

Review paper

Collagen in cosmetics: Friend or Foe?

Abstract

Collagen is one of the natural biomaterial sources that can be used in cosmetic preparation. It is the most abundant protein in mammals which is obtained from many sources such as bovine, porcine and human. There are increasing numbers of people seeking for solutions to improve their appearance. Consumers use different types of collagen cosmetic preparation to look young and beautiful. The collagen can be used for different purposes such as dermal filler, skin substitute and facial products. The objective of this article is to compare the advantages and disadvantages of the collagen when use in cosmetic preparation.

1. Introduction

Cosmetic products and preparations were used by people since they get aware about their look regardless of the gender. 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). Development and researches related to the cosmetic field have grows rapidly together with the advancement in science and technology. This development allows many new discoveries including the uses of biomaterials for cosmetic purposes. This includes the development of the uses of collagen as the biomaterials. Collagen is a type of protein found abundantly in the extracellular matrix, where about 80%-90% in dermis is type I collagen(2,3). The structure of each collagen has a characteristics feature in which it is comprised of three α -chains. Each α -chains is composed of thousands amino acid

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Abstract has to have
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24 and ^{to form} forming polypeptide chains based on sequence -Gly-X-Y-(4). The glycine (Gly) is
 25 positioned at every third position and ^{it} this allows tight packaging along the molecules. The X
 26 and Y position is usually occupied by proline and hydroxyproline(5). There are more than 28
 27 different types of collagen that have been reported. The collagen can be divided into few
 28 different ^{types} class such as fibril-forming collagen, network forming, fibril-associated collagens
 29 ~~with~~ interrupted triple helices (FACIT), membrane-associated collagens with interrupted
 30 triple helices (MACIT) and multiple triple-helix domains and interruptions
 31 (MULTIPLEXINs) (table1)(6-9). ^{Collagen has been} The reported collagen is characterized based on the
 32 diversity of its structure, functions, complexity and the combination of the α -chains. Collagen
 33 is chosen to be used in cosmetic industry due to its biodegradability, availability and
 34 biocompatibility. The common sources of collagen are bovine, porcine, human collagen and
 35 marine organism such as scale of fish(10-12). The collagen can be used for different
 36 purposes such as in dermal filler, skin substitute or scaffolding, wound repair and facial
 37 product. ^{As far as concerning} What is the effect of using collagen in cosmetic? Is it good or give bad effects to the
 38 ^{objective} users? The aim of this review is to emphasize on the effect of collagen that commercially
 39 ^{and And out} used for cosmetic purposes whether it gives good effect or bad adverse reaction. The different
 40 types, uses of collagen, clinical benefits and pathological implication of it are thoroughly
 41 reviewed herein. ^{Further, this review discuss about the}
 42 ^{different types of collagen, and their uses, etc.}

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

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

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2. Collagen in cosmetic

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2.1. Collagen in dermal filler/ cosmetic filler

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Dermal filler is commercially used for several purposes such as for soft tissue augmentation,

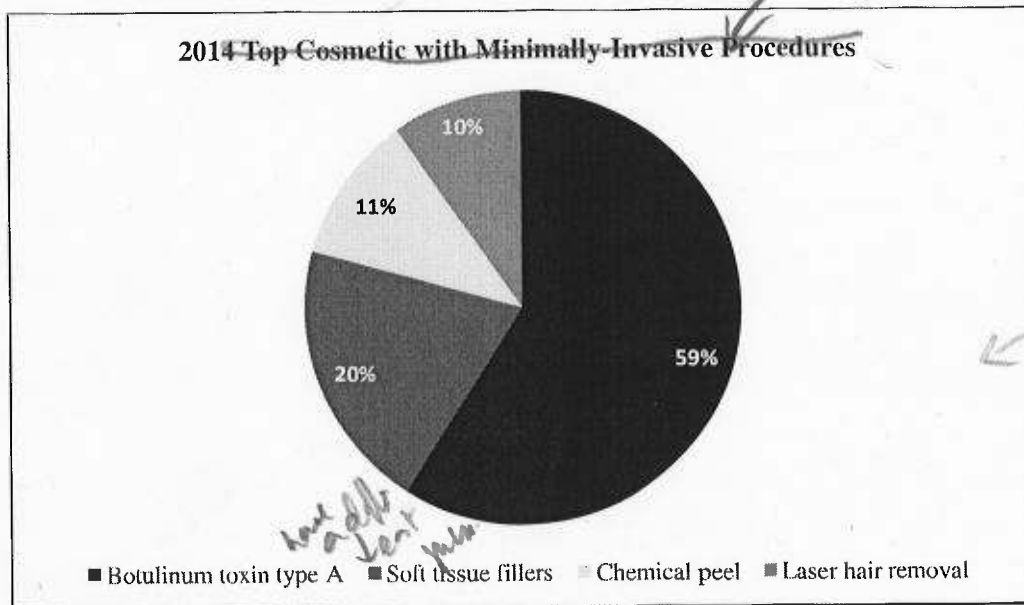
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cosmetic surgery, face and hand rejuvenation, improving the volume deficiencies and contour

49

of face(13–15). The dermal filler will be injected into the deep dermis or the fatty

50 tissue(16) of the particular part of body. Some of the dermal filler requires pre-treatment
 51 before the filler is injected. The most common type of collagen being used is bovine, porcine
 52 and human. In late 1980s, the first injectable filler approved by US FDA was bovine
 53 collagen-based filler(17) . It was followed by the approval of other dermal filler(such as
 54 human CosmoDerm®, porcine Evolence™, and Bovine Zyderm®(13). In United States, by
 55 2014 the use of soft tissue filler has increased by 3% from 2013 and collagen is one of the
 56 sources of the fillers (figure1)(18).



57

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

59 2.1.1 Advantages and disadvantages of collagen dermal filler

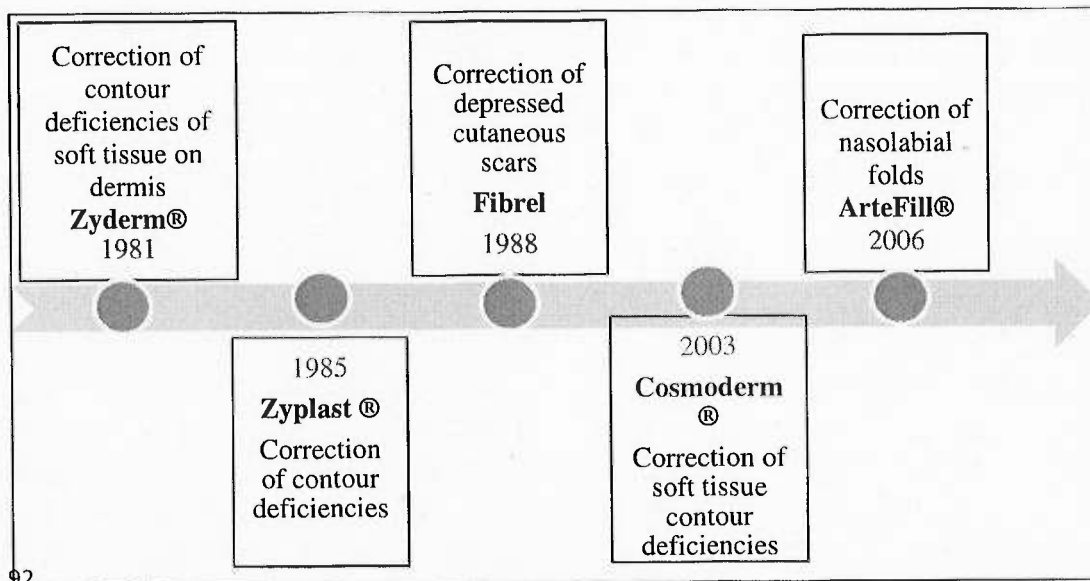
60 Bovine collagen is temporary and biodegradable filler. The sources of this collagen are cows
 61 where it can be found in the muscle, skin and tendons. The most commonly used bovine
 62 collagen-based dermal filler are Zyderm® and Zyplast® (Allergan Inc, Santa Barbara,
 63 California, USA). There are some drawbacks for the uses of bovine collagen. It is unable to
 64 correct the hand appearance because of the low longevity, consistency and causes the skin to

65 be uneven(19). Some adverse reactions were reported due to the uses of the bovine collagen.
 66 Cases of local cutaneous necrosis were reported when Zyplast® was injected to the glabellar
 67 region which is the area between the eyebrows (20). Besides, Cukier et al. from a study of
 68 incidence of dermatomyositis or polymyositis formation after injection of bovine collagen in
 69 8-year period, found that there were nine patients whom developed this disease (21). There
 70 were increases in serum antibodies to the collagen and some had delayed-type
 71 hypersensitivity response(22). The diseases are types of inflammation responses that are
 72 triggered by the usage collagen. Skin test is recommended for the users if they want to use the
 73 bovine collagen and some authors recommend two skin test in interval of two to four weeks
 74 due to inflammatory response and allergic reaction caused by this collagen(22).

75 There was a research conducted by Park et al. regarding iatrogenic retinal artery
 76 occlusion that caused by cosmetic facial filler injections(23). From this study, one case of
 77 central retinal artery occlusion was reported caused by collagen injection at the glabellar
 78 region. Then, Kwon et al. also reported case of branch retinal artery occlusion after injection
 79 of collagenous filler into the left anterior nasal septum(24). Lazzeri et al. in a study regarding
 80 blindness following cosmetic injection of the face included the cases due to the consequences
 81 of using the cosmetic injections and the used of bovine collagen was mentioned in it(25).

82 There is also dermal filler that used naturally sourced porcine collagen. This type of
 83 filler can be used for the cosmetic correction of facial wrinkles and acne scars. This porcine
 84 collagen can stimulate the formation of new collagen in response to the microtrauma that was
 85 induced by the injection of the filler(26). The usage of this type of dermal filler showed no
 86 serious side effect and minimal discomfort(25). It can be considered to be highly safe as
 87 dermal filler.

88 The differences in the contents of the dermal filler used may result in different effect
 89 and for different function. Some may produce side effects and some will show good result for
 90 cosmetic purposes, *depend on the content in the dermal filler.*
 91



92
 93 Figure 2: ~~Some of the collagen product~~ *Time line for the* approved by Food and Drug Administration
 94 (FDA)(13,27) *Fillers?*

96 2.2 Collagen as skin substitute/ scaffolding

97 Skin substitute is required especially when the patient is suffered with full-thickness burns.
 98 This could happen when there is no enough donor skin to cover the wound hence tissue
 99 engineering method is considered as an option(28). Pain, limitation in movement, undesired
 100 cosmetically after the injury and the normal dermis strength of scar tissue contribute to the
 101 discoveries and development of the skin engineering (29,30). *check* *no need*

102

103 2.2.1 Advantages and disadvantages of collagen skin substitute/scaffolding

104 There is a research that combines collagen-based dermal substitute and a fibrin-based
 105 cultured epithelium to replace the damaged skin of acute wounds. The dermal substitute is an
 106 artificial skin that consist of silicone sheet at the upper layer, and lower porous cross-linked
 107 bovine collagen with chondroitin-6-sulfate (glycosaminoglycan)(3,31). From this research, it
 108 showed the development of normal skin on the artificial dermis was able to be done by 83%
 109 of the human epithelium that grown on the fibrin(32). Besides, there are cases reported of
 110 positive long term outcome after using this skin substitute with good formation of the skin
 111 structure and low chance of forming hypertrophic scars(3). The problem with this application
 112 is the high cost and very intensive care is required. This type of skin engineering also has
 113 successfully be used to treat patients with chronic wounds such as foot ulcers due to diabetes
 114 and venous leg ulcers(33). The time needed for the wound closure is lowered with high
 115 percentage of the successful wound healed. Somehow, it cannot be used with patient that
 116 allergic to the bovine collagen and infected wounds.

117 Besides, there is also new type of skin substitute developed in which it is derived from
 118 glycerol preserved human allogeneic skin(34-36). It also consists of collagen and elastin
 119 fibres. This type of dermal substitution is used on partial thickness of burns as temporary
 120 biologic dressing and also for wound bed preparation of excised burns. Patients that are
 121 treated with this type of skin substitute showed improvement in elasticity of the skin when it
 122 is used together with skin graft treatment.

123 When collagen-based scaffold is used, there will be limitation in elasticity and the
 124 scaffold will contract during the repair process. This weakness is improvised by the presence
 125 of elastin in the collagen based scaffold to decrease its stiffness and control the contraction of
 126 the collagen(37). This collagen-elastin composite type of scaffold will promote elastin

127 deposition(38)and it shows good result of cosmetically and functionally on the patients of
 128 burns with total body surface area (TBSA) of less than 20% (9) . It also increased the
 129 elasticity of the skin and minimize the contraction of the wound(39). Somehow, the cost is
 130 quite high with limited quantity.

131 Another findings as skin substitute is the use of collagen hydrogel. This collagen
 132 hydrogel is combined with keratinocytes sheet to treat chronic or acute type of wound(40).
 133 Major advantage of it is the ability to deliver cytokine by dermal fibroblast that will be used
 134 to promote wound healing at the site of injury(41). The drawbacks of this type of materials is
 135 its extensive contraction with the cells and this reduced the surface area after the culture and
 136 poor stability(42). It also has poor neovascularisation so it cannot integrate to the host
 137 organism(43) . New blood vessels are important as it will carry oxygen and feeds the resident
 138 cells (13). Then, it also has poor mechanical properties and hard to handle. If it is used as
 139 scaffold, it is not resistant enough to promote cell remodelling and creation of neodermis, so
 140 this type of skin substitute is not accepted as permanent grafting (14). This collagen hydrogel
 141 is improvised based on a research by concentrating the amount of collagen in it with one of
 142 the methods known as plastic compression(44). This concentrated collagen hydrogel can
 143 stimulate cell growth and the contraction of the materials is inhibited due to the higher
 144 concentration of collagen that helps to improve its stiffness. It also provides easier handling
 145 properties (14). Neovascularisation also observed and it was completely colonized by the host
 146 cells. This make the concentrated collagen hydrogel as a more suitable candidate as dermal
 147 substitute than the normal collagen hydrogel.

148 2.3 Collagen in skin care product

149 Skin-aging is one of the natural processes that occur as the age of the person increases. For
 150 this stage, the skin will start to loss its elasticity and content of collagen. Wrinkles and flabby

151 skin is result of diminishing collagen contents(45). Anti-aging product has gaining interest
152 among consumer especially women either in form of cream or oral supplement.

153 2.3.1 Advantages and disadvantages of collagen skin care product

154 One of the oral supplement is collagen hydrolysate (CH) where specific collagen peptide is
155 its composite material(46). The supplementation of this CH to fibroblast cultures from the
156 research carried out showed that there is increased of type I collagen and proteoglycans with
157 statistically significant increase of skin elasticity. The skin elasticity is improved and this
158 ~~could be~~ due to the increase in the biosynthesis of dermal matrix macromolecules (1).
159 Somehow, the study also reported there is no changed in skin hydration, skin roughness and
160 skin evaporation between CH treatment group and placebo treatment group. From the same
161 study, the supplement is considered as long-lasting effect to dermal as the effect still can be
162 seen at the end of 4-week washout phase(46,47). Basically, the skin elasticity increase up to
163 30% with reduction of wrinkles for about 17.7%(46,47).

164 Somehow, the effect is different from the product that applied topically on the skin. The
165 effects of topically used skin care products as anti-wrinkle is investigated by Xhaufaire-
166 Uhoda et al.(48). The study found that once the treatment of the topical product is stopped,
167 there is no evidence of skin moisturizing observed and low increase in skin hydration. The
168 tested product did not break the skin barrier. The topical type of product should be more
169 effective as it encountered superficial dermis and epidermis part of the skin where it can help
170 to improve skin elasticity by increase epidermal hydration(49). Ineffective topical skin care
171 products could be due to inability of it to penetrate and overcome the structure of skin known
172 as stratum corneum barrier in order to reach the fibroblast cell of dermal layer(50). The
173 stratum corneum is known as part of the skin that function to minimize the passive loss of
174 water and prevent microbial invasion to the body(51,52). From this finding, it can be said

175 that any raw collagen materials that used topically will show no desirable effects to the
 176 consumers. A research by Huey-Jine Chai et al. investigating the effects on facial skin
 177 qualities with penetration through transdermal when fish-scale collagen peptide is used (5).
 178 The result showed that the collagen peptide is still able to penetrate the stratum corneum to
 179 epidermis and dermis of mice model. The fish scale can be considered as ideal choice for
 180 source of collagen as it is cheap, sustainable and rich(10). Overall, collagen is effectively
 181 known to over aging skin but the route and the way the collagen-based product applied to the
 182 skin is also important so that the effect of it can be obtained.

183 There are some limitations in the uses of collagen for the cosmetic purposes. Some futuristic
 184 development that can be done includes genetic modification of the transplanted cell and
 185 improving the anatomy and physiology of the skin substitute. This is a measure to improve
 186 the process of wound healing and performance of the skin substitute used such as improving
 187 the formation of neovascularisation. The tissue engineered implantation that available now
 188 does not have inbuilt capillary network so research regarding this aspects is one of the
 189 important field. Besides, in regenerative medicine, it can be seen clearly that the uses of
 190 medical devices and tissue graft has shifted to a new approach which is by utilising the
 191 synthetic biomaterials. Somehow, the limitation in the ability of the biomaterials to
 192 regenerate tissue for critical size of injury or defects is still a challenge in this field. Further
 193 research should focus on this matter including few aspects such as the host response toward
 194 the biomaterials implanted so that it gives a clear view that important for the development of
 195 biomaterials in the next generation.

3. Conclusion

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 197 Collagen based biomaterials are of utmost importance for cosmetic purposes and tissue
 198 engineering. This is due to its biocompatibility and biodegradability. In cosmetics the

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199 collagen can be used for different purposes such as for dermal fillers, skin substitute and
200 scaffolding and as facial products. The use of these biomaterials is good as when it is used as
201 dermal filler it can stimulate formation of new collagen so it can be used to reduce wrinkles.
202 As skin substitute it can help in development of normal skin in a good formation. It also can
203 promote wound healing. For facial products it can increase the skin elasticity if it is used
204 orally. Somehow, there are bad effects for the uses of collagen in cosmetics. It can cause
205 inflammatory and allergic reactions and also may cause iatrogenic retinal artery occlusion.
206 For certain application, intensive care is needed and the cost is quite high. Some collagen
207 products that used as skin substitute have poor formation of new blood vessels and hard to
208 handle. In conclusion, the usage of collagen can give good and bad effects to the users. It
209 depends on the purposes of the uses of it, sources of the collagen, location and application of
210 the collagen and some other factors. The consumers should aware about the compatibility of
211 the product before using it to reduce the risk of developing any side effects.

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