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Formulation of *halalan toyyiban* radish effervescent tablet

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Abstract

Radish is a vegetable high in nutritional and phytochemical contents that are beneficial to the human body, especially for managing kidney stone disease. However, it is less consumed as compared to other vegetables due to its pungent flavour and odour. Therefore, the objective of the present work was to formulate a radish effervescent tablet to enhance the palatability of the vegetable. The radish effervescent tablet was formulated by using Simplex Lattice Mixture Design where the percentages of sucralose and strawberry flavour were chosen as the factors. Five formulations were generated, and sensory acceptance test was conducted on them. Next, the *halalan toyyiban* principle compliance was evaluated based on the Halal Control Points (HCPs), toxicity assay (brine shrimp lethality assay), anti-urolithiatic properties (turbidimetric assay), and nutritional composition (energy, total protein, total fat, total carbohydrate, and total sugar). Formulation 5 (F5) with 20% citric acid, 12% sodium bicarbonate, 58% radish powder, 2.5% sucralose, and 7.5% strawberry flavour was selected as the most acceptable formulation ($p < 0.05$). For the *halalan toyyiban* principle compliance, F5 was evaluated, and it complied with the *halalan toyyiban* principles. It is *halal*, non-toxic, and safe for consumption as the LC_{50} was greater than 1,000 µg/mL (2,223.31 µg/mL) for toxicity test, and exhibited significant potential as an anti-urolithiatic agent (88.13% inhibition). In the future, prototype development of radish effervescent tablet with potential anti-urolithiatic and fast-dissolving properties can be carried out.

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Introduction

Radish (*Raphanus raphanistrum* subsp. *Sativus* (L.) Domin) belongs to the Brassicaceae family which contains many economically important vegetables. Vitamin C concentration in radish has been recorded to reach a maximum of 122.5 mg per 100 g on a dry weight basis as compared to other underground vegetables (Khattak and Rahman, 2017). However, radish also contains 4-methylthio-3-trans-butenyl isothiocyanate (MTBITC) which gives pungent flavour and aroma to it (Coogan and Wills, 2008). This bioactive compound has anti-inflammatory and anti-cancer effects, and have been shown to reduce abnormal cell growth by promoting apoptosis in human colon cancer cells (Barillari *et al.*, 2008) and lung cancer cells (Wang *et al.*, 2014). Therefore, the present work aimed to formulate a radish effervescent tablet with palatable acceptability to promote the intake of radish so that users can get the benefits from the vegetables. Sweetener and flavouring were used to increase the attractiveness of the effervescent tablet. Sucralose, which is a zero-calorie synthetic sweetener, was used as it has been shown to help in lowering energy intake, which may lead to the reduction and prevention of obesity (Schiffman and Rother, 2013), while strawberry flavour has been found to be preferred by certain subgroups, mainly youths (Hoffman *et al.*, 2016). Apart from that, it also amends the taste of potassium citrate in an effervescent tablet as compared to orange, raspberry, cherry, and lemon flavours (Aslani

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and Fattahi, 2013). Nowadays, the number of people who cannot, or dislike swallowing tablets and capsules is growing, especially kids and old people. So, the effervescent tablet is one of the alternatives as it is administered in liquid form so that people who cannot swallow the solid form of the product can easily consume it. Effervescence is a chemical reaction where gas bubbles evolve from a liquid as the result of foaming or fizzing (Ipci *et al.,* 2016). The application of effervescence in the food industry includes bubbles and foams in champagnes, carbonated soft drinks, and beers. In addition, the effervescent tablet has a significant advantage as the product is already in solution when it is ingested, hence the absorption is quicker and more complete than a traditional tablet (Patel and Siddaiah, 2018).

Halalan toyyiban food product is a product that contains *halal* ingredients and at the same time does not contain any substance that would endanger human health, but provide health benefits for the human body which can help in the prevention of some diseases. A study listed that *halal* and *toyyiban* principles also include other items such as the ingredient, equipment and utensil, packaging, storage, processing, transportation, and waste management (Othman *et al.,* 2016). *Toyyiban* also represents food with ingredients that are clean, pure, free of potential toxin/contaminant/adulterant, and *najis* (Alzeer *et al.,* 2018). Besides, a product is related to a thing that is medically suitable for human consumption, and considered good for health (Ur Raheema and Demirci, 2018). Nowadays, some consumers misunderstand the meaning of *halal* as for them, it is just a religious practice that only focuses on slaughtering. However, the whole concept of *halal* is that the food should be pure, safe, and free of any form of contaminants, not just from pork and alcoholic substances (Baharuddin *et al.,* 2015). Therefore, in the present work, the radish effervescent tablet was formulated and evaluated for its *halalan toyyiban* principle compliance.

Materials and methods

Materials

Radish was purchased from a local supermarket in Pagoh, Johor and the radish powder was prepared following Eveline and Pasau (2019) with slight modification. All chemicals were of analytical grade, and purchased from QRëC (New Zealand), except for calcium chloride trihydrate (HmbG, Germany). Equipment used included electronic balance (OHAUS, Ohaus Corporation, USA), disintegration tester (BJ-2, Guoming, China), texture analyser (Stable Micro Systems, TA.XT*plusC*, United Kingdom), pH meter (Eutech Instruments, pH 700, Singapore), food dehydrator (Hendi, 229026, Austria), ultraviolet-visible (UV-vis) spectrophotometer (PG Instruments, T60 U, United Kingdom), and single-punch press machine.

Formulation of radish effervescent tablet

Sweetener (sucralose) and flavouring agent (strawberry flavour) purchased from a local food additive supplier were selected as independent variables, whereas the dependent response variables measured were weight variation, disintegration time, hardness, pH, and sensory attributes. To study the effect of the ingredients on the physicochemical and sensory acceptance of the effervescent tablets, experiments were systematically conducted by using Simplex Lattice Mixture Design from Design Expert (6.0.4) software to graphically express the influence of each factor on the response by generating the response surface plots (Patel *et al.,* 2015). The radish effervescent tablets were prepared as shown in Table 1. The radish powder with the effervescent agent was weighed and mixed in a blender for 15 min. Then, sucralose and strawberry flavour were added and mixed for 5 min. Finally, the selective excipient including sodium benzoate (10 mg) was added for each 4.5 g of the tablet (Aslani and Fattahi, 2013). Then, by using a single-punch press machine with a

Table 1. Formulation of the radish effervescent tablet.

Ingredient	Formulation (mg)				
	F1	F2	F3	F4	F5
Citric acid	300	300	300	300	300
Sodium bicarbonate	180	180	180	180	180
Radish powder	870	870	870	870	870
Sucralose	75	150	112.5	0	37.5
Strawberry flavour	75	0	37.5	150	112.5

25 mm punch set, the powders were compressed into tablets. The tablets were dried in a food dehydrator with air circulation at 54°C for 1 h to allow the excipient to react and improve the interparticle bonding (Mohd Rosdan *et al.,* 2016), cooled, and packed in air-tight plastic tubes.

Physicochemical properties

The method for the weight variation followed the method described by Patel *et al.* (2015) with slight modification. Three tablets were selected randomly, weighed individually, and the average weight was obtained (Patel *et al.,* 2015). Next, the disintegration test was conducted by using a tablet disintegration machine where the tablets were placed in a cylindrical test tube in the basket-rack assembly. The machine was operated by using water (37°C) as the immersion fluid. For hardness, a texture analyser was used to test the failure behaviour of tablets due to diametral compression using a cylinder probe for each formulation (Joshi *et al.,* 2010). The mode used was a measurement of force in compression with a test speed of 0.03 mm/s. The pH of the effervescent solution was determined by placing one tablet in 100 mL of water (20°C). Then, a pH meter was used to determine the pH value of the solution.

Sensory evaluation (hedonic test)

The radish effervescent tablet drinks were prepared by dissolving one radish effervescent tablet in 100 mL of water to make each drink. The drink sample (10 mL) was poured into a sensory cup, and it was coded with a random number for each formulation. The test involved 55 untrained panellists aged 20 - 50 years old who were served with the drink samples. The critical attributes for scoring included the aroma, flavour, colour, sweetness, and overall acceptance. All product samples were evaluated to obtain liking scores by using a 9-point hedonic scale. The panellists were instructed to evaluate the drink samples by giving the score and rinsing their mouth with water in between samples to minimise the residual flavour effect (Mohd Rosdan *et al.,* 2016).

Halalan toyyiban compliance

The formulation with the highest acceptance for the sensory properties was evaluated for its compliance with the *halalan toyyiban* principles to ensure that the radish effervescent tablet developed would be *halal* and safe to be consumed, and would not cause any harm to the human body. The implementation of *halalan toyyiban* in food industries is essential for the protection of health to prevent food-related diseases (Ambali and Bakar, 2014).

Halal Control Points (HCPs)

The HCPs were identified by the *halal* logo or *halal* certification (Lau *et al.,* 2016) by the Department of Islamic Development Malaysia (JAKIM). Next, all equipment used during the processing was washed before and after to ensure cleanliness. Besides, the *halal* status of the ingredients was maintained during the processing and storage as they did not have contact or were contaminated with *haram* ingredients.

Toxicity assay

Toxicity assay was conducted using brine shrimp (*Artemia salina)* lethality assay. For the stock solution, 10 g of tablets were diluted in 100 mL of distilled water, and then diluted to 1,000, 500, 250, 100, and 10 ppm. Ten matured *A. salina* were placed in a test tube containing 1 mL of artificial seawater solution with 1 mL of prepared diluted solution (Naidu *et al.,* 2014). After 24 h, the number of survived nauplii in each test tube was inspected, and the percentage of death in each tube was counted.

Anti-urolithiatic assay (in vitro)

The anti-urolithiatic properties of the radish effervescent tablet were investigated according to Jagtap *et al.* (2019) using the inhibition of calcium oxalate crystallisation method with slight modifications. An ultraviolet-visible spectrophotometer (UV-vis) at 620 nm was employed to measure the turbidity of the formation of calcium oxalate. First, for the study without inhibitor (negative control), 10 mM of calcium chloride dihydrate solution ($CaCl_2{\cdot}2H_2O$) and 4 mM sodium oxalate solution ($Na_2C_2O_4$) were prepared using sodium chloride solution (0.15 M). Then 1.5 mL of the calcium chloride dihydrate was moved to the cell, and a blank reading was taken. After that, 1.5 mL of sodium oxalate was added to the previous amount, and the absorbance was immediately recorded up to period of 10 minutes.

For the test with the inhibitor, by using Cystone as a standard (positive control), the 100% inhibitor solution (sample) was prepared by dissolving a radish effervescent tablet in 60 mL of sodium chloride

solution, and diluted to produce the inhibitor solutions (10, 20, 30, 40, 50, 60, 70, 80, and 90%). The cell contained a mixture of 1 mL of calcium chloride dihydrate (10 mM) and 1 mL of inhibitor solution. A blank reading was recorded, and 1 mL of sodium oxalate (4 mM) was added to the volume. The absorbance was immediately recorded up to period of 10 minutes. The percentage of inhibition (I%) was calculated using Eq. 1:

$$I\% = 1 - \left[\frac{\text{Turbidimetric slope without inhibitor}}{\text{Turbidimetric slope with inhibitor}}\right] \times 100 \quad \text{(Eq. 1)}$$

Nutritional composition

Total protein content was determined by Kjeldahl method in compliance with AOAC International's method where the value was multiplied by the traditional conversion factor of 6.25, and the species-specific conversion factor of 4.4 for vegetables (Mariotti *et al.*, 2008). Total fat content was determined by a semi-continuous solvent extraction process (AOAC, 2006). Total carbohydrate content was determined by subtraction as shown in Eq. 2:

$$\%\ \text{Carbohydrate} = 100\% - (\%\ \text{protein} + \%\ \text{fat} + \%\ \text{ash} + \%\ \text{moisture}) \quad \text{(Eq. 2)}$$

Energy was determined by multiplying proteins, carbohydrates, and fats by 4, 4, and 9 factors, respectively. Total sugars were determined using high-performance liquid chromatography (HPLC) coupled with an evaporative light scattering detector (ELSD) (Mohd Naeem *et al.*, 2017).

Statistical analysis

All data were expressed as mean ± standard deviation, and analysed using One-way analysis of variance (ANOVA) in Statistical Package for the Social Science (SPSS) software (Version 20.0, IBM, Chicago). The statistical significance was based at a confidence level of 95%. $p < 0.05$ indicated that the model terms were significant in the response variables (Simundic, 2012).

Results and discussion

Physicochemical properties test

The quality of the effervescent tablet was based on the weight variation, disintegration time, hardness, and pH of the solution. The most crucial testing for effervescence is the disintegration time and the pH of the solution obtained after the dissolution, as it verifies the release of carbon dioxide that acts as a buffer to balance the acid and sodium bicarbonate (WHO, 2011).

As shown in Table 2, the mean for the weight variation for all formulations was between 1.34 and 1.40 g with a low standard deviation. The weight of an effervescent tablet depends on its volume, and the lifting effect comes from the bubbles produced on its surface during the effervescence reaction with water (Koimas, 2018). Based on the Drug Registration Guidance Document (DRGD), the weight variation for each formulation of the tablet was acceptable because the differences between individual weight variations were less than 10% from the average weight (NPRA, 2020). As for the disintegration time, Formulation 2 (F2) recorded the shortest time for the tablet to disintegrate ($p < 0.05$). Sucralose is highly water soluble which led to F2 having the shortest disintegration time as it contained the highest percentage of sucralose (Bernadene *et al.*, 2016). On average, all formulations were acceptable as uncoated tablets should not take more than 30 minutes to dissolve, according to DRGD. The disintegration time is related to the hardness of the tablet as F2 also recorded low hardness. Moorthy and Pandey (2016) mentioned that a low hardness value for a tablet resulted in a quick disintegration time. The hardness values for the radish effervescent tablet were also acceptable since the range was within 5 to 10 kg (49 - 98 N) ($p < 0.05$). Effervescent tablets have a lower hardness as compared to regular tablets, with a required minimum hardness of 40 N for uncoated tablets (Lachman *et al.*, 1986). The pH was in the range of 4.0 to 4.8, which was due to different percentages of strawberry flavour and sucralose. Esters, especially methyl and ethyl esters, make up 25 - 90% of the total volatiles in strawberries, and contribute the fruity flavour (Fan *et al.*, 2021). This chemical compound may have some reactions with other ingredients in the tablet, which affected the pH of the effervescent solution. However, it was still acceptable as the pH value was less than 6, and could improve the absorption of effervescent tablets (Aslani and Fattahi, 2013). Therefore, all the formulations were acceptable based on their physicochemical characteristics as effervescent tablets.

Table 2. Physicochemical and sensory properties of radish effervescent tablet.

Property		Formulation				
		F1	F2	F3	F4	F5
Physicochemical	Weight variation (g)	1.34 ± 0.10^{a}	1.39 ± 0.02^{a}	1.36 ± 0.02^{a}	1.36 ± 0.06^{a}	1.40 ± 0.03^{a}
	Disintegration time (s)	125.80 ± 0.70^{e}	47.10 ± 0.90^{a}	64.73 ± 0.35^{b}	77.07 ± 0.35^{c}	91.90 ± 1.68^{d}
	Hardness (kg)	9.03 ± 0.05^{c}	5.72 ± 0.04^{d}	8.93 ± 0.08^{c}	10.37 ± 0.02^{a}	9.67 ± 0.02^{b}
	pH	4.79 ± 0.04^{a}	4.05 ± 0.04^{c}	3.99 ± 0.01^{d}	4.36 ± 0.01^{b}	4.31 ± 0.01^{b}
Sensory	Aroma	6.16 ± 1.58^{a}	5.18 ± 1.52^{b}	5.84 ± 1.56^{ab}	5.67 ± 1.74^{ab}	6.00 ± 1.59^{a}
	Colour	6.64 ± 1.24^{a}	5.89 ± 1.36^{b}	6.24 ± 1.39^{ab}	6.80 ± 1.46^{a}	6.80 ± 1.31^{a}
	Flavour	6.47 ± 1.85^{a}	5.84 ± 1.77^{a}	6.24 ± 1.59^{a}	4.51 ± 1.95^{b}	6.51 ± 1.75^{a}
	Sweetness	6.04 ± 2.12^{a}	5.62 ± 2.04^{a}	5.90 ± 2.00^{a}	4.27 ± 2.05^{b}	6.29 ± 1.84^{a}
	Overall acceptance	6.58 ± 1.75^{a}	5.85 ± 1.73^{a}	6.05 ± 1.70^{a}	4.72 ± 2.02^{b}	6.67 ± 1.49^{a}

Means within a row followed by different lowercase superscripts are significantly different ($p < 0.05$).

Sensory evaluation (hedonic test)

The sensory evaluations were conducted to determine the palatability of the radish effervescent tablet. Hedonic tests were conducted for the five tablet formulations, and the responses were the aroma, colour, flavour, sweetness, and overall acceptance. From Table 2, F4 had the lowest score for aroma, flavour, sweetness, and overall acceptance, despite its short disintegration time. This was because it did not contain any sweetener (sucralose) to help in masking the taste of the radish. Although F2 had acceptable physicochemical qualities, sensory evaluation showed that it had an unpleasant aroma and colour. F5 had the highest overall acceptance ($p < 0.05$) as compared to the others, and panellists liked F5 moderately. Therefore, F5 was chosen as the best formulation as the objective was to enhance the palatability of the radish. A previous study showed that the sweet taste of sucralose is the best suppressor of other taste qualities, including a bitter taste (Green *et al.*, 2010). Besides, masking the undesirable taste can also be improved by adding flavour and effervescent agents (Sohi *et al.,* 2004).

Halalan toyyiban compliance

The *halal* status for all the ingredients used was identified to comply with the *halalan toyyiban* principles. It was *halal*-certified by JAKIM and ARA Halal Certification Services Centre Inc., which is one of the Foreign Halal Certification Bodies (FHCB) recognised by JAKIM where the engagement is in China. Radish comes from a *halal* source in which it is of plant origin. The term *halal* for plant origin applies when the plants are non-toxic and non-hazardous, except the toxic or hazard substances can be removed through processing (Codex Alimentarius, 1997). Apart from that, the handling, processing, and storing activities were also carried out in line with *halalan toyyiban* principles, in which the processes were separated from non-*halal* products to avoid any cross-contamination, and to maintain the *halal* status of the tablet.

For the toxicity assay, after 24 h of exposure of the brine shrimp with the radish effervescent tablet solution, a graph was plotted as the percentage of shrimps killed against the logarithm of the sample concentration. From the graph (Figure 1), the median lethal concentration (LC_{50}) of the test samples was derived. Based on Figure 1, the concentration that killed 50% of the nauplii, or known as LC_{50} value for the radish effervescent tablet, was 2,223.31 µg/mL. Based on Clarkson's toxicity criteria, a sample that has LC_{50} values over 1,000 µg/mL is non-toxic, 500 – 1,000 µg/mL LC_{50} is low toxic, 100 – 500 µg/mL LC_{50} is medium toxic, and 0 – 100 µg/mL LC_{50} is highly toxic (Clarkson *et al.,* 2004). This indicated that the radish effervescent tablet was non-toxic and safe to be consumed.

The results for the anti-urolithiatic assay (*in vitro*) are presented in a bar chart (Figure 2) as the percentages of inhibition for the different concentrations. Cystone was used as a standard, which showed 93.77% inhibition. Even though Cystone was helpful in inhibition, plant extracts also have the potential to inhibit the formation of stone crystal because of their wide range of biomedicinal active ingredients (Devi, 2017).

From Figure 2, 100% consumption of the

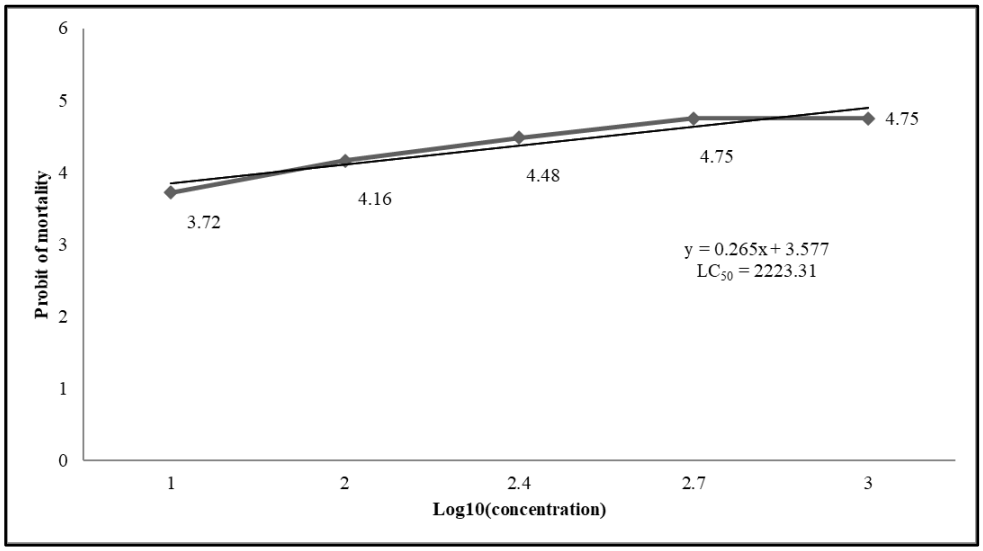

Figure 1. Log concentration against probits of mortality.

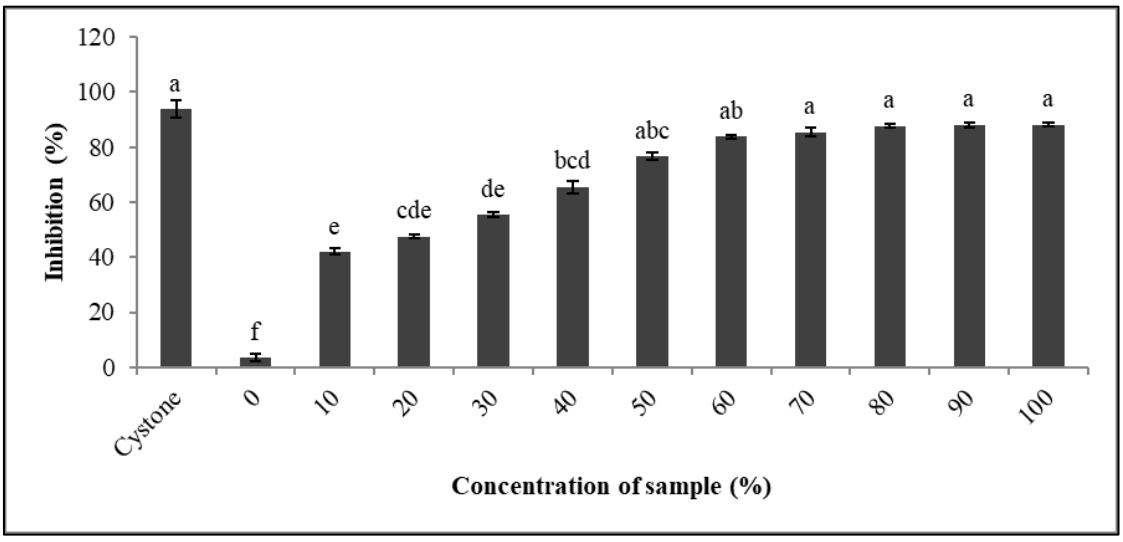

Figure 2. Percentage of inhibition for different concentrations of radish effervescent tablet. Means followed by different lowercase letters are significantly different ($p < 0.05$).

radish effervescent tablet had 88.13% inhibition. A higher inhibition percentage shows a better effect in the dissolution of calcium oxalate crystal. The accumulation of inorganic salts such as calcium, phosphorous, ammonia, oxalate, or uric acid is the main cause of kidney stone. Therefore, as the concentration of the radish effervescent tablet increased, the percentage inhibition of calcium oxalate crystal also increased until 50% concentration of the sample. Phytochemicals in radish inhibit the growth of oxalate crystals since radish itself has antioxidant potentials, as it contains phenolic compounds and ascorbic acid (Falah and Dlshad, 2020). Other than that, a diet that includes radish also resulted in increased excretion of calcium oxalate (Kumar, 2004). Besides, citrate is also an effective stone-forming inhibitor, and the development of kidney stones has been related to low urinary citrate excretion (Zuckerman and Assimos, 2009). Therefore, the radish effervescent tablet formulation had significant potential as an anti-urolithiatic agent.

Based on Table 3, the calories per tablet was 4.8 kcal as it included 1.143 g carbohydrate, 0.005 g protein, 0.002 g fat, and 0.42 g sugar. Lim *et al.* (2015) reported that some consumers were particularly aware and worried about overconsuming nutrients such as fats and sugars, as it might cause obesity and other diet-related diseases. The formulated radish effervescent tablet was low in fat and sugar, and would not contribute high calories to

the diet. It also complied with the *halalan toyyiban* principles where it contained nutrients that can benefit human through consumption.

Table 3. Nutritional composition of radish effervescent tablet.

	Per Serving (1.5 g)	Per 100 g
Energy / calories	4.8 kcal	320 kcal
Total protein	0.005 g	0.300 g
Total fat	0.002 g	1.500 g
Total carbohydrate	1.143 g	76.200 g
Total sugar	0.420 g	28.000 g

Conclusion

The physicochemical properties of the effervescent tablet for each formulation were acceptable and followed the Drug Registration Guidance Document (DRGD), United States Pharmacopeia (USP), and British Pharmacopoeia (BP). F5 with 20% citric acid, 12% sodium bicarbonate, 58% radish powder, 2.5% sucralose, and 7.5% strawberry flavour was selected as the most acceptable formulation as it had the highest overall acceptance ($p < 0.05$) as compared to other formulations following the sensory evaluation. Therefore, F5 was chosen as the best formulation as the objective was to enhance the palatability of radish. The formulation also complied with the *halalan toyyiban* principles. As a result, the number of people that consume this type of root vegetable (*Raphanus sativus*) can be increased. Hence, more people can get the health benefits from consuming radish-based products as radish has high nutritional and pharmaceutical potentials. For future studies, the development of fast-dissolving radish effervescent tablet can be carried out to improve consumers' acceptability. In addition, studies on the packaging material and design can also be conducted as the effervescent tablet is a moisture-sensitive product.

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