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Halal Perspectives on Collagen-Based Biomaterials in Tissue Engineering Applications

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Abstract:

The halal status of biomedical applications has recently been under intense demand due to the utilization of critical ingredients in developing the products. One of the disciplines in biomedical applications, uses various types of biomaterials is tissue engineering. Due to its promising biocompatibility, low antigenicity, and biodegradability, collagen is well known and frequently employed as biomaterials for tissue engineering applications. Most of collagen come from sources including bovine, porcine, marine, and other mammal species. These huge sources end up being one of the most important factors in determining the halal status. Therefore, the purpose of this review is to emphasize collagen's application as biomaterials from the halal standpoint. Additionally, several collagen sources and their status as halal biomaterials for neural, skin, bone, and tissue engineering were covered, with an emphasis on the potential implementation of collagen from halal sources.

Keywords: Collagen; Halal; Biomaterials; Biomedical applications; Tissue engineering

1. Introduction

Animal tissues and their derivatives have long been used as biomaterials in tissue engineering (TE) applications. Collagen is a common natural animal-based biomaterial used in the development of biomedical applications, especially in tissue engineering (TE). However, the use of collagen in manufacturing tissue engineered products has compromised the trust of Muslim consumers due to its non-halal origins, which are mostly derived from porcine and bovine sources. In Islam, halal is defined as permissible (not forbidden by Shariah), and it is not only a religious obligation or observance, but it is also considered the standard of choice for Muslims as well as non-Muslims worldwide. For now, there is no specific guideline or standard that has been published specifying the use of halal biomaterials for TE applications. However, in 2019, the Department of Islamic Advancement of Malaysia (JAKIM) expanded halal certification for medical devices (MS 2636:2019) due to demand in proposals for specific new products, changes in the classification of medical products, and the use of critical ingredients in manufacturing medical devices. In addition, existence halal standard for pharmaceutical products, MS 2424:2019 was also published by Malaysian Standards to cater the needs for pharmaceutical products to be halal certified. These two standards are the closest guidelines that can be referred to determine the principle and halal status of collagen in TE applications.

To the author's concern, there are limited studies focusing on the halal status of collagen sources in biomedical applications, especially for TE applications. The challenge in the TE field regarding halal sources is to select suitable and ideal biomaterials that are compatible with human tissues and yet halal enough to be applied in the human body. Hence, this study aims at reviewing the use of collagen as a biomaterial from a halal perspective and the current applications of halal and non-halal sources of collagen in skin, neural, and bone TE.

2. Basic Principles of Halal Biomaterials for Tissue Engineering

In Malaysia, the Department of Islamic Development Malaysia (JAKIM) is responsible for issuing halal certificates to manufacturers based on the Malaysian Standard and Islamic Laws. Halal certification refers to official gratitude issued by the authorized body of JAKIM for the proper practices of preparation, slaughtering, cleaning, handling, and management. In the context of the use of collagen for TE purpose, there are two halal standards which serve as the closest general guidelines in determining the halal status; "MS 2636 2019 Halal Medical device - General requirement" and "MS 2424:2019 Halal pharmaceuticals – General requirements." Compliance to both standards is on the voluntary basis and serves as a value-added guideline for the biomedical industry's players in providing halal affirmation to consumers.

Based on the general guidelines in the standards, the priority in attaining halal certification is given if: (i) there is a doubt about the potential source of ingredients or potions from halal or non-halal source; (ii) touching or directly contact with human; and (iii) products that have been or are still certified halal by halal authorities under the pharmaceutical product schemes or goods product schemes [1]. One of the requirements for halal certification is that the ingredients, materials, or components do not contain any non-halal part or any non-halal product of an animal, where the product of an animal must be slaughtered according to *Shariah* law and fatwa [2]. Another requirement is the ingredients, materials or components may be from synthetically or naturally derived sources. All types of plants, plant products and their derivatives are known as halal except those prohibited by the competent authority. According to the MS 2636:2019 and MS 2424: 2019 standards, animals can be divided into two categories which are land and aquatic animals. All land animals are considered halal except animals that are not slaughtered according to *Shariah* law, *najs al-mughallazah* animals, i.e. pigs, dogs and their descendants, animals with long pointed teeth or tusks, predator birds, pests, poisonous animals, animals that are forbidden to be killed in Islam, repulsive animals or creatures, farmed halal animals which are intentionally and continually fed with *najs*, other animals forbidden to be eaten in accordance to *Shariah* law and *fatwa*, and all of the above and other animals that are prohibited by the competent authority. Meanwhile, all aquatic animals are considered halal except poisonous, intoxicating, hazardous to health, live both on land and water such as crocodiles, turtles, and frogs, live in *najs* or intentionally and/or continually fed with *najs* and other aquatics animals forbidden to be eaten in accordance with *Shariah* law and *fatwa*.

The development of biomaterials is in line with these halal standards in several ways, ensuring that these materials compliance to Islamic ethical and religious precepts. Here are some important aspects explaining how the development of halal biomaterials is related to halal principles:

1) Haram (forbidden) substances should not be present in halal biomaterials.
2) The procurement and creation of biomaterials are ethical behaviors that are emphasized by halal standards in many facets of life.
3) Halal biomaterials must be reliable and efficient to provide the required benefits without putting consumers or patients in danger.
4) Halal certification can be used to confirm that biomaterials meant for use in medicine and healthcare adhere to the halal principles.
5) Biomaterials must be safe for the human body and respect everyone's values and beliefs.
6) Halal-incompatible procedures or materials should not be used in the production or processing of biomaterials.
7) Getting patients' or consumers' agreement after fully informing them before employing biomaterials in operations or treatments

3. Islamic Perspectives Regarding Halal Status of Collagen-based Biomaterials

In general, collagen or its derivative gelatin is considered halal if it is derived from aquatic animals and halal animals which have been slaughtered in accordance with the Islamic law. However, most commercial collagen and collagen-derived products have been extracted from the processing by-products of land-based animals, primarily cows and pigs. Muslim scholars have different opinions regarding the use of collagen derived from ritually impure animals such as pigs (porcines) or taken from dead animals which are not slaughtered according to the Islamic law. Most of the scholars agreed that collagens originated from these impure animals are haram to be utilized [3].

The jurists agreed that impure animals such as pigs have been declared "*rijs*" or "*najas al-ayn*", meaning essential filth. Therefore, any part of it or its derivatives is considered impure and forbidden to be used except in a dire need, such as a lifesaving situation, where there is no other alternative available [4, 5]. Whereas other opinions supported the idea that the haram status of collagen derived from porcine and carrion should be changed to halal under certain circumstances, which are explained under the principal of *Istihalah,*

Generally, *Istihalah* means the transformation and conversion of one material to another [3]. ***Istihalah*** includes the transformation of physical, chemical, and both physical and chemical properties [3]. In the context of the substances' status, haram can be turned into halal due to the alteration of the physical and chemical properties of a substance derived from haram sources that causes complete changes and produces a new product. The *Istihalah* process involves three elements: raw materials, conversion agents, and final products [6]. The final products that undergo the conversion process must have different physical and chemical properties from the initial materials [6].

There are two groups in the Islamic school of thought that voiced out their opinions regarding the product status of products that undergo the *Istihalah* process. The first group, which consisted of Maliki, al-Shawkani, Hanafi, and Ibn Hazm al-Zahiri schools of teaching, decided that the products resulted from *Istihalah* through natural and/or synthetic transformation could be acceptable as halal [7]. The synthetic transformation could involve human intervention in changing the product matrix. Based on this point of view, collagen-based biomaterials originated from haram sources could be halal if the transformation process of collagen involves the processes of extraction, purification, and polymerization [8, 9]. However, the question arises in a decellularized collagen matrix where its original tissue shape and extracellular matrix (ECM) structure are being preserved. The production of an acellular collagen matrix, or ECM, is being conducted through physical, chemical, and enzymatic methods with the final aim of removing cells, cell debris, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) in a gentle process without damaging the 3D collagen matrix [10]. This technique does not change the product matrix, where the *Istihalah* concept cannot be applied. Therefore, the use of collagen ECM originated from porcine carrion and its derivatives is considered *haram*.

On the other hand, the second group (Hambali and Shafii schools) agreed that the *Istihalah* concept can be acceptable if the transformation process occurs naturally and not by human (synthetic) intervention [8]. For example, the transformation of wine (haram) into vinegar (halal) is naturally conducted without any human intervention at any stage of the process. Based on this ruling, they agreed that the *Istihalah* concept cannot be applied to collagen obtained from haram sources since the process involves human intervention.

In Malaysia, religious guidelines in this regard point towards the ruling of the Shafii school of thought. Even though *Istihalah* is an agreed-upon concept among Islamic jurists and schools of thought, the complexity and ambiguous definition of the alteration process make this concept deniable. Therefore, it should not be used to issue halal certification for collagen derived from haram sources, as it will create confusion among Muslim society.

4. Collagen as a Biomaterial in Tissue Engineering

In TE, the fabrication of scaffolds involves the utilization of biomaterials from either natural sources, synthetically produced ones, or a combination of both. However, naturally derived biomaterials have shown several advantages in terms of biocompatibility, biodegradability, and tissue remodeling compared to synthetically produced materials. There are three main groups of naturally derived biomaterials: protein-based biomaterials (e.g., collagen, gelatin, and silk); polysaccharide-based biomaterials (e.g., chitosan, glucose, and cellulose); and decellularized tissue-derived biomaterials (e.g., decellularized heart valves, blood vessels, and liver).

Among those biomaterials, collagen is considered a halal-critical ingredient as it is typically derived from either bovine or porcine animals (Figure 1). Collagen is actively used in biomedical applications due to its ability to form fibers with high stability and strength through self-aggregation and cross-linking processes [11]. Besides, collagen has ideal characteristics of low antigenicity, being biodegradable, bioresorbable, non-toxic, and biocompatible. These characteristics are crucial to the success of an implanted tissue-engineered organ. There are two basic methods by which collagen-based biomaterials can be created. The first uses a decellularized collagen matrix to maintain the original tissue shape and ECM structure, whereas the second relies on the extraction, purification, and polymerization of collagen and its many components to generate a functional scaffold. Both procedures are subjected to different cross-linking protocols and methodologies that can be used with a variety of tissue sources and species of origin [9]. Bovine skin and tendons, porcine skin, intestine or bladder mucosa, and rat tail are common collagen sources for biomedical use [12]. There are numerous species and sites from which decellularized tissue can be obtained. Currently, the majority of decellularized ECM products that have been approved for use in clinical settings come from mammals which are humans, cows, and pigs.

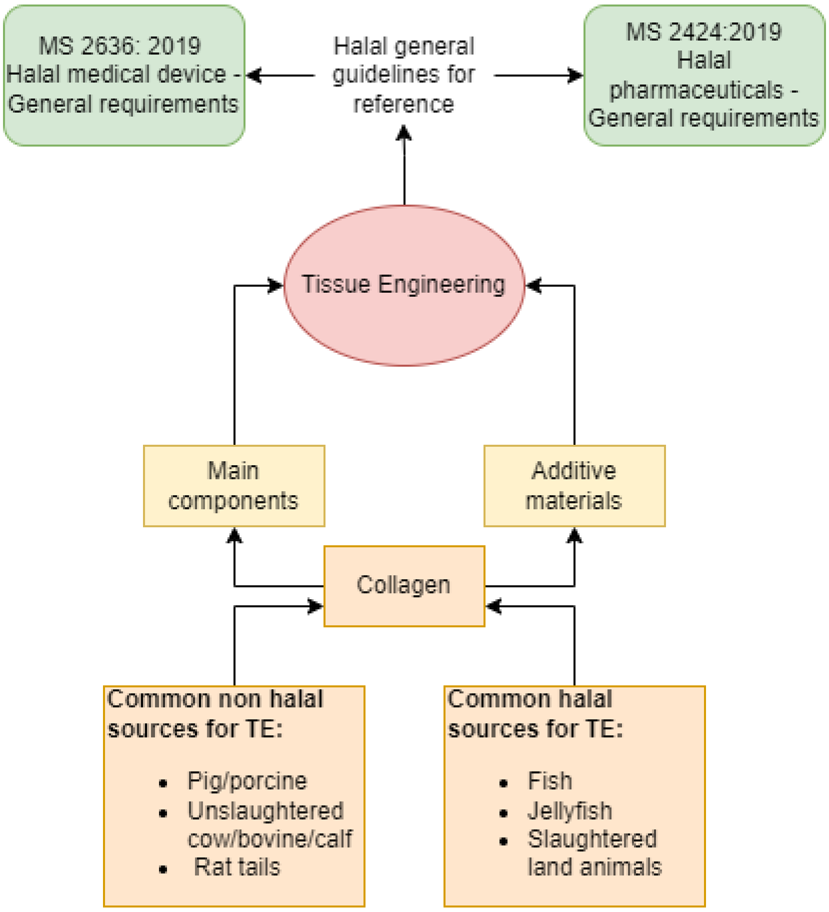

Figure 1 The applications of collagen in TE applications

There are more than 25 types of collagen that occur naturally in the human body, of which type I collagen is abundant in tendinous and ligamentous tissues that serve as connective tissues. In TE, collagen type I is the gold standard for fabricating ECM due to its high biocompatibility. Besides, most people do not possess humoral immunity against collagen type I and are not susceptible to an allergic reaction in response to these collagen-based biomaterials, where both complications can be easily verified through a simple serological test [13]. Collagen type I sources derived from skin, bone, teeth, tendon, ligament, and the vascular ligature of porcine, bovine, and rat-tail tendon are the common types of collagens used in the field of TE. There is a sizeable amount of scientific research focusing on the use of type I collagen from different sources in combination with other biomaterials and cross-linking agents in various types of TE applications. The applications of collagen-based scaffolds in TE have covered different parts of tissues such as nerve tissues, bone and cartilage tissues, tendon and ligament tissues, vascular grafts, and skin tissues [14]. Table 1 summarized the halal status of current applications of collagen-based biomaterials for neural, skin and bone TE.

Table 1 - Halal status of current applications of collagen-based biomaterials for neural, skin and bone TE

Field of TE	Source of Collagen	Halal Status	Important Finding(s)	Reference
Neural TE	Collagen type I from porcine tendon.	Non-halal	The results showing porosity of 95% with an open structure and large surface area that may allow surface-cell interactions for neural tissue engineering purposes	[15]
	Collagen type I from porcine skin.	Non-halal	Collagen hydrogel that acted as an extracellular matrix in peripheral nerve *in vitro*.	[16]

	Collagen type I from bovine tendon.	Non-halal	The neoglucosylated collagen matrices were able to drive cell differentiation.	[17]
	Collagen from rat-tail tendon.	Non-halal	Hydrogels that provide 3D microenvironmental conditions for mesenchymal stem cells growth.	[18]
	Collagen type I from rat-tail	Non-halal	The collagen/PPy-b-PCL hydrogels possessed better printability and biocompatibility	[19]
	Collagen type I from rat-tail	Non-halal	Schwann cell-loaded engineered neural tissues using collagen gel aspiration ejection (GAE) support and guide neuronal regeneration	[20]
	Collagen type I from calf skin	Non-halal	The collagen scaffold promoted neuronal survival and axonal growth inside the wounded site and stopped glial scar growth by regulating astrocyte production for their normal functioning	[21]
Skin TE	Collagen from porcine, bovine, and ovine tendon.	Non-halal	All collagen scaffolds showed no difference in physical and mechanical properties.	[22]
	Collagen type I from porcine.	Non-halal	Scaffolds have good dispersion within skin cells.	[23]
	Collagen from tilapia scale	Halal	The nanofibers can induce skin regeneration along with enough tensile strength and antibacterial activity.	[24]
	Collagen type I from tilapia skin	Halal	The electro-spun nanofibers demonstrated good biocompatibility and low immunogenicity.	[25]
	Collagen from *Arothron stellatus* fish	Halal	The collagen sponges showed good swelling ability, increase in porosity, in vitro enzymatic degradability, and antibacterial property.	[26]
	Collagen from *Paralichthys olivaceus* (Olive flounder fish)	Halal	The synergetic effect of fish collagen polycaprolactone (FCP) and chitooligosaccharides (COS) enhanced healing process for full-thickness wound	[27]
	Collagen from bovine	Non-halal	Ciprofoxacin-loaded collage–chitosan scaffold shown excellent hemocompatibility and cell attachment, proliferation, growth, and migration of fbroblast on scaffolds as well as anti-bacterial effects.	[28]
Bone TE	Collagen type I from rat-tail	Non-halal	Nucleic-acid collagen complexes (NACC) microfibers resemble native extracellular matrix architecture and allow bone mineralization and remodelling	[29]
	Collagen from jellyfish	Halal	Jellyfish 3D scaffold promoted pre-osteoblast and fibroblast cells growth suggesting that collagen from jellyfish can be further use as scaffolds in bone tissue engineering	[30]
	Collagen from fish scales	Halal	The collagen membrane prepared from fish scales had good thermal stability, cytocompatibility, and osteogenic activity.	[31]
	Collagen from porcine	Non-halal	The composite improves the mechanical degradation properties for collagen-based materials.	[32]
	Collagen from porcine	Non-halal	Scaffolds display well-controlled and interconnected pore structures with high mechanical strength, steady release of DEX and good biocompatibility.	[33]

Collagen from fish scales	Halal	Collagen/bioactive glass composite structure enhances osteogenic and angiogenic properties, possessed mechanical property comparable to bone and support cell migration and spheroidal formation.	[34]
Collagen type I from calf skin	Non-halal	Collagen scaffolds containing Hydroxyapatite-CaO fiber fragments promoted the differentiation of MG63 osteoblast-like cells and bone regeneration.	[35]

4.1 Applications of collagen in neural, skin and bone tissue engineering

Neural TE serves as a great platform to treat traumatic brain or spinal cord injury by providing a selection of suitable scaffold. Apart from the brain and spinal cord injuries, scaffolds are also used in other applications such as neural degenerative disorders, neural implant and peripheral nerve injury [21]. The creation of in vitro scaffolds with an optimum composition and micro-architecture suitable for stem cells culture and differentiation are crucial to develop the next generation of scaffolds for nervous system repair [14]. An ideal scaffold for neural TE should closely mimic the natural ECM due to the constitution of ECM in one-fifth of the normal brain. One of the first considerations in designing a scaffold for neural TE is the choice of materials where collagen is a well-known biomaterial in accommodating neural TE based on its ECM and characteristic capability.

In neural TE, collagen is used in the form of ECM components and has been pre-clinically studied using a variety of animal models, including primates. Additionally, collagen is the only biopolymer that has been approved to be studied clinically at the peripheral nerve generation stage. However, due to its poor mechanical properties, researchers often combine collagen with synthetic or electroconductive polymers. Based on the previous research, various collagen sources were used as components in fabricating scaffolds (Table 1). Even though fish collagen has been extensively studied as a potential biomaterial due to its great biocompatibility, low antigenicity, high level of cell adhesion, and excellent biodegradability, there has been little to no work done on the application of fish collagen for neural TE [36]. In other soft and hard tissue applications, fish collagen scaffolds were proved to exhibit considerable cell viability, comparable to bovine collagen.

Despite the great potential of fish collagen in replacing mammalian collagen for different biomedical engineering purposes, scaffold fabrication using this type of collagen for nerve tissue is limited. In the future, more fish or other marine collagen sources should be explored to replace mammalian sources for neural TE as an assurance of halal medical devices.

In skin TE, collagen type I is commonly used to support and facilitate cell proliferation in cell culture tests. The combination of collagen from different sources, and other biomaterials has resulted in a highly compatible cell scaffold for skin-engineered substitutes. Recently, more skin-engineered tissue research has focused on the use of collagen from marine sources especially fish (Table 1). This might be due to the safety and religious security issues and other features, possessed by this source such as excellent bioactive properties, biocompatibility, low antigenicity, high biodegradability, and cell growth potential. The marine-sourced collagen has no disease risk and possesses properties like those of traditional collagens [37]. Different methods such as freeze-drying and electrospinning have been employed to fabricate collagen-based scaffolds for skin TE.

In bone TE, scaffolds are designed to mimic the native of bone tissue micro-environment, so that natural biological response to tissue damage can be exploited [38]. In promoting cell migration and differentiation into a scaffold, the synthetic bone scaffolds must provide temporary mechanical support while holding a porous structure. The infiltration of cells within bone scaffolds will encourage osteoinduction and osteointegration. One of the main challenges in developing bone scaffold is the tailoring of mechanical properties, biocompatibility, biodegradability, and scaffold architecture for optimum cell integration, proliferation, and organization.

Therefore, a wide range of biomaterials has been studied for the preparation of bone scaffolds including natural materials such as collagen. However, pure collagen cannot be directly used to substitute bone due to its poor mechanical strength [39]. Thus, collagen is combined with bioactive ceramics to produce composites that are being fabricated in many forms such as 3D scaffolds [40], dry powders [41] and hydrogels [42]. The source of collagen used for scaffold development is often neglected, which can indicate the halal status of those natural biomaterials. Here, the authors briefly compile previous studies of collagen composite scaffolds for bone TE, focusing on the sources of collagen as summarized in Table 1.

5. Conclusion

An increase in attention towards halal was not only applied to food products, which created a great demand for new halal sources of biomaterials that can be applied for tissue engineering. The use of collagen is widely applied in tissue engineering. There are different sources of collagen being used, mostly from pig skin, bovine hide, and pork and cattle bones, which makes the sources of halal collagen limited and not well known yet in biomedical applications. Recently, there have been more studies on collagen from halal sources to be used as a substitute in tissue engineering due to the high demand from Muslims and non-Muslims worldwide. There is a lot of interest in collagen from fish sources as a possible alternative to collagen from porcine and bovine sources. However, the mechanical strength and stability in the aqueous environment of marine collagen scaffolds need enhancement to be considered as a suitable substitute option. Fish skin collagen is being considered for halal tissue engineering biomaterials due to its biocompatibility properties and characterizations.

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Conflict of Interest

The authors declare no conflict of interest.

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