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Systematic Literature Review on Alternative Options For Halal Critical Ingredients In Halal Pharmaceutical and Cosmetics

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Abstract

The global halal market is expanding fast as halal products establish themselves as a new standard for safety and quality assurance. The constituent of a product, whether pharmaceutical or cosmetic, determines its halal classification. Ingredients that do not correspond to the halal standard are commonly known as critical ingredients. As a result, various substitutes for critical ingredients should be developed to raise global demand for the halal market. This study aims to review the current research development on the alternatives for halal critical ingredients in halal pharmaceuticals and cosmetics and to explore the testing methods used to test the alternative option for halal critical ingredients. This systematic study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards and all the publications in this review meet the research eligibility requirements, which were searched and selected using electronic databases such as PubMed, Scopus, and MyCite. This study examined approximately 21 publications that proposed various substances derived from sources such as plants, animals, marines, and microbes. Three publications illustrated the possible use of the choice in insulin-resistant patients, whereas seven articles discussed on the potential replacement for gelatine. Insulin and gelatine are the most frequently explored topics among the publications included in this review. Their alternative possibilities, whether derived from plants, marine sources, or microbe-based substances, are thoroughly evaluated to determine their desired effect or activity. The testing methodologies demonstrated that the alternative possibilities are far superior to the critical ingredients in terms of texture, morphology, activity, composition, and even the cost of synthesis.

Keywords: halal; critical ingredients; systematic literature review; insulin; gelatine

Introduction

The Arabic word "halal" implies "permissible" or "lawful". According to the law of Islam, halal refers to any act, way of life, or even object that is regarded as permissible or authorized, whereas "haram" refers to any action or way of life that is deemed prohibited or interdicted. Halal and haram refer to any product used by consumers, such as food, cosmetics, and medicinal products.

In an article written by Mustafa[1], the halal worldwide industry is fast expanding as halal-certified products receive widespread recognition as they set a new standard for safety and quality. Goods that conform to halal norms and rules, regardless of type, can simply receive a halal certificate from the authorities. As a result, when a halal-certified product is presented to the market, consumers accept it with confidence, particularly Muslim consumers, who have religious considerations. Because Muslims

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make up the vast majority of Malaysia's population, the halal market has surely grown into a global industry. The halal industry is a new concept in the twenty-first century; therefore, to adapt to the changes, producers take advantage of chances to make a product with improved strategies and innovations to certify it as halal.

Because of technical advancements, the halal concept now includes pharmaceutical and cosmetic products in addition to food products. In a publication by Siddiqui[2], the concept of Halal in pharmaceuticals especially in the global market is something new which is not surprising given the embryonic state of Halal supply chain and logistics management in general. Global Islamic Economy Summit (2013) states that halal has evolved largely into three categories: Food, Cosmetics, and Pharmaceuticals [2]. Even though halal pharmaceuticals are quite new Nain [3]elaborates that halal pharmaceuticals are gaining popularity, with the global Halal pharmaceutical business valued at approximately US$800 billion per year.

In Malaysia, the authorities, Jabatan Kemajuan Islam Malaysia (JAKIM), established a standard known as the Malaysian Standard – Halal Pharmaceuticals and Halal Cosmetics, which serve as a guide for manufacturers to design a halal product. They must also comply with the requirements to facilitate the halal certification procedure of cosmetics and medicinal items. The halal status of a product, whether pharmaceutical or cosmetic, is determined by the ingredient used because it determines the efficacy and safety of the product. As a result, the ingredients must be certified halal before being used in a product composition. According to Sugibayashi [4], substances that do not correspond to the halal system are frequently referred to as critical ingredients. Thus, to determine their halal certification, their properties must be investigated as well as their efficacy if employed in a product. If the critical ingredient is halal, it can be incorporated into the formulation to facilitate the product's halal certification. Furthermore, halal items may also see an increase in demand among non-Muslims if the halal critical ingredients are more effective and safer than non-halal critical ingredients.

However, there are several obstacles in determining the halal status of the critical ingredient. This is because most producers were unwilling to provide extensive information about their products, and the halal status of the critical ingredient has yet to be determined. To overcome these challenges, authorities in charge of Halal products must address them, explain the importance of Halal, and enforce the law governing product formulation to ensure that manufacturers use the appropriate ingredients according to the Halal Standards and Guidelines. Therefore, this systematic literature review provides more insights into the alternatives for halal critical ingredients in halal pharmaceuticals and cosmetics so that the halal market not just broadens in food but also in cosmetics and pharmaceuticals.

Methodologies

Research design

This study's design is a Systematic Literature Review (SLR). SLR is a type of literature review that uses a systematic and rigorous process to discover, analyze, and synthesize all available research related to a certain research issue or topic. In SLR, research questions are created and then conducted a systematic search for studies or previously published papers that were appropriate for our study. The publications will be locatedusing specificsearch phrases and parameters in predetermined databases. To avoid outliers in data collecting, inclusion and exclusion criteria are used while searching for relevant papers. The data-gathering procedures are pre-defined and stored in an Excel sheet, which can then be utilized to support our

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findings and discussions. After collecting relevant and suitable papers, it will beanalyzed and summarized to reach a conclusion based on our research questions and objectives. The major concern of this systematic literature review is to provide a high-quality and comprehensive study that includes all the relevant previously published papers used in this investigation. In this systematic literature review, keywords relating to systematic literature reviews will be entered into each database's search column. Boolean operators "AND" will be used to combine keywords to narrow down certain search titles. Meanwhile, "OR" will be utilized to combine the terms to broaden the search titles.

Preferred reporting items for systematic reviews and meta-analyses (prisma)

PRISMA refers to Preferred Reporting Items for Systematic Reviews and Meta-Analyses. It is an evidence-based minimal set of things to report in systematic literature reviews and meta-analyses. PRISMA was selected as one of the data-collecting and analysis methods because it establishes a widely accepted standard for reporting evidence in systematic literature reviews and meta-analyses.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were developed before proceeding with the systematic literature review study as they are essential to make sure all applicable data are presented properly. The inclusion criteria that are included in this study are the publication of the article should be in either Malay or English language and the publications should be ranged from the year 2013 until 2023. In addition to that, original research studies only were selected to maintain the quality of the study. On the other hand, the exclusion criteria are the publication's language other than English and Malay language and the publications that are not related to the research questions and objectives. Publications that are related to review articles were also excluded from this study.

Study selection

Articles that showed in the database results after conducting keyword searches were carefully checked and eliminated if they were duplicated. The recovered articles were then carefully examined so that they met the inclusion and exclusion criteria that were predetermined and specified at the start of the investigation. Following an assessment of each publication, the articles that met the eligibility standards were incorporated into this research. The reasons for the excluded articles were briefly stated in the PRISMA flow chart (Figure 1).

Data extraction

The key information from the included articles was extracted and tabulated, as shown in the results and appendices. Examples of information extracted include the author, year of publication, database source, country, research methodology used in the study, summary of the article, types of journals, critical ingredients in pharmaceuticals and cosmetics, alternatives for the critical ingredients, testing methods for halal authentication, and study conclusions.

Critical appraisal

Quality assessment is a critical stage in completing a systematic literature review. This is because it will aid in determining the risk

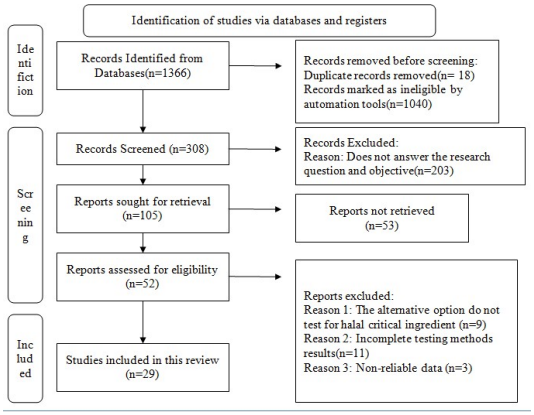

Figure 1: PRISMA Flow Diagram

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of bias in particular studies and overall trust in the review findings. To conduct a quality assessment, a standard form should be produced and given to reviewers for use in evaluating each publication[5]. The standard form is commonly referred to as an assessment tool for reviewing research papers and determining the validity of the study mentioned in the article. There are various types of tools based on the study design. In this review study, JBI Checklist appraisal instrument was selected for the quality assessment of the papers, which are based on the research methodology of the study.

Results and Discussion

Article selection and screening process

The article searches yielded 1366 articles from four databases. Table 1 presents an overview of the search results. A total of 308 papers were screened for prospective inclusion in this study. In comparison, the remaining 1058 publications were removed from this study since they did not meet the inclusion criteria and the records were duplicated. Approximately 207 articles were excluded because they were not retrievable from the database. To finish the search results, 29 publications were selected and included in this review study during the last stage of the data selection procedure. Among the 29 articles, there are 8 articles achieved through PubMed, another 9 collected through MyCite, and 12 from Scopus. Figure 1 demonstrates the selection of the articles through the PRISMA flow diagram.

Descriptive statistics

A descriptive analysis was conducted on the retrieved papers used in this study. Analysis, such as the number of publications by year, the number of papers published by publisher nation, the research methodology employed in the study, and the number of publications by journal type, were conducted and sorted accordingly. According to the number of publications by year, 2018 had many papers published as shown in Figure 2A. This could be attributable to an increase in global demand for halal products. As a result, researchers and producers work together to make halal products that are more dependable and of higher quality. Before the year 2018, there were not many papers written since the halal concept was a new idea in the cosmetic and pharmaceutical sector therefore there was not much demand for halal cosmetic and pharmaceutical products. In terms of the number of articles published based on the country of publisher, Malaysia had the most based on Figure 2B. This is because Malaysia has a larger Muslim population than other countries, therefore halal has become a primary issue in their daily lives, resulting in a rise in halal-related research. Based on Figure 3A experimental type research was discovered to be the most common in the research methodology employed by the gathered publications because the study focuses on critical substances, hence testing for an ingredient must be done experimentally. Finally, the number of publications by journal type revealed that journals classified as others published many papers linked to the study. The other type of publication has a large number of conference papers from many mediums; thus it cannot be divided into the types of journals as shown in Figure 3B. Five of the included publications indicated important chemicals that are commonly used in the beauty and pharmaceutical industries. This research employed a variety of approaches to determine the halal status of the key ingredient. Magnesium stearate's halal certification was verified using FTIR and chemometric analysis as shown in Table 2. However, the halal status remains dubious because the acquired FTIR data show no substantial difference between the various magnesium stearate sources[7]. On the other hand, three articles have shown that collagen and allantoin are important elements. Even though allantoin was synthesized, the process of istihalah was unable to occur due to many factors, making allantoin's halal

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Table 1: Critical ingredients commonly used in the pharmaceutical and cosmetic industry (*Contd.*)

No	Themes	Sub-themes/ Supporting Evidence
1	Pharmaceutical	Magnesium Stearate - The halal status of magnesium stearate was conducted by chemometric investigation. The results showed that magnesium stearate from animal sources such as bovine is not entirely halal whereas plant and kosher sources are halal based on the peaks of chemometric [7]. - The halal status of magnesium stearate was conducted by FTIR study. In this study we couldn't make a conclusion on the halal status of magnesium stearate as there were no prominent peaks of the FTIR raw spectra, hence their halal standards remain unclear[7].
		Enzyme (Trypsin in Insulin) - A study showed that insulins from animals that have been slaughtered according to Islamic law are considered halal however if it's a non-halal animal source then the insulin is not permissible[8].
2	Cosmetic	Keratin - Keratin is a type of protein that can be found in human hair and soybeans. Hence, the protein from the human hair or non-permissible animal is considered non-halal [9].
		Hyaluronic Acid - Hyaluronic acid is considered forbidden according to the Syariah law if the sources are from animals and humans because it is commonly present in the ocular fluid and the fetus [9].
		Allantoin and its derivatives -Found in various biological materials so allantoin is found to be haram if they derived from humans or animals [9]. - Typically, the extraction of allantoin from plant sources requires alcohol. Even though, the source of the substance is halal the extraction process makes the halal status of allantoin doubtful [10]. - According to the Islamic perspective, synthetic allantoin is halal, as is allantoin obtained from animal urine through several processes such as oxidation and hydrolysis, which do not change the chemical properties of the ingredients allantoin even though their physical properties change. This prevents the process of istihalah from occurring. Because of this, its halal status remains unclear [10].

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Table 1: Critical ingredients commonly used in the pharmaceutical and cosmetic industry (*Contd.*)

No	Themes	Sub-themes/ Supporting Evidence
		Collagen - Animal-derived collagen does not conform to the halal system, whereas plant-based collagen is made from hydrolyzed wheat proteins and contains an extension composed of hydroxyproline, a similar amino acid residue to that found in mammals that contributes to collagen properties. As a result, it is halal but not as effective as animal-derived collagen [11]. - Is a connective tissue present in various biological materials. Haram whether it comes from people or animals [9].
		Protease Enzyme - This can be acquired from either animals or plants. Halal if derived from plants [11].
		Riboflavin - Colour; Halal if derived from synthetic sources. Otherwise, it requires further inquiry to determine its source [11].
		Fast Yellow AB - It is a chemical colour that is Halal when used as a dry powder; however, its liquid form is only Halal when Halal solvents are utilized [11].
		Mono Starch Phosphate - Phosphate from animal bones is not halal; however, phosphate from minerals is halal[11].
		Quinoline Yellow - Colour. It is a chemical colour that is halal when used as a dry powder. Its liquid form is only Halal when Halal solvents are used [11].
		Patent Blue V - Colour. It is a dry petroleum basis. It is halal when used as a powder colour. When Halal solvents are employed, the liquid dye is Halal [11].
		Carmine - Colour. It was once harvested from plants, but it is now synthesized synthetically. It is Halal if it is made synthetically from Halal ingredients. The liquid form is Halal if the solvents used are Halal [11].
		Chlorophyll -Colour. It is a plant pigment that is Halal if the extraction solvents employed are Halal rather than alcohol [11].
		Copper Complex of Chlorophyll - Colour. It is a plant pigment that is Halal if the extraction solvents employed are Halal rather than alcohol [11].

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Table 1: Critical ingredients commonly used in the pharmaceutical and cosmetic industry (*Contd.*)		
No	Themes	Sub-themes/ Supporting Evidence
3	Cosmetic and Pharmaceutical	Gelatin - There are two varieties of gelatin. Type A is derived from non-halal animals, usually pigs. This form of gelatin is acid-processed and can create large quantities of high-quality gelatin, whereas form B gelatin is derived from the bones or skin of cows and buffaloes and is alkaline-treated. Because the halal status for both types does not conform to the halal system, it requires full research from the Islamic perspective [8].
		Glycerin and its derivatives - It can be obtained naturally or synthetically. If the source of the substance from haram animal fat then it is considered not permissible [9]. - If it is from an animal source (bone), it is classified as mushbooh according to the E code, indicating that further clarification and study are required [11].

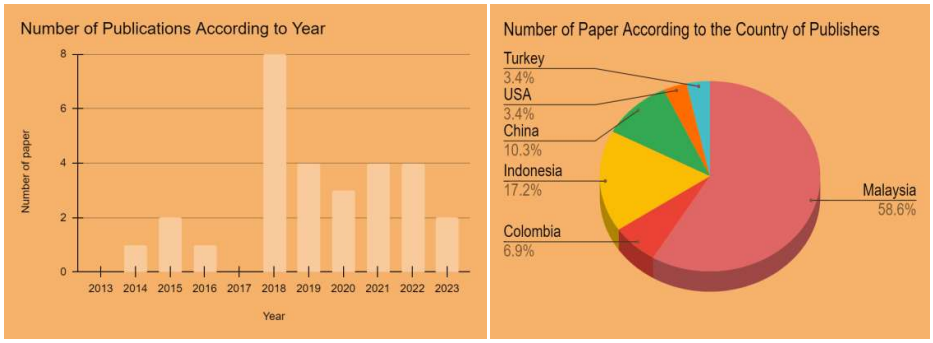

Figure 2: Number of published articles based on (A) year throughout 2013–2023 and (B) publication distribution according to the country of origin

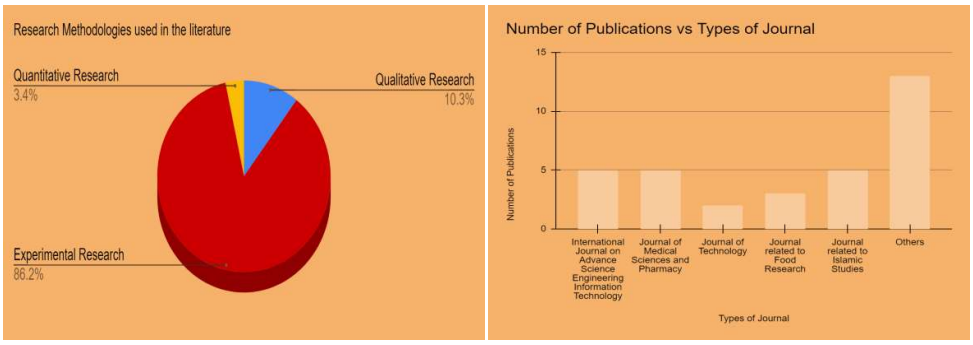

Figure 3: Number of published articles based on (A) research methodologies and (B) Different types of journals used

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Table 2: Alternative options for halal critical ingredients used in pharmaceuticals and cosmetics

No	Themes	Sub-themes/ Supporting Evidence
1	Plant-based Ingredient	Okara - Acts as a substitute for important ingredients in cosmetics. Okara oil contains a high concentration of functional lipids, making it a viable alternative source of essential oil for cosmetic purposes. Okara showed excellent potency as a functional cosmetic ingredient, primarily for improving skin conditions, acting as a skin whitening agent, and providing UV ray protection [12].
		Gum Arabic - Alternative to gelatine, a versatile hydrocolloid. The results revealed that the optimal formulation in terms of physicochemical properties, antioxidant activity, and sensory acceptability was a sample containing 12% gum Arabic and 4% gelatin. Thus, gum Arabic is an appropriate alternative to gelatine [13]
		Aquilaria malaccensis Leaf - An alternative to nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids. The study found that (Gas chromatography-mass spectrometry) GCMS of leaf (supercritical fluid extract) SFEX revealed a peak of a tricyclic sesquiterpene that was tested for possible analgesic and anti-inflammatory effects [14].
		Pea Protein Isolate -An alternative to gelatin. The results showed that at a protein concentration of 9-16%, thermo-reversible gels were generated, with several of them having strong gelling properties and increasing the pH up to 4.2. The pea protein gel is translucent, thermo-reversible, and has strong mechanical properties, making it suitable for substituting gelatin [15].
		Plant-based Cellulose - An alternative to commercial cellulose. The Fourier Transform-Infrared (FTIR) demonstrated the usual peaks of conventional cellulose. The results revealed that cellulose produced from Borassus flabellifer fruit peel fibres had remarkable similarities with the conventional cellulose employed and a 12.4% of large cellulose yield was produced [16].

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Table 2: Alternative options for halal critical ingredients used in pharmaceuticals and cosmetics (*Contd.)*

No	Themes	Sub-themes/ Supporting Evidence
		Flower Extracts - An alternative to commercial sunscreens with titanium dioxide or zinc oxide as active components. The UV filtering effectiveness of flower extracts from Rosa centifolia L., Posoqueria latifolia (Rudge) Schult, and Ipomoea horsfalliae was evaluated. The P. latifolia extract was shown to be the most promising for use as a sunscreen due to its significant photoprotective efficacy, antigenotoxicity, photostability, and comparatively low cytotoxicity and genotoxicity in human fibroblasts [17].
		Bolanthus spergulifolius (Caryophyllaceae) - An alternative to synthetic insulin. The data imply that extracts of B. spergulifolius promote programmed cell death, enhance lipid excretion, and, up-regulate glucose transporter levels, and may leads to increasing insulin sensitivity in DM [18].
		Acer truncatum leaves -An alternative to synthetic insulin. Myricitrin which is the active component can repair aberrant mRNA sequence of pro-inflammatory cytokine in diabetic conditions, mostly via interfering with toll-like receptor pathways so that they can improve glucose absorption and reduce blood glucose level in the body. [19].
		Curcumin - An alternative to synthetic steroids. Curcumin consumption was found to suppress the development of hypersensitivity and anaphylaxis reactions in susceptible mice.Th2 responses were similarly decreased, and curcumin inhibited mast cell activation. The study found that curcumin decreased the activation of the pro-inflammatory gene induction in susceptible mice [20].
		Moringa Oleifera Leaves -Alternative to collagen, which is frequently utilized as an active ingredient in facial mask formulations. The results revealed the percentage of protein content in conventional facial mask samples is lower compared to the protein content in the moringa leaves which are 16.67% and 33.33% respectively [21].

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Table 2: Alternative options for halal critical ingredients used in pharmaceuticals and cosmetics (*Contd.)*

No	Themes	Sub-themes/ Supporting Evidence
		Xanthan Gum - An alternative to gelatine. A study shows that xanthan gum is a suitable release-retarding agent in the formulation of halal sustained release gliclazide tablets using the wet granulation technique [22].
		Pectin(Mango peel) - An alternative to gelatine. According to the results of its gelling properties and sensory evaluation, (crude mango peel pectin) CMPP has a high potential to be utilized as low-methoxyl pectin. It also serves as a low-cost gelatin alternate [23].
		Brewer's Rice - The study found that fermented brewer's rice extract increased total flavonoid and total phenolic content while also improving ferric-reducing and antioxidant activities. Furthermore, fermented brewer's rice extract inhibits tyrosinase and elastase more than unfermented extract, by roughly 7- and 57-fold, respectively. Ferulic and kojic acid, two of the most essential components in cosmetic formulations, were also found in fermented brewer's rice extract [24].
2	Animal-based Ingredient	Cyprinus Carpio - An alternative to non-halal animal collagen. The study found that the yield of collagen from carp is around 8.62%, with the characteristic of yellowish-white and a pH of 6.59. Furthermore, the analysis of the carp reveals a fibril structure with chemical interactions dominated by amide groups [25].
		Camel Skin - An alternative to commercial gelatin. According to the study, camel skin was able to produce a yield of 29.1% of gelatin after 2.58 minutes at 71.87 degrees Celsius and pH 5.26. The bloom value of the gelatin from camel skin was 340.4 g. The study also found that the isolated gelatin had a significant proline and glycine content through the amino acid analyzer tool [26].
		Cobia (Rachycentron canadum) skin - An alternative to gelatine. The study indicated that cobia skin gelatin (CG) can binds to fat easily compared to bovine gelatin (BG). However, CG has low moisture retention compared to BG.The lowest concentration of gelling for BG was measured at 1%, while for CG it was 2%. [27].
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Table 2: Alternative options for halal critical ingredients used in pharmaceuticals and cosmetics (*Contd.)*

No	Themes	Sub-themes/ Supporting Evidence
3	Marine-based ingredient	Seaweed - The antioxidant test revealed that P.pavonica (brown macroalgae) had the highest (1,1-diphenyl-2-picrylhydrazyl) DPPH activity, with an inhibition percentage of 61% . All of the seaweed samples shown high antibiotic activity against E. coli and P. aeruginosa when it was tested for antimicrobial test. The overall antifungal test findings showed that all seaweed samples had moderate antifungal activity against M. gypseum and Fusarium sp [28].
		Microalgae - Alternative to synthetic colourants. The study found that Chlorella vulgaris has the highest carotenoid content. Lutein is found in all six microalgae species, while Pandorina morum contains all three forms of carotenoids: lutein, β-carotene, and β-cryptoxanthin [29].
4	Microbe-based ingredient	Bacteria-producing cellulose - An alternative to commercial cellulose-gelatine. The results of this investigation indicated that bacterial cellulose can be manufactured from Enterobacter sp. M003 with continuous stirring conditions and good carbonaceous materials such as fructose to replace glucose for bacterial cellulose (BC) synthesis [30].
		- An alternative to cellulose. The study discovered that optimum bacterium cellulose was achieved at around 2.28 g/L at 32°C and pH 4 during a 7-day fermentation period. Coconut water is utilised as a medium to ferment bacterial cellulose [31].
		Amillariella Mellea - An alternative to synthetic insulin. This study found that Amillariella mellea, an edible fungus, improved on a dexamethasone (DEX)-induced insulin resistance together with high fat diet(HFD) by regulating lipid metabolism. Our findings suggested that Amillariella mellea extract can be a potential medication in diabetic patient [32].

status unclear[10]. If the substance comes from a different source than synthetic, it will be considered haram[9], although collagen's halal status remains uncertain because it comes from a variety of sources, including humans, animals, and plants. Human and animal collagen is considered haram, while plant collagen is considered halal[11][9]. Aside from that, glycerin's halal status was reviewed because it can be derived from a variety of sources. The supported articles demonstrate that animal-based glycerin requires additional explanation and inquiry into its halal validity when compared to

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Table 3. The testing methods used to test the alternative option for halal critical ingredients

No	Themes	Sub-themes/ Supporting Evidence
1	Morphology Analysis	(Scanning Electron Microscopy) SEM - The current collagen from the market, morphology revealed a heterogeneous fibril form, while microcollagen from cyprinus carpio revealed homogenous particles [25]. - SEM analysis revealed a fine-stranded network structure with thin connective walls in 10% and 13% protein gels made at pH 3.4. The morphology explain the gel's transparency since the homogeneous fine-stranded network allows more light to pass through without scattering [15]. - SEM was used to investigate the morphology of bacterial cellulose. The scanning reveals the compact structure of cellulose generated using the air-drying process[30].
		Field Emission Scanning in Electron Microscopy (FESEM) - FESEM visualizes the bacterial cellulose(BC) that has an entangled structure with mild porous spread through it permitting the impregnation of various compounds into the BC matrix. Hence, the flexibility and stiffness properties of BC are improved [31].
2	Functional groups and Chemical bond Analysis	(Fourier-Transform Infrared) FTIR - This study used FTIR to determine the collagen's functional groups and chemical bonds. The results indicated the presence of both an amide A bond and an amide B position [25]. - The study results showed that both spectra of lard and EVOO seem fairly similar. However, they revealed some differences in peak intensities and the specific wavenumbers at which the highest absorbance were seen in LD(Lard) and EVOO, due to the different nature and composition of both LD and EVOO [33]. - The study's results revealed that the two samples have identical FTIR peaks, with the exception of some areas where bacterial cellulose did not produce a strong peak like microcrystalline cellulose due to its compacted structure. However, the study proves that Enterobacter sp. M003 produces an authentic bacterial cellulose [30].
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No	Themes	Sub-themes/ Supporting Evidence
		UV-Vis spectrophotometer - In this study, UV absorption was assessed on collagen samples isolated from carp scale waste using a UV-visible spectrophotometer. The results show that the benzene causes a bathochromic shift, particularly in the K band (204nm), which shifts to a wavelength of 268nm. The shift results not just from benzene aromatics, but also from alkyl substituents and functional groups. It denotes the existence of carboxyl and hydroxyl groups [25].
		(Gas chromatography-mass spectrometry) GCMS - The volatile components of the triplicate A.malaccensis leaf extract samples were determined using a gas chromatography equipment. The findings revealed that different types of extracts produced varying numbers of peaks and compounds [14].
3	Particle Size Analysis	(Particle Size Analyzer)PSA - PSA was used to measure the size and distribution of micro-collagen particles.The obtained results ranged from 668 nm (d10 < 10%) to 1581 nm (d90 < 90%). The micro-collagen particle size with the highest distribution intensity was 1146 nm [25].
4	Activity Analysis	2, 2-diphenyl-2-picrylhydrazyl (DPPH) Scavenging assay - The sample with high antioxidant activity has a high amount of Gum Arabic (GA). Recent studies have also shown that GA has antioxidant qualities because it plays a role in lipid metabolism and improves kidney failure and cardiovascular treatment [13]. - This test was designed to investigate the antioxidant effects of fermented brewer's rice extracts. The results revealed that fermented samples had higher biological components and antioxidant activity than their unfermented counterparts which is favourably connected with total phenolic content [24].
		Quantitative reverse transcription polymerase chain reaction (qRT-PCR) - The results showed that myricitrin therapy prevented alloxan-induced gene expression degradation or diabetes development. Among the altered genes, IκBα, STMN1b, and IL1b were associated with toll-like receptor pathways. The toll-like receptor detects β-cell death. Furthermore, inhibiting toll-like receptors can reduce β-cell mortality in diabetes [19].

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No	Themes	Sub-themes/ Supporting Evidence
		Ferric reducing antioxidant power (FRAP) Assay - This experiment was designed to investigate the antioxidant effects of fermented brewer's rice extracts. The results revealed that fermented samples had higher biological components and antioxidant activity than their unfermented counterparts which is favourably connected with total phenolic content [7].
5	Texture profile analysis	Texture Analyzer - The study results revealed that Gum Arabic had decreased hardness, cohesiveness, and springiness. Furthermore, it has a lower gumminsess value than gelatine, therefore it does not require a lot of energy to break down the pastille [13]. - The study found that the Bloom value (gelatin strength) of camel skin gelatin was 340 ± 0.5 g. This number is comparable to gelatin from bovine which was higher (267g) and almost similar amount to porcine source gelatin(350g) [26].
6	Component/ Content Analysis	HPLC System - HPLC tool was used to quantify the total carotenoid content. The content of chlorophyll for both P. pavonica and C. lentillifera is similar .It was found that the chlorophyll composition in K. striatum is 4.6 µg/g DW, G. tikvahiae at 2.9 µg/g DW, and E. denticulatum at 3.0 µg/g DW so it showed that the chlorophyll content in these 3 compound are lower compared to P. pavonica and C. lentillifera [28]. - Protein amino acid analysis was performed using an HPLC system. Both asparagine and aspartic acid, as well as glutamine and glutamic acid, were considerably greater in ASE-PPI (pea protein isolate extracted via ammonium sulphate precipitation technique) than in AE-PPI [15]. - The HPLC technique found three significant carotenoid peaks, including lutein, β-cryptoxanthin, and β-carotene.Lutein and β-carotene concentrations were highest in C. fusca (63.39 ±5.99 µg/g DW) and C.vulgaris (18.42 ± 5.31 µg/g DW), respectively [29]. - Amino acids were analysed using an HPLC technique. Camel skin gelatin has high glycine, proline, and lysine levels, similar to bovine and porcine gelatins. Camel skin gelatin contained more lysine than porcine or bovine gelatin [26].

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Table 3. The testing methods used to test the alternative option for halal critical ingredients (*Contd.)*

No	Themes	Sub-themes/ Supporting Evidence
		Chemometrics - Using the score plot projection, cream containing lard, EVOO, and commercial samples are highly separated, indicating that PCA (Principal Component Analysis) can classify them. Based on this profile, commercial samples (region B) do not contain lard in their formulation [33]. - Fuzzy Autocatalytic Set (FACS) is a novel chemometrics method where it discovered the FTIR spectra peaks of bovine, porcine, and fish gelatins.The method was successful because prominent peaks were able to observed and they are differ among the different types of gelatins. Hence, this method provides a warrant for halal authentication [34].
		LC-MS/MS Analysis - The research revealed that the active content which was myricitrin, higher than the other compounds which are myricetin-3-rutinoside,,myricetin-3-O-pentoside, and myricetin. It remained steady throughout tree age samples [19].
		Amino acid analyser - According to the findings, the total amino acid content in (Bovine Gelatin) BG and (Cobia Gelatin) CG is 99.51% and 86.65%, respectively [27].
		Modified Quartz Crystal Microbalance (QCM) sensor method - The modified QCM sensor produced a satisfactory frequency response for distinguishing bovine and porcine gelatin. The measurements produced negative frequency shifts for bovine gelatin and positive frequency shifts for porcine gelatin, indicating that bovine gelatin is halal and porcine gelatin is non-halal [35].

alternative sources, such as plant-based, microbial-based, or even propylene gas. According to this review, there are several alternate options for insulin as listed in Table 3. Three articles show that *Bolanthus spergulifolius*, *Amillariella mellea*, and *Acer truncatum* leaves, respectively, provide an excellent replacement for insulin as a halal critical ingredient. A study found that Acer truncatum leaves containing myricitrin can repair gene expression associated with diabetes by interfering with toll-like receptor pathways, improving glucose absorption, and relieving hyperglycemia levels[19]. On the other hand, a study found that *Bolanthus spergulifolius* had a similar impact as insulin when the substance was treated on adipocytes and produced a positive effect in

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terms of gene expression[18]. Furthermore, Amillariella Mellea dramatically lowered fasting blood glucose levels, lowering glucose intolerance and insulin resistance via raising the expression of two important lipases[31]. As a result, all these drugs are effective alternatives to insulin. Finally, gelatine also was found to have many alternatives according to this review where 6 articles suggested an alternative option such as gum arabic, xanthan gum, pea protein isolate, pectin, camel skin, and cobia skin respectively. All these alternative options possess similar efficacy and features as gelatin. For example, Gum Arabic is an important hydrocolloid that can be used in pastille production and acts as a stabilizer and fat emulsifier[13] on the other hand xanthan gum possesses the best release-retarding agent so it can used in various formulations of drug for a sustained-release effect[22]. These effects are also performed by gelatin. Since all the alternative options can be obtained naturally it will produce a much more cost-effective halal product and at the same time, it maintains the quality of the product. Hence, these substances can be confidently used by the manufacturers to produce a halal product. This review also covers the testing methods that were used to analyze the alternative halal critical ingredients so that they can be used for future product formulations which are shown in Table 4. A total of 24 articles used different types of testing methods to characterize the alternative halal critical ingredient. Scanning Electron Microscopy (SEM) is one of the common testing methods used to analyze the morphology of the compound. 5 articles used SEM as one of their testing methods to visualize the compound. Besides that, FTIR was used commonly to study the functional groups and chemical bonds of a compound. 8 articles used FTIR to analyze their compound. Furthermore, the researchers

Table 4: The testing methods used to test the alternative option for halal critical ingredients

No	Themes	Sub-themes/ Supportive evidence
1	Morphology Analysis	**(Scanning Electron Microscopy) SEM** – The current collagen from the market, morphology revealed a heterogeneous fibril form, while microcollagen from cyprinuscarpiorevealed homogenous particles [25]. – SEM analysis revealed a fine-stranded network structure with thin connective walls in 10% and 13% protein gels made at pH 3.4. The morphology explains the gel's transparency since the homogeneous fine-stranded network allows more light to pass through without scattering [15]. – SEM was used to investigate the morphology of bacterial cellulose. The scanning reveals the compact structure of cellulose generated using the air-drying process [30]. **Field Emission Scanning in Electron Microscopy (FESEM)** – FESEM visualizes the bacterial cellulose (BC) that has an entangled structure with mild porous spread through it permitting the impregnation of various compounds into the BC matrix. Hence, the flexibility and stiffness properties of BC are improved [31].

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Table 4: The testing methods used to test the alternative option for halal critical ingredients (*Contd.*)

No	Themes	Sub-themes/ Supportive evidence
2	Functional groups and Chemical bond Analysis	**(Fourier-Transform Infrared) FTIR** – This study used FTIR to determine the collagen's functional groups and chemical bonds. The results indicated the presence of both an amide A bond and an amide B position [25]. – The study results showed that both spectra of lard and EVOO seem fairly similar. However, they revealed some differences in peak intensities and the specific wavenumbers at which the highest absorbance were seen in LD(Lard) and EVOO, due to the different nature and composition of both LD and EVOO [33]. – The study's results revealed that the two samples have identical FTIR peaks, with the exception of some areas where bacterial cellulose did not produce a strong peak like microcrystalline cellulose due to its compacted structure. However, the study proves that Enterobacter sp. M003 produces an authentic bacterial cellulose [30]. **UV-Vis spectrophotometer** – In this study, UV absorption was assessed on collagen samples isolated from carp scale waste using a UV-visible spectrophotometer. The results show that the benzene causes a bathochromic shift, particularly in the K band (204nm), which shifts to a wavelength of 268nm. The shift results not just from benzene aromatics, but also from alkyl substituents and functional groups. It denotes the existence of carboxyl and hydroxyl groups [25]. **(Gas chromatography-mass spectrometry) GCMS** – The volatile components of the triplicate A.malaccensis leaf extract samples were determined using a gas chromatography equipment. The findings revealed that different types of extracts produced varying numbers of peaks and compounds [14].

(*Contd.*)

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Table 4: The testing methods used to test the alternative option for halal critical ingredients (*Contd.*)

No	Themes	Sub-themes/ Supportive evidence
3	Particle Size Analysis	**(Particle Size Analyzer)PSA** – PSA was used to measure the size and distribution of micro-collagen particles.The obtained results ranged from 668 nm (d10 < 10%) to 1581 nm (d90 < 90%). The micro-collagen particle size with the highest distribution intensity was 1146 nm [25].
4	Activity Analysis	**2, 2-diphenyl-2-picrylhydrazyl (DPPH) Scavenging assay** – The sample with high antioxidant activity has a high amount of Gum Arabic (GA). Recent studies have also shown that GA has antioxidant qualities because it plays a role in lipid metabolism and improves kidney failure and cardiovascular treatment [13]. – This test was designed to investigate the antioxidant effects of fermented brewer's rice extracts. The results revealed that fermented samples had higher biological components and antioxidant activity than their unfermented counterparts which is favourably connected with total phenolic content [24]. **Quantitative reverse transcription polymerase chain reaction (qRT-PCR)** – The results showed that myricitrin therapy prevented alloxan-induced gene expression degradation or diabetes development. Among the altered genes, IκBα, STMN1b, and IL1b were associated with toll-like receptor pathways. The toll-like receptor detects β-cell death. Furthermore, inhibiting toll-like receptors can reduce β-cell mortality in diabetes [19]. **Ferric reducing antioxidant power (FRAP) Assay** – This experiment was designed to investigate the antioxidant effects of fermented brewer's rice extracts. The results revealed that fermented samples had higher biological components and antioxidant activity than their unfermented counterparts which is favourably connected with total phenolic content [7].

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Table 4: The testing methods used to test the alternative option for halal critical ingredients (*Contd.*)

No	Themes	Sub-themes/ Supportive evidence
5	Texture profile analysis	**Texture Analyzer** – The study results revealed that Gum Arabic had decreased hardness, cohesiveness, and springiness. Furthermore, it has a lower gumminsess value than gelatine, therefore it does not require a lot of energy to break down the pastille [13]. – The study found that the Bloom value (gelatin strength) of camel skin gelatin was 340 ± 0.5 g. This number is comparable to gelatin from bovine which was higher (267g) and almost similar amount to porcine source gelatin(350g) [26].
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No	Themes	Sub-themes/ Supportive evidence
		– Fuzzy Autocatalytic Set (FACS) is a novel chemometrics method where it discovered the FTIR spectra peaks of bovine, porcine, and fish gelatins.The method was successful because prominent peaks were able to observed and they are differ among the different types of gelatins. Hence, this method provides a warrant for halal authentication [34]. **LC-MS/MS Analysis** – The research revealed that the active content which was myricitrin, higher than the other compounds which are myricetin-3-rutinoside,,myricetin-3-O-pentoside, and myricetin. It remained steady throughout tree age samples [19]. **Amino acid analyser** – According to the findings, the total amino acid content in (Bovine Gelatin) BG and (Cobia Gelatin) CG is 99.51% and 86.65%, respectively [27]. **Modified Quartz Crystal Microbalance (QCM) sensor method** – The modified QCM sensor produced a satisfactory frequency response for distinguishing bovine and porcine gelatin. The measurements produced negative frequency shifts for bovine gelatin and positive frequency shifts for porcine gelatin, indicating that bovine gelatin is halal and porcine gelatin is non-halal [35].

commonly used the DPPH Scavenging assay to study the activity of a compound, especially the antioxidant properties. 3 articles that study the antioxidant properties used this DPPH assay. Other methods were also used to analyze the activity such as qRT-PCR and FRAP assay. However, these methods were only used in a maximum of 1 article respectively. The texture of a compound was analyzed using a texture analyzer commonly. To support this statement, 3 articles had used this method. On the other hand, HPLC systems and chemometrics are commonly used to study the content or composition of a substance. 5 and 3 articles used this method to figure out the content of their study compound respectively. In conclusion, the testing methods that were discussed above are commonly used in the research setting. However, there are other methods too such as the methods that were listed in Table 3. This review will serve as a guide for researchers on the different types of testing methods that can be used for the analysis of a product or substance.

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Conclusion

In conclusion, this study suggested alternative options for halal critical ingredients in halal pharmaceuticals and cosmetics. All the research objectives and the aim of this study were achieved. Hence, this studyconcludes that among the articles that were collected for this review study, insulin, and gelatine are the most commonly studied. Their alternative options whether it's from plant sources, marine sources, or microbe-based ingredients are tested extensively to assess for their desired effect or activity. The testing methods proved that the alternative options are much better than the critical ingredients in terms of their texture, morphology, activity, composition, and even the cost of synthesis.

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