Bovine Based Collagen Dressings in Wound Care Management

Rameshkumar Santhanam¹, Mohd Adha P. Rameli², Azleena Al Jeffri³ and Wan Iryani Wan Ismail⁴,⁵∗

¹Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia.
²Laboratory of Molecular Biomedicine, Institute of Bioscience, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia.
³Bio-Collagen Technologies Sdn Bhd, No 11, Jalan Perindustrian Balakong Jaya 2/3, Taman Perindustrian Balakong Jaya 2, 43300, Selangor, Malaysia.
⁴Cell Signaling and Biotechnology Research Group (CeSBTech), Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia.
⁵Biological Security and Sustainability (BioSeS) Research Group, Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia.

Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Collagen plays a significant role in treating acute and chronic wounds such as cuts, burns, ulcers associated with other illness via enhancing the debridement of infected tissues, angiogenesis and promoting natural growth. There are several types of collagen, which can be obtained from various animal sources such as chicken, bovine, porcine, fish etc. Among that bovine based collagen contributed many shares towards biomedical application. Nowadays using bovine based collagen biomaterials for wound care is in trend to minimize the negative impacts such as infection, pain and other side effects. However, its applicable and effectiveness are not fully revealed. At the same time, clinicians and researchers are exploring and implementing advanced techniques and

*Corresponding author: E-mail: waniryani@umt.edu.my;
treatment procedures to reduce the wound healing burden effectively. In this review, we aimed to focus on the fundamental information about types of wound dressings, collagen dressings and the clinical utility of bovine based collagen dressings in providing essential knowledge in advanced wound care management.

Keywords: Collagen dressings; bovine based; chronic wounds; wound care; wound healing.

1. INTRODUCTION

Collagen is one of the major components in extracellular matrix where it comprises about 70 – 80% of the dry weight of the human skin. It can also be found in connective tissues such as bones, cartilage and tendon. As a structural protein, collagen maintains the structural and biological integrity of several organs and tissues. Initially, collagen was believed to provide only support and tensile strength later it has been established that it is responsible for various essential functions such as cell migration, cell differentiation, cell behaviour through regulation of extracellular matrix (ECM) and synthesis of several proteins [1]. Approximately one-quarter of all proteins in the human body is made up of collagen, making it the most abundant protein. There are up to 28 different collagens carrying different functions depending on the location of where the protein is located. For instance, collagen in the ECM provides cell strength, regulates cell adhesion, supports chemotaxis and migration, and directs tissue development [2]. Meanwhile, the collagen found in the bone provides shear strength to absorb energy (i.e., the toughness) and ductility [3].

A single collagen monomer consists of three individual polypeptide chain, which is alpha-1, alpha-2 and alpha-3. These amino acids sequence which known as alpha chain intertwined together to create elongated triple-stranded alpha helix via hydrogen bond. The most common types of collagen are summarized in Table 1. Among all collagens, type I collagen is the most abundant, as it forms 80 – 85% of dermal extracellular matrix and type III constitutes 8 – 11% [4].

The key function of the type I, type II and type III collagen in connective tissues is to act as scaffolds. This is the vital feature recommended in early wound healing process apart from that collagen has the ability to induce growth factors, cytokines, signal transduction, migration and epithelization etc [5]. Additionally, it acts as a natural framework or substrate for new tissue growth. Due to their versatility, collagen plays a significant role in advance wound care management where it has been utilized as a biomaterial in the form of wound dressings.

In this review, the wound healing process, types of wound dressings, collagen wound dressings, bovine based collagen and clinical utilization of bovine based collagen are discussed.

2. WOUND HEALING

Skin is the largest organ in the human body, and it consists of three different regions; epidermis, dermis and subcutaneous layer (Fig. 1). The first region of skin; epidermis consists mostly of keratinous cells, which are responsible for the skin’s impermeability to water. Other components of the epidermis are melanocytes, Langerhans cells and Markel cells, which are responsible for melanin production, immunity and skin sensation respectively [6]. The lowest epidermis of the skin is known as stratum basal, which contains melanocytes and stem cells that will later differentiate into keratinocytes. Overall, epidermis functions as a protection or physical barrier to the skin.

| Table 1. The structure and localization of most common collagen types in the body |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Collagen                        | Type I          | Type II         | Type III        | Type IV         |
| Structure                       | Consists of two alpha-1 chains and one alpha-2 chain | A homotrimer of alpha-1 chain [α1(I)I]3 | A homotrimer of alpha-1 chain [α1(III)]3 | Consists of six alpha chain |
| Location                        | Bone, tendons, skin, teeth, and ligament | Cartilage and intervertebral discs | Blood vessel, skin, and muscle | Basement membrane and basal lamina |
The second layer; dermis contains a network of proteins (the largest component being the ECM). Dermis is divided into two layers; the papillary layer and reticulum layer. The papillary has connective tissues that extend into the dermis, while the reticulum contains collagen fibers (made up of primarily collagen type I and type III) and elastin fibers which gives the skin its strength and flexibility. It also contains blood vessels, sebaceous gland, and sweat gland, the root of a hair follicle and various nerves and receptors. As it contains a plethora of components for the skin, dermis acts as the center of the skin with collagen acting as a support. Finally, the subcutaneous layers, which are the lowest portion of the skin, contain adipose cells which act as an insulator for the human body. There is also a network of elastin fibers, collagen and larger blood vessels found in this region. This layer allows the dermis to stick to the rest of the body [6].

Wound is defined as any injury to living tissues, and it can be classified as an open or closed wound. The open wound is exposed to the environment, whereas the closed one is a non-penetrating wound. Both types of wound can be further classified as acute wound based on their rate of healing such as acute and chronic. Acute wounds will heal in some specific amount of time, whereas chronic wound would take a longer time to heal. Further wound also be classified as fresh, clean wound or infected wound based on the time of occurrence and appearance. Infected wounds reveal the presence of pus and high levels of exudates in the wound area. Wounds are generally caused by internal factors such as low blood supply, oxygen or nutrients to immune and nervous system function as well as by external factors such as penetrating object, abrasion (a scraping of outer skin layer) due to accident, or other miscellaneous factors such as animal bites, fractures, chemical and thermal substances [7].

Wound healing is a complex and dynamic process, where it undergoes four major phases, i.e. hemostasis (clot formation), inflammation (controls bleeding and infection), proliferation (re-epithelialization) and maturation (granulation tissue formation) to replace the damaged tissues [8-10]. It occurs as a progressive cascade that involves a variety of cellular activities such as chemo taxis, phagocytosis, mitogenesis, and synthesis of collagen and other matrix components via overlapping the four phases (haemostasis, inflammation, proliferation, and remodelling) of wound healing process [11]. These phases involve several growth factors such as platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), and transforming growth factor-beta (TGF-β), granulocytes, vasoactive amines, cytokines, chemokines, immunoglobulins, fibroblasts, lymphocytes, macrophages, MMPs, etc. Disruption in the healing phases especially occurs in the inflammatory and proliferation phases. At these phases, white blood cells, thrombocytes, neutrophils and other cells release growth factors, cytokines, chemokines to accelerate the inflammatory process and decontaminate the wound. However due to individual immune condition with associated aging factors and other health disorders such as diabetes, stress and obesity, improper management and altered cellular response elevated levels of inflammatory cytokines, free radicals, endotoxins and matrix metalloproteinase such as collagenase, gelatinases, stromelysins, serine proteases,
neutrophil elastases, (microbial contamination) and decreased levels of tissue inhibitor of metalloproteinases (TIMPs) will result in the wound atmosphere. This condition prolongs the inflammatory and proliferative phase with low blood circulation, less nutrition and oxygen supply, biofilm formation, antibiotic prevention, migration barrier, reduced collagen synthesis and increased level of free radicals, inflammatory cytokines and matrix metalloproteinases (MMPs) [12,13]. MMPs are the proteolytic enzymes belonging to the zinc dependent-endopeptidase group. These enzymes play a major role in the pathogenesis of wound, in which they cleave the peptide bonds in the dermal protein, mainly collagen and elastin. Increased level of matrix metalloproteinases (MMPs) degrades the viable as well as nonviable collagen present in the extracellular matrix which prevents the proliferation and remodeling phase. Overall, the healing processes halted and the wound becomes chronic. Studies revealed that balancing the biochemical alterations at the wound atmosphere could trigger the formation of new blood vessels, granulation tissue, migration of fibroblasts and keratinocytes [12-16].

Different types of treatments are available to treat the acute and chronic wounds such as cleaning, debridement, wound dressings, compression stockings and bandages, antibiotics, hyperbaric oxygen therapy, ultrasound and electromagnetic therapy, negative pressure wound therapy, skin grafts etc [13]. One of the most widely used method to promote the wound healing process in advance wound care management is wound dressings. At present, wound healing is one of the common health issues, where it was estimated that chronic non-healing wounds impact around $8.2 billion (15%) of Medicare beneficiaries. Consequently, it was also conservatively estimated that around $31.7 billion to $96.8 billion were spent annually for primary and secondary diagnosis of the wounds [17].

3. WOUND DRESSINGS

Wound dressings are materials used to fix the wound through direct contact. It stimulates the healing process by initiating the clot followed by bleed control, increase oxygen supply, absorb excess fluids, supply growth factors, increase wound debridement and prevention of microbial infection [18,19]. Since ages, various types of wound dressings are utilized to treat the acute and chronic wounds. Based on their composition and applications, wound dressings are classified as traditional, modern, bioactive, tissue engineered skin substitutes, medicated and composite wound dressings which can be further classified based on the usage of ingredients as shown in Fig. 2. Conventional/Traditional wound dressings are used for primary/secondary coverings which are made up of woven or non-woven gauze. They are made up of cotton, wool, polyesters (synthetic or natural) which are mainly used to protect the wound from the external environment via preventing contamination and absorb the excessive fluids drain out from the wounds. These types of dressings are utilized for one time/short term and are still in practice. Modern wound dressings have multifunctional properties to enhance the healing properties instead of just covering it. These types of dressings are made up of synthetic polymers and are classified as non-occlusive, semi-occlusive or occlusive. These products act as a barrier to prevent dehydration of wound and microbial contamination. They are in different form such as film, foam, hydrogels, hydrocolloid, alginate, fibers etc [7].

Bioactive dressings are made up of materials derived from natural sources where it could deliver the active substances towards the wound atmosphere and stimulates the healing process endogenously. These materials can be pure collagen or it can be incorporated with other modern wound dressing materials such as hydrocolloids, hydrogels, biopolymers, alginites, honey dressings, chitin and chitosan derivatives. Another type of wound dressings is tissue engineered skin substitutes, mainly used in the place where extensive skin loss or untreatable injuries. It is a mimic of normal skin which are of three types, epidermal, dermal, and dermo-epidermal with the desired compositions. The other types of dressings are medicated and composite dressings. Medicated dressings are multifunctional drugs where growth factors, antimicrobial agents and proteinase enzymes are incorporated. These dressings enhance the wound healing potential via preventing microbial infection, chemotactic recruitment, cell proliferation, angiogenesis and removal of necrotic tissues. Composite dressings generally consist of three layers where the outer layer is to prevent microbial infection, middle layer maintains moisture content and assist autolytic debridement and the inner layer prevents adhesion to young granulation tissues. Wound dressings and their application in the types of wound are discussed in Table 2.
Table 2. Most common types of wound dressings available in the market and their application

<table>
<thead>
<tr>
<th>Wound Dressings</th>
<th>Types of dressings</th>
<th>Type of wounds</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cloth.</strong> Woven and non-woven fibres made up of cotton, rayon, polyesters</td>
<td>Conventional</td>
<td>Open wounds – scraped knee / an uncomfortable cut / an injury in a sensitive area</td>
<td>Versatile, first layer of protection</td>
</tr>
<tr>
<td><strong>Foam.</strong> Semipermeable polyurethane</td>
<td>Modern</td>
<td>Acute/Chronic wounds – leg ulcers, minor burns/cuts, abrasions, skin graft, pressure ulcers, wound cavities</td>
<td>Maintains healthy moisture balance, prevent foul smelling odours. Allow water vapour to enter and prevent bacteria</td>
</tr>
<tr>
<td><strong>Transparent.</strong> Thin sheets of transparent polyurethane (polymer) coated with an adhesive</td>
<td>Modern</td>
<td>Complicated wounds such as surgical incision sites, IV sites, ulcers, burns</td>
<td>Wound clean, speed up healing, allow monitor for complications, flexible</td>
</tr>
<tr>
<td><strong>Hydrocolloid.</strong> Polysaccharides and other polymers</td>
<td>Modern</td>
<td>Burns, light to moderately draining wounds, necrotic wounds, compression wraps, pressure/venous ulcers</td>
<td>Create moist conditions for speedy heal up. Absorb moist and form gel, flexible</td>
</tr>
<tr>
<td><strong>Hydrogel.</strong> Synthetic polymers</td>
<td>Modern</td>
<td>Second degree burns and infected wounds</td>
<td>Promote cell growth, adds moisture, breaks down dry and dead tissues</td>
</tr>
<tr>
<td><strong>Alginate.</strong> Polysaccharide fibres derived from sodium and calcium salts</td>
<td>Modern</td>
<td>Extreme deep wounds, burns, venous ulcers, packing wounds, higher state pressure ulcers/injuries</td>
<td>Act as extreme absorbent in the wounds that have excessive fluid drainage</td>
</tr>
<tr>
<td><strong>Collagen.</strong> Structural protein from various sources such as bovine, porcine, ovine, etc</td>
<td>Bioactive</td>
<td>Chronic wounds – pressure sores, transplant sites, ulcers, injuries, surgical wounds, burns</td>
<td>Remove dead tissue, stimulate the growth of new cells, encourage formation of new blood vessels, assist to tighten the wound’s edges</td>
</tr>
<tr>
<td><strong>Human skin or dermal skin equivalent cell containing matrix.</strong> Keratinocytes and fibroblasts on collagen matrix</td>
<td>TSSE</td>
<td>Diabetic foot ulcer and venous leg ulcer</td>
<td>Secrete and stimulate wound growth factors and cytokines – Epithelialization</td>
</tr>
<tr>
<td><strong>Acellular matrix.</strong> Dermal elements with fibroblasts on collagen matrix</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antimicrobial agents, growth factors and enzymes</strong></td>
<td>Medicated</td>
<td>Diabetic foot ulcers</td>
<td>Prevents infection and promotes tissue regeneration</td>
</tr>
<tr>
<td><strong>Multiple Layer of dressings – each layer physiologically distinct.</strong></td>
<td>Composite</td>
<td>Partial and full thickness wounds</td>
<td>Outer layer – prevent microbial infection Middle layer (absorptive material) – maintains moist environment Inner layer (non-adherent material) – prevents sticking to granulation tissues</td>
</tr>
</tbody>
</table>
Collagen wound dressings (Figs. 3 and 4) belongs to the bioactive wound dressings which are made up of collagen obtained from various sources such as bovine, porcine, marine, avian, chicken, equine and many more [1,17,18]. They are commonly available in the form of particles, powders, pastes, gels, pads, ropes, sheets or solutions. It is one of the advanced wound dressings that is impermeable to bacteria as well as exhibiting superior healing capabilities compared to conventional dressings. It has the ability to uphold the healing process via maintaining the moist environment around the wound as well as it absorbs the exudate. Collagen dressings are suitable to address moderate to chronic wounds such as minor injuries, burns, sores, foot ulcers, surgical wounds, cuts and traumatic wounds. As discussed, collagen is a triple-helix protein molecule, which comprises about 70 – 80% of the dry weight of the dermis in animal tissues. It helps to drift numerous cells such as keratinocytes and fibroblasts. It was reported that the global collagen dressings market in 2019 was $926 million and it was anticipated to inflate at a CAGR (compound annual growth rate) of approximately 5% in 2020 – 2030. In the Asia Pacific it was expected to increase at a CAGR of 5.8% in 2020 – 2030 [19].
Collagen can interact with a various regenerative process that ranges from angiogenesis to re-epithelialization in wound healing [15]. Currently, it is used in different scaffolds to enhance the wound healing process. Collagen was first utilized as a modern biomaterial in 1881 by Joseph Lister and William MacEwan as “catgut” obtained from a sheep’s small intestine [20]. Since then, collagen biomaterial as dressing has evolved countless times until today, where it flavoured numerous types of wounds with a faster healing rate [21,22]. Its biocompatibility with tissues, biodegradability and non-toxicity nature are among the advantages conferred by the collagen dressing [7].

As mentioned previously, collagen for wound dressing can be obtained through various sources [20], where bovine and porcine are among the most common. There is a high demand for bovine based wound dressing instead of using porcine due to certain religious beliefs. Bovine based collagen biomaterial derived from the cartilage, joints and bones of the cattle, used in the dressings are suitable to treat wounds effectively as it is highly compatible in human skin. Bovine collagen displays low immunogenicity and positive characteristics with limited immune response. Despite its biocompatibility, a small percentage of the population (3%) were reported to be allergic to the bovine based collagen [23].

Currently, there is a lack of study investigate the differences between human and bovine based collagen and how exactly is bovine based collagen compatible with most wound tissues. It is assumed that collagen from different species has similar features. Histological observation of human and bovine cartilage by Rieppo et al., indicated a typical characteristic feature between collagens in both cartilages [24]. Another comparative study by Parenteau-Bareil et al., on bovine, avian and porcine collagens for tissue-engineered dermis application concluded that scaffold-biocompatibility and cell proliferation were similar for all collagen types [25]. However, few significant differences also observed between different species. Nevertheless, for wound healing application, collagen-based biomaterial from bovine and other species has been proven to be effective in multiple studies [21,26,27,28,29].

Collagen wound dressing is suitable for wound healing treatment due to various reasons. Collagen has also been known to promote the migration of epidermal keratinocytes during the healing process. Guo et al., has demonstrated that type I collagen is one of the factors that induce the activation of human keratinocyte cell migration (in-vitro) [30]. Thus, integration of collagen in the dressing promotes re-epithelialization, which is the migration of keratinocytes across the wound, and this leads to faster or more successful wound closure [31]. Additionally, the body will produce multiple responses during the wound healing process, among them by synthesizing the ECM of skin to replace the damaged wound matrix or loss of tissues [1]. The contact of the wounded site with collagen, which is one of the building blocks of the ECM could influence the matrix deposition and boost the formation of new collagen.
Normally MMPs secreted in the wound tissues will breakdown the collagen that prevents the wounds from healing quickly, whereas in collagen wound dressings, the normal breakdown of collagen in the host will be replaced by the new material [32]. Moreover, collagen stimulates fibroblasts and macrophages, which enhances wound healing [18].

5. BOVINE BASED COLLAGEN

Bovine based collagens (type I – V) are obtained from cows and they are mostly isolated from Achilles tendon followed by tissues and skin (type I – tendons, bones, skin and ligaments, type II – cartilage and eyes, type III – lungs, arteries and liver, type IV – kidneys, type V – cell surface, hair and placenta). Bovine collagens are widely used in food, pharmaceutical and cosmeceutical industries for their health benefits [33,34]. It has the ability to alleviate osteoarthritis symptoms, prevent bone loss, and limits the visual signs of aging etc. Recent report on the biomedical market revenue of bovine based collagen was $660.4 million in 2019 and it was expected to make income around $1350 million by 2026. The demand for biomedical applications of bovine based collagen are hovering all over the world such as North America, Latin America, Europe, Asia pacific, Middle East and Africa [35].

The biomedical products of bovine based collagen are in the form of scaffolds, haemostats, skin grafts and wound dressings. Biocompatibility, low risk of infection and low immunogenicity strongly supported the usage of bovine based collagen as wound dressings. Though several advantages and demand for bovine collagen rises certain limitation such as isolation protocols, batch to batch inconsistency, manufacturer’s difference, and pathogen contamination influence the quality and content of the collagen [36]. To overcome the limitations, it was suggested to follow uniform protocols, sterile conditions and utilize same donor population. Combinational therapy with bovine based collagen and other wound healing agents strappingly fast-tracked the wound healing rate. Currently, different range of bovine based collagen products are available in the commercial market, and many clinical trials are in line to determine the efficacy of bovine based collagen wound dressings. Bovine based collagen plays a remarkable role in hospitals to treat various types of wounds such as first-, second- and third-degree burns, diabetic foot ulcers, bed sores, surgical wounds etc [37]. Table 3 summarizes a few lists of bovine based collagen wound dressings available in the global market.

6. CLINICAL UTILIZATION OF BOVINE BASED COLLAGEN IN WOUND CARE

Tsai et al., reported that the effect of combinatorial collagen-based dressings consists of silver-impregnated dressing from Atrauman Ag® (Paul Hartmann AG, Germany) as the inner layer, type-I collagen dressing from Collawound® (Collamatrix, Taiwan) as the middle layer, and sponge dressing from Mepilex® (Moleke, Sweden) as the outer layer in 33 patients (age 20 – 40) in comparison with neomycin containing antibiotic ointment covered with sterile gauzes in Taiwan [38]. The results obtained revealed that the multi-layered collagen-based dressing has highly accelerated the wound healing rate and minimizes the exudates compared to the traditional ointment.

Waghmare et al., reported that the management of paediatric fresh burns of first and second degrees with the collagen sheet obtained from bovine yields good recovery, avoids trauma and pain of the conventional dressings [39]. They tested the collagen sheet on 100 paediatric patients up to 12 years old those suffered from first- and second-degree burn, where almost 92% of the patients showed good healing progress at day 7 – 10. It was also stated that the collagen sheet could easily be applied on an uneven surface such as face, chest, around the neck and at a joint area [39].

In a comparative study between the treatment of collagen sheet and heparin dressing against second-degree burns, it was concluded that the group treated with collagen showed better results than the group treated with heparin in terms of toleration towards the dressing and overall cost-benefit [39]. One more comparative study between collagen dressing and paraffin gauze on 20 adult patients that require 40 cm² of the skin by Sreekumar et al., revealed that the group treated with collagen dressing had less pain and high collagen epithelialization was observed at day 10 compared to paraffin gauze [40]. Additionally, the frequency of re-dressing was also lesser in the collagen dressing group compared to the paraffin gauze group.
### Table 3. Bovine based collagen in the global market

<table>
<thead>
<tr>
<th>Bovine based collagen</th>
<th>Company</th>
<th>Composition</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apligra®</td>
<td>Organogenesis</td>
<td>Neonatal foreskin-derived keratinocytes and fibroblasts with bovine Type I collagen</td>
<td>Non-infected partial and full-thickness skin ulcers, full-thickness neuropathic diabetic foot ulcers</td>
</tr>
<tr>
<td>Catrix®</td>
<td>Lescarden Inc</td>
<td>Fine white powder (bovine cartilage)</td>
<td>Pressure ulcers (stages I-IV), stasis ulcers, first- and second-degree burns, diabetic ulcers, post-surgical incisions, radiation dermatitis, cuts, abrasions and irritations, partial thickness wounds, skin conditions associated with peristomal care</td>
</tr>
<tr>
<td>CellerateRX®</td>
<td>Sanara MedTech</td>
<td>Hydrolysate of Type I bovine collagen</td>
<td>Surgical wounds, traumatic wounds, partial and full-thickness wounds, first- and second-degree burns</td>
</tr>
<tr>
<td>Collatek®</td>
<td>Human BioSciences Inc.</td>
<td>Bovine collagen fibers bioengineered with the proprietary Kollagen™ technology in gel</td>
<td>Abrasions, cuts, superficial injuries, severe sunburns, partial- and full-thickness wounds, venous stasis ulcers, first- and second-degree burns, ulcers caused by mixed etiologies, surgical wounds, donor sites and grafts</td>
</tr>
<tr>
<td>Collawound</td>
<td>Collamatrix Co Ltd</td>
<td>Bovine based collagen with Polyhexamethylene biguanide</td>
<td>Third-degree burns</td>
</tr>
<tr>
<td>Collieva™</td>
<td>CollMed Laboratories</td>
<td>Bovine collagen (Type I)</td>
<td>Pressure ulcers, venous stasis ulcers, diabetic ulcers, first- and second-degree burns, partial and full thickness wounds, superficial injuries</td>
</tr>
<tr>
<td>Collogel</td>
<td>ColoGenesis</td>
<td>Highly purified Type I collagen from bovine source.</td>
<td>Bed sores, dermal lesions, first-degree burns, donor sites, stretch marks and scar management</td>
</tr>
<tr>
<td>Colloskin®</td>
<td>ColoGenesis</td>
<td>Bovine collagen</td>
<td>Burns and wounds with HIV and hepatitis infection</td>
</tr>
<tr>
<td>DermaCol™</td>
<td>DermaRite Industries, LLC</td>
<td>Type I bovine collagen powder/sheet</td>
<td>Chronic wound, diabetic foot ulcer, neuropathic, pressure ulcers, stages 3 and 4, venous insufficiency ulcers</td>
</tr>
<tr>
<td>Fibracol®</td>
<td>Systagenix</td>
<td>90% collagen and 10% alginate</td>
<td>Full-thickness and partial-thickness wounds, diabetic ulcers, pressure ulcers, venous ulcers, second-degree burns, donor sites, trauma wounds</td>
</tr>
<tr>
<td>Gentell Collagen</td>
<td>Gentell</td>
<td>100% bovine derived Type I collagen</td>
<td>Burns, sores, blisters, scrapes and ulcers</td>
</tr>
<tr>
<td>HELIX3® Bioactive Collagen</td>
<td>AMERX Health Care</td>
<td>100% non-hydrolyzed Type I bovine collagen</td>
<td>Acute/ cavity/ deep/ dehisced/ infected/ palliative/ sloughy/ surgical/ superficial/ traumatic diabetic foot/ granulating/ epithelializing wounds, exuding wounds, non/ minimally exuding wounds, burns, pressure/ venous ulcers</td>
</tr>
<tr>
<td>Bovine based collagen</td>
<td>Company</td>
<td>Composition</td>
<td>Application</td>
</tr>
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</tr>
<tr>
<td>Hycol®</td>
<td>Sanara MedTech</td>
<td>Type 1 bovine hydrolyzed collagen</td>
<td>Partial and full-thickness wounds, arterial ulcers, pressure injuries I-IV, diabetic ulcers, venous stasis ulcers, traumatic wounds, skin tears, first and second-degree burns</td>
</tr>
<tr>
<td>Integra® (Integra Dermal Matrices, Integra PriMatrix Scaffolds)</td>
<td>Integra Lifesciences</td>
<td>Bovine tendon collagen and glycosaminoglycan</td>
<td>Diabetic and venous ulcers</td>
</tr>
<tr>
<td>Medifil® II</td>
<td>Human Biosciences, Inc</td>
<td>Type I fibrillar bovine collagen particles</td>
<td>Acute/chronic/deep wounds, burns, diabetic foot, infected wounds, moderate/highly exuding wounds, non/minimally exuding wounds, sloughy/superficial/surgical/traumatic wounds, pressure/venous ulcers</td>
</tr>
<tr>
<td>Promogran ™</td>
<td>Systagenix</td>
<td>55% collagen (bovine), 45% oxidized regenerated cellulose (ORC)</td>
<td>Diabetic ulcers, venous ulcers, pressure ulcers, ulcers caused by mixed vascular aetiologies, traumatic and surgical wounds</td>
</tr>
<tr>
<td>Promogran Prisma®</td>
<td>Systagenix</td>
<td>44% oxidized regenerated cellulose, 55% collagen and 1% silver-ORC</td>
<td>Diabetic ulcers, venous ulcers, pressure ulcers, ulcers caused by mixed vascular aetiologies, traumatic and surgical wounds</td>
</tr>
<tr>
<td>Puracol ® (Puracol® Plus, Puracol® Plus Ag+, Puracol® Ultra ECM, Puracol® Ultra Powder)</td>
<td>Medline Industries</td>
<td>Type I 100% native collagen</td>
<td>Venous ulcers, pressure injuries, diabetic ulcers, and surgical incisions</td>
</tr>
<tr>
<td>Simpurity™ (Powder/ Pad)</td>
<td>Safe n’ Simple</td>
<td>100% non-bleached, native undigested bovine collagen</td>
<td>Partial and full-thickness wounds, tunneled/undermined wounds and surgical wounds, sores, low to moderately exuding chronic wounds such as diabetic foot ulcers and venous leg ulcers</td>
</tr>
<tr>
<td>Skintemp® II</td>
<td>Human Biosciences, Inc</td>
<td>Bovine collagen scaffolds</td>
<td>Arterial/venous/diabetic neuropathic ulcers, pressure injury stage 2/3/4, blisters, donor sites, second-degree burns, superficial abrasions, dehisced surgical wounds, traumatic wounds healing by secondary intention</td>
</tr>
<tr>
<td>Stimulen™</td>
<td>Southwest Technologies, Inc.</td>
<td>Bovine collagen</td>
<td>Acute/ superficial/ trauma wounds, diabetic/pressure/venous ulcers, donor sites, partial-thickness burns</td>
</tr>
<tr>
<td>Triple-Helix Collagen Dressings</td>
<td>Mpm Medical, Inc</td>
<td>Bovine collagen</td>
<td>Burns, scrapes, sores, ulcers, blisters, and other wounds</td>
</tr>
<tr>
<td>Xenoderm</td>
<td>Helix Pharma</td>
<td>100% pure re-constituted collagen of bovine origin</td>
<td>Non-infected superficial burns, traumatic wounds, donor site</td>
</tr>
<tr>
<td>Bio Coll – Skin Dry Skin</td>
<td>Bio-Collagen</td>
<td>Collagen from bovine Achilles tendon</td>
<td>First- and second-degree, non-infected burns, superficial and deep</td>
</tr>
</tbody>
</table>
### Bovine based collagen

<table>
<thead>
<tr>
<th>Company</th>
<th>Composition</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Reconstituted Collagen Sheet)</td>
<td>Technologies</td>
<td>dermal wounds, skin donor site, surgical and traumatic wounds; skin, pressure and diabetic foot ulcer</td>
</tr>
<tr>
<td>Bio Coll – Skin Wet Skin (Meshed)</td>
<td>Bio-Collagen Technologies</td>
<td>Collagen</td>
</tr>
</tbody>
</table>
Another clinical study for partial thickness burns on 60 patients who were admitted at Tirunelveli Medical College Hospital by Kumar et al., found that the collagen dressings adapted well on the patient’s wound surface with moderately acceptable pain score [27]. Moreover, it also reduces the need for analgesics in early healing, excellent tolerance and limits the associated complications such as infections of the burn wounds. Therefore, the researchers recommended it as an effective temporary biological dressing for the management of partial-thickness burns.

Khurram et al., conducted a study on 38 paediatric patients with scald wounds at Jawaharlal Nehru Medical College Hospital. Collagen dressings were applied on the wound together with paraffin gauze dressing impregnated with chlorhexidine followed by dry gauze, cotton and bandage application [26]. The results revealed that the wound was completely healed in 10 – 14 days. None of the patients demonstrated any adverse reaction towards collagen dressing application, and fewer dressings, lesser blood transfusions and shorter duration of hospital stay were recorded.

Collagen membrane dressings manufactured by the Laboratory of Central Leather Research Institute (CLRI), Chennai, India is taken from a bovine source. The manufacturer prepared the collagen membrane through two major approaches i.e.; treatment of serosa layer of bovine intestine through mild enzymes and solubilization of collagen with acetic acid [41,42]. These membranes are suggested to be beneficial for burn patients that could enhance the complete epithelialization process.

7. BOVINE BASED COLLAGEN DRESSINGS FROM BIO-COLLAGEN TECHNOLOGIES SDN. BHD.

For the Malaysian and South-East Asian market, bovine based collagen dressings can be obtained from a local company, Bio-Collagen Technologies Sdn. Bhd. The company manufactures bovine based collagen sheet from the same technology provider i.e.: Laboratory of Central Leather Research Institute, CLRI. Bio-Collagen Technologies has also started distributing this product in the healthcare market since 2011. During the introduction of the product in the market, Bio Collagen Technologies Sdn Bhd had conducted many clinical studies in Malaysia in collaboration with local government and private hospitals. In an observational study performed at the Burn Unit, Hospital Sungai Buloh from September 2012 until January 2013, seven patients were enrolled in this study. Bio Coll-Skin Wet Skin collagen sheet was applied on different types of wounds (one chemical burn wound (Fig. 5), thermal burn wound, and abrasion wound respectively, four donor skin graft sites and two recipient skin graft sites). From this study, a total of nine wounds were analysed, with eight out of nine wounds healed by two weeks. All patients were satisfied with the progress of wound healing [43]. The results obtained from Sungai Buloh Hospital was comparable to the findings discussed previously.

**Fig. 5.** Chemical burn accident patient treated with collagen based wound dressing from Hospital Sungai Buloh
Aside from this study, a non-healing surgery wound or chronic wound (Fig. 6) that does not improve for more than four weeks was investigated. It was conducted to evaluate the closure of the non-healing surgery wound (diabetic) at the neck region upon application of Bio Coll-Skin Wet Skin collagen dressing compared to conventional dressing treatment. Application of collagen-based dressing (Bio Coll-Skin Wet Skin) onto the surgery wound was found to result in the epithelization of new skin in 28 days and closure of non-healing wound. The results demonstrated that the application of Bio Coll-Skin Wet Skin, a bovine based collagen dressing as a primary wound dressing is beneficial in wound management [44]. The duration of wound healing described by Samuel was comparable to the healing duration discussed earlier in this review [44].

Fig. 6. Collagen based wound dressing product application of non-healing surgery

Next, collagen-based wound dressing (Bio Coll-Skin Wet Skin) was used on a 3-year-old child for the treatment of first- and second-degree burns (Fig. 7) at Serdang Hospital, Malaysia, due to boiling water. The patient was discharged on the third day of application, and the wound recovered within 10 days [45]. A similar case at Hospital Salam, Shah Alam, Malaysia, was observed in a 3-year-old child with similar results [46]. The application of the product resulted in the epithelization of new skin and minimal scarring on the patient skin, and the patient required fewer dressings and shorter duration of hospital stay as described in the clinical study by Khurram et al. [27].

Fig. 7. Collagen based wound dressing product application for paediatric patient

8. CONCLUSION

In advance wound care management, the role of collagen is inevitable. Though collagen from bovine sources offer appreciable acceleration in the phases of wound healing process with the constructive faces such as biocompatibility and low immunogenicity other factors such as batch variation, origin, age, isolation procedure, genetic inheritance, and pathogenic hazards limits their wide application. Advanced techniques such as nanotechnology, electrospinning, recombinant technology, anti-biofilm technology play a substantial role in utilizing bovine based collagen in hospitals and surgical institutes.
CONSENT
It is not applicable.

ETHICAL APPROVAL
It is not applicable.

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COMPETING INTERESTS
Authors have declared that no competing interests exist.

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