Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 6[11] October 2017: 01-07

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.876
Universal Impact Factor 0.9804
NAAS Rating 4.95

REVIEW ARTICLE **OPEN ACCESS**

Collagen –A Bounteous Animal Protein For The New Era Of Wound Treatment

K. Rajamanickam[1,*], Jayashree Gogoi[1], V.Leela[1], S.Gowrishankar[2]
[1] – Department of Veterinary Physiology, Madras Veterinary College, Tamilnadu Veterinary and Animal Sciences University, India.
[2] – Department of Veterinary Parasitology, Madras Veterinary College, Tamilnadu Veterinary and Animal Sciences University, India.
* - Corresponding author
Email ID- rajapk92@gmail.com

ABSTRACT
The whole animal kingdom is bestowed with a protein named as collagen. With human ingenuity this abundant protein is made into well organized, three dimensional scaffolds those are nontoxic, biodegradable and biocompatible on exogenous usage. These facets make the collagen as the key material for the new era of wound treatment. This article reviews about the various sources [such as animals and birds], reconstituted forms [such as sponges, films, membranes, injectable and hydrogels]and different uses of the collagen. Moreover, the way of extraction of collagen from animal sources and commercially available collagen based products are delineated.
Key words: Collagen, Biodegradable, Biocompatible, Scaffold, Wound treatment.

Received 01.06.2017 Revised 15.07.2017 Accepted 19.08.2017

INTRODUCTION

Wound healing is a dynamic, complex and well-orchestrated physiological process which involves a series of cellular, molecular and biochemical events that are necessary to restore the structural and functional integrity of damaged tissues following injury. In chronic wounds, the normal sequence of healing events is impaired due to defective remodelling of the extracellular matrix [ECM], failure of re-epithelialisation and prolonged persistence of inflammation. Collagen is the triple helix protein molecule present abundantly in ECM and connective tissues of animals[1]. Since 1881, collagen is used as the biomaterial[2].About 25-30% of total protein content of animal body is made up of collagen[3]. Fibroblast of connective tissue is the major source of collagen formation [4-5]. Collagen is the key for ECM to maintain its biological and structural integrity. The cellular behaviour and functions are taken care by this dynamic and flexible material, which has constant remodelling property [6]. Collagen is inherited with properties like biodegradability, nontoxicity, biocompatibility and weak antigenicity [7], so it is the predominant biomaterial used for soft tissue regeneration.

The Collagen

Collagen molecule comprises of right handed triple helix arrangement of three polypeptide chain [8-9]. This triple helix structure has three chains of which two are identical [α1] and third one differs from others [α 2]. Each chain comprises of 1050 amino acid, approximately of 300nm long. Every third amino acid position is occupied by the glycine [Gly] to make this structure highly stable. Xaa-Yaa-Gly, this repeating unit is most commonly noticed in the triple helix structure. Emil Fischer identified [2S] – proline[Pro][10] 92S, 4R] - 4- hydroxyproline[Hyp][11] occupies the Xaa and Yaaposition, so Pro-Hyp-Gly is the most common triplet seen in the collagen structure [12].

As on date 29 different collagen types are discovered [type 29th is the collagen containing Von willebrand factor type A dominant][13].All of them has thetriple helix structure [14]. Among the 29 types type I-V are the most common, in that type I constitutes about 90% of totalcollagen content of the body [15].Collagen has high tensile strength, protects skin from toxins and pathogens [16] and causes quick healing of the

damaged blood vessels, bones and maintain their structural integrity [17].Each type of collagen have their own location in the body of animals, Table 1. [18].

SOURCES OF COLLAGEN

Collagen can be extracted from tissue of any animals, even the extinct dinosaurs [19-20], but the most common sources are bovine tendons and sins, intestine, skin and bladder mucosa of porcine, sometimes from other animals also [21].Bovine is the major collagen source but this can be complicated by diseases transmission [e.g., BSE, TSE, FMD, etc.] and allergic reactions [7,22]. Porcine collagen is another important source, it shows minimal allergic reactions but the risk of pathogen transmission is noted. This potential risk can be minimized by the use of other important newly identified marine source, whichis the area of interest for many researchers now [23-25].

Marine collagen has ample advantages over collagens obtained from other sources, Table – 2.[18]. Marine sources includes fishes, sponges, jellyfishes, sea urchin, octopus, squids, cuttlefish, sea anemone, prawn and starfishes [26- 29].Scales, fins, skin and bones of salt and fresh water fishes are the main parts considered for collagen extraction, this can reduce the environmental pollution because they are the main waste products coming from the fish industries [30,31]. Type I collagen is obtained from the skin of *Gadusmorhua*, Silver carp [*Hypophthalmich thysmolitrix*], Japanese sea- bass, chub mackerel bullhead shark, sole fish and bones of *Thunnusobesus*, skipjack tuna, Japanese sea-bass, ayu, yellow sea bream, Horse mackerel and fin of Japanese sea-bass and scales of *Pargus major*, *Oreochromisniloticas*, crap. Other mammalian sources includes kangarootail, duck feet, rat tail tendon, equine tendon [32], alligators bone and skin, sheep skin, frogs skin and birds feet. Heterogeneous expression of collagen in mammalian, yeast and insect cells proved as a better alternative source without any risk of pathogen transmission and allergic reactions [33]. Expression of recombinant type – I collagen from *Pichiap astoris* yeast is used for collagen film formation [34].

STEPS FOR GETTING COLLAGEN FROM VARIOUS SOURCES

Basic steps involved in extracting collagen from various sources are delineated below; complete analysis[Amino acid analysis, denaturation temperature analysis, X-ray diffraction analysis and electrophoresis] for physical and chemical properties of obtained collagen has to be done [35].Extraction of collagen includes dialysis with acetic acid or disodium hydrogen phosphate.

Covalent cross links are the sole reason for the proteolytic resistant and high tensile strength of collagen [36]. Such linkages can be disintegrated during extraction procedures or during formation of reconstituted forms of collagen e.g., collagen films, membranes, hydrogels, injectable and sponges. Hence generating new cross links are important to preserve the properties of collagen. Various methods can be employed for the cross-linkage formation, which needs different materials, Table 4.

COLLAGEN BASED BIOMATERIALS

Collagen is widely used for skin tissue engineering as coating materials and it is known to be one of the most promising biomaterial for diverse applications.Two main categories of collagen based biomaterials are available; one is decellularized collagen matrices and another one is refined scaffolds. Decellularized collagen materials retain ECM structure and original tissue properties. They are prepared by physical [snap or high pressure freezing], chemical [acid or alkali treatment] and enzymatic[trypsin digestion] methods [47]. Scaffolds are prepared by extraction, purification and collagen polymerization processes.

RECONSTITUTED FORMS OF COLLAGEN

Collagen Sponges

Cow, horses and pigs are the main sources of the collagen sponges. These collagen sponges has the properties like exudate absorption, smooth adherence to wound surface, maintenance of moist environment and protect wound from mechanical damage and microbial infection [48]. Sponges leads to intense infiltration of neutrophils that can lead to quick healing of burn wounds [49]. Collagen sponges are the vehicle for delivery of drugs, growth factors like fibroblast growth factor [FGF][50], platelet derived growth factors [PDGF][51] to the wound bed to promote quick repair of 'hard-to-heal' wounds. Sponges can also transport antimicrobials like gentamicin, cefataxim, fusidicacid, clindamycin or vancomycin effectively [99.9%] to the wound surface in vitro [52,53]. Sponges can act as the template for the growth of cells, so they are used in cell culture as well[54, 55].

Injectable collagen solutions

Collagen in injectable form are used to treat the dermatological defects. The slow delivery of local anaesthetics and central analgesics can be achieved when they are formulated with the collagen [56]. This property is due to high binding efficiency of the drug to the collagen or high micro viscosity of the

collagen which reduces the rate of diffusion. The collagen solutions containing FGF and transforming growth factor [TGF] are used for the effective treatment of intestinal wounds in porcine model [57].This suggests that collagens can also act as a suitable delivery moiety.

Collagen Hydrogels.

Hydrogel formulations have large uniform surface area those can be used for delivery of growth hormone and insulin in effective manner [58]. Gel loaded with chondrocytes is useful for treatment with cartilage defects [59].

Collagen films and membranes.

Collagen films are about 0.1-0.5 mm thickness, which are made from collagen solutions.They are used as wound-barriers and also help in slow release of drugs [60]. Collagen membranes are used for tissue regeneration and wound dressing;it allows addition of many pharmaceutical products and growth hormone for their sustained release in the wound surface [61].

Table 1: Common types of collagen and their location in body

COLLAGEN TYPE	LOCATION
Type I	Skin, bone, teeth, tendon, ligament, vascular ligature, organs [mainly in organic parts of bone]
Type II	Eye and Cartilage [mainly in cartilages]
Type III	Reticular fibres, skin, muscles, blood vessels [mainly in reticular fibres]
Type IV	Basement membrane and basal lamina
Type V	Hair, cell surface and placenta

Table 2: Advantages of marine source over land animal source.

ADVANTAGES OF MARINE SOURCE
• High collagen content • Eco- friendly • No pathogen transmission [like BSE, TSE, FMD, etc.] • Greater absorption due to lower body temperature than land animals. • Lower molecular weight facilitates greater absorption. • Presence of spare amount of toxins and biological contamination. • Reduced inflammatory response and low immunogenicity. • Metabolically compatible.

Table 3: Steps in extracting collagen.

Source/ Raw material

↓

Maintain raw material at -25°c or -4°c

↓

Remove non- collagenous substance using
Sodium Chloride / sodium hydroxide/ calcium hydroxide

Demineralization using Hcl/ Acetic acid

↓

Acid/ enzymatic digestion

↓

Morphological analysis

Table 4: Different types of cross linking techniques and materials used.

CROSSLINKING METHOD	MATERIALS USED	REFERENCES
Chemical method	Formaldehyde Glutaraldehyde Carbodiimides Polyepoxy compounds Acyl azides Hexamethylenediisocyanate	37 38,39 40,41 42 43 44
Physical method	Ultraviolet light @ 254nm and dehydrothermal treatment	45
Enzymatic method	Transglutaminase	46

Table 5: Currently available animal source collagen products [list is not exhaustive].

PRODUCT NAME	SOURCE
Permacol®	Porcine dermis
Interga®	Bovine tendon / Synthetic polysiloxane
Puracol	Bovine collagen
Oasis®	Porcine small intestine submucosa
Catrix®	Bovine collagen [powder]
Cellerate®	Bovine collagen
Collieva®	Bovine collagen
Medifil®	Bovine collagen
Decutastar®	Equine collagen
Mediskin	Porcine dermis
EZ- Derm®	Aldehyde linked porcine dermis

COLLAGEN IN WOUND DRESSING

Porcine collagen and polyglutamic acid are used as a novel surgical adhesive because of their physical properties [62]. Collagen has inherent biocompatibility and low antigenicity with most of the body tissues, these properties make them more suitable for treating 'hard-to-heal' wounds. Collagen facilitates the wound healing by up regulation of fibroblast production, inhibits or deactivates of Matrix Metalloproteiases[MMP] and by preservation of macrophages, leukocytes, fibroblast and epithelial cells from damage. They also conserve the micro environment of the wound and aid in uptake of fibronectin[63].Reconstituted type I collagen can also be used directly for replacement of damaged skin due to its mechanical strength and biocompatibility [64]. As a mile stone in the collagen therapy, collagen mimetic peptides are identified and made into large polypeptide chains which are used to treat chronic wounds which show lesser allergic reactions [65].

COLLAGEN IN VARIOUS INDUSTRIES.

Collagen paved a new scientific way in many industries like pharmaceutical, biomedical, medical and tissue engineering. Type I collagen is the gold standard for many field to make their products of high aesthetic value. In the veterinary field, collagen therapy for wounds gained more importance during these years because of their biochemical nature. Many number of commercial collagen products are available[63], which are listed below,Table 4. Any product that uses collagen may act as reservoir to increase the contact time with host, reversible binding with drugs such that they are released in delayed mode and reduce the likelihood of systemic toxicity.

CONCLUSION

Collagen, a unique animal protein has manycompatible properties with the body tissue on their exogenous administration, so itthrown the colourful lights in veterinary and medical field to treat the ailing patients. Collagen not only involved in wound healing but also helps in targeted drug and hormone delivery to the wound surface. Development of newer collagen products like sponges, injectable, films, membranes, hydrogels and collagen mimetic peptides had generated newer therapeutic option for the wound care. Exploring more of marine sources for collagen will provide more of economically reliable collagen products. Collagen created tremendous change in the wound therapy during this era.

REFERENCES

1. Ramshaw JA, Peng Y, Glattauer V, Werkmeister JA.[2009] Collagens as biomaterials. *J. Mater.Sci.Mater. Med.,* 20 [1]: S3–S8.
2. Gibson T . Evolution of catgut ligatures: the endeavours and success of Joseph Lister and William Macewen.[1990].*Br J Surg.,* 77[7]:824-825.
3. Muller and Werner EG. [2003].The Origin of Metazoan Complexity: Porifera as Integrated Animals. *Integrated Computational Biology*., 43 [1]: 30-10.
4. Lullo DD, Gloria A, Shawn SM, Jarmo K, Ala-Kokko, Leena, Antonio S, James D.[2002]. Mapping the Ligand-binding Sites and Disease associated Mutations on the Most Abundant Protein in the Human, Type I Collagen. *J. Biol. Chem*., 277 [6]: 4223-4231.
5. Kadler KE, Baldock C, Bella J, Boot-Handford RP.[2007]. Collagens at aglance. *Journal of cell science*.,120: 1955-1958.
6. Aszódi A, Legate KR, Nakchbandi I, Fässler R. [2006]. What mouse mutants teach us about extracellular matrix function.*Annu Rev Cell Dev Biol.,* 22:591-621.
7. Maeda M, Tani S, Sano A, Fujioka K. [1999]. Microstructure and release characteristics of the minipellet, a collagen-based drug delivery system for controlled release of protein drugs.*J Control Release.,*62[3]:313-24.
8. Shoulders MD, Raines RT. [2009]. Collagen structure and stability. *Annu Rev Biochem.*,78:929-58.
9. Okuyama K, Hongo C, Fukushima R, Wu G, Narita H, Noguchi K, Tanaka Y, Nishino N. [2004]. Crystal structures of collagen model peptides with Pro-Hyp-Gly repeating sequence at 1.26 A resolution: implications for proline ring puckering.*Biopolymers.*,76[5]:367-77.
10. Fischer,E. [1901]. On the hydrolysis of casein by hydrochloric acid.*Z. Physiol.Chem*.,33;151-176.
11. Fischer E. [1902].Übereineneue Aminosäureaus Leim. *ChemBer*. 35:2660–2665
12. Ramshaw JA, Shah NK, Brodsky B. [1998]. Gly-X-Y tripeptide frequencies in collagen: a context for host-guest triple-helical peptides.*J Struct Biol.*,122[1-2]:86-91.
13. Söderhäll C, Marenholz I, Kerscher T, Rüschendorf F, Esparza-Gordillo J, Worm M, Gruber C, Mayr G, Albrecht M, Rohde K, Schulz H, Wahn U, Hubner N, Lee YA. [2007]. Variants in a novel epidermal collagen gene [COL29A1] are associated with atopic dermatitis.*PLoS Biol.*, 5[9]:242
14. Miller, EJ. [1984]. Biomedical and industrial application of collagen. [Eds. K. A. Piez and A. H. Reddi]. Extracellular Matrix Biochemistry, Elsevier,New York pp. 41-81.
15. Cheah KSE. [1985]. Collagen genes and inherited connective tissue disease.*Biochem. J.,*229: 287-303.
16. Fratzl P. [2008]. Collagen: Structure and Mechanics,Springer, New York,pp 1-496.
17. Buehler, MJ. [2006]. Nature designs tough collagen: Explaining the nanostructure of collagen fibrils. *PNAS.,*103[33]: 12285-12290.
18. K. S. Silvipriya, K. Krishna Kumar, A. R. Bhat, B. Dinesh Kumar, Anish John, Panayappanlakshmanan. [2015].Collagen: Animal Sources and Biomedical Application.*Journal of Applied Pharmaceutical Science*.,5[03]: 123-127.
19. Asara JM, Schweitzer MH, Freimark LM, Phillips M, Cantley LC.[2007].Protein sequences from mastodon and Tyrannosaurus rexrevealed by mass spectrometry.*Science.*,316[5822]:280-285.
20. Schweitzer MH, Zheng W, Organ CL, Avci R, Suo Z, Freimark LM, Lebleu VS, Duncan MB, Vander Heiden MG, Neveu JM, Lane WS, Cottrell JS, Horner JR, Cantley LC, Kalluri R, Asara JM. [2009].Biomolecular characterization and protein sequences of the Campanianhadrosaur B. canadensis.*Science*.,324[5927]:626-631.
21. Badylak SF.[2004].Xenogeneic extracellular matrix as a scaffold for tissue reconstruction.*TransplImmunol.,*12[3-4]:367-377.
22. Koide T. [2007]. Designed triple-helical peptides as tools for collagen biochemistry and matrix engineering.*Philos Trans R SocLond B Biol Sci*.,362[1484]:1281-1291.
23. Addad S, Jean-Yves E, Faye C, Sylvie Ricard-Blum S, LethiaC. [2011]. Isolation, Characterization and Biological Evaluation of JellyfishCollagen for Use in Biomedical Applications. *Mar Drugs*.,9 [6]:967-983.
24. Krishnan S, Perumal P. [2013]. Preparation and Biomedical Characterization of Jellyfish [*Chrysaora Quinquecirrha*] Collagen fromSoutheast Coast of India. *International Journal Of Pharmacy and Pharmaceutical Sciences.,*5 [3]: 698-701.
25. Exposito JY, Cluzel C, Garrone R, Lethias C, Garrone Q. [1999]. Shortchain collagens in sponges are encoded by a family of closely relatedgenes. *J. Biol. Chem.*, 266: 21923-21928.
26. Subramanian A, Lin HY. [2008]. Crosslinked chitosan: its physical properties and the effects of matrix stiffness on chondrocyte cellmorphology and proliferation. *J. Biomed. Mater. Res.,*75A:742-753.
27. Sugiura, H, Yunoki S, Kondo E, Ikoma T, Tanaka J, Yasuda K. [2009].*In vivo* biological responses and bioresorption of tilapia scale collagen as apotential biomaterial. *J. Biomater. Sci. Polym.* 20, 1353-1368.
28. Song E, Yeon Kim, ChunT, Byun HJN, Lee Y. M. [2006]. Collagen scaffolds derived from a marine source and their biocompatibility.*Biomaterials.,*27: 2951-2595.
29. Strawich E, Nimni ME. [1971]. Properties of a collagen molecule containing three identical components extracted from bovine articularcartilage. *Biochemistry*., 10 [21]:3905-3911.
30. Liang J, Pei XR, Wang N, Zhang ZF, Wang JB, Li Y. [2010]. Marinecollagen peptides prepared from chum salmon [*Oncorhynchus keta*] skin extend the life span and inhibit spontaneous tumor incidence in Sprague-Dawley Rats. *J Med Food*.,13[4]: 757-770.
31. Tzaphlidou M, Berillis P. [2002]. Structural alterations caused bylithium in skin and liver collagen using an image processing method. *Journal of Trace and Microprobe Techniques*.,20 [4]: 493-504.

32. Cortial D, Gouttenoire J, Rousseau CF, Ronzière MC, PiccardiN, Msika P, Herbage D, Mallein-Gerin F, Freyria AM. [2006]. Activation by IL-1of bovine articular chondrocytes in culture within a 3D collagen-basedscaffold. An in vitro model to address the effect of compounds withtherapeutic potential in osteoarthritis. *Osteoarthritis Cartilage.,*14[7]: 631-640.
33. Olsen D, Yang C, Bodo M, Chang R, Leigh S, Baez J, Carmichael D, Perälä M, Hämäläinen ER, Jarvinen M, Polarek J. [2003]. Recombinant collagen and gelatin for drug delivery.*Adv Drug Deliv Rev.,*55[12]:1547-1567
34. Yang C, Hillas PJ, Báez JA, Nokelainen M, Balan J, Tang J, Spiro R, Polarek JW. [2004]. The application of recombinant human collagen in tissue engineering.*BioDrugs*.,18[2]:103-119.
35. Mocan E, Tagadiuc O, Nacu V.[2011]. Aspects of Collagen Isolation Procedure. *Clinical Research Studies.,* 2: 3-5
36. Weadock KS, Miller EJ, Keuffel EL, Dunn MG. [1996]. Effect of physical crosslinking methods on collagen-fiber durability in proteolytic solutions.*J Biomed Mater Res.*,32[2]:221-226.
37. Robert J. Ruderman,Clarence W. R. Wade,William D. Shepard,Fred Leonard. [1973].Prolonged resorption of collagen sponges: Vapor-phase treatment with formaldehyde.*J of biomedical materials res.*,7[2]: 263–265.
38. Harriger MD, Supp AP, Warden GD, Boyce ST. [1997]. Glutaraldehyde crosslinking of collagen substrates inhibits degradation in skin substitutes grafted to athymic mice.*J Biomed Mater Res.*,35[2]:137-145.
39. Wu X, Black L, Santacana-Laffitte G, Patrick CW. [2007]. Preparation and assessment of glutaraldehyde-crosslinked collagen-chitosan hydrogels for adipose tissue engineering. *J Biomed Mater Res Part A.*,81:59–65.
40. Powell HM, Boyce ST. [2006]. EDC cross-linking improves skin substitute strength and stability.Biomaterials.,27[34]: 5821-5827.
41. Powell HM, Boyce ST. [2007]. Wound closure with EDC cross-linked cultured skin substitutes grafted to athymic mice.Biomaterials.,28[6]:1084-1092.
42. Tu R, Lu CL, Thyagarajan K, Wang E, Nguyen H, Shen S, Hata C, Quijano RC.[1993].Kinetic study of collagen fixation with polyepoxy fixatives.J Biomed Mater Res.,27[1]:3-9.
43. Petite H, Rault I, Huc A, Menasche P, Herbage D.[1990]. Use of the acyl azide method for cross-linking collagen-rich tissues such as pericardium.J Biomed Mater Res., 24[2]: 179-187.
44. Zeugolis DI, Paul GR, Attenburrow G. [2009]. Cross-linking of extruded collagen fibers--a biomimetic three-dimensional scaffold for tissue engineering applications.J Biomed Mater Res A.89[4]:895-908
45. Weadock KS, Miller EJ, Bellincampi LD, Zawadsky JP, Dunn MG. [1995]. Physical crosslinking of collagen fibers: comparison of ultraviolet irradiation and dehydrothermal treatment.J Biomed Mater Res.,29[11]:1373-1379.
46. Khew ST, Yang QJ, Tong YW. [2008]. Enzymatically crosslinked collagen-mimetic dendrimers that promote integrin-targeted cell adhesion.Biomaterials.,29[20]:3034-3045.
47. Gilbert TW, Sellaro TL, BadylakSF. [2006].Decellularization of tissues and organs. Biomaterials.,27[19]:3675-3683.
48. Yannas, I.V. [1990]. Biologically Active Analogues of the Extracellular Matrix: Artificial Skin and Nerves." Angew Chem. Int. Ed, England. 29: 20–35.
49. Boyce ST, Christianson DJ, Hansbrough JF. [1988]. Structure of a collagen-GAG dermal skin substitute optimized for cultured human epidermal keratinocytes.J Biomed Mater Res.,22[10]:939-957.
50. Marks MG, Doillon C, Silver FH. [1991]. Effects of fibroblasts and basic fibroblast growth factor on facilitation of dermal wound healing by type I collagen matrices.J Biomed Mater Res.,25[5]:683-696.
51. Lepistö J, Kujari H, Niinikoski J, Laato M. [1994]. Effects of heterodimeric isoform of platelet-derived growth factor PDGF-AB on wound healing in the rat.EurSurg Res.,26[5]:267-272.
52. Wachol-Drewek Z, Pfeiffer M, Scholl E. [1996]. Comparative investigation of drug delivery of collagen implants saturated in antibiotic solutions and a sponge containing gentamicin.Biomaterials.,17[17]:1733-1738.
53. Vaneerdeweg W, Bresseleers T, Du Jardin P, Lauwers P, Pauli S, Thyssens K, Van Marck E, Elseviers M, Eyskens E. [1998]. Comparison between plain and gentamicin containing collagen sponges in infected peritoneal cavity in rats.Eur J Surg.,164[8]:617-621.
54. Fujisato T, Sajiki T, Liu Q, Ikada Y. [1996]. Effect of basic fibroblast growth factor on cartilage regeneration in chondrocyte-seeded collagen sponge scaffold.Biomaterials.,17[2]:155-162.
55. Toolan BC, Frenkel SR, Pachence JM, Yalowitz L, Alexander H. [1996]. Effects of growth-factor-enhanced culture on a chondrocyte-collagen implant for cartilage repair.J Biomed Mater Res.,31[2]:273-280.
56. Horakova Z, Krajicek M, Chvapil M, Boissier JR. [1967]. Prolongation by collagenous substances of several pharmacologic actions.Therapie.,22[6]:1455-1460.
57. Slavin J, Nash JR, Kingsnorth AN.[1992]. Effect of transforming growth factor beta and basic fibroblast growth factor on steroid-impaired healing intestinal wounds.Br J Surg.,79[1]:69-72.
58. Weiner AL, Carpenter-Green SS, Soehngen EC, Lenk RP, Popescu MC. [1985]. Liposome-collagen gel matrix: a novel sustained drug delivery system.J Pharm Sci.,74[9]:922-925.
59. Uchio Y, Ochi M, Matsusaki M, Kurioka H, Katsube K. [2000]. Human chondrocyte proliferation and matrix synthesis cultured in Atelocollagen gel.J Biomed Mater Res., 50[2]:138-143.
60. Rubin AL, Stenzel KH, Miyata T, White MJ, Dunn M. [1973]. Collagen as a vehicle for drug delivery. Preliminary report.J ClinPharmacol.,13[8]:309-312.
61. Maeda M, Kadota K, Kajihara M, Sano A, Fujioka K.[2001]. Sustained release of human growth hormone [hGH] from collagen film and evaluation of effect on wound healing in db/db mice.J Control Release.,77[3]:261-272.
62. Sekine T, Nakamura T, Shimizu Y, Ueda H, Matsumoto K, Takimoto Y, Kiyotani T. [2001]. A new type of surgical adhesive made from porcine collagen and polyglutamic acid.J Biomed Mater Res.,54[2]:305-310.

63. AravindanRangaraj, Keith Harding, David Leaper. [2011].Role of collagen in wound management. WoundsUK., 7[2].
64. Rao KP. [1995]. Recent developments of collagen-based materials for medical applications and drug delivery systems.J BiomaterSciPolym Ed.,7[7]:623-645.
65. SayaniChattopadhyay and Ronald T. [2014].RainesCollagen-Based Biomaterials for Wound Healing. Biopolymers., 101[8]: 821–833.

CITATION OF THIS ARTICLE

K. Rajamanickam, J Gogoi, V.Leela, S.Gowrishankar. Collagen –A Bounteous Animal Protein For The New Era Of Wound Treatment. Bull. Env. Pharmacol. Life Sci., Vol 6[11] October 2017: 01-07