

Collagen: New dimension in cosmetic and healthcare

Abstract

Collagen is one of the natural biomaterials used in cosmetic preparation. It is the most abundant protein in mammals which is obtained from many sources such as bovine, porcine and human. Collagen based cosmetics are in demand now a days though safety issues related with allergies are still main concern of consumers. The collagen is used for different purposes in cosmetic and medical field such as dermal filler, skin substitute and facial products. Use of collagen in medical field is useful depending upon the patient's requirement. It is useful in pathological conditions like in severely burn patients, patients with chronic wounds such as foot ulcers due to diabetes and venous leg ulcers etc however, use of collagen injection as anti aging/anti wrinkle biomaterial need to be further investigated in large population study to check the side effects in long term.

Keywords: Dermal filler, scaffolding, skin care product

1. Introduction

Cosmetic products and preparations were used by people since they get aware of their look regardless of the gender. The US Federal Food, Drug and Cosmetic Act written in 1938, defined cosmetic as “articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part for cleansing, beautifying, promoting attractiveness, or altering the appearance”, without affecting any structure or function of the body(1). Studies on cosmetics have been grown rapidly together with the advancement in science and technology. Advancement in science and technology allows many new discoveries including the uses of biomaterials for cosmetic

24 purposes. The objective of this review is to emphasize on the effect of collagen that is
25 commercially used for cosmetic purposes, clinical benefits of collagen and to compare the
26 advantages and disadvantages of the collagen in a cosmetic products.

27

28 2. Collagen

29 Collagen is a type of protein that has found abundantly in the extracellular matrix and about 80
30 to 90% in dermis is type I collagen(2,3). The structure of each collagen has a characteristics
31 feature in which it is comprised of three α -chains. Each α -chains is composed of thousands
32 of amino acid to form polypeptide chains based on the sequence –Gly-X-Y(4). The glycine
33 (Gly) is located at every third position and it allows tight packaging along the molecules. The
34 X and Y position is usually occupied by proline and hydroxyproline amino acids. There are
35 more than 28 different types of collagen that have been reported (5). Collagen are of different
36 types: such as fibril-forming, network forming, fibril-associated collagens with interrupted
37 triple helices (FACIT), membrane-associated collagens with interrupted triple helices
38 (MACIT) and multiple triple-helix domains and interruptions
39 (MULTIPLEXINs)(6,7,8,9). Collagen has been classified based on the diversity of its
40 structure, function, complexity and the combination of the α -chains as shown in Table 1.

41

42 Table 1: Collagen class, types and distribution (4,5,6).

Class	Type	Distribution
Fibril-forming (Fibrillar)	I	Bone, skin, tendon, ligaments, cornea
	II	Cartilage, vitreous humor in the eyes
	III	Skin, blood vessels
	V	Bone, dermis, co-distribution with type I
	XI	Cartilage, intervertebral discs, co-distribution with type II

	XXIV	Bone, cornea
	XXVII	Cartilage
Fibril-associated collagens with interrupted triple helices (FACIT)	VII	Bladder, dermis
	IX	Cartilage, cornea
	XII	Tendon, dermis
	XIV	Bone, dermis, cartilage
	XVI	Kidney, dermis
	XIX	Basement membrane
	XX	Cornea of chick
	XXI	Kidney, stomach
	XXII	Tissue junctions
	XXVI	Ovary, testis
Network-forming	IV	Basement membrane
	VI	Muscle, dermis, cornea, cartilage
	VIII	Brain, skin, kidney, heart
	X	Cartilage
	XXVIII	Dermis, sciatic nerve
Membrane-associated collagens with interrupted triple helices (MACIT)	XIII	Dermis, eyes, endothelial cells
	XVII	Hemi desmosomes in epithelia
	XXIII	Heart, retina
	XXV	Heart, testis, brain
Multiple triple-helix domains and interruptions (MULTIPLEXINs)	XV	Capillaries, testis, kidney, heart
	XVIII	Liver, basement membrane

43

44 Collagen is chosen to be used in cosmetic industry due to its biodegradability, availability
45 and biocompatibility. The common sources of collagen are bovine, porcine, human collagen
46 and marine organism such as scale fish (10,11) and fish skin (12). The collagen can be used
47 for different purposes such as in dermal filler, skin substitute or scaffolding, wound repair
48 and facial product

3. Applications of collagen in cosmetics

3.1 Dermal filler/ cosmetic filler

Dermal filler is commercially used for several purposes such as for the soft tissue augmentation, cosmetic surgery, face and hand rejuvenation, improve volume deficiencies and improve oncontour of face(13,14,15). The dermal filler will be injected into the deep dermis or the fatty tissues of the particular part of the body (16). Some of the dermal fillers require pre-treatment before the filler is injected. The most common type of collagen being used is bovine, porcine and human. In late 1980s, the first injectable filler approved by US FDA was bovine collagen-based filler(17). It was followed by the approval of other dermal fillers such as human CosmoDerm®, porcine Evolence™, and Bovine Zyderm®(13). In the United States, the use of soft tissue filler has increased by 3% from 2013 and then collagen become one of the source of the fillers as shown in Figure 1 (18).

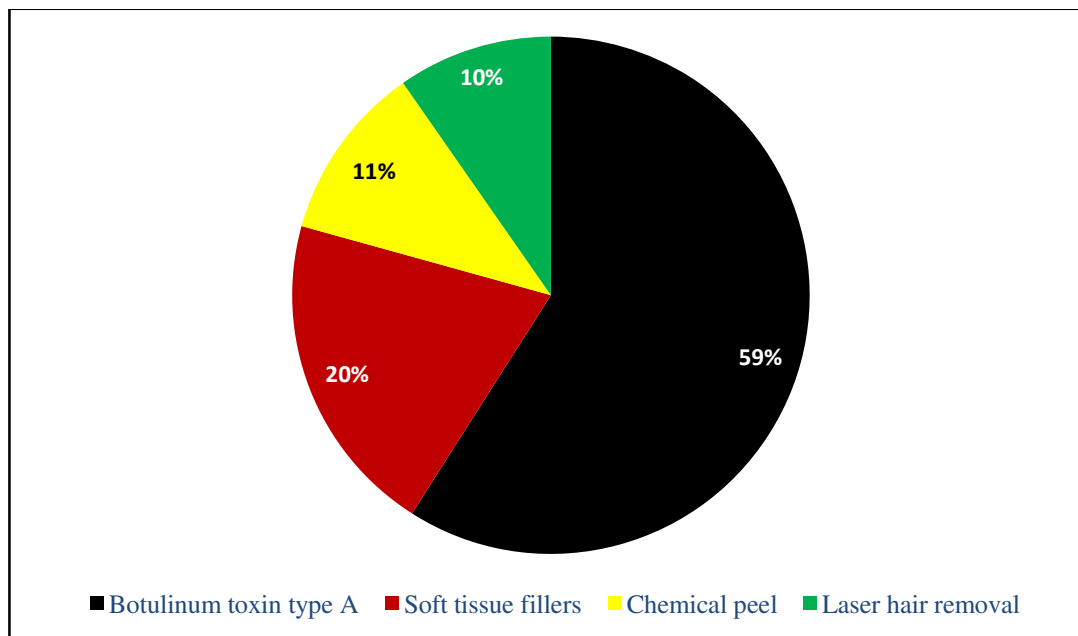


Figure 1: Cosmetics with minimally invasive procedures in 2014 in United States(18).

3.2 Skin substitute/ scaffolding

64 Skin substitute is required especially when the patient is suffered with severe burns (full
65 thickness). This could happen when there is not enough donor skin to cover the wound hence
66 tissue engineering method is considered as one of the option(19).

67 **3.3Skin care product**

68 Skin-aging is one of the natural processes that occur during senescence where the skin will
69 start to loss its elasticity and content of collagen. Wrinkles and flabby skin is one of the
70 results of diminishing collagen contents(20). Anti-aging product has been gained interest
71 among consumersespecially women who are using cream or oral supplement.

72 **4. Advantages and disadvantages of dermal filler**

73 The most common sources of collagen is cow and it can be found in the muscle, skin and
74 tendons. The most common use of bovine collagen-based dermal filler is Zyderm®and
75 Zyplast® (Allergan Inc, Santa Barbara, California, USA).There are some disadvantages of
76 use of bovine collagen. It is unable to correct the hand appearance because of the low
77 longevity, consistency and make the skin to be uneven(21). Some adverse reactions were
78 reported due to the uses of the bovine collagen. Cases of local cutaneous necrosis were
79 reported when Zyplast® was injected to the glabellar region which is the area between the
80 eyebrows (22). In addition, Cukier et al., found that there were nine patients whom developed
81 this disease (23). According to Kleindelayed-type hypersensitivity responses were reported
82 during use of serum antibodies with collagen. The diseases are types of inflammation
83 responses that are triggered by the usage of collagen. Skin test is recommended for the users
84 if they want to use the bovine collagen and some authors recommend two skin tests in
85 interval of two to four weeks due to inflammatory response and allergic reaction caused by
86 collagen(24).

87 There was a research conducted by Park et al. in 2012, related to iatrogenic retinal
88 artery occlusion that caused by cosmetic facial filler injections(25). This study on case of
89 central retinal artery occlusion caused by collagen injection at the glabellar region. In
90 addition, Kwon et al. also reported case of branch retinal artery occlusion after injection of
91 collagenous filler into the left anterior nasal septum(26). Lazzeri et al; 2012 discussed the
92 cases in which scientist reported cases of blindness as a consequences of using a bovine
93 cosmetic injections on face (27).

94 There is also dermal filler that made out of natural porcine collagen. This type of filler
95 can be used for the cosmetic correction of facial wrinkles and acne scars. Porcine collagen
96 can stimulate the formation of new collagen in response to the microtrauma that was induced
97 by the injection of the filler(28). The usage of this type of dermal filler showed no serious
98 side effect and also minimal discomfort(27). Therefore porcine collagen can be considered to
99 be highly safe as dermal filler.

100 Some may produce side effects and some will show good result for cosmetic purposes
101 which depends upon the contents in the dermal filler.

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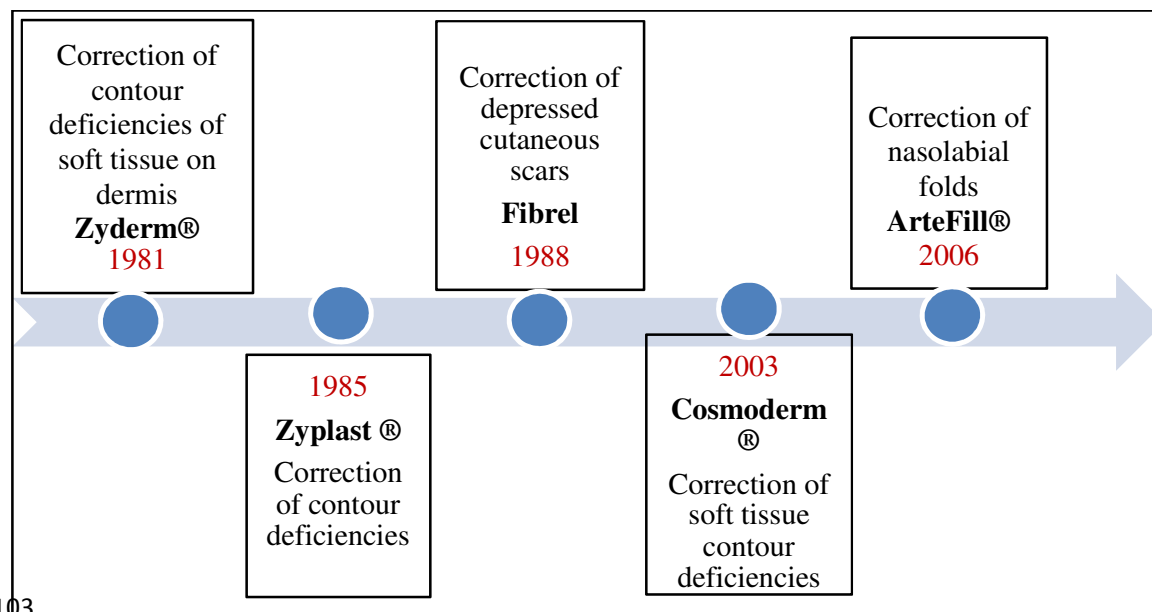


Figure 2: Time line for some of the collagen products approved by Food and Drug Administration (FDA)(13,29)

5. Advantages and disadvantages of scaffolding

There is a research that combines collagen-based dermal substitute and a fibrin-based cultured epithelium to replace the damaged skin of acute wounds. The dermal substitute is an artificial skin that consist of silicone sheet at the upper layer, and lower porous cross-linked bovine collagen with chondroitin-6-sulfate (glycosaminoglycan)(3,30). This research study showed that the development of normal skin on the artificial dermis was able to be done by 83% of the human epithelium that grown on the fibrin(31). In addition, there were cases reported about positive long term outcome after using skin substitute with better formation of the skin structure and low chance of forming hypertrophic scars(3) . High cost and intensive care are the two main concerns with this application. This type of skin engineering also has successfully been used to treat patients with chronic wounds such as foot ulcers due to diabetes and venous leg ulcers(32). The time needed for the wound closure is lowered with

118 high percentage of the successful wound healed. Somehow, bovine collagen cannot be used
119 to patient with allergic reactions.

120 There is also new type of skin substitute developed in which derived from glycerol
121 preserved for human allogeneic skin(33,34). It also consists of collagen and elastin fibres.
122 This type of dermal substitution is used on partial thickness of burns as temporary biologic
123 dressing and also for wound bed preparation of excised burns. Patients that are treated with
124 this type of skin substitute showed improvement in elasticity of the skin when it is used
125 together with skin graft treatment (35).

126 When collagen-based scaffold is used, there is a limitation in elasticity and the
127 scaffold will contract during the repair process. This challenge is improvised by the presence
128 of elastin in the collagen based scaffold to decrease its stiffness and control the contraction of
129 the collagen(36). Collagen-elastin composite type of scaffold will promote elastin deposition
130 and also showed good result of cosmetic and functionality on the patients of burns in total
131 body surface area (TBSA) of less than 20% (9, 37) . It also increases the elasticity of the skin
132 and minimize the contraction of the wound(38).

133 Another finding for skin substitute is the use of collagen hydrogel. Collagen hydrogel
134 is combined with keratinocytes sheet to treat chronic or acute type of wounds (39). Major
135 advantage of this is the ability to deliver cytokine by dermal fibroblast that will be used to
136 promote wound healing at the site of injury(40). The drawback of this type of materials is its
137 extensive contraction of the cells that reduce the surface area after the culture and poor
138 stability of the skin(41). It also has poor neovascularisation that cannot integrate to the host
139 organism(42) . New blood vessels are important as they will carry oxygen and feeds the
140 resident cells (13). Then, it also has poor mechanical properties and hard to handle. If it is
141 used as scaffold, it is not resistant enough to promote cell remodelling and creation of

neodermis; therefore this type of skin substitute is not accepted as permanent grafting (14). Collagen hydrogel is improvised with method known as plastic compression(43). Concentrated collagen hydrogel can stimulate cell growth and the contraction of the materials is inhibited due to the higher concentration of collagen that helps to improve its stiffness. It also provides easier handling properties (14). Neovascularisation also observed and it was completely colonized by the host cells. This makes the concentrated collagen hydrogel as more suitable candidate as a dermal substitute than the normal collagen hydrogel.

6. Advantages and disadvantages of Skin care product

One of the oral supplement of collagen hydrolysate (CH) where specific collagen peptide is its composite material(44). A research study showed that the supplementation of CH to fibroblast cultures will increase type I collagen and proteoglycans with statistically significant increase of skin elasticity. The skin elasticity could be improved due to the increase biosynthesis of dermal matrix macromolecules (1). Study also reported there is no change in skin hydration, skin roughness and skin evaporation between CH treatment group and placebo treatment group. From the same study, the supplement is considered as long-lasting effect to dermal as the effect still can be seen at the end of 4-week washout phase. The skin elasticity increase up to 30% will reduce wrinkles for about 17.7%(44,45).

However, the effect of product that applied topically on the skin is different. The effects of topically used skin care products for anti-wrinkle was investigated by Xhaufaire-Uhoda et al.(46) and they found that once the treatment of the topical product is stopped, there were no evidence of skin miniaturization however low increase in skin hydration was observed. The tested product did not break the skin barriers. The topical type of product should be more effective as it encountered superficial dermis and epidermis part of the skin where it can be helped to improve skin elasticity by increase epidermal hydration(47). Ineffectiveness

oftopical skin care products could be occur due to the inability of it to penetrate the structure of skin known as stratum corneum barrier in order to reach the fibroblast cell of dermal layer(48). The stratum corneum is known as part of the skin that function to minimize the passive loss of water and prevent microbial invasion to the body(49,50). These researchers also found that any raw collagen materials used topically will show no desirable effects to the consumers. A research by Huey-Jine Chai et al. 2010, investigating the effects on facial skin qualities with penetration through transdermal when fish-scale collagen peptide is used (5). The result showed that the collagen peptide is still able to penetrate the stratum corneum to epidermis and dermis of amice model. The fish scale could be considered as a choice for source of collagen as scales composition is rich in collagen, cost effective and sustainable(10). Overall, collagen is known as an important content of skin but the route and the way the collagen-based product applied to the skin is important.

7. Conclusion

Collagen based biomaterials are used in cosmetic and tissue engineering purposes due to its biocompatible and biodegradable characteristics. In cosmetics, collagen can be used for different purposes such as for dermal fillers, skin substitute and as facial products. The use of these biomaterials is good when they are used as a dermal filler that can stimulate the formation of new collagen to reduce wrinkles. Skin substitute can be helpful in the development of normal skin with good formation and to promote wound healing. However, there are some side effects for the uses of collagen in cosmetics. It can cause inflammatory and allergic reactions and it may also cause iatrogenic retinal artery occlusion. For certain application, intensive care is needed and the cost is very high. Some collagen products that used as a skin substitute have a poor formation of new blood vessels and hard to handle. In conclusion, the usage of collagen may give good and bad effects to the users depending upon the purpose of the uses of collagen, sources of the collagen, location and application of the

collagen etc. The consumers should be aware about the compatibility of the product before use to reduce the risk of any side effects. There are some limitations to use collagen for cosmetic purposes. Some futuristic development of use of collagen includes genetic modification of the transplanted cell and improvement of the anatomy and physiology of the skin substitute. This is one of the measure to improve the process of wound healing and performance of the skin substitute used to improve the formation of neovascularisation. Since, tissue engineered implantation technique does not have inbuilt capillary network so further research are needed in this aspects.

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