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Synthesis, Characterisation, and Density Functional Theory Study of Encapsulated Bioactive Components of Ginger

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ABSTRACT

In this paper, we encapsulated ginger bioactive components in maltodextrin nanocapsules. Ginger nanocapsules were characterised using Transmission Electron Microscope (TEM) and Particle Size Analyser (PSA). The results show that the nanoparticles have a generally globular shape with particle size under 200 nm. In addition, the simulation of gingerol and dextran, as a representative for maltodextrin, was also investigated using Density Functional Theory (DFT) calculation. From the DFT calculation, gingerol exhibited a physisorption interaction with dextran by forming hydrogen bonds. Furthermore, the density of state analysis shows that the gingerol-dextran system has a conductive-like behaviour that promotes the nanocapsules' cell uptake.

Keywords: DFT, encapsulation, ginger, gingerol, TEM

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INTRODUCTION

Ginger (*Zingiber officinale* Roscoe) has been widely used for beverages, food, and medicine since ancient times due to its

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health benefits (White, 2007). Ginger is ubiquitously grown in Indonesia due to the suitable climate for ginger cultivation; therefore, ginger-based products are widely popular among Indonesians, particularly those who seek to use it for medicinal purposes. Traditionally, people process ginger by boiling the roots in water to get the extract as herbal drink or using ginger roots directly in foods as a spice. However, these traditional processing methods need a large amount of ginger to produce the desired benefit, not to mention the short durability of the processed product. It is, therefore, necessary to seek new methods for ginger processing to enable its effective utilisation.

Bioactive compounds of ginger include hydrophobic phenolic compounds (gingerol, shogaol, gingerdiol, and gingerdione) and hydrophilic polysaccharides (Kou et al., 2018). Gingerol has many pharmacological benefits such as antioxidant, anticancer, anti-inflammation, analgesic, and antipyretic (Shahrajabian et al., 2019). The main challenge to utilize hydrophobic compounds such as gingerol in the pharmaceutics and the food industry is the low bioavailability and sustainability of these hydrophobic compounds that can be overcome by using the nanoencapsulation technique. Nanoencapsulation is one of the most recent techniques that can be an excellent strategy to protect hydrophobic compounds against unsuitable environments and processing conditions such as light, high temperature, and humidity. In addition, the Nanoencapsulation technique could also enhance the bioavailability of hydrophobic compounds such as controlled release, improvement in water solubility, and increase in antioxidant activity (Rezaei et al., 2019).

In practice, nanoencapsulation involves incorporating of ingredients, bioactive compounds, or other desired materials into the encapsulated material for the delivery of the contents at the appropriate time (King, 1995). On the other hand, encapsulation is a process to entrap active agent within another wall material to improve the quality of foods by protecting micronutrients through processing and storage until the foods are consumed (Ghayour et al., 2019; Ahmad et al., 2019; İnanç Horuz & Belibağlı, 2018). The wall material used for coating or encapsulating ginger bioactive compounds must be food-grade, biodegradable, and form a barrier between the internal phase and its surroundings (Nedovic et al., 2011). It may be made from sugars, proteins, gums, and natural and modified polysaccharides, but polysaccharides are the most widely used.

Since previous studies of encapsulation technique show the stability of functional food components and toxicity reduction (Suganya & Anuradha, 2017), nano-encapsulated ginger bioactive compounds could theoretically exhibit faster gastrointestinal absorption compared to the traditionally processed ginger, as well as a slower degradation without compromising its unique taste and flavour (Lakshmi et al., 2012). Therefore in this study, a maltodextrin-based nanoencapsulation method of ginger bioactive compounds was performed to synthesise ginger nanocapsules used in a food product. Synthesised nanocapsules were then characterised using Particle Size Analyser (PSA) and Transmission Electron Microscope (TEM) to clarify the shape and size of the nanoparticle.

To understand the encapsulation process of nano-encapsulated ginger bioactive compounds, theoretical methods from an atomistic scale point of view can help describe the interaction within the system (Setzer, 2010; Khayer & Haque, 2020; Michailidou et al., 2020). Thus, to seek the physical-chemical properties and the electronic properties and elucidation of interaction between ginger bioactive compounds and nanocapsule wall, we performed a computational analysis based on a quantum-mechanical description of the electron-core interaction using the Density Functional Theory (DFT) method. It has been predicted that DFT could offer to solve advanced quantum chemistry and material science problems.

MATERIALS AND METHODS

Materials

n-hexane (CAS-No:110-54-3) and Tween 80 (CAS-No:9005-65-6) were obtained from Merck KGaA (Germany). Maltodextrin was obtained from a local commercial market. Both reagents, *n*-hexane and Tween 80, used without purification because it is already in the pro-analysis grade category. While for maltodextrin, there is no purification to maintain the low production cost, especially for mass-scale production.

Nanoencapsulation of Ginger Bioactive Components

Fresh ginger was washed, cut, and dried at 60°C for 24 hours. The dried ginger was soaked in n-hexane for 24 hours to extract the bioactive compounds, which were put in a rotary evaporator at 70°C and 150 rpm to eliminate the solvent. The evaporated extract was then prepared to create nanocapsules with maltodextrin as the capsule material. The first step of nanoencapsulation was preparing oil-in-water nanoemulsion based on the method described by Silva et al. (2011) and Jaganathan and Kumar (2017) with slight modifications described as follows. First, an organic solution of 0.3% (w/w) extract was dissolved in n-hexane at 40°C. Then, an aqueous solution of 0.5% (w/w) Tween 80 in the distilled water was prepared. The organic solution was then added to the aqueous solution with the volume ratio of 1:6 and homogenised by ultrasonication at 20 kHz to create the oil-in-water nanoemulsion. Next, the n-hexane was removed from the nanoemulsion using a rotary evaporator at 70°C and 150 rpm. The next step was to create a separate maltodextrin solution by adding 2% maltodextrin and 0.5% Tween 80 to 100 ml distilled water. Finally, the maltodextrin solution was added dropwise to oil-in-water nanoemulsion under constant stirring at 2000 rpm for 3 hours. The final ginger nanocapsule dispersion was stored at 4°C before being characterised.

Nanocapsule Characterisation

PSA. The ginger nanocapsule dispersion was diluted in distilled water until it reached 0.1% to 1% (w/w) concentration and homogenised with ultrasonication at 20 kHz for 2 min. Then, the dispersion was placed in a disposable plastic cuvette, and PSA measurements were done with Horiba SZ-100 Particle Size Analyser. The settings used for the measurements were as follows: water as the dispersion medium, measurement temperature 25°C, three measurement repeats, and monodisperse and narrow size range for the calculations.

Morphological Analysis using TEM. TEM Hitachi HT7700 at the Research Center for Nanoscience and Nanotechnology, Bandung Institute of Technology, was used for morphological observation of ginger nanocapsules. The operational voltage was set to 100 kV with the magnification of 40,000 times. The diluted nanocapsule dispersion used for PSA characterisation was further thinned by distilled water and then sonicated for about 5 min to prevent the agglomeration of nanocapsules. After that, 2-3 drops from the thinned dispersion were dropped onto a carbon-coated TEM copper grid. The nanocapsules were observed with TEM after the n-hexane was evaporated from the TEM grid.

Model and Computational Analysis on the Nanocapsule System

Gingerol was reported as the main bioactive compound in ginger roots and had antioxidant, analgesic, anti-inflammatory, and antipyretic properties (Kundu & Surh, 2009; Ippoushi et al., 2003; Koo et al., 2001; Suekawa et al., 1984). Therefore, the model used in our calculation was limited to gingerol ($C_{17}H_{26}O$) as the representative bioactive compound and dextran ($H(C_6H_{10}O_5)_3OH$) as the encapsulation material. Aside from maltodextrin, the use of dextran was also considered in the calculation. All calculations were performed using the density functional theory (DFT) with plane-wave basis set as implemented in the Vienna Ab-initio Simulation Package (VASP) (Kresse & Furthmüller, 1996a; Kresse & Furthmüller, 1996b). The projector augmented wave (PAW) method was used, and the generalised gradient approximation (GGA) within the Perdew-Burke-Ernzerhof (PBE) functional was applied for the exchange-correlation energy (Blöchl, 1994; Perdew et al., 1996). The energy cutoff used was 520 eV, and the Brillouin zone was sampled using 3×3×3 k-points of Monkhorst-Pack grids (Monkhorst & Pack, 1976). In this work, optimisation was done for gingerol alone and dextran alone. We designed a gingerol-dextran system after the optimisation was done by combining gingerol and dextran in an extensive vacuum system, as shown in Figure 1. Then, a full relaxation calculation was done to get the optimised gingerol-dextran system.

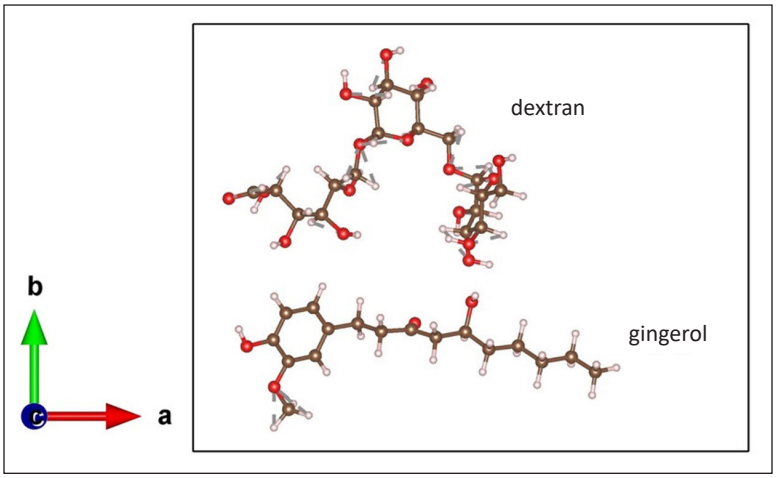


Figure 1. (Color online). The initial structure of the gingerol-dextran system

The binding energy of dextran on gingerol, Eb, was determined using Equation 1:

$$Eb = E_{(gingerol-dextran)} - \left[E_{(gingerol)} + E_{(dextran)}\right] \quad [1]$$

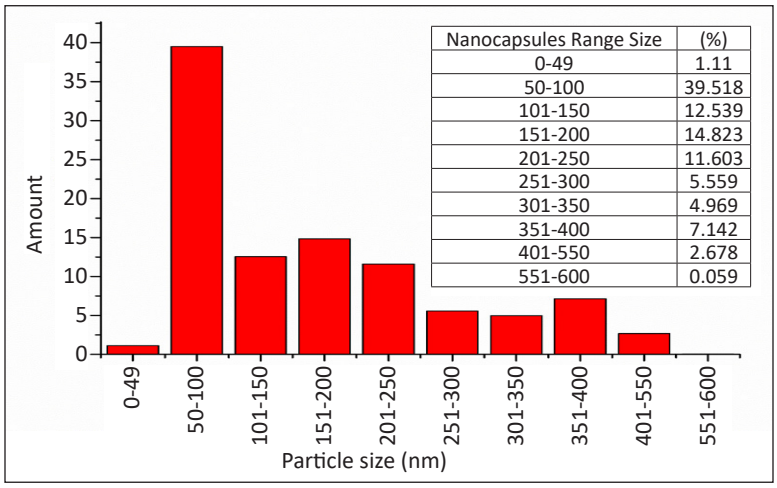
where $E_{(gingerol\text{-}dextran)}$ is the total energy of gingerol-dextran system, $E_{(gingerol)}$ is the total energy of isolated gingerol, and $E_{(dextran)}$ is the total energy of isolated dextran.

RESULT AND DISCUSSION

Nanocapsule Characterisation

Size distribution and homogeneity particle characterisation were done with a PSA and transmission electron microscopy (TEM to determine the nanocapsules' shape). PSA was employed to determine the average particle size and overall size distribution of the nanocapsules. This method can provide a more extensive statistical sampling size than electron microscopy observation and therefore, is useful for quantitative judgments.

The particle size distribution profile (Figure 2) shows that most of the nanocapsules (39.518 %) are in the 50-100 nm range. 1.11% of the nanocapsules were observed at the smallest measurement size range of 0 to 49 nm, and 0.059% of the nanocapsules were observed at the biggest measurement size range of 551 to 600 nm. Overall, the nanocapsules were measured in all size ranges in varying degrees of frequency, which means the nanocapsules are possibly not homogenous. It could be caused by inadequate optimisation of the ultrasonication process, which produced a non-uniform droplet size of the ginger extract before being encapsulated by maltodextrin. However, we cannot discount the possibility that some nanocapsules measured at the more extensive size ranges were aggregates. However, the percentage of the nanocapsules measured under the size of 200



Nanocapsules Range Size	(%)
0-49	1.11
50-100	39.518
101-150	12.539
151-200	14.823
201-250	11.603
251-300	5.559
301-350	4.969
351-400	7.142
401-550	2.678
551-600	0.059

Figure 2. Distribution of nanocapsule size

nm was 67.99%, which means the encapsulation was successfully performed in the nanoscale range.

Polydispersity Index (PI) of nanocapsules solution was measured at 0.347, showing that the particle size on the solution has a good size distribution. PI values range from 0 to 1, where the PI value < 0.1 shows a very homogeneous particle size. Materials intended for general purposes require PI values of 0.3 and 0.5 (Shah et al., 2014). The PI value of 0.347 in this study shows that the ginger nanocapsule particle size distribution is already acceptable for the intended purpose as food products.

As PSA only measures the diameter of the nanocapsules, there was also the possibility that the synthesised nanocapsules were not globular in shape, which made the size measurement varied. Therefore, qualitative analysis by TEM was employed to see the shape of the nanocapsule, to ensure the encapsulation of the ginger bioactive compounds inside the maltodextrin walls, and, to a lesser degree, confirming the size of the nanocapsules measured by PSA.

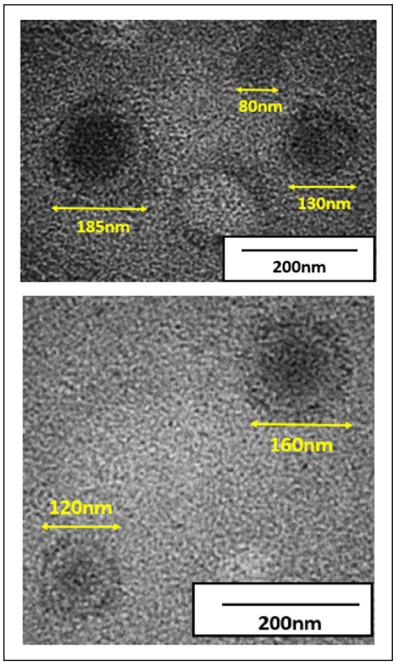


Figure 3. The TEM results showing nanocapsules

TEM results in Figure 3 show that the nanocapsules have a perfectly globular shape. The dark area located at the centre of the nanocapsule indicates the bioactive component at the core of the nanocapsules. The dark circle surrounding the outer surface of the nanocapsule

is composed of maltodextrin, which acts as a shell material for the nanocapsules. The observed nanocapsule size was small enough to categorise the nanocapsules as nano-scaled particles, even though TEM observation also shows slight varieties on nanocapsule size.

Computational Result

Geometry. The DFT studies confirmed the interaction between dextran and gingerol, wherein the binding energy of dextran on gingerol is -0.34 eV. The initial and optimised structures of gingerol-dextran are shown in Figures 4 and 5. It was observed that the interaction between dextran and gingerol occurred via the rotation of the hydroxyl moiety

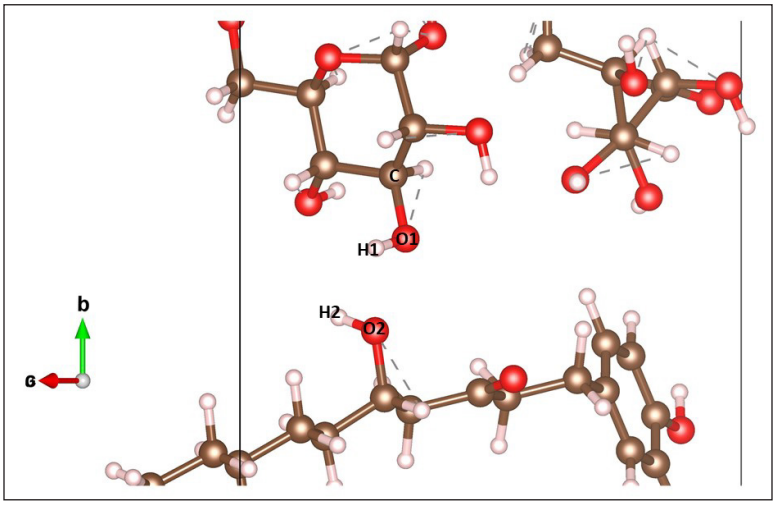


Figure 4. (Colour online). The initial structure of the gingerol-dextran system. For clarity, some atoms are not involved in both dextran and gingerol

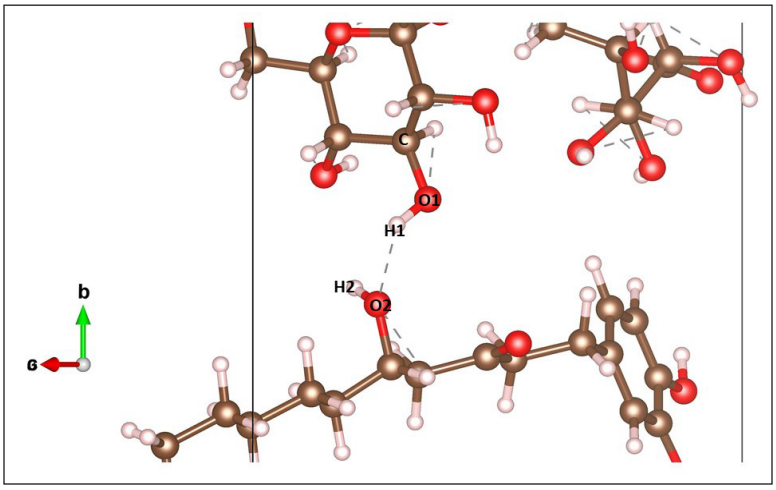


Figure 5. (Colour online). The optimised structure of the gingerol-dextran system. For clarity, some atoms are not involved in both dextran and gingerol

from dextran (O_1H_1) towards the oxygen moiety from gingerol (O_2). This rotation was due to Coulombic repulsive interaction between a dextran (H_1) and a hydrogen atom from gingerol (H_2) hydrogen atom. As listed in Table 1, the O_1H_1 rotation increased the C-O_1-H_1 angle by 5.94º, and this caused the H_1 to approach the oxygen moiety from gingerol and form a hydrogen bond with a length of 2.01 Å. This hydrogen bond is considered physisorption because of its relatively large distance. Table 1 also shows that the H_1-O_2 bond length was shortened by 0.1 Å, indicating the initiation of the encapsulation process. As the encapsulation was formed by physisorption, it should be theoretically accessible for the nanocapsules to be dissolved after consumption.

Table 1
The O-H, H-H, O-O bond lengths and C-O-H angle before and after dextran bind to gingerol

	O_1-O_2 (Å)	H_1-H_2 (Å)	H_1-O_2 (Å)	C-O_1-H_1 (deg)
Before	2.10	2.39	2.11	107.82
After	2.60	2.33	2.01	113.76

Density of States. The density of states analysis was employed to study the electronic structure of the gingerol-dextran system. Figure 6 shows the density of states (DOS) of isolated gingerol, isolated dextran, and gingerol-dextran systems. The DOS intensity near the Fermi level for isolated gingerol and isolated dextran is much higher than in the gingerol-dextran system. Furthermore, the peak height decreased when dextran and gingerol were bound together—from Figure 6, isolated gingerol, isolated dextran, and bound gingerol-dextran show conductive-like behaviours as shown by the density of states crossing the Fermi level.

In biological environments, conductivity is especially relevant to cell membrane permeability. It is because conductivity depends on the particle surface charge, which is one of the major variables determining particle uptake into the cells, particularly in human cells.

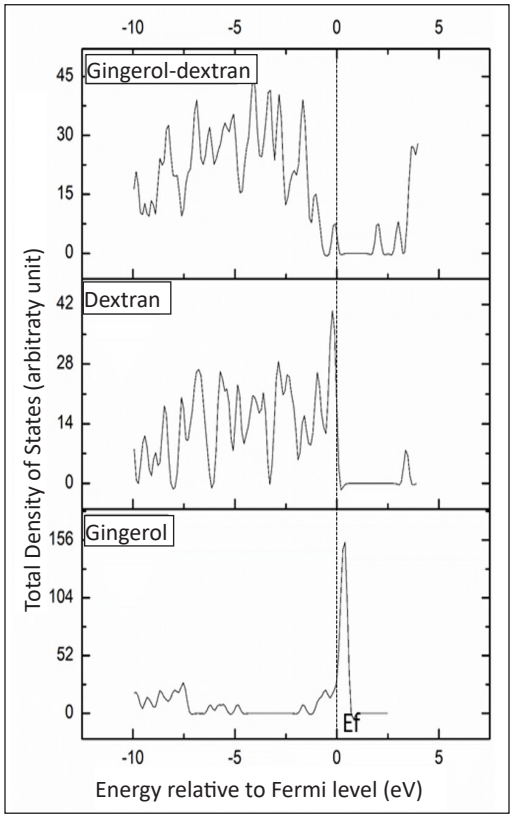


Figure 6. The total density of states of gingerol, dextran, and gingerol-dextran. The Fermi level is set to zero axes.

Nanoparticle Surface Charge and Cell Uptake

Nanoparticle uptake into cells is affected by several factors, including shape, size, and surface charge. The outer structure of animal cells consists of a phospholipid bilayer barrier and transmembrane proteins, which regulate whether the particle may be imported inside or exported outside the cell. The DFT calculation result, particularly from the density of states, shows that the interaction within the nanoparticle (between the dextran and gingerol) exhibits conductive-like behaviour, assuming that changing ions in molecules will affect the electronic structure of the nanoparticle and thus the cell uptake. A previous computational model shows that the negative charge of the phospholipid bilayer is relatively stable at a specific location due to the depth of the potential wells where the ions can be found (Pekker & Shneider, 2014), thus tweaking the surface charge of the nanoparticle will have a major effect on its interaction with the cell surface, and by extension, the cell uptake.

Admittedly, the surface charge of the phospholipid bilayer varies significantly in different cells and species as a result of the heterogeneous spatial distribution of macromolecular structures across the phospholipid bilayer (Klausen et al., 2016). However, as a general rule, this phospholipid bilayer has polar heads facing the external environment and lipid tails in the reverse direction. The interaction between polar or charged nanoparticles with the polar heads of the phospholipid bilayer is usually strong enough to make the nanoparticles unable to pass this barrier freely, and the nanoparticles tend to adhere to the membrane surface. These nanoparticles possibly use active transport methods of cell uptake with the aid of transmembrane proteins. Likewise, less charged nanoparticles are more easily passed through the cell membrane.

The nanoparticles used in this study are intended for gastrointestinal absorption to circulate in the cardiovascular system. Therefore, the nanoparticles should not strongly adhere to the gastrointestinal cell membrane surface. We can assume that more conductive nanoparticles will adhere to the cell membrane surface due to strong surface charge interactions and thus are difficult to penetrate further into the mucosal cells. Less charged nanoparticles are predicted to pass more easily through this barrier and thus are more desirable. The benefits and disadvantages of nanoparticles' ability to pass the cell membrane depend on the intended use. As a carrier for drugs intended to treat stomach ulcers, it is indeed more advantageous to have the nanoparticles adhere to the cell membrane surface, as the ulcer lies on the surface. On the other hand, nanoparticles are intended to reach systemic circulation. Therefore, they have to pass the cell membrane barrier.

It has been observed that the cell uptake mechanism differs between positively and negatively charged nanoparticles. In contrast, the positively charged particles tend to stick to the inner hydrophobic part of the phospholipid bilayer; negatively charged particles usually only interact with the outer hydrophilic surface and are difficult to pass the phospholipid bilayer (Tatur et al., 2013). From our DFT study, it can be seen that the nano-encapsulated ginger is less conductive compared to free gingerol. Less conductive particles tend not to

adhere strongly to either the phospholipid bilayer's inner hydrophobic or outer hydrophilic side. Therefore, they can be assumed to be able to pass through the phospholipid bilayer. Although a certain amount of conductivity is still needed to adhere to the outer hydrophilic side in the first stage of absorption through the phospholipid bilayer, predicting the exact conductivity value needed for optimal absorption through the phospholipid bilayer is beyond the scope of this study.

Other studies observed that the cell uptake of nanoparticles was more influenced by individual cell membrane composition than the different uptake routes taken by the nanoparticles of different charges (Fröhlich, 2012). However, these two factors may also be linked. Furthermore, the relations between nanoparticle surface charge and cell viability has also been recently explored, with increasing evidence to support that higher nanoparticle charge content may lead to structural cell damage to some extent (Tatur et al., 2013; Fröhlich, 2012; Hosseinidoust et al., 2015), which urges the need to tailor the surface charge of nanoparticles, such as by encapsulation. Our study proves that nano-encapsulated gingerol is less charged than free gingerol, and based on the previous studies by Tatur et al. (2013), Fröhlich (2012), Hosseinidoust et al. (2015), it can be inferred that nano-encapsulation of gingerol potentially lessens structural damage. However, further studies of nano-encapsulation with different materials should be done before we can safely assume that this is caused by nano-encapsulation and not a singular observation from a specific nano-encapsulated material.

SUMMARY AND CONCLUSION

In this study, we conducted the synthesis and characterisation of nano-encapsulation of ginger bioactive components and computational studies to analyse the geometry and the density of states of the ginger-dextran system. The bioactive components of ginger were encapsulated by maltodextrin. Particle characterisation was done using a PSA and TEM. PSA results show that the particle size of the ginger nanocapsules had a relatively homogenous particle distribution, with most of the particles measured under 200 nm. TEM observation confirms the nano-scale size of the ginger nanocapsules and shows that the ginger nanocapsules are perfectly globular in shape. The DFT calculation of the dextran-ginger system was conducted to measure the electronic properties and geometric structure. The hydrogen bond formation between dextran and gingerol indicates that the ginger nanocapsules were formed via physisorption. The density of states analysis shows that the gingerol-dextran system has a conductive-like behaviour to promote cell membrane permeability of the nanocapsule system. Ginger nanocapsules have similar characteristics to the gingerol-dextran system. Hence, they are expected to have a good cell membrane permeability to be easily absorbed by human cells.

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