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Collagen: New Dimension in Cosmetic and Healthcare

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Authors' contributions

This work was carried out in collaboration between authors NABAS and ARC. Author NABAS wrote the first draft of the manuscript and managed the literature searches whereas author ARC designed, supervised and edited the manuscript. Both authors read and approved the final manuscript.

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Review Article

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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.

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1. INTRODUCTION

Cosmetic products and preparations were used by people since they get aware about their looks (regardless of the gender). The US Federal Food, Drug and Cosmetic Act written in 1938, defined cosmetic as an "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 purposes.

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

2. COLLAGEN

Collagen is a type of protein that has found abundantly in the extracellular matrix and about 80 to 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 of amino acid to form polypeptide chains based on the sequence –Gly-X-Y [4]. The glycine (Gly) is located at every third position and it allows tight packaging along the molecules. The X and Y position is usually occupied by proline and hydroxyproline amino acids. There are more than 28 different types of collagen that have been reported [5]. Collagen are of different types: such as fibril-forming, network forming, fibril-associated collagens with interrupted triple helices (FACIT), membrane-associated collagens with interrupted triple helices (MACIT) and multiple triple-helix domains and interruptions (MULTIPLEXINs) [6,7,8,9]. Collagen has been classified based on the diversity of its structure, function, complexity and the combination of the α-chains as shown in Table 1.

Collagen is chosen to be used in cosmetic industry due to its biodegradability, availability and biocompatibility. The common sources of collagen are bovine, porcine, human collagen and marine organism such as scale fish [10,11] and fish skin [12]. The collagen can be used for different purposes such as in dermal filler, skin substitute or scaffolding, wound repair 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, to improve volume deficiencies and to improve on contour 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 Fig. 1 [18].

3.2 Skin Substitute/ Scaffolding

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

3.3 Skin Care Product

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

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, inverterbral 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

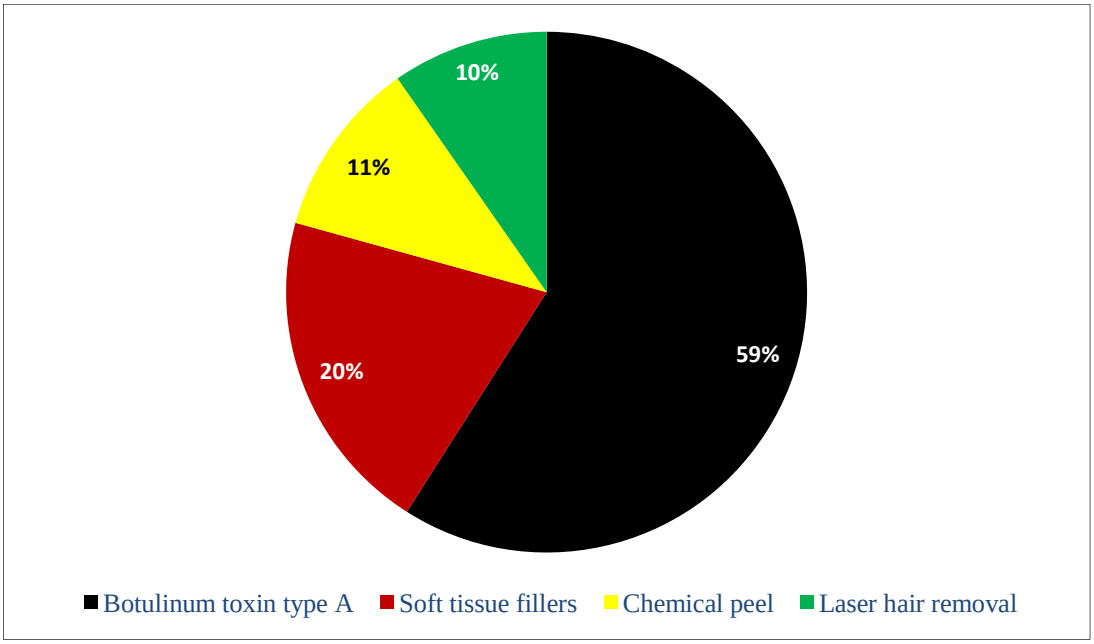

Fig. 1. Cosmetics with minimally invasive procedures in 2014 in United States [18]

4. ADVANTAGES AND DISADVANTAGES

4.1 Dermal Filler

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

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

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

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

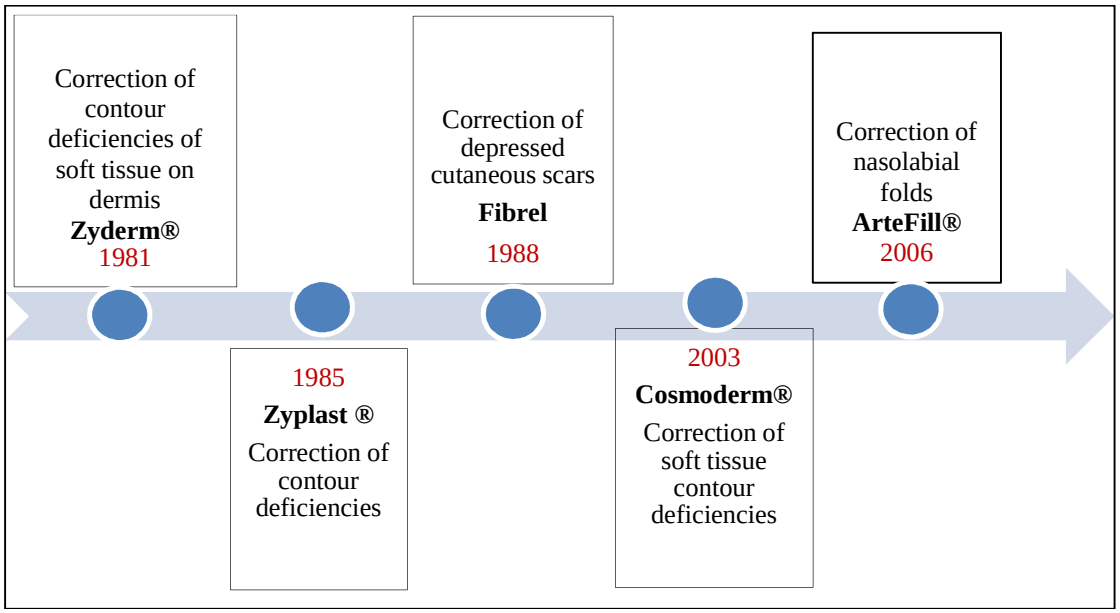

Fig. 2. Time line for some of the collagen products approved by food and drug administration (FDA) [13,29]

4.2 Scaffolding

Study was conducted in which researcher's combine 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]. Researchers were able to develop normal skin on the artificial dermis by 83% of the human epithelium that grown on the fibrin [31]. In addition, there were cases reported on 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 minimised with high percentage of the successful wound healing. Somehow, bovine collagen cannot be used to patient with the allergic reactions.

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

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

Another finding for skin substitute is the use of collagen hydrogel. Collagen hydrogel is combined with keratinocytes sheet to treat chronic or acute type of wounds [39]. Major advantage of this is the ability to deliver cytokine by dermal fibroblast that will be used to promote wound healing at the site of injury [40]. The drawback of this type of materials is its extensive contraction of the cells that reduce the surface area after the culture and poor stability of the skin [41]. It also has poor neovascularisation that cannot integrate to the host organism [42]. New blood vessels are important as they will carry oxygen and feeds the resident cells [13]. Then, it also has poor mechanical properties and hard to handle. If it is 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 the 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 the collagen that helps to improve its stiffness. It also provides easier handling properties [14]. Neovascularisation was also observed with complete colonization by the host cells. This makes the concentrated collagen hydrogel more suitable as a dermal substitute than the normal collagen hydrogel.

5. 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 that there is no change in skin hydration, skin roughness and skin evaporation between CH treatment group and placebo treatment group. The supplement is considered as long-lasting effect to dermal as the effect still can be seen at the end of 4^{th} week washout phase. The skin elasticity increased up to 30% will reduce the 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 Xhauflaire-Uhoda et al. [46] Researchers found that once the treatment of the topical product is stopped, there were no

evidence of skin miniaturization however low improvement 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 helpful to improve skin elasticity by increase in epidermal hydration [47]. Ineffectiveness of topical 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]. Researchers also found that any raw collagen materials used topically, will not show desirable effects to the consumers. A research by Huey-Jine Chai et al. 2010, investigated the effects on facial skin qualities with penetration through transdermal when fish-scale collagen peptide was used [5]. The result showed that the collagen peptide was able to penetrate the stratum corneum to epidermis and dermis in mice 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 an important content of the skin but the route and the way the collagen-based product applied to the skin is important.

6. 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 as depends upon many different factors such as, 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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