatory phase, debris and bacteria are phagocytized and removed. At this stage some biological factors are released that cause the migration and division of cells involved in the proliferative phase (1, 9).

**Clotting cascade**

Clotting cascade is the first process of restoration of tissue integrity in the inflammatory phase of wound healing. Coagulation is a rapid-fire response to initiate homeostasis and protect the host from excessive blood loss. This fibrin-fibronectin complex is the main structural support for the wound until collagen is deposited (1).

**Platelets**

Dasu et al (24) observed that platelets are the cells usually present in highest numbers shortly after injury occurs. The growth factors from platelets stimulate cells proliferation to facilitate wound healing.

**Vasoconstriction and vasodilation**

Inflammatory factors such as thromboxanes and prostaglandins are released from ruptured cell membranes, and cause blood vessel spasm and thus prevention of blood loss. This causes vasoconstriction that lasts for 5-10 min (1, 9).

**Polymorphnuclear neutrophils**

Ovinghton (25) and Aschcroft et al (26) pointed out that polymorphonuclear neutrophils (PMNs), are attracted to the wound site by fibronectin, growth factors, and substances such as kinins and neutropeptides. Neutrophils clean the wound by secreting proteases that break down damaged tissue.

**Macrophages**

Macrophages are attracted to the wound site by growth factors released by platelets and other cells. Macrophages are stimulated by the low oxygen content of their environment to produce factors that induce and speed angiogenesis (25, 26).
PROLIFERATIVE PHASE
The proliferative phase occurs when tissue reconstruction begins. This includes angiogenesis, epithelialization, and granulation. Fibroblasts begin to enter the wound site 2-3 days post injury, after a wound develops. With time the steps in this stage partially overlap as reported by Stadelmann et al (2), and Diegelmann et al (6). This means that one stage does not stop completely before another stage starts.

Angiogenesis
This process is also called neovascularization. It occurs concurrently with fibroblast proliferation during endothelial cells migration to the area of the wound. LaVan and Hunt (27), reported that angiogenesis is imperative for other stages of wound healing, like fibroblast and epidermal migration; as such cells require oxygen. Mulder et al (28), pointed out that endothelial cells are the stem cells that originate from parts of uninjured blood vessels which develop pseudopodia that push through the extracellular matrix into the wound site. Li and Li (29) observed that in a low-oxygen environment, macrophages and platelets produce angiogenic factors which attract endothelial cells chemotactically.

Fibroplasia and granulation tissue formation
Fibroblasts mainly proliferate and migrate in the first 2-3 days after injury. They are the main cells that lay down the collagen matrix at a wound site, by migrating from normal tissue into the wound area from its margins. Granulation tissue begins to appear in the wound 2-5 days post injury.

Epithelialization
The re-epithelialization phase starts after formation of granulation tissue in an open wound. The epithelial cells migrate across the new tissue to form a barrier between the wound and the environment. Santoro and co-worker (30) observed that this occurs 17 times more than in normal tissue.

Contraction
Fibroblasts later differentiate into myofibroblasts to initiate wound contraction. Contraction continues even after the wound has completely reepithelialized (9).

MATURATION AND REMODELING PHASE
The maturation phase of tissue repair starts when levels of collagen production and degradation are equal. The tensile strength of the wound increases up to 50% - 80% that of normal tissue at the end of this phase (1, 9).

Factors affecting wound healing
There are numerous factors that can affect wound healing. The size of wound is inversely proportional to the wound healing rate. The presence of an infectious agent in the wound can adversely affect the healing process. Robson et al (31), observed that wound infection occurs when the bacterial count in the wound exceeds $10^5$g of tissue. The wound type determines the wound healing rate. Superficial (surface) wounds heal faster than deep or major wounds. The wound in a well nourished patient heals faster than wound in a malnourished patient. Falcone and co-worker (7) suggested that nutritional supplements such as zinc, vitamin C, folate, iron, and copper are the key minerals and vitamins that can be given such patients. In a wound patient that has compromised immunity, the rate of wound healing is usually slow. This leads to delay in the wound repair process as all other healing phases are equally delayed as observed by Zhu et al (32). Age and stress factors also lead to delay in healing. Sinclair et al (33), stated that in chronic wounds there is high level of protease activity that results in delayed wound healing caused by an increase in tissue destruction. Cocks et al (34) and Doumas et al (35) observed that leucocytes are up-regulated in such wounds. Grinnell and co-worker (36), also pointed out that protease can
degrade growth factors which will lead to delay in wound healing. McDonad et al (37), and Herrick et al (38), reported in their various studies that protease causes delay in wound healing. Other factors that can lead to delay in wound healing include: radiation, foreign bodies, chemotherapeutic agents, smoking, steroids and diabetes mellitus (1, 9).

**Histopathology of wound**

Tissue disruption in higher vertebrates results in tissue regeneration. The disruption of the integrity of a tissue leads to histological imbalance which in turn results in pathological effect. This incapacitates the tissue from carrying out its normal physiological functions. The body has the ability to commence the repair process to restore the integrity of the tissue. Keswani et al (39) suggested that the aim of this process is to restore histological normality in the tissue.

**Histological characteristics of wounds**

The type of cells that appear in the wound depends on the stage of the healing process. The healing cascade begins immediately following injury when the platelets come into contact with exposed collagen. Usually, platelet aggregation and clotting factors are released, resulting in the deposition of a fibrin clot at the site of injury. Hackam et al (40), pointed out that cytokines (endogenous peptides), enhances fibroblast and smooth muscle cell chemotaxis and modulates collagen and collagenase expression. The result of this role is vigorous response of the matrix producing cells to ensure a rapid deposition of new connective tissue at the injury site during the proliferative phase that follows the inflammatory phase.

Cejkova (41) and Herrick et al (42) in their work observed that neutrophils are the predominant cells in the wound, 24 hours post injury. The main function of the active amines released from the mast cells is to cause surrounding vessels to become leaky and allow the speedy passage of the mononuclear cells into the injured area.

Young et al (43), stated that within 48 hours post wound development, fixed tissue monocytes become activated and turn into wound macrophages. The presence of wound macrophages is a sign that the inflammatory phase is nearing an end and that the proliferative phase is beginning. The phagocytic macrophages are responsible for removing nonfunctional host cells, damaged matrix, bacteria filled neutrophils, bacteria and foreign debris from the wound site.

In the proliferative phase of the wound, the predominant cell is the fibroblast. The fibroblast cell is of mesenchymal origin and is responsible for producing the new matrix needed to restore structure and function to the wounded tissue. Santoro and co-worker (30) stated that the final stage of the wound healing is characterized by proliferation of collagen cells for remodeling. The enzyme lysyl oxidase acts on collagen to form stable cross-links. As the collagen matures the intramolecular and intermolecular cross-links are formed, which give healed wound tissue its strength and stability over time.

**Wound scar**

Wound scar can be defined as the replacement of the normal structural elements of the tissue by distorted, nonfunctional and excessive accumulation of fibrotic tissue in order for scar to form; there is 2 - 3 times production of fibroblast in the wound from that of the normal skin. There is also increased density of mast cells that process procollagen into excessive collagen (8.9).

**Enzymology of wound**

Enzymes can be classified into six groups according to their mechanism of action namely: oxidoreductases, transferases, hydrolases,
lyases, isomerases and ligases (44, 45). Changes in pH affect the activity of the enzyme on the substrate (46, 47) with the enzyme-substrate interaction similar to kinetics reactions in physical chemistry (47).

**Matrix proteins and proteases in wound**

Proteases are a family of enzymes that include the endopeptidases and exopeptidases, which catalyse the hydrolytic breakdown of proteins into peptides or amino acids. Ovington (26) pointed out that proteases are associated with the early inflammatory stage of wound healing in many ways. During angiogenesis, proteases are expressed significantly at the growing tip of blood vessels to facilitate vascular invasion. Aschcroft et al (25) reported that this class of enzymes also assists in wound debridment and cleansing of necrotic tissue, bacteria and foreign bodies. Proteases digest the extracellular matrix and assists in tissue remodeling during reconstructive and remodeling phase in normal wound healing.

Studies have shown that the biochemical environment of the non-healing wound is different from that of a healing wound. A chronic non-healing wound has a biochemical environment with evidence of excessive proteases and inflammatory cytokines and low levels of growth factors. The presence of a high level of bioburden in wound is prone to increase the levels of proteases. Okada et al (48), indicated that there are higher protease activity levels and endogenous enzyme inhibitors called tissue inhibitors of metalloproteases (TIMPs), observed in older patients. Borregaard et al (49), reported that for a wound to heal, a balance is needed between the protein degrading activities of matrix metalloproteases (MMP’s) and other cellular activity that synthesizes and deposits protein components of granulation tissue.

In tissue remodeling and wound repair there are different types of proteases involved. Increase in the levels of these enzymes in the wound indicate tissue damage or tissue repair. The assay of such enzymes will indicate whether the wound healing rate will be slow or fast. Cullen et al (50) in their investigations observed that this assay can be used as a prognostic test to monitor wound healing.

**The role of neutrophil elastase in wound healing**

Neutrophil-derived elastase, plasmin and MMP’s are major proteases present in chronic wounds and have a role in delaying healing with the neutrophil-derived elastase being the predominant protease in chronic wounds. In their various studies, the view is corroborated by Aschoft et al (25), and Jahovic et al (51).

**WOUND DRESSINGS**

**Categories of wound dressings**

There are several classes of wound dressings, some of which are described below:

**Absorbent**

Absorbents are the oldest class of dressings. Absorbent wound dressing medicament has attempted to maximize absorption based on fiber type, content and weave. The disadvantage of this type of wound dressing is adherence to wound.

**Impregnated dressings**

These types of dressings have been used for many centuries. They are usually paraffin gauze (tulle gras) which create non-adhesive or semi-occlusive surface. They equally include other fabrics impregnated with petrolatum or other substances that create non-adherent surfaces. Some are impregnated with antimicrobial agents (e.g neomycin) that minimally diffuses into the exuding wound (52).
**Hydrocolloids**

Hydrocolloids as wound dressings are extremely useful and versatile. They contain a pressure sensitive adhesive layer and a hydrophilic polymer. They are also available in paste. When in contact with the wound, the exudate is absorbed from the wound and a gel is formed that expands into the wound cavity. Because of their absorptive characteristics, they usually require less frequent dressing changes, than conventional dressing materials (52, 53).

**Foams**

Foams are polymeric dressings that maximize absorbency and vapour permeability to provide optimal exudate handling. Foam dressings fit into deep wounds and expand as they absorb exudates. They create gentle pressure on the wound, which may contribute to reduction in peri-wound edema (49). This may enhance granulation tissue formation because reduced peri-wound edema may limit exudates production and improve peri-wound oxygenation.

**Transparent films**

These are transparent synthetic adhesive films that are semipermeable, and highly flexible. They have been used as dressings within the last two decades. Films reduce evaporative losses due to the skin stratum corneum, which can result in the loss of 3000 to 5000 g/m² of water over 24 hours (52).

**Alternative dressings**

A lot of substances known to man have been tried as wound dressings. The commonly used agents include vinegar, aloe vera, bleach, sugar and honey. It has been shown that sugar’s hypertonicity reduces peri-wound edema, which can improve tissue oxidation. The sugar may ferment within the wound, leading to antiseptic alcohol formation. The pH of the wound can have antiseptic effects (51).

Honey contains several proteins that have beneficial effects for wounds. Honey contains inhibine which is an enzyme that creates metabolic by products including hydrogen peroxide and gluconic acid that act as mild antiseptic.

**MUCIN**

Mucins are mucoproteins secreted by cells. Mucins can raise the viscosity of the medium around them. Mucin is the major glycoprotein component of mucus (53). They are conjugated proteins in which protein is combined with a polysaccharide containing hexosamines or glycoproteins as reported by Adikwu et al (54). Mucins form a protective biofilm on the surface of epithelial cells, where they can provide a barrier to particulate matter and bind microorganisms. They have about 80% of their sugar glycosylated with large molecular weight glycoprotein (2.14-14×10⁶ Da). There are peptide cores that are rich in serine and threonines which are attached by O-glycosidic linkages composed of N-acetyl-glucosamine, N-acetyl-galactosamine, galactose, fructose and sialic acid. A lot of mucins are membrane bound due to the presence of a hydrophobic membrane-spanning domain that favors retention in the plasma membrane while some are secreted on mucosal surfaces and saliva (55).

Mucin can generally be defined as glycoproteins, which contribute to the mucus gel barrier and are part of the dynamic, interactive mucosal defensive system with protective, adhesive and lubricative functions. Mucin has many biophysical properties that have made it a good candidate for pharmaceutical studies (56). Glycoproteins are now known to interact in various ways with many biologically important compounds such as enzymes, polymer, cations, drugs, viruses, particulate matters and bacteria. In the past 15-
30 years several authors, including Anosike (57), Ganon (58) and Pasternak (59) have written on mucus glycoproteins from different organs which have revealed that these macromolecules consist of sub-units held together by interchain disulphide bonds. Harding (60) in his work stated that these multiple crosslinks confer a kind of random gel network which confers mucus/mucin with visco-elasticity property. Ofakansi (61) reported that bioadhesiveness of gelatin/mucin increase with increase in concentration of the admixture, while Nnamani (62), reported also that the mucoadhesive force required to separate snail mucin applied to two surfaces increase as mucin concentration increases. Certain studies have indicated the healing property of mucin (11, 12). It can be used as medicament, or as biomaterial to be formulated as suitable delivery system for application in wound (13).

**Classification of mucin**
Young et al (63), observed that mucin being a major glycoprotein component of mucus is found in living systems such as egg white, plasma, connective tissues, blood and enzymes. It can be classified as a structural polysaccharide that has a high content of clustered oligosaccharides with O-glycosidically linked to polypeptides. Mucins can also be classified based on their sources, which may be snail, bovine, guinea pig, porcine, rat, rabbit and nematodes. It can also be classified based on the body part that secrets it, such as eye, ovary, saliva and gastro-intestinal tract (64 - 66).

**Composition of mucin**
In mucin, the protein unit is about 20 % w/w, while the carbohydrate portion is about 80 % w/w oligosaccharide. The sugar unit of the glycoprotein, which may be branched, or straight chain contains short or long chain carbohydrates of 2 to 20 residues. The carbohydrates that can be found in mucin include N-acetylglucosamine, sialic acid, N-acetylgalactosamine, mannose, L-fructose, xylose, galactose and arabinose. The protein portion of the mucin contains mostly amino acids, which form the linkage with the carbohydrates. Such amino acids include asparagines, threonine, serine, glycine, hydroxylysine, proline, phenylalanine, cysteine, alanine and valine. Threonine and serine are the most predominant amino acids in mucin (55, 60).

Acharan sulphate, a recently discovered glycoprotein isolated from snails of the species *Achatina fulica*, has a major disaccharide repeating unit of \( \rightarrow\text{4})-2\text{-acetyl,2-deoxy-alpha-D-glucopyranose}(1\rightarrow\text{4})-2\text{-sulfo-alpha-1-idopyranosyluronic acid making it structurally related to both heparin and heparin sulphate. Acharan sulphate is a main constituent of the mucus of snail (60).**

**Physico-chemical properties of mucin**
The gel-like characteristic of mucin is due to the carbohydrate portion of the glycoprotein. Adikwu et al (13) reported that the presence of sialic acid gives the mucin its dense negative charge. This gives mucin a pKa value of about 2.6 and mucin molecule behaves eventually as anionic polyelectrolyte, at pH values greater than 2.6. Blood (67) in his studies found that the amino acids in the glycoprotein confer amphipatic properties to mucin and as such can buffer small amounts of acid or alkali. The mucin gel is held together by primary (disulphide) or secondary (electrostatic or hydrophilic) bonds. In other words, the glycoprotein molecules are held in association with each other by means of non-covalent interaction to form a gel matrix that is responsible for the physiological and rheological properties of mucin (68). The flow of mucin is not proportional to the force applied due to increase in viscosity (60, 69). Mucin has the ability to form self-assembly of drug-polymer or polymer-polymer complexes. In a study by Oliva et al (70) a spontaneous
The nanoencapsulation process (monitored by atomic force microscopy which is the force required to extract nano-particles from a polymer) occurred. The results demonstrate that polymer-polymer molecules can nanoencapsulate spontaneously, which offers possibility of controlling the release rate of a drug without the need of complex technological processes.

**Mucin as a pharmaceutical material**

Mucin has been widely investigated for a variety of microparticulate pharmaceutical forms. It also has potential applications in the delivery of radiopharmaceuticals, genes and peptides. It has also been used in mucoadhesive formulations for ocular, nasal, gastro-intestinal, buccal and vaginal drug administration (71, 72).

**Assay of mucin immunoradiometric assay (IRMA)**

In this assay, radiolabelled glucosamine is incorporated into the mucin. This radio-immunometric assay method was developed using monoclonal antibodies against epitopes which are associated with peptide core of gastric mucins (60). IRMA technique has been applied in supernatants of pancreatic cell culture to detect mucin in pancreatic cyst in order to diagnose the mucinous pancreatic cyst that is precancerous (13). The disadvantage of this technique is that it characterizes the high molecular weight glycoproteins containing glucosamine and does not detect mucins specifically.

**Atomic force microscopic assay of mucin**

In atomic force microscopic assay of mucin, quantitative measurements of biophysical characteristics of individual mucin molecules and molecular assemblies are measured (69). To enhance the characterization of human ocular mucins, purified mucins have been used to demonstrate the capabilities of this technique and derive biophysical properties unavailable through other techniques. The result showed that the antibodies bound to short polymers and longer polymers required longer reaction times. Influence of length and charge distribution on diffusion through gels is investigated by comparing the forces needed to extract mucin and DNA polymers from agarose gels (60).

**Analytical ultracentrifuge assays**

In this method, there are two principle approaches to assay mucin. The first approach is to use change in molecular weight using sedimentation equilibrium, but has the disadvantage of having an upper limit of about 50 MDa. Since complexes are large, a more efficient assay procedure is to use sedimentation velocity with change in sedimentation coefficient. There is a special procedure known as sedimentation fingerprinting where mucin is assayed for its effect on the mucoadhesion (60).

**Current development and uses of mucin**

**Antibacterial activity**

Snail mucin from *Archachatina marginata* (Family Ariondiae) has been reported to have antimicrobial activity, while mucin in tears prevents infection and decrease in commensal bacterial load. Rudolph *et al* (73) in their work reported that purified ocular mucin inhibited bacterial growth while Adikwu *et al* (12) have suggested that due to its surfactant activity it prevents bacteria attaching to host cells. Similarly, a study has shown mucin could bind microorganisms preventing them from spreading to adjacent tissues (77).

**Mucoadhesion**

Blood (67) and Mortazavi *et al* (68), in their studies suggested that mucin as a polymer has a lot of interaction forces such as electrostatic interaction, van der Waals forces, hydrogen bonding, etc. Mucoadhesion can be explained considering interfacial energy theories as pointed out by Adamson (74). In aqueous solutions, mucin which is usually negatively
charged interacts with cationic ions, drugs, or polymers that are positively charged. Non-ionic macromolecules, however, could interact with mucin mainly through hydrogen bonding.

**Analgesic activity**
Adikwu et al. (13) reported that a new compound extracted from snail mucin is found to ease pain. The compound known as ACVI is more efficacious and has longer effects when compared to morphine. The compound does not have addictive effect and or side effect as morphine does.

**Tumor marker**
Scientists have proved that mucin can be used as a tumor marker. Rudolph et al. (73) in a study where dimethylhydrazine was used to induce tumors in rats reported that there was abnormal increase in expression of sialomucins (type of mucin in colon cancer of mammals). Similar sialomucins were detected in precancerous lesions and in the colon mucosa around the adenocarcinomas. No sialomucins were seen in normal colon mucosa. This implies that an alteration in mucin expression is an early event in colon carcinogenesis.

**Wound healing property**
In a study by Adikwu et al. (12), it was reported that snail mucin from the giant African snail, *Archachatina marginata*, (Family Arionidae) has wound healing effects. The extract (mucin) remarkably increased the wound healing capacity of Cicutrin® powder. King et al. (75) in their study reported that mucin secretion in pig mucosa enhanced ulcer healing of the cell wall. Mucins from other sources have not been reported to have the same wound healing effect as snail mucin. Similarly, Adikwu and Enebeke (78) showed that mucin dispersed in *Brachystegia euphycoma* gum showed marked wound healing effect. It has also been reported that *Detarium microcarpium* gum enhanced the wound healing effect of mucin (79).

**HONEY**

Honey is carbohydrate-rich syrup produced by bees, primarily from floral nectars. The British Pharmacopoeia (76) defines purified honey as obtained by purification of the honey from the comb of the bee, *Apis mellifera* L., and other species of *Apis*. Honey has an extensive history of traditional human medicinal use, in a number of societies. Molan (15) stated that it may be used alone or in combination with other substances, and has been administered both orally and topically.

**Classification of honey**
Generally, we have purified honey and natural honey. The purified honey is natural honey standardized to meet stipulated pharmacopoeia standard. The natural honey is sugar syrup produced by worker bees from plant nectars, plant secretions and excretions of plant sucking insects (80).

**Composition of honey**
The two major sugars present in honey, are fructose (38 %w/w) and glucose (31 %w/w). Sucrose (1 %w/w), and other disaccharides and oligosaccharides are also know to be present. Gluconic acid, other acids and small amounts of proteins, enzymes (including glucose oxidase), amino acids and minerals may also be present. Potassium is the major mineral present (16).

The chemical composition of honey is highly variable because of the broad range of plants visited by honey bees when collecting the substance. Deinzer et al. (21) reported that the plant species available in a given geographic area determine the kinds and amounts of important compounds present in honey. Storage conditions may also influence the final composition of honey, with the proportion of disaccharides increasing over time. Molan and Allen (16) and Bergman et al. (18) reported that there are a range of other, largely
uncharacterized, substances present in some honeys that have antibacterial effects.

**Physico-chemical properties of honey**

Honey is yellow-amber colored sticky viscous, translucent syrup. It has low moisture content (17%) and is mildly acidic with a pH of 3.2 and 4.5 (16, 18). The acidic pH is mostly due to the presence of gluconic acid which is formed when bees secrete the enzyme glucose oxidase, that catalyses the oxidation of glucose to gluconic acid and hydrogen peroxide. The low pH alone is inhibitory to many pathogenic bacteria.

**Uses of honey**

Many reports have indicated that honey is an effective remedy for stomach upsets. A report in the British Medical Journal (48) suggested that it shortened the duration of bacterial diarrhea and was as effective as glucose at promoting the re-absorption of sodium and water from the intestine. Ali (20) reported that honey has been used to treat gastritis, duodenitis and duodenal ulcers.

Molan and co-worker (16) observed that honey has been used successfully as replacement for carbohydrate in oral rehydration therapy in acute diarrhea. The use of honey in ophthalmic conditions has been reported in Egypt. Such conditions treated included chronic, non-specific conjunctivitis and persistent blepharitis (16). Honey has a very long history of low-risk food use. Daily intake as a food could easily reach 100 g in some individuals, a dose far higher than is likely to be achieved when honey is consumed in therapeutic forms. It is often consumed alone, as a spread, or may be mixed with a wide range of other foods.

Deinzer *et al* (21), Gupta *et al* (22) and Ndayisaba *et al* (23) in various studies have shown that honey has antibacterial effects, attributed to its low pH, high osmolarity, hydrogen content and other uncharacterized compounds. The low water activity of honey is inhibitory to the growth of the majority of bacteria, and many moulds and yeasts (16, 47). Honey is used in pharmaceutical preparations and cosmetics, as adjuvant, thickener, sweetener and vehicle (46).

Molan (15) in his study stated that honey is effective in treatment of wounds while Ghaderi *et al* (17) observed that it is effective in the treatment of skin wound in mice. There are other reports of the use of honey to treat wounds such as ulcers, burns, surgical wounds and gastric ulcers (18-20, 21-23). There are many reports of the traditional medicinal use of honey in a large number of cultures. The Bible and Koran recommend its use. It has been used in a wide range of conditions, including gastrointestinal, respiratory, skin, measles and eye ailments (15). It has been shown that admixture of mucin and honey accelerates wound healing, including the reduction of scar formation (81). Apart from the synergistic effect, the native honey stabilized the mucin because of its preservative effect (81).

**CONCLUSION:**

Mucin and honey possess wonderful therapeutic activities as regards wound healing. With the upsurge in bee- and snail-keeping, mucin and honey sources are readily now available for therapeutic uses. Apart, from the food uses of snail, the mucin extracted from it during processing for culinary uses, offers another useful product for medical application.
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