ORIGINAL ARTICLE

Adsorption Onto Solid Carriers Enhances the Flow Properties and Release of *Alpinia galanga* Ethanolic Extract

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ABSTRACT

Introduction: There are many natural products which have the potential of ameliorating the deterioration in health due to aging. Some of the natural products are in the form of ethanol extract which is frequently difficult to develop into viable products for oral consumption. The use of solid carriers as an excipient to adsorb the extract is a cost-effective and feasible technique. **Methods:** Ethanolic extraction of *Alpinia galanga* was performed and preformulation studies were conducted to assess the extract. Organoleptic and physicochemical evaluations were conducted, and five established pharmaceutical excipients namely β-cyclodextrin, corn starch, carrageenan, gum arabic and microcrystalline cellulose, were formulated into granules with the *A. galanga* extract. The flow properties of the resulting granules, the compatibility of the granule components and the release of the marker compounds were assessed. **Results:** The ethanolic extract of *A. galanga* was sticky and bitter, and adsorption onto the five different solid carriers gave varying results. Granules formed with β-cyclodextrin, corn starch and carrageenan were subjected to flow studies and the highest flowability was shown by the granules fabricated with corn starch. No incompatibility was detected from the thermal profiles of the individual components and the granules. Release studies showed that formulation into granules using corn starch has increased release of the marker compounds by 3-4 folds. **Conclusions:** Solid carriers can improve the capability of a plant extract to be processed into viable products, and can facilitate the production of a batch for preclinical and clinical tests in the local industrial settings.

Keywords: Solid carriers; Formulation; Ethanol extract; *Alpinia galanga*; Natural products.

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INTRODUCTION

Demand for plant-based products, whether marketed as pharmaceuticals, nutraceuticals, health supplements or functional foods, has been growing over the years with increasing number of consumers turning to such products for health promotion and disease prevention. In an aging population, bioactives from plants are attractive solutions towards health maintenance and they are regarded as effective in halting deterioration of body functions. Malaysia has a wealth of resources in terms of natural products, and its biodiversity presents a wide range of flora and fauna from which compounds can be tapped. There has been many research on Malaysian plants, and numerous studies have also suggested that many of these contain ingredients which have medicinal properties (1-3). However, the potential of many of these plants has not been fully realised due to poor development of the active ingredients into viable final products. On the other hand, unethical producers and sellers have no qualms about putting low quality herbal products and traditional medicine into the market, almost all of which are accompanied by unsubstantiated therapeutic claims (4).

Many of the marketed natural products are presented as grinded plant parts encapsulated in hard gelatin or sachets. Simple tablets can also be produced if the natural ingredient is in the form of an aqueous extract. Difficulty in formulating the natural bioactives into oral solid dosage forms arises when solvent extract is used or the compounds contained in the extract show substantial physicochemical variability between the different components. Selecting formulation excipients which will be compatible with each component is frequently challenging, but critical in ensuring that the product remains safe, efficacious and of high quality throughout its shelf life. The physicochemical properties of the types of compounds extracted from natural sources frequently render the raw material being processed with poor organoleptic and flow properties. One of the strategies proposed to overcome these challenges is to formulate the natural compounds into novel drug delivery systems (5). Nevertheless, the practicality of manufacturing such novel forms on a large scale in an industrial setting remains to be seen. The major producers of herbal-based products are traditional medicine and supplement

manufacturers, and not many of them would have the resources nor the technical capabilities to transform the novel preparations into viable products, especially in the local context. Moreover, novel delivery systems frequently use new compounds and materials which toxicological profiles have not been robustly established yet. Whilst this may not be a major issue for products designed to be applied to the external parts of the body, it becomes a critical concern when the product will be ingested or targeted to an internal organ.

The current study aimed to investigate the use of common excipients to improve processing properties and in vitro release of active ingredients obtained from *Alpinia galanga*. *A. galanga*, also known as greater galangal or "lengkuas" locally in Malaysia, is one of the members of Zingiberaceae family and its rhizome is widely used in Asian cuisine and traditional medicine (6). The rhizomatous part is used traditionally mainly for digestive and carminative purposes, improving vascular health, as well as for its anti-spasmodic and anti-bacterial properties including in women undergoing confinement (6,7). Although folk medicinal use of the leaves to treat cough in a local population in Sumatera, Indonesia has been reported (8), its leaves are less commonly used in general. However, our previous work had shown the potential of the ethanolic extract in ameliorating the detrimental effects of aging, postulated to be due to the high phenolics content in the extract. Hence, the current work focused on the use of solid carriers which are already commonly used in the pharmaceutical industry and generally recognised as safe, to transform the crude ethanolic extract of *A. galanga* into a product through the utilisation of a cost-effective and simple technique.

MATERIALS AND METHODS

Preparation of extract

The grinded leaves of *Alpinia galanga* were obtained from a local herbal supplier (Herbagus, Pulau Pinang).) A 400 g quantity of the leaves was steeped in 1000 ml ethanol 95% (Fisher Scientific, Malaysia) and placed in a water bath at 45°C with regular shaking. After 24 hours, the mixture was filtered and the process was repeated twice with fresh ethanol on the same leaves. The filtrates were pooled and rotary evaporated at 45°C under reduced pressure.

Preformulation studies

Organoleptic properties of the extract were recorded by describing the colour, odour and taste of the extract using terminology previously proposed (9). A 1 % w/v solution of the extract in distilled water was prepared, filtered and its pH value was read using a pH meter (Accumet Research AR10, Fisher Scientific, Singapore). The mean of triplicate readings was reported. Moisture content of the extracts was determined by placing 1.0 g extract in a dry Petri dish and weighed with an analytical balance (AB54, Mettler Toledo, Switzerland). The dish was placed in an oven (Memmert GmbH, Germany) set at 60 °C and the extract was dried to constant weight (approximately for 3 hours). It was then cooled over silica gel in a desiccator and reweighed. The percent loss in weight was taken as moisture content. The mean value of triplicate samples was recorded (10).

Partition coefficient (Log P value) of the extract was determined by dissolving an amount of the extract in distilled water and shaking the solution together in a separating funnel with an equal volume of octanol. After the phases separate, the amount of extract remaining in the aqueous phase was analysed, from which the amount that has partitioned into the octanol can be calculated. The log of the ratio of the extract amount in the organic phase to its amount in water is the Log P value. In addition, the solubilities of the extract in water and ethanol were determined by dissolving an excess amount of the extract in a measured volume of solvent, until an equilibrium concentration has been reached.

Formulation of *A. galanga* extract into granules

Several excipients such as β-cyclodextrin, corn starch, λ-carrageenan (Sigma Aldrich, USA), gum arabic (Colorcon, USA) and microcrystalline cellulose (Avicel PH-101) (FMC Biopolymer, USA) were investigated for their compatibility with the *A. galanga* extract for formulation of granules. Wet granulation technique similar to Gupta et al. (11) was utilised with slight modifications. The extract weighing 1 g was dissolved in 10 ml ethanol and mixed in a mortar and pestle with an amount of an excipient to form a wet mass before placing it in the oven at 70°C for 1 hour. This mass was then passed through a sieve with the orifice size of 500µm to obtain semi-dry granules and these granules were further dried in the oven at 40°C for 24 hours. The organoleptic and physical characteristics, pH, loss on drying percentage, solubility and partition coefficient value were determined for the granules as previously described for the extract.

Characterisation of flow properties

An accurately weighed amount of granules, M, was carefully poured into a dry 100 ml cylinder without compacting. Apparent volume, V_o was read from the cylinder where the granules were leveled. The bulk density, ρ_b was calculated using the following formula (12):

$$\rho_b = M/V_o \qquad \text{Equation 1}$$

The cylinder containing the granules was then tapped 500 times using a tap density tester (Electrolab ETD-1020, Globe-Pharma, Ireland) initially followed by an additional 500 taps until the difference between successive measurements was less than 2%. The tapped volume, V_f was measured and the tapped density, ρ_{tap} was calculated using the following formula:

$$\rho_{tap} = M/V_f \quad \text{Equation 2}$$

Compressibility index, or also known as Carr's index, is a measure of the propensity of a powder or granules to be compressed. It can be calculated from the bulk and tapped densities. Theoretically, a material which is less compressible has better flowability. In a free-flowing material, interparticulate interactions are minimal, and the bulk and tapped densities will be closer in values. For poorer flowing materials, the greater interparticle interactions will cause a greater difference between the bulk and tapped densities to be observed. These differences are reflected in the index which is calculated using the following formula:

$$\text{Compressibility index} = \frac{(\rho_{tap} - \rho_b)}{\rho_{tap}} \times 100 \quad \text{Equation 3}$$

Hausner ratio measures the ease of granules flow. It is calculated by the following formula:

$$\text{Hausner ratio} = \frac{\rho_{tap}}{\rho_b} \quad \text{Equation 4}$$

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height, h, above a graph paper that was placed on a flat horizontal surface. The granules were carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius of the base, r, of the conical pile was measured. The angle of repose (θ) was calculated using the following formula:

$$\tan \theta = \frac{h}{r} \quad \text{Equation 5}$$

Differential Scanning Calorimetry

Thermal profiles of the extract, excipients and granules were analysed using a differential scanning calorimeter (Pyris 6 DSC, Perkin Elmer, Netherlands). Accurately weighed samples ranging from 7-10 mg were placed into an aluminum pan and then sealed using a crimper. The thermal runs were performed in the temperature range of 0-400°C at a rate of 10°C/min under nitrogen gas.

HPLC analysis of *A. galanga* marker compounds

HPLC system equipped with a double LC-20AD pump, a SPD-20A UV-Visible detector and SIL-20AHT auto-sampler (Shimadzu, Japan), used with a C18 column (Hypersil Gold, Thermofisher Scientific, USA) of 250 × 4.6 mm, 5 µm pore size and temperature maintained at 45°C, was utilised for the quantification of *A. galanga* marker compounds. The analysis will be necessary for the quantification of the extract released from the granules. The mobile phase consisted of 0.1 % acetic acid and methanol (HPLC grade, Fisher Scientific, Malaysia) at the ratio of 60: 40, and was run through the isocratic elution program at a flow rate of 1.0 mL/min, Detection was at 258 nm. The method was previously validated following ICH guidelines (13) to ensure consistency, reliability, and accuracy in the analysis of data using standard solutions of reference chemical markers, kaempferol and quercetin (Sigma-Aldrich, USA). Although many phytochemical analyses have been performed on the rhizomatous part of *A. galanga*, there is scarcity of information instead for its leaves. Data on the overall antioxidative properties such as total phenolic content (TPC) and ascorbic acid equivalent antioxidant capacity (AEAC) were favoured by the researchers working on *A. galanga* leaf extracts, as bioactivity of natural products is commonly related to those properties (14). However, for product development and quality control, chemical markers need to be identified. According to the seminal work on the phytochemistry of Zingiberales leaves, a number of genera have distinctive flavonol profiles, and for the Alpinia species kaempferol and quercetin were distinguished (15). Moreover, kaempferol and quercetin were ascertained to have antiaging properties by ameliorating molecular damage in the cells (16).

***In vitro* release profiles of *A. galanga* extract and granules**

In vitro release was determined by using VK 7000 dissolution apparatus (Varian, USA) and performed according to USP guidelines (12) using Apparatus 1 (basket). Dissolution media used was 500 ml distilled water or simulated gastric fluid (SGF) set at 37± 0.5°C, and the basket speed used was 100 revolutions per minute. SGF was prepared by dissolving 2.0 g of sodium chloride in 7.0 mL of hydrochloric acid and adding enough distilled water to make 0.1N hydrochloric acid with the final volume of 1000mL. It was then adjusted to pH of 1.2 with hydrochloric acid. Extract or granules weighing 5g each was placed in a basket and placed in each of the six vessels of the dissolution apparatus. Samples of the dissolution medium (3mL) were withdrawn from each vessel at 5, 15, 30, 45, 60, 90, 120 and 180 minutes, and filtered with a 0.45mm syringe filter. The sample withdrawn was replaced with an equal volume of fresh medium to the vessel. The concentrations of the marker compounds were determined using the developed HPLC method as stated above for the analysis of *A. galanga* marker compounds.

Statistical Analysis

Data were analyzed by using one-way ANOVA and when the results showed statistically significant difference ($p<0.05$), Tukey's Honestly Significant Difference (HSD) test was used for pairwise comparison of means at $p< 0.05$.

RESULTS

Preformulation and formulation of *A. galanga* extract into granules

After the extraction process of *A. galanga* leaves and

upon drying in the rotary evaporator, it was observed that the extract was a sticky mass and difficult to remove from the vessel. Preformulation studies revealed properties as noted in Table I, which indicated that the extract had poor organoleptic characteristics such as a pungent smell, bitter taste, sticky and greasy texture, and an unattractive brownish-green colour. As the extract is intended to be administered orally to humans, modifications to make the extract more palatable for consumption were deemed necessary. The extract was also found to be sparingly soluble in water, needing more than 5ml to dissolve 100mg of extract, which may lead to difficulties in extract solubilisation in gastrointestinal fluids and eventual low bioavailability.

The properties observed were typical of ethanolic extracts of plant parts whereby a bitter and sticky mass was often obtained after rotary evaporation, and this mass will require a judicious formulation approach to allow it to be converted to a workable and manufacturable product. The excipient was progressively added to the extract as a solid carrier, to give structure and form to the previously sticky mass. The amount of the different excipients needed to form granules and the description of granules obtained are stated in Table II.

Table I : Organoleptic and physical properties of *A. galanga* preparations

Properties	Extract	Granules
Colour	Brownish-green	Green
Odour	Pungent	Slightly pungent
Taste	Bitter	Bitter
Texture	Sticky greasy mass	Well flowing granules
pH (25°C)	4.61	4.80
Loss on drying (65°C)	0.28%	0.309 %
Partition coefficient (25°C)	Log P = 0.493	Log P = 0.677

Table II : Granules of *A. galanga* extract formed with various excipients

Excipient	Ratio	Observation
Corn starch	1: 2.5	Forms well flowing granules
β-cyclodextrin	1: 2.5	Forms slightly sticky granules
Carrageenan	1: 2	Forms well flowing granules
Gum Arabic	1: 3	Forms sticky granules
Microcrystalline cellulose	1: 2	Extract and excipient do not mix well

From the results obtained, it can be seen that only corn starch and carrageenan formed well flowing granules from general visual and sensory observations. Granules formed with gum Arabic was excluded from further investigation due to its stickiness whilst microcrystalline cellulose could not mix well with the extract. Granules formed with β-cyclodextrin was included for further tests as the excipient is widely used to promote aqueous solubility and may facilitate in the release of extract.

Characterisation of flow properties

The flow indices were calculated for the granules formed from β-cyclodextrin, corn starch, and carageenan (Table III). With reference to the index scales and the corresponding description of flow (Table IV) (12), the compressibility index and Hausner ratio values indicated that the three types of granules had excellent flow. Among the three types, angle of repose distinguished the granules made from corn starch as having better flow, with its values falling within the fair flow category, in comparison to the β-cyclodextrin and carrageenan granules which values fell within the passable flow category.

Differential Scanning Calorimetry

The thermal profiles of corn starch, the ethanolic extract of *A. galanga*, the physical mixture of corn starch and extract, and the granules were obtained from the DSC scans (Fig. 1). Thermal profile of the corn starch shows endothermic peaks at 56.9°C and 280.6°C. On the other hand, the thermal profile of the ethanolic extract of *A. galanga* showed several peaks starting from 117.4°C to 170.0°C due to the various components present in the extract. Simple physical mixing of the corn starch with the extracts did not substantially cause any physicochemical alterations to either material as evidenced by the continued presence of the corn starch peaks at 57.45°C and 287.75°C, and the extract peak at 120.9°C respectively. The formulated granules of *A. galanga* gave endothermic events at 48.3°C and 306.4°C, and no corresponding peak for the extract. This suggests that a disruption in the crystalline structure of the corn starch and the total incorporation of the extract as a solid solution have occurred during the granule formation. No new additional peaks were observed, suggesting incompatibility between the excipient and extract components was not present.

***In vitro* release profiles of *A. galanga* extract and granules**

Incorporation of *A. galanga* ethanolic extract into granules using corn starch has enhanced its release, as indicated through the quantification of the release of its marker compounds, quercetin and kaempferol. In distilled water medium at 5 minutes, cumulative percentage quercetin release was 11% from the

Table III : Flow indicators of *A. galanga* granules

Excipient	Ratio	Bulk density (g/ml)	Tapped density (g/ml)	Compressi-bility index (%)	Hausner ratio	Angle of repose (θ)
Corn starch	1: 2.5	0.36	0.40	9.60	1.11	36.61
β-cyclodextrin	1: 2.5	0.35	0.36	4.59	1.05	40.69
Carrageenan	1: 2	0.32	0.35	7.83	1.09	41.23

Table IV : Index scales and flow property

Compressibility Index	Hausner Ratio	Angle of Repose	Flow property
≤10	1.00-1.11	25-30	Excellent
11 – 15	1.12-1.18	31-35	Good
16 – 20	1.19-1.25	36-40	Fair
21 – 25	1.26-1.34	41-45	Passable
26 – 31	1.35-1.45	46-55	Poor
32 – 37	1.46-1.59	56-65	Very Poor
> 38	> 1.60	> 66	Very, Very Poor

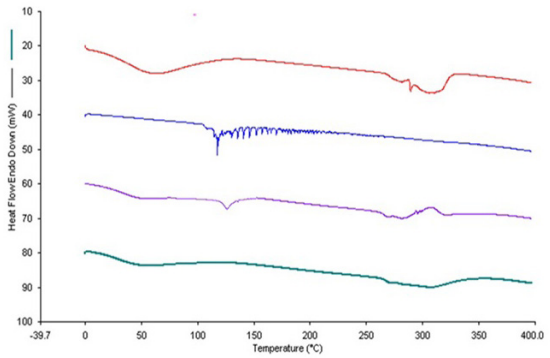

Figure 1 : DSC thermal profiles of corn starch (a), ethanolic extract of *A. galanga* (b), physical mixture (c) and granules (d).

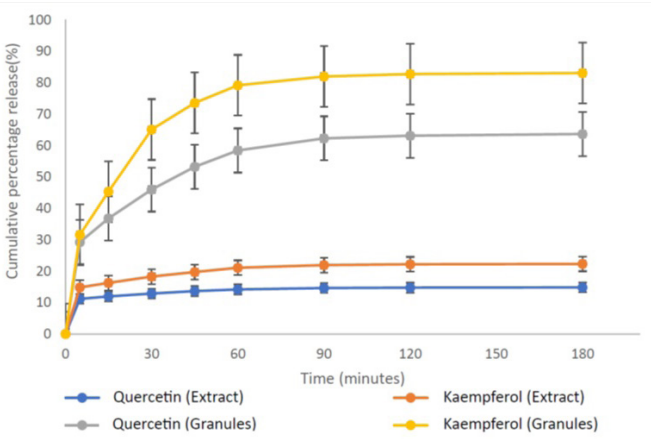

Figure 2 : Percentage released profile of *A. galanga* extract and granules in distilled water.

extract and 29% from the granules; hence quercetin release was promoted by 2.6 times in the granule form compared to the extract at the start of the study (Fig. 2). By the end of the study at 180 minutes, this value has elevated to 4.3 times. Similarly, the release of kaempferol was increased through the granular formulation by a factor of 2.1 at the initial stage of the study, and progressively increased until the end of release period by a factor of 3.7.

The rise in release due to the granular form was also seen in simulated gastric fluid (Fig. 3). Quercetin release increased by 2.3 times initially and reached its maximum of 3.1 times at the end of the study, whilst for kaempferol the values were 1.9 at the beginning and 3.2 at the completion, respectively.

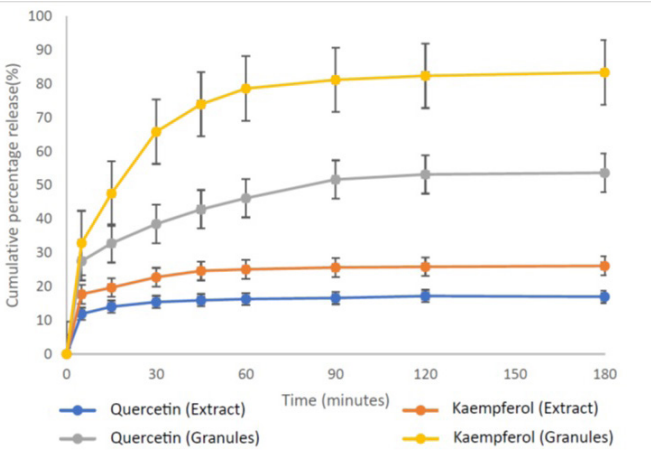

Figure 3 : Percentage released profile of *A. galanga* extract and granules in simulated gastric fluid.

DISCUSSION

Ethanolic extract of *A. galanga,* from the preformulation studies, showed poor organoleptic properties and unfavourable physicochemical conditions for further processing into viable preparations. Adding excipients to function as a solid platform onto which the extract can adsorb onto, allowed a physical barrier to be introduced in between the components of the extract that were responsible for the sticky texture. Table I also displayed the improvement in organoleptic properties of the granule form. The granules were less pungent and not sticky, there was no substantial change in pH and the loss on drying remained low indicating that the granules were not hygroscopic. The log P value in Table I and the solubility evaluation which showed that the granules were freely soluble, suggests that the bioactives in the granules could show better bioavailability due to increased solubilisation in the gastrointestinal fluids and permeation through its membranes. No chemical modification was introduced by this technique; physisorption was postulated to have caused the adherence of the extract components to the solid carriers, evidenced by the thermal profiles in DSC which displayed lack of new peaks resulting from new chemical complexes. Furthermore, a similar release enhancement of both marker compounds, quercetin and kaempferol, by the granule form in both distilled water and simulated gastric fluid suggests that the extract components were bound to the solid carriers by physical bonds. The production of a solid dosage form through the granulation technique also avoided the use of spray-drying, which is the technique usually employed to form dry powders of natural products (17). Spray-drying of solutions containing high concentrations of ethanol is hazardous, costly and gives low yield in industrial settings.

In comparison to aqueous extracts, many plants give greater pharmacological effects with their ethanolic extracts which could be due to more bioactive compounds being present (18, 19). The ethanolic extract of Hopea ponga stem bark demonstrated higher antidiabetic activity compared to the water extract (20). The ethanol extracts of Jamu pahitan exerted significant glucose uptake and insulin secretion stimulatory activity in L6 and RIN-m5F respectively, in a more potent manner than the water extract (21). Moreover, phenolics and flavonoids which are frequently acknowledged to be the compounds with therapeutic attributes, are substantially more soluble in ethanol than water. Mixtures of water and ethanol are also sometimes used to allow the more polar compounds to be extracted (22, 23). The use of plant extracts is more common in food supplements, hence the use of ethanol as the main or co-solvent is less regarded as a complication. Some of the ethanol may be left in the extract to aid solubility when it is used in colourings, flavourings or preservatives, and in nutraceuticals such as ginseng-based products (24, 25). However, when the extract is to be used as a phytopharmaceutical which effective dose is usually very high, or when it will be consumed over a long period of time to ameliorate chronic conditions, total removal of the ethanol should be the aim. In addition, in countries with large Muslim populations such as Malaysia, consumption of products with high residual ethanolic content is avoided.

Preliminary studies had shown that for *A. galanga* leaves, the extract that demonstrated the most promising anti-aging potential in vitro and in vivo was the one obtained with ethanol. Hence, the current study focussed on developing the *A. galanga* ethanolic extract into a dosage form that can be manufactured in a large scale and at the same time improve the delivery of the active ingredient. Many products containing plant ethanolic extracts are in liquid dosage forms including oral solutions, elixirs, tisanes and tinctures (24). In these forms, dissolution in the gastrointestinal media and the eventual absorption of the bioactive compounds are non-issues. Nevertheless, to achieve the desired pharmacological effect, large volumes need to be consumed. Coupled with the unpalatability of the extract due to poor tasting compounds being extracted by the ethanol together with the bioactive ones, the inconvenience of liquid forms may reduce compliance. One of the objectives of the current study was to incorporate *A. galanga* extract into a solid dosage form which will promote the release of the bioactive compounds, but at the same time maintaining a form which is feasible for upscaling. The profiles in the in vitro study displayed an increase of quercetin and kaempferol release when formulated into granules compared to the crude extract. This study demonstrated that the amount of the two important compounds in *A. galanga* that are made available for absorption into the systemic circulation can be raised by 3 to 4 times by adsorbing the bioactives onto a solid carrier, allowing the compounds to be released in molecular form or small discrete particles when the carrier dissolves in the media. The fabrication of free-flowing granules also allows it to be placed into hard gelatin capsules, hence avoiding the poor taste of the extract from being detected orally. The use of carriers to improve dissolution of drugs is an established technique in pharmaceutical technology. A non-steroidal anti-inflammatory drug, celecoxib, was successfully developed into a dosage form with 3-fold increase in in vitro dissolution and with excellent flowability when the solution of the drug in an organic solvent was loaded onto a mesoporous carrier (26). The dissolution of a hydrophobic antihyperlipidemic drug, fenofibrate, was significantly enhanced by physically adsorbing the drug onto a high-surface-area-carrier, Aerosil 200 (27). However, such methods are less explored in nutraceuticals and supplements fields, postulated to be due to the difficulties introduced by

the numerous components that exist in a plant extract. There is a need to adopt formulation strategies to overcome obstacles to producing plant extract-based preparations which are safe, efficacious and of high quality and which are eventually permitted to make therapeutic claims. The current study has demonstrated the viability of using solid carriers as a simple technique to make an *A. galanga* preparation that can be manufactured at a pilot scale, that can be brought further in the development of a final product by submitting it for pre-clinical safety tests and clinical trials.

CONCLUSION

This study has demonstrated the feasibility of using solid carriers to overcome the formulation problems inherent in many ethanolic plant extracts. Adsorption of the *A. galanga* components onto corn starch and the subsequent fabrication into granules could potentially improve on the pharmacokinetic profiles of the bioactives, as the in vitro release study showed enhancement in quercetin and kaempferol releases in both aqeuous and simulated gastric acid media. Finally, the solid carriers were capable of forming granules with good flow which can be further processed into viable products such as capsules, and can facilitate the production of a batch for preclinical and clinical tests in the local industrial settings.

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