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Harnessing the Potential of Several Local Indonesian Tuber-derived Starches as Pharmaceutical Excipients

Ronald Horison, Silvia Surini*
Faculty of Pharmacy, Universitas Indonesia, Depok, West Java, Indonesia

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ABSTRACT

Starch is one of the widely required excipients in pharmaceutical dosage forms manufacturing. Indonesia's rich biodiversity, encompassing tubers like arrowroot, taro beneng, porang, ganyong and yams, harbours the potential for novel starch excipient sources. These tubers provide starch variations with distinct functional properties influenced by the natural starch granules' properties and amylose-amylopectin ratio. Previous research utilizing natural and modified starches from these tubers has demonstrated their potential in pharmaceutical formulation. These starch tubers have been studied and provided promising results in tablet formulation and film development. Additionally, they could be involved in developing more advanced dosage forms, such as starch nanoparticles and nanocrystals. The rich versatility of these tuber starches solidified a promising future for their development, offering significant advantages for both pharmaceutical technology and economic value perspectives. Optimization of the starch yield, mainly through extraction, is crucial to fully realizing the economic prospect of tuber-derived starches.

Keywords: *starch; tuber-starches; Indonesian tuber; pharmaceutical excipients; excipients development*

**corresponding author*
Email: silvia@farmasi.ui.ac.id

INTRODUCTION

Excipients are crucial in ensuring that pharmaceutical dosage forms meet the required quality specifications. Starch, prevalent excipients in the pharmaceutical industry, impacts drug performance, quality, safety, efficacy, acceptance, and stability across various dosage forms (Adetunji, 2020). Equivalently, starch is also extensively used in the food industry as a gelling agent, thickener and ingredient in diverse food and beverage products (Egharevba, 2020). The demand for starch in the market has grown significantly in recent years. Despite the considerable growth, global starch production mainly came from corn, cassava, potato, and wheat sources (Vilpoux et al., 2018).

Indonesia, despite possessing rich biodiversity within the tropical belt and harboring a wider variety of starch-bearing crops compared to sub-tropical regions (Vilpoux et al., 2018), relies heavily on import trade to fulfil its domestic needs of pharmaceutical-grade starch excipients. Among the vast sources of tuber starches, solely cassava starch has been commercially exploited as a significant source of starch (Moorthy et al., 2017). Nevertheless, other than cassava, Indonesia is rich in various underutilized tubers such as arrowroot (*Maranta arundinacea* L.), taro beneng (*Xanthosoma undipes* K.Koch), porang tuber (*Amorphophallus muelleri Blume*), gembili yam (*Dioscorea esculenta*), ganyong tuber (*Canna edulis Kerr*) and various species of other tubers. Despite their potential as rich starch sources, these tubers hold limited economic value due to their restricted use in small-scale traditional food production. Consequently, developing excipients from these underutilized and readily available tubers presents a promising solution to meet the rising demand for starch in diverse pharmaceutical dosage forms. Furthermore, understanding the tuber starch's rheological, gelling and thermal properties can provide valuable insights for understanding and predicting the pharmaceutical application of these starch (Sukhija et al., 2016).

In this review, detailed explanations about starch properties and their relationship to starch granules' properties and composition, followed by a brief discussion of the principle of starch extraction. The review also highlighted the development of tuber starch excipients and their applications in the formulation of several pharmaceutical dosage forms. This review's tuber discussion is limited to arrowroot, taro beneng, porang, ganyong, and gembili yam, which are the most prevalent in Indonesia.

METHODS

Based on previous studies, this review presents the potential of starch production from several Indonesian tubers to be developed as pharmaceutical excipients. A detailed literature review was 'Indonesian tubers', 'tuber starches', 'tuber starch properties', 'tuber

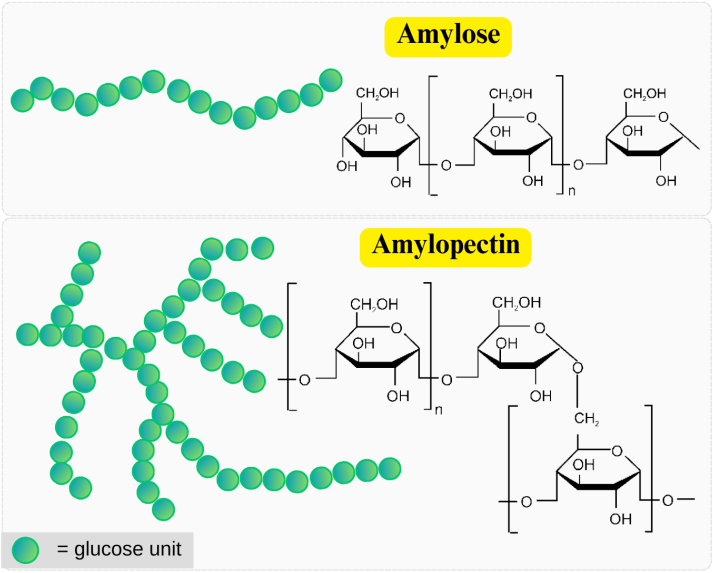

Figure 1. Amylose and amylopectin chain structure

starch extraction', 'tuber starches excipient', '*Maranta arundinacea*', 'arrowroot', '*Xanthosoma undipes* K.Koch', 'taro beneng', '*Amorphallus muelleri* Blume', 'porang tuber', '*Canna edulis* Kerr', 'ganyong', '*Dioscorea esculenta*', 'gembili', 'starch nanoparticles', and 'starch nanocrystals' on various search engines such as Google and ScienceDirect.

RESULTS AND DISCUSSION

Starch Granules Properties in Determining Starch Functionality

The versatility of starch applications is defined by its physicochemical properties due to variations in starch granule morphology and size. Starch granules comprise semi-crystalline and amorphous concentric layers (Sholichah et al., 2019). The starch granule size, morphology, and shape depend on the composition and arrangement of amylopectin and amylose and their biological origins. The tuber starch granules are primarily oval-shaped, with smaller portions varying from polygonal to lenticular (Kunle, 2020). Starch granule's size and shape were primarily influenced by the botanical sources, along with genetics and environmental conditions during growth (Bajaj et al., 2018).

Starch granule size can be classified into four categories: large (>25 µm), medium (10–25 µm), small (5–10 µm), and very small (<5 µm) (Builders & Arhewoh, 2016). The granule's size affects the starch dispersion properties even at similar amylose-amylopectin content, where small granule starches tend to have a lower pasting temperature compared to larger granules due to increased water absorption and water hydration, leading to a higher amount of amylose leaked out. The smaller granule signifies a higher amorphous arrangement of the polysaccharide chains, rendering them susceptible to water hydration.

The starch granule complex is composed primarily of amylopectin and amylose. Amylopectin forms a concentric core within the granule, with amylose dispersed at the matrix. Amylopectin is a nonrigid branched structure of anhydroglucose molecules, while amylose is a linear molecule of glucose linked with a glycosidic bond, as depicted in Figure 1 (Builders & Arhewoh, 2016). Amylose, rigid due to tight packing from its straight chain, is insoluble in water. However, it can disperse in hot water without gel formation due to a sparse amount of hydroxide groups providing restricted interaction with water. Amylopectin, which is nonrigid in a structure equipped with many hydroxide groups, favours the interaction with water, resulting in gel formulation. Amylopectin contents correlates with granule size, as smaller granules possess more amylopectin chains with lower degrees of polymerization, while amylopectin chains with higher degrees of polymerization are seen in large starch granules (Kunle, 2020).

Variations in amylopectin–amylose composition at starch granules lead to variations in paste profile, retrogradation, gel and rheological properties (Tarique et al., 2021). Biduski et al. (2018) reported that gel formed from starch with elevated amylose content possessed a compact, rigid gel microstructure, whereas gel from higher amylopectin resulted in a loose network structure (Biduski et al., 2018). Tian et al. (2023) also observed that a gel made from rice flour with higher amylose content resulted in higher retrogradation enthalpy, which indicates higher energy is required to disrupt the crystalline structures (Tian et al., 2023).

Tuber starches are comparable with commercially available starch excipients from various sources with varied starch granule characteristics and starch compositions. Commercially available starch mostly came from maize starch (Starch 1500, C*PharmGel), potato starch (Solani Amylum) and wheat starch (Wheat Starch TB). Tuber starches have distinctive differences in terms of starch properties due to their native origin. Compared with wheat (26.27%) and maize starch (26.28%), tuber starch (35.20%) generally contains higher amylose and larger granule size (Nuwamanya et al., 2011; Tarique et al., 2021). Tuber starch with higher amylose possesses great structure integrity and is suitable for hydrogel, film-based dosage forms, and matrix-forming agents. Additionally, cereal starches have weaker gel structures with higher hydrophilicity (Tarique et al., 2021).

Starch minor constituents significantly affect starch functional characteristics. Regarding starch compositions, wheat and maize starches have significantly higher lipid and protein contents than tuber starch (M. Li et al., 2022). Lipid and proteins is absorbed at starch granule surface which could form a hydrophobic barrier coating the starch granules, thus limiting the starch wettability and water penetration (M. Li et al., 2022; A. P. Putri et al., 2017). Higher protein and lipid in wheat and maize starch resulted in lower starch wettability, which plays a role in lower viscosity, higher gelatinization temperature, and limited disintegration potential (Builders & Arhewoh, 2016; M. Li et al., 2022). Adjei et al. (2017) compared the disintegration potential of wheat, maize and cassava starch in paracetamol tablets. The study reported that native cassava starch, with a faster disintegration time compared with wheat and maize starches, had the potential to be utilized as a tablet disintegrant (Adjei et al., 2017). Compared with wheat and maize starch, potato and cassava starch with larger granule size and higher amylose content possess higher amylose leaching percentages, an indicator of starch thermal stability due to the disruption of crystalline amylopectin region than wheat and maize starch. The studies postulated that weaker amylopectin regions are generally observed within tuber starch granules (Nuwamanya et al., 2011). Therefore, tuber starches could excel as substitute for wheat and maize starch as disintegrants at tablet formulation, encapsulant materials, and film-forming agents (Malki et al., 2023; Patomchaiviwat et al., 2011; Sholichah et al., 2019).

Tuber Starch Extraction

Starch extraction from tubers involves several processes, as depicted in Figure 2. The precipitation method is mainly adopted to extract starch from the cassava industry (Vilpoux et al., 2018). The main purpose of starch extraction is to isolate starch in its purest form (M. Li et al., 2022).

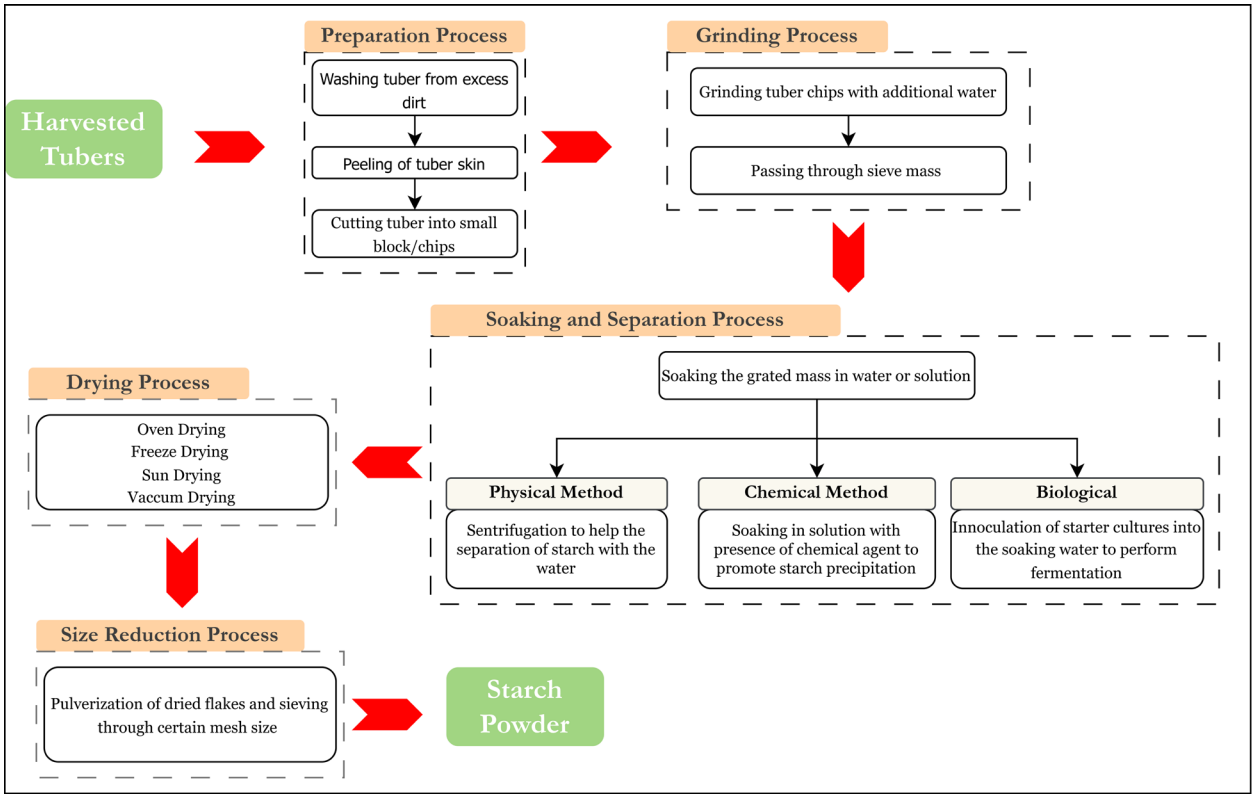

Figure 2. Starch extraction process from tuber source

In general, starch extraction from tubers starts by washing tubers to remove any excess dirt before getting peeled and subjected to a grinding process with the aid of water until it passes through a mesh sieve. The grinding process exposed the starch granules and made them more accessible to extract (Guilherme et al., 2018). The disintegrated mass was then submerged in water for 24 hours (Sukhija et al., 2016; Wahyusi et al., 2022). The submersion or steeping steps promote water diffusion into the tuber starch cellular components to promote hydration. In nature, starch is insoluble in water because it has numerous crystalline regions in its granules. The precipitated mass is gathered. The effectiveness of the soaking method in producing high yield is determined by soaking time, temperature, and soaking liquid composition. The obtained mass is later washed to remove the excess protein and chemical residue. The washed mass is subjected to the drying process to obtain dried flakes, which were then pulverized into fine powder (Sukhija et al., 2016).

The separation methods involve additional stimuli to physically, chemically, or biologically enhance precipitation and protein removal. Physically, addition of centrifugal force through mixing could promote the starch precipitation and promote higher starch surface area contacted with water. While starch separation could be done by centrifuge, it is only possible in small lab-scale production and required further process to removing protein that act as impurities (Thuppahige et al., 2023). Chemical methods involve soaking water with additional compounds such as alkalinizing agents (sodium metabisulphite, sodium bisulphite, and sodium hydroxide), sulphur dioxide (SO_2) (Ghoshal & Kaur, 2023). Sodium salts and NaOH create an alkaline solution for the soaking water. Alkali extractions solubilize the protein in the starch granules, which separate from the starch. This method's drawback is that it potentially degrades the starch double-helix and crystalline structure, resulting in low starch yield at high alkali concentrations. A combination of proteolytic enzymes such as bromelain with alkali treatment is required to reduce the amount of alkali concentration. Another viable agent is soaking in SO_2 solution, which helps control the spoilage microbe growth and preserves the color by denaturing the browning enzymes and softening the protein matrix bonds with starch. Therefore, employing SO_2 causes environmental concerns since proper wastewater treatment and washing processes are required (M. Li et al., 2022; Sukhija et al., 2016). Biologically, the involvement of proteolytic enzymes (pepsin, bromelain and papain) could help attack the protein-starch complex adsorbed at the surface of granules to promote the separation of protein. Another attempt could involve an enzymatic reaction provided by fermentative microbes. Alternatively, the fermentation-based isolation method involved soaking tuber mass in an aqueous solution containing *Spectrococcus lactis* due to its enzymatic reaction (Z. Li et al., 2008).

Table 1. Comparison of tuber starches physcochemical properties with commercially available starch excipients

Parameters	Potato Starch	Wheat Starch	Maize Starch	Cassava Starch	Sweet Potato Starch
Trade name	Solani Amylum	Wheat Starch TB	Starch 1500, Lycatab, C*PharmGel	-	-
Moisture content	13.01 ± 0.02 13.67	10.0 to 12.15 ± 0.01	7.2 to 11.29 ± 0.07	10.93 ± 0.05 to 16.50	9.33 to 9.72 ± 0.04
Ash content (%)	0.26	0.60	0.54	0.31	0.28
Protein content (%)	1.82	6.44	2.20	0.52	1.13
Lipid content (%)	0.15 – 0.46	0.74 ± 0.01	0.62 ± 0.01	0.14 ± 0.04	0.13 ± 0.01
Total starch (%)	86.80 ± 0.41	86.87 ± 0.23	87.63 ± 0.76	88.95 ± 0.16	89.97 ± 0.35
Amylose content (%)	24.16 ± 1.16 – 31.09	24.50 – 26.40	28.49 – 29.20	17.71 ± 4.87	18.82 ± 2.05 to 19.57 ± 0.2
Amylopectin content (%)	75.84 ± 1.16	73.60 ± 3.75	71.51 ± 2.15	82.29 ± 4.87	81.18 ± 2.05
Granule size (μm)	35.74 ± 0.1 to 70.7	19.19 ± 0.1	5.85 ± 0.07	23.3 to 306.27	16.67 ± 0.1 to 90
Granule shape	Oval, ellipsoidal, spherical	Disk, irregular, lenticular	Polygonal, spherical, oval	Oval, bell spherical	Oval, polygonal, irregular

Sources: (Bajaj et al., 2018; Guo et al., 2023; He et al., 2020; Lyu et al., 2021; Nuwamanya et al., 2011; Tong et al., 2023; D. Zhang et al., 2017)

Established tuber starch drying methods include oven drying (Sukhija et al., 2016; Wahyusi et al., 2022), sunlight drying (Jufrinaldi et al., 2023) and freeze-drying (Thuppahige et al., 2023). Oven drying, significantly impact the product properties like porosity and density. Zhao et al. (2024), in the previous studies, stated that oven drying caused the collapsed structure of kudzu tuber starch (*Pueraria montana* var. lobata) due to the dissociation of starch molecules along with water to break the surface structure of granules (Zhao et al., 2024). The phenomenon was also reported in oven drying of cassava starch, which weakened the starch granule's integrity (Aviara et al., 2010). Higher granule porosity will lower starch density while improving the granule's wettability. While sun drying is cost-effective and straightforward, oven drying offers a more widespread, reliable and affordable alternative. Regardless of their higher costs, freeze-drying and vacuum-drying minimize the oxidation of phenol compounds by decreasing the emitting heat at lower temperatures to preserve their white colour. Compared with starch functional characteristic, there was not a significant difference in viscosity and swelling capabilities of starch characteristics due to the drying method, as demonstrated by Jufrinaldi et al. (2023) to understand the impact of oven and sunlight drying methods towards starch functional characteristics (Jufrinaldi et al., 2023).

Indonesian Tuber-Derived Starches as Pharmaceutical Excipients

An overview of tuber starch properties was covered in this section, as presented in Table 1. Various tuber starches have been studied to develop as potential pharmaceutical excipients. Several chemical or physical modifications have been performed to improve its application as an excipient.

1. Arrowroot (*Maranta arundinacea* L.)

Arrowroot is a perennial herb with a tuberous rhizome mainly found in the West Indies, Brazil, Indonesia, the Philippines, India and Sri Lanka. Arrowroot is categorized as a perpetual plant with 90 – 150 cm in height and green leaves with 10 – 20 cm in length. The white rhizomes have 2.5 cm width and 20 – 40 cm length, as shown in Figure 3 (Tarique et al., 2021). Arrowroot was originally from West Brazil, where Indonesia's climate suits arrowroot cultivation (Sholichah et al., 2019). 14-month-old arrowroot rhizomes show the highest dry mass and starch content, ready to be processed (Tarique et al., 2021). Arrowroot starch contained 10.8%-21.1% crude protein, 11.1%-30.2% crude fibre, and 3.8%-17.0% ash (Amante et al., 2021). The starch granules are considered large (10 µm to 35 µm) with an ellipsoid shape (Guilherme et al., 2018). Arrowroot starch contain 0.14-21.1% protein, 0.01-1.43% fat content, 0.33-3.60%, 80.77-84.2% total starch content, 7.06-15.24% moisture content, 0.33-3.60% ash content (Amante et al., 2021; Chit, 2016; Waraczewski et al., 2022). Arrowroot starch have varied amylose content ranging from 21.9% (Aprianita et al., 2014), 24.95 ± 1.49% (Malki et al., 2023), 25.64 ± 1.32% (Astuti et al., 2018), 35.20% (Tarique et al., 2021) to 42.01 ± 0.24% (Valencia et al., 2015). The amylopectin content from arrowroot starch are varied from 62.3% to 84.79% (Waraczewski et al., 2022).

The development of arrowroot starch as a pharmaceutical excipient has been done in natural and modified forms, either at tablet formulation or film formulation, as presented in Table 3. Utilization of arrowroot starch as a binding agent in the wet granulation process has been done by Yulyadah et al. (2021) in the formulation of ibuprofen tablet using wet granulation.

Figure 3. Arrowroot plant (left) and arrowroot rhizomes (right)

Table 2. Compilation of various tuber starch characteristics

Parameters	Arrowroot	Taro Beneng	Ganyong	Gembili Yam
Color parameters	L*: 75.52 ± 0.12 to 92.92 ± 0.97 a*: 0.83 ± 0.01 to 1.17 ± 0.18 b*: 6.00 ± 0.07 to 7.22 ± 0.81	L*: 81.14 ± 0.01 to 85.30 ± 0.01 a*: 0.94 ± 0.01 to 3.14 ± 0.01 b*: 11.29 ± 0.81 to 12.35 ± 0.01	L*: 57.93 to 73.00 a*: 0.82 ± 0.23 b*: 9.20 ± 0.40	L*: 84.09 ±0.20 to 87.22 ±0.12 a*: -3.06 ±0.03 to 1.84 ±0.00 b*: 9.87 ±0.04 to 11.19 ±0.03
Whiteness Index (%)	4.12 ± 0.49 to 18.84 ± 0.09	n.d	84.58 ± 0.47	n.d
Starch content (%)	51.97 ± 4.33 to 66.00 ± 0.48	79.80 to 84.10	83.82 ± 1.08	86.69 ± 0.22
Granule size (μm)	44.99 to 127	1.344 to 4.695	24.40–102.53	6 to 23
Granule morphology	Oval, spherical and irregular	Spherical and irregular	Polygonal and irregular	Polygonal, oval and irregular
Amylose content (%)	24.95 ± 1.49 to 42.01 ± 0.24	19.27 to 28.91	21.24 ± 0.26 to 41.59 ± 1.59	14.2 to 29.92 ± 5.09
Amylopectin content (%)	32.80 ± 1.70 to 39.56 ± 0.48	37.02	44.4 ±1.41	37.0 ±7.32
Swelling capabilities (%) or swelling power (g/g)	868.71 ± 80.9 to 1120 ± 23.2 %	22.45 to 29.17 (g/g)	14.49 ± 0.22 (g/g)	3.00 ± 0.23 to 4.67 ± 0.18
Viscosity (Cp)	7660 ± 2910 (12%)	1075 (12%)	146.7 (5%)	n.d
Bulk density (g/ml)	0.69 ± 0.01	n.d	n.d	n.d
Tapped density (g/ml)	0.88 ± 0.02	n.d	n.d	n.d
Carr's Index	19.16 ± 1.86	n.d	n.d	n.d
Hausner ratio	1.24 ± 0.03	n.d	n.d	n.d
Oxalate content (ppm)	n.d	154.38 to 212.27	n.d	n.d

* n.d : no data
Sources: Arrowroot (Aprianita et al., 2014; Astuti et al., 2018; Malki et al., 2023; Sholichah et al., 2017; Tarique et al., 2021; Valencia et al., 2015), taro beneng (Jufrinaldi et al., 2023; Kusumasari et al., 2024; Nurtiana & Pamela, 2019; Pamela et al., 2019; N. Putri et al., 2021; Saadah et al., 2021), ganyong (Aprianita et al., 2014; Cáceres et al., 2021; Harmayani et al., 2011; Purwitasari et al., 2023; Yovani et al., 2022), and gembili yam (Aprianita et al., 2014; Houngbo et al., 2023; Jambomias et al., 2024; Retnowati et al., 2018, 2019; Rukmini & Santosa, 2019).

The formulation utilizes 10%, 15% and 20% arrowroot starch which resulted in 7.23 to 7.75 kg tablet hardness, 0.56 – 0.66% friability (Yulyadah et al., 2021). Another application of arrowroot starch as wet binder also reported by Sugiyono et al. (2012) in formulation of paracetamol tablet. The formulation was done with 5%, 7.5%, 10%, 12.5%, and 15% of arrowroot starch in addition of lactose as filler, sodium starch glycolate as disintegrant and magnesium stearate as lubricant. The developed tablet hardness is ranged from 4.86 ± 0.87% to 6.19 ± 1.24%, which improve alongside increasing of arrowroot starch concentration.

Improvement of the starch concentration also decrease the friability rate from 0.60 ± 0.12% for 5% concentration to 0.28 ± 0.07% for 15% concentration (Sugiyono et al., 2012). Patomchaiviwat et al. (2011), successfully utilized arrowroot starch as a disintegrant in tablet formulation at various concentration at 2%, 4%. 6%, and 10% along with corn starch and Explotab®. The study also evaluates the gelatinization effect in starch characteristics, showing that the pregelatinized arrowroot starch possesses a faster disintegration time (100 s) than native starch in tablet formulation (269 s). The disintegrability improvement at lower concentration could be explained by the higher swelling capabilities found at pregelatinized arrowroot (678.89 ± 56.80%) compared with the native starch (119.82 ± 56.80%) at 2% concentration. That swelling improvement could be explained by the disruption of the ordered crystalline region through leaching, which becomes more available to interact with water (Mateescu et al., 2015). However, at higher arrowroot starch concentration the pregelatinized arrowroot starch possess slightly lower disintegration time than the tablets with native starch due to viscious gel mass formed resulting in retardation of tablet disintegration (Patomchaiviwat et al., 2011). Another usage of modified arrowroot starch in tablet formulation was done by Sriamornsak et al. (2010), utilizing it as a matrix-forming agent due to its high gel strength characteristic due to the starch modification.

Table 3. Application of arrowroot starch as pharmaceutical excipients

Developed excipients	Application	Role in Formulation	References
Natural and pregelatinized arrowroot starch	Placebo tablet	Disintegrant	(Patomchaiviwat et al., 2011)
Microwave-heated arrowroot starch	Theophylline tablet	Matrix-forming agent	(Sriamornsak et al., 2010)
Arrowroot starch	Glipzide buccal film	Film-forming agent	(Gayathri & Jayakumari, 2019)
Arrowroot starch	Microencapsulated probiotic bacteria	Matrix beads	(Samedi & Charles, 2019)
Arrowroot starch	Ibuprofen tablet	Binder	(Yulyadah et al., 2021)
Arrowroot starch	Paracetamol tablet	Binder	(Sugiyono et al., 2012)

Figure 4. Taro beneng plant (left) and harvested taro beneng tuber (right)
Sources: (Kusumasari et al., 2019; Susilawati et al., 2021)

The study also concluded that modified arrowroot starch, due to microwaved heating possesses better retardation properties caused by higher gel strength value and lower swelling capabilities (Sriamornsak et al., 2010). Starch swelling capability can be reduced by rearranging the crystalline region within the starch granules after the heating treatment, which might become randomly distributed within the granules after the heating treatment (Oyeyinka et al., 2021).

Other than tablets, arrowroot starch is also suitable in film composite formulation with other polymers. Utilization of arrowroot proposed promising potential, as reported by Gayathri & Jayakumari (2019) in antidiabetic buccal glipizide film formulation using a combination of arrowroot starch with Na-CMC (sodium carboxymethyl cellulose). The combination at 70:30 (arrowroot starch: Na-CMC) ratio shows the synergistic relationship in tensile strength observed by highest folding endurance 315 ± 2.3 fold (Gayathri & Jayakumari, 2019). Chin-San and Liao (2017) also successfully formulated film membranes from arrowroot starch and polyhydroxyalkanoate (PHA) through crosslinking reaction mediated by tetraethoxysilane as a coupling agent. The developed crosslinked composite membranes exhibited elevated water absorption compared with the PHA-arrowroot starch physical mixture membrane alone due to the hydrophilicity of the arrowroot starch. In addition, the incorporation of arrowroot starch into the composition contributed to inferior mechanical strength, resulting in lower membrane film tensile strength (8.3 MPa) compared to the crosslinked-PHA formula alone (16.3 MPa). Therefore, the ratio of crosslinked 20:80 (arrowroot starch: PHA) is considered optimal, as confirmed by SEM observation promoting the uniform distribution of coupling agent in the film surface (Chin-San & Liao, 2017). Sholichah et al. (2017) also reported similar attempts to develop arrowroot and polyvinyl alcohol (PVA) blended films through crosslinking reactions using citric acid. The developed films at lower PVA content (0.25-0.75%) did not significantly affect the water absorption capacity, film tensile strength, and film elongation. On the contrary, citric acid concentration greatly affected the composite film properties by developing covalent bonds between glucose and PVA molecules, which improve water holding capacity and film mechanical properties (Sholichah et al., 2017).

2. Taro Beneng (*Xanthosoma undipes* K.Koch)

Taro beneng is one of Indonesia's local tubers abundantly grown in the Banten region (Suhaendah et al., 2021). Taro beneng is known for its massive size and weight compared to another tuber. The tuber weight ranged from 8–12 months and could reach 2.4-15 kg,

affected by soil fertility and climate as depicted at Figure 4 (Fetriyuna et al., 2016; Susilawati et al., 2021). Taro beneng starch contains 0.66% protein, 6.21% moisture, 10.56% lipid, 0.25% ash and 56.29% - 82.32% starch (Kusumasari et al., 2019; Nurtiana & Pamela, 2019). Several amylose and amylopectin values are reported for taro beneng starch varied from 19.27% amylose with 37.02% amylopectin content (Kusumasari et al., 2019), 16.40-20.35% amylose content (Saadah et al., 2021) and 28.91% amylose with 53.41% amylopectin content (Nurtiana & Pamela, 2019).

One notable challenge in using taro beneng is rich in oxalate content in the form of oxalic acid and calcium oxalate (Agustin et al., 2022; Pancasasti, 2016). These oxalate content could be reduced by washing and soaking treatment with NaCl solution. Agustin et al. (2022) study showed that utilization of 10% NaCl concentration with 90 min soaking duration leads to a higher reduction of oxalate content (Agustin et al., 2022).

Previous studies discussing the utilization potential of taro beneng starch as a pharmaceutical are reported. The development of taro beneng-derived starch as pharmaceutical excipient has been done before by Awidah et al. (2021). The isolation of starch from the beneng taro was done using a fermentation method that resulted in modified starch that fulfilled the essential characteristic requirement of excipient (Awidah et al., 2021). Furthermore, taro beneng starch has been successfully utilized as disintegrant in paracetamol tablet formulation along with Avicel PH 102, copovidone, and magnesium stearate. The study confirming the potential as a disintegration in the formulation of the paracetamol tablet at various concentration (5%; 10%; 15%), utilizing its swelling capabilities. The developed tablet show slower disintegration time at 64.67 s (5%), 42.17 s (10%), and 25.83 s (15%) compared with tablet without taro beneng starch at 76.11 s (Indriatmoko et al., 2019). Improvement of taro beneng starch functionality has been done by Wibisana et al. (2022) by chemical modification through acetylation reaction with acetic anhydride. The modified starch with 10:50 ratio of acetic anhydride and taro beneng starch possesses lower solubility and higher swelling power (5.2 g/g) due to substitution of hydroxyl groups with acetyl groups, lead to higher water interaction (Wibisana et al., 2022).

Taro beneng starch demonstrates promising potential for development as a film-forming agent. Maghfirah et al. (2023) successfully produced composite biodegradable film utilizing taro beneng starch to enhance its physical properties along with chitosan as additional material and glycerol as the plasticizer. The developed film shows increased density along with higher starch concentration and lower chitosan concentration, with an optimal composition at 70:30 (starch: chitosan). This study also reported improved water absorption capacity at higher starch concentrations due to improved hydrophilicity (Maghfirah et al., 2023). Puspita et al. (2022) successfully develop edible film based on taro beneng starch (2.5%) with carrageenan (7.5%) blend at various plasticizer type (sorbitol, glycerol, and polyethylene glycol) and various concentration concentration (1%; 3%; 5%). The optimal formulas is the edible film developed formulated from sorbitol at 3% concentration which produce 17.7567 MPa tensile strength, 9.0637% elongation and 0.1214 g/m^2.hour water vapor transmission rate (Puspita et al., 2022).

Figure 5. Porang tuber plant (left) and porang bulb tuber (right)
Source: (Pusat Penelitian dan Pengembangan Porang & Indonesia, 2013)

Figure 6. Ganyong tuber plant (left) and ganyong tuber (right)
Sources: (Elik et al., 2022; Sukarsa, 2010)

Table 4. Application of ganyong starch as pharmaceutical excipients

Developed excipients	Application	Role in Formulation	References
Pregelatinized ganyong starch	Acetylsalicylic acid tablets	Binder	(Azhary et al., 2019)
Ganyong starch	Ibuprofen tablets	Filler	(Maghfiroh et al., 2018)
Crosslinked ganyong starch	Ondansentron granules	Matrix-forming agent	(Putri et al., 2017)
Hydrolyzed ganyong starch	-	Microcapsule-forming agent	(Purwitasari et al., 2023)
Ganyong resistant starch (RS-3)	Colon targeted curcumin and Fe_3O_4	Microcapsule-forming agent	(Zhang et al., 2024).

3. Porang (*Amorphallus muelleri* Blume)

Porang comes from the Araceaea family, which is nowadays cultivated in South Asia and Southeast Asia. Porang perennial plants that could grow up to 1.5 meters tall with round yellowish bulbil tubers weighed up to 2 kg, as depicted in Figure 5 (Putri et al., 2022). Porang is primarily utilized in its extracted forms, such as glucomannan, a hydrocolloid carbohydrate. Despite that, porang starch still has the potential to be used as a pharmaceutical excipient. Dried porang starch has 15.29% moisture content, 2.59% lipid content, and 2.75% protein, with 20.44 % of amylose content and 42.85% amylopectin content (Nurman et al., 2022). Porang starch in forms of flour potential as pharmaceutical excipients has been studied before in tablet and film. Konjac flour has been successfully utilized as a matrix-forming agent, as reported by Liang et al. (2015) in the formulation of a metronidazole floating tablet. The floating tablet matrix comprises of two drug-free shell parts with a combination of konjac flour (20%), MCC (20%), PVPP (10%), and metronidazole (50%), with a drug-layered matrix in the central part. The study also reported the impact of konjac flour particle size due to variation of ball-milling time towards the drug release profile. Konjac flour which was milled for 4 hours succeeded in prolonging the drug release over 14 hour with the shortest floating lag time (Liang et al., 2015).

4. Ganyong Tuber (*Canna edulis* Kerr.)

Originally from South America, ganyong, also known as achira, is a known tubers which is cultivated in Southeast Asian countries, including Indonesia (Khoi et al., 2023). The tuber part has thick rhizomes as shown at Figure 6, with high starch content, with amylose at 13.77% and amylopectin at 86.23% (Cáceres et al., 2021). Ganyong starch also contain protein 0.44% protein, 6.43% lipid, 7.42% moisture and 1.37% ash (Fatkhiyah et al., 2020). Due to its high starch content due to low fiber content, ganyong starch is a promising candidate for starch development (Munfarida, 2023). Ganyong starch granules are typically large with variation in ganyong starch granules size can be attributed to the biological origin, cultivation practices, and plant physiology (Cáceres et al., 2021; Khoi et al., 2023).

Several studies have explored the potential of ganyong tuber starch in natural and modified forms has been done before as as a pharmaceutical excipient for tablets, granules and encapsulants as reported at Table 4. Azhary et al. (2019) developed pregelatinized ganyong starch, which possesses better compressibility and flowability. Ganyong starch was pregelatinized in different temperatures at 50ºC, 55ºC and 60ºC. The developed excipients were later utilized as direct compression disintegrant in acetylsalicylic acid tablets at 10%.

The developed tablet has hardness value varied from 5.80 ± 0.21 kg to 6.70 ± 0.29 kg. Besides that, the developed tablet also fulfills the friability value requirement (<1%) for every formula ranged from 0.13 ± 0.00% to 0.34 ± 0.00%. The tablet developed from pregelatinized ganyong starch at 55ºC posess the higher hardness and lower friability value (Azhary et al., 2019). In another study, ganyong starch was successfully physically blended with gembili starch and employed as a filler in formulation of ibuprofen tablets. The developed tablets show optimum physical properties at (82.11%:17.89%) of gembili starch: ganyong starch ratio with hardness at 7.45 ± 0.38 kg and friability values at 0.81 ± 0.01% (Maghfiroh et al., 2018). Utilization of modified ganyong starch as a matrix-forming agent was done by Putri et al. (2017) through cross-linking reaction using $CaCl_2$. This modification resulted in higher starch swelling index of 3.44 ± 0.11% than native starch at 2.13 ± 0.10%. Improvement of starch swelling due to increased amylopectin accessibility to interacting with water. The developed ondansetron granules possess similarities with the controlled drug release profiles (A. P. Putri et al., 2017). Improvement of ganyong starch swelling and water absorption capacity has been studied before by Purwitasari et al. (2023) through enzymatic hydrolysis. The modified starch hold potentials for applications in microencapsulation (Purwitasari et al., 2023). The potential of ganyong starch as an encapsulant has been proven in the development of retrograded resistant starch particles for colon targeting (C. Zhang et al., 2024).

5. Gembili Yam (*Dioscorea esculenta.*)

Yams are a well-known source of carbohydrates and several bioactive compounds correlating with their applicability potential. Indonesia has a long history of yam cultivations and uses several varieties of yam, such as gembili yam (*Dioscorea esculenta*), gadung yam (*Dioscorea hispida*), purple yam (*Dioscorea alata*) and white yam (*Dioscorea rotundata*) being prominent. However, their utilization is limited to preparing traditional dishes such as pounded yam or yam porridge and as complementary food cooked through boiling, steaming, or baking (Retnowati et al., 2018).

One of the concerns regarding using *Dioscorea* sp. is the presence of bioactive compounds, such as toxic dioscorine alkaloids and toxic cyanogenic compounds (Ashri et al., 2014; Estiasih et al., 2022). Only 600 of the 1137 *Dioscorea* sp. varieties are safe to consume (Ashri et al., 2014). Therefore, an additional detoxification process through soaking in brine or rubbing with ash for a specific amount of time has been successfully studied and employed (Estiasih et al., 2022).

In this section, gembili yam which more utilized and studied will be discussed further. Gembili yams have a potato-like shape with a grey colour, as can be seen in Figure 7. Gembili yam successfully developed into gembili flour through fermentation process which contains 8.39% moisture content, 0.72% ash content, 0.15% lipid content, 3.92% protein content, and 86.84% total starch content (Saskiawan & Nafiah, 2014). Jayakody et al. (2007) reported gembili yam starch consist of 9.90 ± 0.13 to 10.97 ± 0.11% moisture, 0.17 ± 0.00% to 0.32 ± 0.00% ash, 0.40 ± 0.00% to 0.47 ± 0.00% lipid, and the rest as carbohydrate with starch content (>80%) (Jayakody et al., 2007). Sulistyawati et al. (2024) reported that *D. esculenta* starch comprises of 12.08% moisture, 0.00% lipid, 3.00% protein, 1.27% ash, 9.04% fiber and 86.69% carbohydrate (Sulistyawati et al., 2024).

Figure 7. Wild gembili yam plant (a), and harvested gembili yam (b)
Source: (Estiasih et al., 2022)

Gembili yams starch contains amylose varied from several previous studies: 14.2% (Rukmini & Santosa, 2019), 20.89% (Jambomias et al., 2024), 20.93% (Bahlawan et al., 2020) and 29.92 ± 5.09% (Retnowati et al., 2019). Meanwhile, the amylopectin content of gembili yams starch is 79.07% (Bahlawan et al., 2020).

Yam starches have been studied to be utilized as a pharmaceutical excipient in tablet development through some modifications. Nattapulwat et al. (2009) successfully developed carboxymethyl yam starch, which resulted in higher viscosity and swelling power, where at a higher substitution degree, more water can penetrate the starch granules due to the presence of hydrophilic groups. The modified excipients functioned optimally as disintegrant at 2% carboxymethyl starch, whereas 3% and 4% concentration caused slight retardation in the disintegration, likely caused by the viscous gel formed after contact with water, which resulted in decreased water penetration towards the tablet (Nattapulwat et al., 2009). Dewi et al. (2019) has successfully developed the development of co-processed excipients based on pregelatinized gembili yam with hydroxypropyl methylcellulose (HPMC) (2019). The developed excipients act as filler-binders that aid the tableting process through direct compression at 52% with ibuprofen (40%), Starch®1500 (5%), talc (1%), and magnesium stearate (2%). Compared with the excipients from native starch, the pregelatinized starch exhibited better flow properties from repose angle (37.13 ± 0.14º) and compressibility index (14.33 ± 1.15%) than the native starch with higher repose angle (47.63 ± 0.31º) and compressibility index (17.66 ± 0.58%). Therefore, the developed co-processed excipients possess of pregelatinized starch and HPMC (2:1) possess superior flow properties with the lowest repose angle (31.94 ± 0.92º) and compressibility index (6.83 ± 0.81%). The co-processed excipients superior properties as filler-binder were reflected in sufficient tablet hardness (7.20 ± 0.05 N) and friability (0.81 ± 0.23%). Regarding the disintegration time, co-processed pregelatinized starch and HPMC (2:1) have longer disintegration time attributed to hydrogel-forming, which limits water penetration (Dewi et al., 2019).

Utilization Potential of Tuber Starch in Starch Nanoparticles

In addition to its potential as an excipient in tablet formulations, starch presents significant potential for developing nanoparticles and nanoencapsulation technologies. These technologies hold promising potential in the pharmaceutical, food and bio-material industries (Mateescu et al., 2015). The broad applicability of starch nanoparticles underscores the substantial opportunities associated with developing tuber-derived starches. The development of starch nanoparticles enhances their properties, yielding particles with a small size (less than 1000 nm) and a correspondingly large surface area (Marta et al., 2023). In pharmaceutical technology, nano-sized starch has promising potential to be developed as a drug carrier for various applications that could be developed as a drug carrier with a modified release, mucoadhesive properties or a suitable carrier for protein and hydrophobic drugs (Han et al., 2013; Jain et al., 2008).

1. Starch Nanoparticles

Starch nanoparticle preparation can be broadly classified into two primary approaches: bottom-up and top-down. The bottom-up method involves the formation of atoms to develop nanoparticles at specific conditions, such as nano-precipitation. In contrast, the top-down approach mainly focuses on breaking down large bulk starch materials into nanoparticles.

Table 5. Previous studies of starch nanoparticles development

Application	Methods	Starch Excipients	References
Starch nanoparticles	Ultrasonication	Cassava starch, corn starch, and yam starch	(Minakawa et al., 2019)
Starch nanoparticles	Nanoprecipitation	Corn starch, potato starch, sweet potato starch, tapioca starch	(Qin et al., 2016)
Ascorbic acid and oxalic acid nanoparticles	Ultrasound assisted acid hydrolysis	Potato starch	(Shabana et al., 2019)
Tea polyphenols pickering emulsions	Milling	Taro starch	(Shao et al., 2018)
Starch nanoparticles	Nanoprecipitation and acid/alkaline hydrolysis	Andean potato starch	(Torres et al., 2019)
Andrographolide starch microcapsules	Nanoprecipitation	Acid hydrolyzed arrowroot starch	(Winarti et al., 2014)
Temulawak oleoresin starch microcapsules	Nanoprecipitation	Acid hydrolyzed arrowroot starch	(Winarti et al., 2019)
Starch nanoparticles	Solvent evaporation	Acetylated *Dioscorea abyssinica* yam starch	(Paulos et al., 2016)

This can be achieved through various methods such as chemical hydrolysis, physical grinding (milling), ultrasonication, high-pressure homogenization, and irradiation (Abid et al., 2022; Marta et al., 2023; Qin et al., 2016). While the top-down approach offers greater scalability for lab and industrial settings, it typically requires a higher initial investment than the bottom-up approach. Additionally, the bottom-up, which is difficult to control on large-scale production methods, generally results in fewer byproducts of degraded starch, commonly observed with top-down methods (Marta et al., 2022).

Numerous studies have explored the development of starch nanoparticles from various sources, including tuber starches such as cassava, arrowroot, elephant yam, and potato, for diverse applications, as presented in Table 5. Notably, the botanical source of starch significantly influences the morphology and properties of the resulting nanoparticles. Qin et al. (2016) proved this theory by developing nanoparticles from various starches consisting of corn starch, pea starch, potato starch, sweet potato starch, and tapioca starch. The starch granules possess spherical, oval and irregular shapes with varied granule sizes. The obtained nanoprecipitated starch was mainly spherical and elliptical in shapes ranging from 20 to 200 nm, correlating with the granule sizes; the smaller the starch granules lead to smaller starch nanoparticles. Besides, the higher starch amylose content of native starch reflected higher crystallinity and lower degradation temperature of nanoparticles that varied between each botanical source (Qin et al., 2016). Similar trend was reported by Minakawa et al. (2019) in the development of starch nanoparticles from cassava, corn and yam starches. Yam starch with higher amylose content led to high crystallinity nanoparticles, while cassava with the lowest amylose content resulted in mostly amorphous results. Interestingly, the thermal properties did not follow that principle compared to their native starches. Starch nanoparticles resulted in lower thermal properties due to the semi-crystalline structure shifting into a more amorphous region that is more susceptible to degradation (Minakawa et al., 2019).

The selection of preparation methods also affects the morphology and properties of yield nanoparticles, as Torres et al. (2019) reported in developing Andean potato starch nanoparticles by combining acid hydrolysis or alkaline hydrolysis with nanoprecipitation. The difference was observed through XRD analysis, where the acid treatments degraded the starch amorphous region, and the alkaline treatment eroded the outer part of the starch granule and gelatinized it (Torres et al., 2019). Ultrasound (physical method) and ultrasound-assisted acid hydrolysis (chemical method) of potato starch have been successfully done in the development of potato starch nanoparticles by Shabana et al. (2019). Compared with conventional sonication, ultrasonication leads to smaller particle size (80 nm), and combined treatment with acid hydrolysis produces smaller particles (40 nm) as the hydrolysis provides starch degradation. Ultrasonic with acoustic cavitation energy promotes the breakage of the starch network through starch pores (Kim & Suslick, 2018). Additionally, the acid treatment resulted in lower starch molecular weight, indicating starch structural breakdown as proven by gel permeation chromatography (GPC) (Shabana et al., 2019).

The implementation of tuber starch was done before involving the development of microcapsules to facilitate the delivery of several active ingredients. Winarti et al. (2015), studied the potential of arrowroot starch in developing microcapsules containing andrographolide. The nano arrowroot starch was obtained through the precipitation of acid-modified starch for 24 hours. The encapsulation was done by spray-drying a mixture of maltodextrin and arrowroot starch nanoparticles. The obtained composite microcapsule possesses an average particle of 14.84 ± 1.36 – 15.06 ± 3.66 μm, with a polydispersity index (PDI) valued from 0.526 – 0.528. On the contrary, encapsulation using starch alone resulted in lower particle size and PDI index showing more uniformity (Winarti et al., 2014, 2015). Winarti et al. (2019) also conducted similar research in developing composite microcapsules containing *Curcuma xanthorrhiza* oleoresin from nanoprecipitated starch. The produced microcapsule has an average particle size ranging from 196.7 to 256.74 nm (Winarti et al., 2019).

2. Starch Nanocrystals

Nanocrystals are unique nanostructures with high crystalline content that are also known as hydrolyzed starch or microcrystalline starch. Starch nanocrystals are derived from starch granules due to disruption of the amorphous region, resulting in nanoscale particles with high crystallinity (Li et al., 2023; Odeniyi et al., 2019). Compared with the crystalline region, the amorphous part in starch granules is more susceptible to hydrogen ions. Therefore, starch nanocrystals are commonly prepared with selective processes to remove the amorphous region, such as acid hydrolysis and enzymatic hydrolysis. Starch nanocrystals are identified as having lower solubility compared to native starches as a result of their high crystallinity purity (Li et al., 2023).

Starch nanocrystals, have shown great potential in pharmaceutical applications. Alwaan et al. (2019) reported the potential of starch nanocrystals for controlled drug delivery of hydroxyurea in a formulation of hydrogel composed of hydrolyzed starch cross-linked with arabic gum. The study shows that adding starch nanocrystals reduces the swelling ratio, reflecting lower

drug release (Alwaan et al., 2019). Martins et al. (2022) utilized rice starch and potato starch nanocrystals as barrier agents in the development of rice starch films. The study shows that the addition of starch nanocrystals interferes with the film characteristics with higher tensile strength and elongation, reduced solubility and decreased water vapor permeability (Martins et al., 2022).

Future Prospectives and Challenges

Tuber starches have been gaining attention in the last decades because of their abundance and properties, which could fulfil the growing characteristic requirements in the pharmaceutical and food industries, which keep growing. In the pharmaceutical industry, other than being used as a tablet excipient and film-forming agent, starch also has the potential to be developed into advanced drug delivery systems such as starch nanoparticles and nanocrystals (Sivamaruthi et al., 2022; J. Zhang et al., 2022). Utilization of starch is primarily limited to its native characteristics, which urgently require excipient modification either by physical modification (gelatinized starch, co-processed excipients) or chemical modification (hydrolyzed starch, esterified starch, cross-linked starch, oxidized starch) to improve the natural starch excipient applicability furthermore (Moorthy et al., 2017). Consequently, it is possible to utilize several local Indonesian starches in the future. The local tubers' value would be improved by being utilized as an alternative starch source to fulfil the domestic demand for starch from the pharmaceutical and food industries in the future. One of the significant hurdles facing the development of starch from tubers is the manufacturing stage's feasibility. Principally, starch extraction from tubers faces challenges related to starch extraction efficiency Therefore, an optimization study about starch extraction parameters based on soaking time and concentration of sedimentation agent salts is needed to improve its efficiency. Another limiting factor is the high oxalate, alkaloid and cyanide concentration found in tubers, which require additional processes (Agustin et al., 2022; Ashri et al., 2014; Estiasih et al., 2022).

While cereals are dried at 12%-14% moisture content and can be stored for years, fresh rhizomes, tubers, and roots present more than 60% moisture content (Vilpoux et al., 2018). From a practical point of view, fresh tubers' high moisture content is also a crucial issue. Fresh tubers are very perishable due to high water activity, which promotes spoilage microbe growth that induces rotting. Additionally, post-harvest physiological activities (sprouting, transpiration), regulated by storage temperature and humidity, also play a role in weight loss during storage. Therefore, tuber must be processed as dried chips or flour after being harvested to prolong its storage time (Omohimi et al., 2019).

CONCLUSION

As proven by several application and extraction studies, Indonesian tuber starches from arrowroot, taro beneng, porang tuber, ganyong tuber, and gembili yam possess enormous potential to be utilized as pharmaceutical excipients. These starches possess several unique characteristics reflected by their starch composition and granule properties. Enhancing tuber starches functional characteristics through physical and chemical modification could further improve its applicability as an excipient. In the future, these tuber-derived starches could be a staple excipient utilized in tablet formulation and film formulation either in native or modified forms. Besides that, tuber starches also potentially to be utilized in starch nanoparticles development.

CONFLICT OF INTEREST

The authors already agree with the contents of the manuscript and declare no conflict of interest regarding the publication of this article.

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