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Modifications and Pharmaceutical Applications of Glucomannan as Novel Pharmaceutical Excipient in Indonesia: Review Article

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Abstract: Currently, Indonesia is excessively dependent on imported raw materials, such as pharmaceutical excipients. In this regard, the current pandemic should remind the critical nature of independence in purchasing raw resources to cope with future dynamics. One of the causes of dependence is the lack of raw materials management, specifically from biological sources abundantly available. A significant advantage is directed towards natural excipients because large quantities of more affordable plants ensure sustained availability in nature. Therefore, this study highlighted the possibility of using excipients derived from natural resources that are commonly used yet underutilized in Indonesia, such as glucomannan (GM). Indonesia has the potential to produce GM, considering the high natural resources as its source. However, it has not been applied extensively in pharmaceutical preparations due to diverse uses in several countries' drug, food, and cosmetic industries. This study aimed to discuss the modifications of GM and their use as pharmaceutical excipients with better physical properties. Additionally, the potential of melinjo seeds that have not been widely used was also analyzed. Melinjo seeds can be used as a source of GM due to their fairly large polysaccharide of about 64.11%. This issue will promote national autonomy in developing novel pharmaceutical excipients derived from natural resources that are highly economical and innovative.

Keywords: glucomannan; modification; natural excipients; pharmaceutical application

1. Introduction

Indonesia has 10% of the world's plant species, making it one of the most varied countries in terms of flora diversity (Rintelen *et al*., 2017). Based on Scopus data 2021, we were looking for several research studies on native plant species in Indonesia, both as medicinal ingredients and pharmaceutical excipients. While those that are not related to the two things were excluded. The results showed that research studies in Indonesia have a dominant tendency to find an active medicinal ingredients rather than the natural excipients (Figure 1) (Scopus, 2021). However, excipients are the most significant component of any pharmaceutical formulation derived from natural or synthetic with their respective advantages. Natural excipients are still used because

they are biodegradable, low-cost raw materials that are more readily available than synthetic ones and are renewable (Tekade & Yogita, 2013). Furthermore, they can provide a steady supply of raw materials in the future when cultivated or harvested sustainably. Therefore, the demand for those materials is growing, and new sources are being developed. The potential of natural ingredients that can be used as excipient raw materials in pharmaceutical applications was discussed while responding to these conditions.

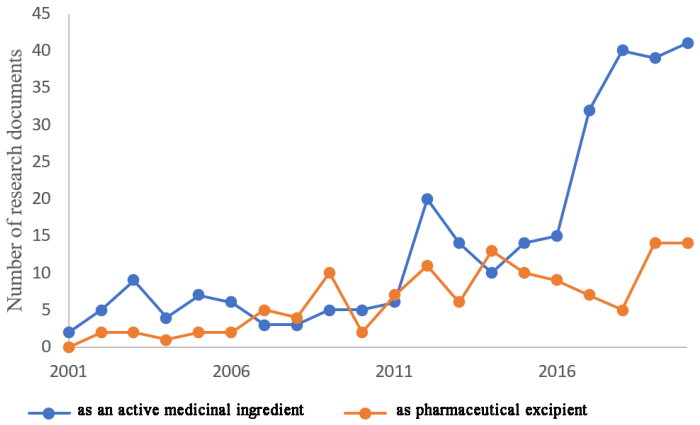

Figure 1. Number of scientific publications on the use of native plant species in Indonesia (Scopus, 2021).

In general, plant parts that are potential as raw materials for pharmaceutical excipients are based on their high content of polysaccharides (Pettolino *et al*., 2012; Willför *et al*., 2003). Polysaccharides are natural polymers most widely used as excipients in pharmaceutical preparations as binders (Owusu *et al*., 2021), fillers (Singh *et al*., 2020), disintegrants (Daglio *et al*., 2019), gelling agents (He *et al*., 2017), film formers (Gao *et al*., 2019), emulsifier (Chivero *et al*., 2015), stabilizers (Xu *et al*., 2019), and others (Maniruzzaman *et al*., 2013). However, the function of these excipients is not limited only to the pharmaceutical industry since it is useful in the food and cosmetic industries.

Glucomannans (GM) are among the polysaccharides that have not been optimally utilized as excipients. Based on Scopus (2021), the study on the use of GM in research journals in the last 20 years has been the lowest among all polysaccharides in the world (Figure 2). GM is one of the main constituent groups of hemicellulose in plant cell walls and can be useful in pharmaceutical preparations. It has adhesive properties and swells to form colloids when in contact with water (hydrocolloids). The adhesive properties are used as fillers, disintegrants, and tablet binders. Meanwhile, excellent swellability is used as a gelling agent, surfactant in cosmetics, stabilizing agent, coating film-forming, and texture-forming (Pan *et al*., 2011; Wu *et al*., 2018; Zhang *et al*., 2017; Zhou *et al*., 2013). Swelling GM can form a hydrogel layer that regulates the release of active substances such as diclofenac sodium extended-release tablets

(Korkiatithaweechai *et al*., 2011), ketoprofen (Yu & Xiao, 2008), theophylline (Nair & Jyothi, 2013), and diltiazem sustained-release tablets (Alvarez-Manceñido *et al*., 2008).

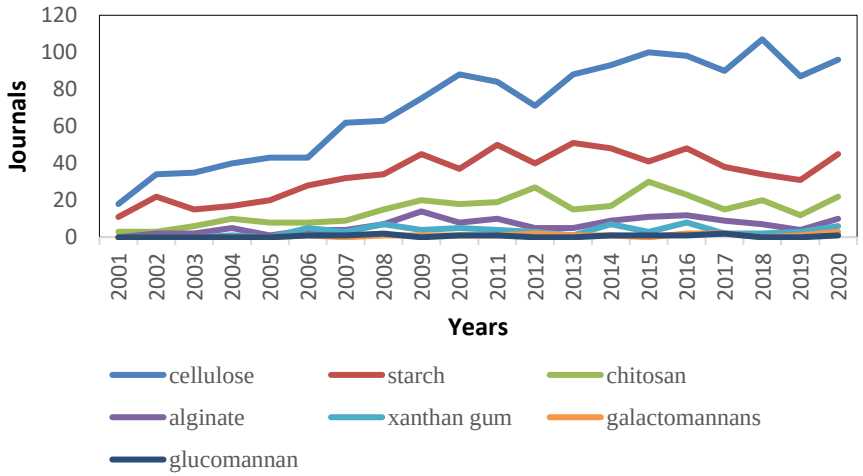

Figure 2. Plant polysaccharides used as pharmaceutical excipients in the world (Scopus, 2021).

GM is an excipient that has not been explored much with various applications in the pharmaceutical, food, and cosmetic sectors. In Indonesia, its use is limited because of the rare native plant (*Amorphophallus konjac* K. Koch); therefore, it has not received much attention. Currently, only about 100 scientific publications use GM as a pharmaceutical excipient. This number is minimal compared to other countries such as China which reached 1,100 articles. Meanwhile, Japan dominates the patent, having developed a consumable GM strain of *Amorphophallus konjac* K.Koch called konyaku (Boettger *et al*., 2011). It also has antioxidant activity used as a polymer to manufacture hydrogels, microparticles, and nanoparticles in China and Japan (Alves *et al*., 2020; Chen *et al*., 2018; Guerreiro *et al*., 2019; Liu *et al*., 2015).

Using local materials for pharmaceutical excipient is an opportunity to answer the high dependence of imported raw materials in Indonesia. Around 96% of raw materials for medicine are still imported from other countries, especially China, India, Europe, and America (Ministry of Health of the Republic of Indonesia, 2013). Lack of domestic raw material production contributes to a country's reliance on foreign suppliers. As a result, the pharmaceutical industry will eventually find it challenging to produce pharmaceutical products, or drug prices will rise, making access more difficult. One of the causes of dependence on imports of raw materials is the limited upstream sector of the pharmaceutical industry, including the development of excipient raw materials.

Meanwhile, GM has many functions in pharmaceutical applications. On the other hand, the research interest in Indonesia is still limited due to the lack of its plant source availability. Therefore, this study aimed to outline the optimization of GM extraction, modification and the

applications as well as its plants source while also motivating the procurement of novel and highly economical excipients.

2. Material and Methods

The method used to prepare article review is through library searches from both national and international journals downloaded from electronical databases such as Google Scholar, Scopus, and PubMed. The keywords used were “glucomannan as pharmaceutical excipient”, “optimization of glucomannan properties” and “modified glucomannan”. The number of libraries obtained was 85 journals, but those included in the inclusion criteria were 50 journals. The inclusion criteria are research articles published in 2011 – 2021 that discuss glucomannan excipients as pharmaceutical excipients. In contrast, the exclusion criteria were review articles, research articles that could not be accessed entirely and did not discuss glucomannan's optimization as an excipient in pharmaceutical preparations.

3. Physicochemical Characteristics

Mannan is one of the main constituent groups of hemicellulose in plant cell walls, consisting of four subfamilies, namely linear mannans, glucomannans, galactomannans, and galacto-glucomannans (Figure 3). Among the four types of mannan, glucomannan (GM) has a more natural abundance (Kuang *et al*., 2021; Mikkelson *et al*., 2013)

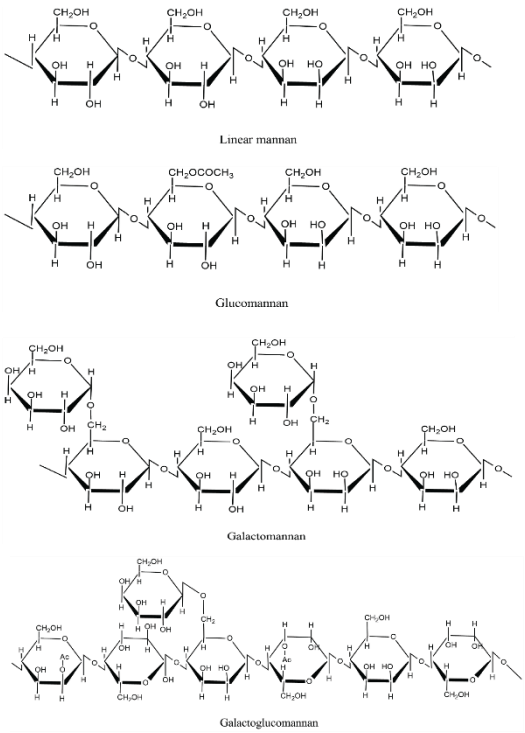

Figure 3. Four different subfamilies of Mannan (a) Linear mannan, (b) Glucomannan, (c) Galactomannan, (d) Galactoglucomannan.

GM is a linear chain β-1,4 heteropolysaccharide composed of D-glucose and D-mannose in a molar ratio of 1:1.6 or 1:1.4; where the glucose and mannose ratio depends on the plant

source. Studies on melinjo seeds showed GM with a glucose and mannose ratio of 1:1.4 in hardwoods and 3 to 4 times higher in softwoods (Nawawi *et al*., 2016). However, GM extracted from melinjo seeds has not been commercialized in the market. The most commonly used is konjac glucomannan (KGM), extracted from *Amorphophallus konjac* K.Koch and consumed as food in some parts of China and Japan. The Food Chemicals Codex has approved KGM as a gelling agent, viscosity enhancer, film-forming agent, and stabilizer (Du *et al*., 2012).

GM is hydrophilic due to the abundance of hydroxyl and carbonyl groups in its molecular chain. However, its solubility in water is affected by strong hydrogen bonds after drying and purification. The stronger the bonds between the molecules, the more difficult it is to dissolve in water (Chen *et al*., 2011). However, by increasing the concentration of the polymer, the swelling capacity will increase. This is because the hydrogen bonds limit the junction zone between GM molecules and promote interactions to form a network in the continuous liquid phase (gelation) (Zhang *et al*., 2014)

GM has a low acetyl group branch (5-10%) at the C-6 atomic position at every 9-19 sugar residues (Wardhani *et al*., 2017) to inhibit the formation of intramolecular hydrogen bonds, thereby increasing the solubility of GM (Wang *et al*., 2015; Xiao *et al*., 2015b). Consequently, an increase in the degree of acetylation causes a delay in the gelation process which affects drug release in GM (Huang *et al*., 2015; Wardhani *et al*., 2017).

The molecular weight (Mw) of GM as measured by light scattering and gel permeation chromatography showed an average molecular weight range of 10 to 2,000 kDa. The high molecular weight causes GM to have the highest intrinsic viscosity among other polysaccharides, reaching 30,000 cps at a concentration of 1%. Generally, commercial GM has a viscosity of about 19,679 cps The high viscosity of GM is explained by a solute-solvent or solute-solute interaction mechanism rather than by hydration Several methods have been carried out to obtain GM with low Mw, namely through depolymerization GM gelation is thermally reversible through physical agglomeration or cross-linking with other polysaccharides (such as xanthan, k-carrageenan, acetan and acetan deacetylation) The description of the physicochemical characteristics of GM is summarized in Table 1.

Table 1. Physico-chemical characteristics of Glucomannan (GM).

Physico-chemical characteristics	GM
Chemical composition	• consists of a linear chain of ß-1,4 linked D-glucose and D-mannose • has an acetyl group branch randomly at the position of the C-6
Molecular weight	10 – 2,000 kDa
Solubility	Soluble in boiling water (hydrophilic)

Viscosity and rheological properties	The viscosity of GM depends on the molecular weight and temperature of the solution. Solution temperature above 85°C indicates lower viscosity.

4. Modified Glucomannan

Table 2. Effect of structural modification on the physical properties of GM and its application.

No.	GM modification	Explanation	Optimized properties	Pharmaceutical application	Ref.
1.	Carboxymethyl konjac glucomannan (CMKGM)	• Carboxomethyl incorporation in GM produces negatively charged GM derivatives • Carboxymethylation and deacetylation decrease the hydrophilicity of GM depending on the type of activator	The nature of CMKGM relies on the degree of substitution (DS) i.e., higher DS gives: • increased thermal stability • denser network structure • particle size reduction • greater elasticity • decrease in molecular weight • increased solubility in water	• coat pH-sensitive drugs in gastric and upper gastrointestinal acids • matrix system for colon targeted drug delivery due to enzyme-induced degradation	(Neto *et al*., 2019; Liang *et al*., 2015; Long *et al*., 2011; Luan *et al*., 2017; Magalhães *et al*., 2009; Xiao *et al*., 2015a)
2.	Acetylated konjac glucomannan (AceKGM)	Acetylation weakens the hydrogen bonds that are abundant in the GM molecular chain, thereby limiting its water absorption	• reduce water absorption improved thermoplastic properties	• modulate macrophage activity to accelerate wound healing • applications in nutraceuticals and pharmaceuticals, where the lowest possible water absorption is required • Production of biodegradable plastic	(Campestrini *et al*., 2013; Koroskenyi & McCarthy, 2001; Lin *et al*., 2010; Wang *et al*., 2020)
3.	Oxidized konjac glucomannan (OKGM)	GM undergoes oxidation in the β-(1,4) molecular chain, which produces a reactive aldehyde group. The aldehyde group can be used as a crosslinking agent for macromolecules for	• form a tighter structure • increase tensile strength • drug release depends on the pH of the medium	The aldehyde group formed can be an agent for hydrogel formation through cross-linking and achieve long-term drug release	(Korkiatithaweechai *et al*., 2011; Liu *et al*., 2020; Lu *et al*., 2015; Luo *et al*., 2018)

No.	GM modification	Explanation	Optimized properties	Pharmaceutical application	Ref.
		the manufacture of hydrogels	• increase the adsorption efficiency of the hydrogel		

GM has weak mechanical properties; indicating it has a low tensile strength, hence it is susceptible to degradation, most notably when exposed to high amounts of water. This is due to the high number of hydroxyl groups in the polymeric chain, which can easily interact with water molecules and increase water absorption, thereby the gelation process decreases. Consequently, the improvement of the mechanical properties of GM was carried out to prevent the brittleness of the polymer. Additionally, several structural modifications and new processing technology were carried out through the co-process method to increase the mechanical strength of GM (Chen *et al*., 2011).

Modification is also an effective way to expand GM applications. Chemical and physical approaches have been used to modify KGM, including structural modification and novel processing technologies through co-processing. Table 2 describes some structural modifications of GM to optimize GM properties and applications.

4.1. Carboxymethyl konjac glucomannan

Modifying GM structure through carboxymethylation is one way to change the charge of polysaccharides. GM carboxymethylation (CMKGM) produces negatively charged GM derivatives. It can be applied as a vehicle for drug delivery systems through electrostatic interactions with positively charged polymers such as chitosan. The properties produced using a base depend on the degree of substitution (DS). Higher DS lowers molecular weight and particle size but produces a denser network structure, increased elasticity, solubility in water, and thermal stability. Wang *et al*. (2019) explained that the type of alkaline activator played a role in the properties of the CMKGM produced. Different effects are shown by using strong and weak bases as activators. Using sodium acetate (a weak base) as an activator cannot degrade GM since there is no decrease in molecular weight. The inclusion of a carboxymethyl group removes a small portion of the acetyl group to prevent water molecules from approaching the hydrophilic group and decreasing water solubility (Wang *et al*., 2019; Xiao *et al*., 2019; Xiao *et al*., 2015b).

4.2. Acetylated konjac glucomannan

Acetylation is an excellent method of reducing the extremely high-water absorption of native konjac glucomannan. Furthermore, KGM (AceKGM) acetylation was carried out using the reflux method in acetic anhydride using NaOH as a catalyst. The acetylation reaction and DS rate can be increased by increasing the catalyst concentration or temperature. DS depends

on reaction conditions and affects water absorption. The original KGM DS was low at 0.05-0.08 and was not measured. A 5-fold increase in DS occurred at reflux temperature (~120 °C) compared to 70 °C. Water absorption reduces fast as DS increases, to the point where a very moderate DS (0.5-1.0) is adequate to reduce water absorption drastically. AceKGM swells and floats in organic solvents such as chloroform due to its increased hydrophobicity (Koroskenyi & McCarthy, 2001).

KGM is a promising material for manufacturing plastics that can be decomposed by temperature. However, it lacks thermoplasticity which typically undergoes thermal decomposition before reaching the glass transition temperature (Tg) and melting temperature (Tm). Therefore, Lin *et al* (2010) analyzed the effect of acetylation on the thermal stability and thermoplastic properties of KGM. The thermoplasticity of KGM increases with acetylation because it reduces hydrogen bonding. AceKGM with a DS of more than 1.25 has thermoplastic properties and can melt before thermal decomposition. The manufacture of biodegradable plastics using AceKGM can be conducted using the melt-processing or the casting method.

AceKGM can modulate macrophage activity in the pharmaceutical industry to accelerate wound healing. The enzyme-linked immunosorbent assay results (ELISA) showed that AceKGM fibrous membrane increased macrophage expression of anti-inflammatory and pro-regenerative cytokines and significantly accelerated wound healing through re-epithelialization, tissue remodeling, and collagen deposition (Wang *et al*., 2020).

4.3. Oxidized konjac glucomannan (OKGM)

KGM is oxidized in the β-1,4 molecular chain due to a reaction with sodium periodate, which produces a reactive aldehyde group. The aldehyde group can be a macromolecular crosslinking agent for hydrogel formation and achieve sustained drug release. Hydrogels consist of a three-dimensional network of hydrophilic polymers, which, when placed under conditions of excess water, are able to swell and hold large amounts of water without being dissolved (Luo *et al*., 2018).

The crosslinked polymer between OKGM and chitosan can increase the adsorption efficiency of diclofenac sodium (DFNa). CTS:OKGM:DFNa ratio of 1:2:1 (w/w) showed the slowest release of DFNa and gave the highest % adsorption efficiency. The amount of OKGM used affects the number of cross-links formed, thereby increasing the adsorption of diclofenac sodium (Korkiatithaweechai *et al*., 2011).

4.4. Combination of GM with other polymers

Non-ionic KGM has limited use as a vehicle for drug delivery systems through electrostatic interactions. So that incorporation with other positively charged polymers can help

improve the mechanical properties of GM, which produces a hydrogel film that is elastic. The technique of combining two or more excipients designed to modify physical properties in a way that cannot be achieved by simple physical mixing is called a co-processing method. The co-processing method does not induce chemical interactions so that the co-processed excipients formed can be considered safe to use and therefore do not require additional toxicological studies, which will save manufacturing time. Another advantage of using the co-processing method in making excipients is that the co-processed excipients will cover each other's shortcomings and increase GM's stability, solubility, and gelling properties (Erdemir *et al*., 2019; Narang & Boddu, 2015)

The co-process method helps to optimize the physical properties of each excipient. For example, stabilization of GM gels can be achieved by combining them with other polysaccharides such as xanthan gum using a freeze-drying method that results in controlled drug release (Abbaszadeh *et al*., 2016). Hydrogels with a combination of two polysaccharides (XG and KGM) without chemical crosslinkers can form in-situ thermo-reversible hydrogels. In the healing of burns, treatment indicates immediate wound closure.

The co-processing method with milling on GM affects the particle properties. The results showed that longer milling time resulted in a higher angle of repose, lower molecular weight, and coarser powder surface. KGM powder milled for 4 hours achieved the shortest float time, longest float duration time, and optimum controlled release properties when used as excipient in the floating drug delivery system. Then, it forms a hydrogel layer for controlled drug release (Liang *et al*., 2015).

Liu *et al*., (2020) reported that OKGM and cassava starch prepared by dry heat showed low solubility and swellability, which was beneficial for the preparation of sustained-release tablets. Furthermore, in the same study showed that incorporation with sucrose ester with an HLB value of 5 significantly reduced the porosity and swellability of tablets and slowed drug release from 94.36% to 83.29%, and mean dissolution time increased from 4.50 hours to 5. 79 hours. Meanwhile, Lu *et al*., (2015) reported the potential of microspheres made of oxidized konjac GM (OKGM), which were cross-linked by Fe^{3+} through the emulsification method and coated with positively charged chitosan oligosaccharides (COS) to be able to sustainably release anthocyanin antioxidants in the intestine.

5. Application of Glucomannan

GM has been investigated as an excipient in tablet preparations, hydrogels, and wound dressing films because it has good gelation properties and is biodegradable. The Food Chemicals Codex has approved GM as a gelling agent, viscosity enhancer, film-forming agent,

and stabilizer (Du *et al*., 2012). Interestingly, recent studies have raised the potential of GMs for targeting nanocarriers to specific receptors, namely the mannose receptors on the cell surface. The presence of mannose on the particle surface increases the uptake of mannose receptors by M cells and macrophages (Guerreiro *et al*., 2021). Several GM modifications as shown in Table 2 are useful for expanding GM applications, such as:

5.1. Glucomannan-based hydrogels

CMKGM can form hydrogels through electrostatic interactions. The hydrogel formed exhibited a significant increase in density and tensile strength also improved the solubility of GM in water. In addition, the cross-linked CMKGM modulates the swellability and the rate of moisture transmission, thereby accelerating tissue regeneration. In addition, OKGM was used to form a network on the gelatin hydrogel (GL) which slowed the release of the drug ketoprofen, and the release rate could be adjusted according to the OKGM/GL ratio (Hongbo *et al*., 2019; Luo *et al*., 2018; Yu & Xiao, 2008).

5.2. Glucomannan-based oral colon targeting drug delivery system

In the pharmaceutical field, GM is widely studied as an oral colon targeting drug delivery system (OCDDS) or to treat colon disease specifically because of the presence of β-mannanase in the colon, which substantially accelerates the degradation of GM. For instance, CMKGM is used as a delivery system for nutrients such as curcumin to the gastrointestinal tract. This system did not change the particle size and morphology of curcumin but increased the efficiency of curcumin encapsulation and then released curcumin sustainably (Wu *et al*., 2021). Carboxymethylated KGM (CMKGM) as a matrix in colon targeted drug delivery system capable of coating the pH-sensitive drugs and degraded by hydrolysis of β-mannanase enzyme (Wang *et al*., 2019; Xiao *et al*., 2015b).

5.3. Glucomannan-based microparticles

The presence of mannose in the structure of GM polymers can be used as a material for targeting macrophages. Macrophages recognize GM because it has a mannose receptor so that GM can be used as a biodegradable polymer for drugs that target macrophages. Spray-drying GM was used as a carrier matrix for tuberculosis therapy. The results showed that the microparticles consisting only of KGM displayed the most suitable characteristics compared to other spray drying excipients such as mannitol. The drugs isoniazid and rifabutin are mostly associated with microparticles of biocompatible GM (88-104% efficiency) and the obtained microparticles have an aerodynamic diameter of about 3 μm which allows deeper lung penetration (Guerreiro *et al*., 2021; Wardhani *et al*., 2020).

5.4. Glucomannan-based nanoparticles

The combination of GM-chitosan used as a promising nanoparticulate peptide and protein carrier. These nanoparticles exhibit increased stability in ionic media and delayed release of proteins that depend on the degree of cross-linking. The resulting particle size is about 200-700 nm with varying zeta potential (-2 to +39 mV). Recently, silver nanoparticles have been synthesized using the combination of KGM-Montmorillonite to produce antimicrobial films. The qualitative test of antibacterial activity of silver nanoparticles coated with KGM-Montmorillonite (MTM) proved to be efficient in suppressing bacterial growth, which makes it potential as an antimicrobial film in the biomedical field. The layered structure of the KGM-MTM silver nanoparticle composite film is beneficial for the continuous release of silver particles resulting in an extended antibacterial effect (Alonso-Sande *et al*., 2006; Cuña *et al*., 2006; Zhu *et al*., 2018).

6. Isolation of Glucomannan

GM can be extracted using mechanical, enzymatic, and chemical methods. The mechanical method starts with milling the slices of the plant parts, and then they are dried and sieved. However, this method results in low GM purity sold as processed foods at low prices. The enzymatic method uses a starch hydrolysis enzyme of alpha-amylase, with an incubation temperature of 50 °C. The enzymatic purification method is not optimal because it is not selective in starch degradation. The most common GM flour purification method uses chemical methods with ethanol as a solvent because it is simple and highly efficient. Ethanol acts as a GM anti-solvent to remove impurities, and it dissolves impurities such as ash, starch, fat, protein, oxalate, and crude fiber to obtain high GM extract (Ardhany *et al*., 2019; Nurlela *et al*., 2021; Pasaribu *et al*., 2020). Furthermore, Xu *et al*., (2014) illustrates that GM does not expand when in an ethanol/water system but not in water-soluble sugar compounds and proteins. During this process, water-soluble sugar particles and proteins separate, then the presence of heating also helps remove ash adhering to the GM surface.

Pasaribu *et al*., (2020) reported that washing GM flour from *Amorphophallus muelleri* Blume with 50% ethanol and 2% NaHSO3 for 4 hours while stirring increases the GM content from 32.65% to 83.96%. Subsequently, this washing process did not show a decrease in GM flour's iron and calcium content as sources of minerals that can be consumed.

GM can be purified using many techniques, such as non-solvent precipitation, ultrafiltration, membrane filtration, and column chromatography. Non-solvent precipitation usually uses ethanol, methanol, isopropanol, acetone, ammonium sulfate, and polyethylene. This process does not need specialized equipment, allowing for more adaptability in production size to purify GM from various sources. Therefore, the non-solvent precipitation method has

great potential to be used for the large-scale production of fractionated GM in the future. The ultrafiltration method uses a membrane to separate high molecular weight substances such as protein, starch, dextran from the solution. Compared to the other fractionation techniques discussed above, column chromatography is the most extensively utilized and successful, but purification using this method has been challenging to use for a long time. Therefore, this technique is expensive and not suitable for large-scale industrial preparations (Al-Rudainy *et al*., 2020; Tang *et al*., 2020; Zhang *et al*., 2007).

The GM isolation method described above shows that the Indonesian industry can produce the polysaccharide. Moreover, GM has great use in the pharmaceutical, cosmetic, and food industries. The use of GM as a biodegradable, biocompatible, and sustainable medication delivery system has enormous promise. In addition, the effect of the β-mannanase enzyme produced by the microflora Bacillus sp. in the human colon can target the delivery of drugs or pH-sensitive proteins-peptides (Wang *et al*., 2019).

7. Future Perspective and Limitation

GM as an excipient has not been widely used in Indonesia. Meanwhile, as discussed above, GM shows a very wide use in the drug, food, and cosmetic industries in several countries. The utilization of abundant biological resources in Indonesia is a strategic way to promote the independence of raw materials. Therefore, GM should be isolated from sources other than *Amorphophallus konjac* K.Koch. considering the limited sources of these plants in Indonesia. One of the plants with significant resources but small utilization is melinjo seeds. This plant is used as a source of GM, but research conducted on this matter is still limited.

The production of melinjo in Indonesia, which is not limited to seasons (BPS, 2020), has enormous potential to be used as raw material for excipients. This improves the added value of melinjo, transforming it into a high-value commodity. There has been no scientific article discussing the potential of melinjo seeds as an excipient raw material other than a processed food product. Based on research, melinjo seeds contain a reasonably large polysaccharide, about 64.11% of which GM dominates (Bhat & Yahya, 2014; Melvin & Stewart, 1969; Nawawi *et al*., 2016). This is undoubtedly an excellent opportunity to produce GM from melinjo seeds.

Kato *et al*., (2009) extracted metabolites from melinjo seeds using 50% ethanol using the soxhlation method. The polysaccharides in the seed extract were washed with distilled water then eluted using methanol in reverse phase ODS chromatography. The eluate was evaporated under vacuum and followed by column chromatography of Sephadex LH-20 with 50% methanol to produce a pale brown amorphous powder of gnemonoside. Several studies also used ethanol to extract melinjo seeds, but this procedure did not show the optimum purity (Bhat

& Yahya, 2014; Mun'Im *et al*., 2017). Melvin & Stewart, (1969) extracted GM from melinjo seeds using 5% and 24% KOH. Cellulose polysaccharides were washed with 0.01 N HCl (cold extraction), then with water until free of chloride and dried. Cellulose polysaccharides were extracted with alkaline borate for 1 hour at 20 °C. The residue was neutralized, dialyzed, and freeze-dried to yield crude GM. However, this method produces a tiny glucomannan fraction of the cellulose polysaccharide, which is 2.3% from wood. Several methods have been carried out to analyze the components of melinjo, and more efforts should be devoted to optimize the extraction and purification procedure of GM from melinjo seeds and obtaining a large amount of GM from it.

The excipient raw material industry can produce GM from melinjo seeds. This is because the source is not difficult to obtain, and the amount is very abundant in Indonesia. The technology for production is also available, and using local materials as excipients can improve the welfare of Indonesian farmers in planting melinjo. Moreover, melinjo seeds are not only used traditionally and simply for local confectionery; they can also be developed into pharmaceutical excipients with high economic value.

In terms of limitations, this study uses a database with specific keywords, as listed in the methodology. Second, it recommends one of Indonesia's local plants as a source of GM raw material, which is still underutilized, namely melinjo. However, studies concerning the optimization of GM extraction on melinjo seeds are very limited; therefore, it should be investigated further to be applied as a pharmaceutical excipient.

This study has discussed GM's broader applications and can be used as a pharmaceutical excipient with some modifications to produce GM with better physical properties. The potential of melinjo as a natural resource and many studies related to glucomannan are further boosted to develop the excipient raw material industry. The pharmaceutical industry, assisted by academics, and the government, should be improved and transformed, hence have the ability to promote self-sufficiency in meeting domestic raw material needs by utilizing widely available local materials.

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Conflict of Interest

All authors declared that there was no conflict of interest.

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