Original Article

Gingerol supplementation does not change glucose tolerance, lipid profile and does not prevent weight gain in C57BL/6 mice fed a high-fat diet

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ARTICLE INFO

SUMMARY

We hypothesized that gingerol supplementation would exert protective effects against high-fat diet (HFD)-induced weight gain via regulation of lipid and glucose homeostasis. To test our hypothesis, forty C57BL/6 mice were fed a standard diet (SD), SD plus gingerol (SDG), high-fat diet (HFD) and HFD plus gingerol (HFDG) for 12 weeks. Gingerol dose was 500 mg/kg/d. HFD groups presented higher total food intake (grams) as compared to SD groups (97%). Nevertheless, there were no significant differences in weight gain between the groups. Gingerol supplementation did not prevent retroperitoneal, epididymal, and brown fat gain on HFDG, as well did not change liver weight. In addition, no difference was observed on lipid profile and glucose tolerance test. These results suggest that gingerol supplementation in mice fed high-fat diet has limited effects to prevent

weight and fat gain, and do not inhibit the increase on area under serum glucose curve.

1. Introduction

Obesity is defined as a chronic noncommunicable disease, caused by an imbalance between energy intake and expenditure and is characterized by excess lipid accumulation in adipocytes [1]. The evidence-based literature describes obesity as a chronic medical condition of multifactorial etiology, including genetic, environmental, metabolic and behavioral factors [1]. This disease is growing and has become one of the biggest public health concerns in the world. Estimates indicate that by 2030, approximately 38% of the adult world population will be overweight [2].

The complications of obesity are related to the development of chronic diseases, such as type 2 diabetes (DM2), hypertension, hepatic steatosis, coronary heart disease, among others [3]. The prevention and treatment include a healthy lifestyle with regular physical exercise and a balanced diet, accompanied in some cases by pharmacological therapy and/or surgical procedures [4].

Recently, interest has been growing in spice-based medicines, because they are associated with fewer side effects, exert anti-inflammatory, hypoglycemic and antioxidant function, showing beneficial effects on obesity [5–7]. According to Yun [8], herbal medicines act in five different ways in obesity: 1: decrease lipid absorption, 2: decrease carbohydrate absorption, 3: increase energy expenditure, 4: decrease pre-adipocyte differentiation and proliferation, 5: decrease lipogenesis and increase lipolysis. However, the ability of plants, herbs and their derivatives to prevent or treat obesity is still poorly investigated and may be a pathway for the safe and effective development of anti-obesity medicines based on natural products.

One herbal medicine that has been described for obesity treatment is the Ginger, derived from the rhizome of *Zingiber officinale* Roscoe (Zingiberaceae) [7]. Ginger contains various phytochemicals and biologically active components, such as gingerols and shogaols, which have been investigated for their anti-inflammatory, anti-diabetic and antioxidant effects [7,9,10]. Research with C57BL/6 mice fed with high-fat diet (HFD) and supplemented with ginger (500 mg/kg) showed that supplementation significantly reduced the final body weight and consequently prevented the weight gain [10]. Moreover, ginger was effective to avoid the increase in serum glucose, total cholesterol (TC) and triglycerides (TG) levels [10].

Although some studies indicate positive effects of ginger supplementation, little has been reported about its use in the prevention of weight gain and the development of insulin resistance, diabetes and dyslipidemia [10,11]. Thus, considering the epidemic proportions of obesity and the urgency of new strategies for its prevention, this study aimed to investigate the effects of gingerol on weight gain, lipid and glucose profile of mice fed a high-fat diet.

2. Materials and methods

2.1. Animals and design

The experimental protocol was approved by the Animal Research Ethics Committee of Ribeirão Preto Medical School, University of São Paulo (protocol no. 088/2013) and followed the ethical principles from the ARRIVE guidelines and the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978).

Forty C57BL/6 male mice (6–8 weeks after birth) were obtained from the Central Animal Facilities of the Ribeirão Preto Campus, University of São Paulo. The animals were kept in cages under standard laboratory conditions (25 ± 1 °C, 12-h light/dark cycle) with free access to food and drinking water for 2 weeks to stabilize their metabolic condition (adaptation). After the 2-week adaptation, the animals were randomly separated into two groups of twenty animals each: animals that received standard diet

(SD) and animals that received high-fat diet (HFD) and remained in that division for one week for adaptation with the diet. After this period of adaptations, they started the treatment and were randomly separated into four groups of ten animals each: standard diet (SD), standard diet supplemented with gingerol (SDG), high-fat diet (HFD) and high-fat diet supplemented with gingerol (HFDG).

The total period of supplementation with gingerol was twelve weeks.

2.2. Ginger extract and diets

Ginger dry extract was powdered and mixed in food and the supplemental dose of gingerol was 500 mg/kg/day. The diet ingredients were crushed, hydrated and offered in the form of pellets.

Ginger dry extract contained 5% of gingerol was analysed by high-performance liquid chromatography (HPLC) and purchased from local market. The animals from HFD groups were fed the diet composed of 400 g of standard chow, 100 g of sucrose, 100 g of lard, 170 ml of soybean oil, 400 g of milk powder and 0.04 g of butylated hydroxytoluene (BHT). The animals from SD groups were fed a commercial Nuvilab CR1 chow, based on the recommendation of the American Institute of Nutrition (AIN-93), for growing rodents. The nutritional compositions of experimental diets (SD and HFD) are described in Table 1.

2.3. Weight gain analysis

The body weight (BW) was checked weekly using a digital scale with a maximum capacity of 15 kg (Filizola S.A., São Paulo, Brazil). The percentage of weight gain was calculated by the difference between the final weight and initial weight using the following equation:

[(final weight − initial weight)] x 100/initial weight

2.4. Dietary intake analysis

The dietary intake of animals was recorded daily, by means of the difference between the amount of food offered and the amount remaining in the feeder on the following day, which allowed the determination of the 24-h food intake.

2.5. Biochemical and Tissue analysis

At the end of the experiment, the animals were euthanized by decapitation and blood samples were collected for lipid profile analysis. During the euthanasia, the blood was collected and promptly centrifuged at 3500 rpm, 4 °C for 15 min to obtain the serum, which was kept in a freezer at −70 °C for subsequent biochemical analysis. Glucose concentrations were measured at 12 weeks by the Accu-Chek glucometer (Accu-chek Performa Roche, Mannheim, Germany) according to the manufacturer's

Table 1
Nutritional composition of the standard and high-fat diets (g/100 g diet).

	Standard[a]	High-fat[b]
Carbohydrates	44.8 g (42%)	48.47 g (34.5%)[c]
Lipids	3.4 g (4%)	31.85 g (51%)[d]
Proteins	24.8 g (22%)	20.37 g (14.5%)
Energy (Kcal/weight)	309 Kcal	562 Kcal

[a] Standard. Source: Nuvilab. (NUVILAB-CR1 Nuvital-Colombo, Brazil), contains the following nutritional composition: protein 22%; lipids 4%; carbohydrate 42%; minerals 10%; phosphorous 0.8%; vitamins 1%; fibers 8%; humidity 12.5%. To the bromatological analysis, 100 g of dry matter of the diet contained: 309 kcal; 24.8 protein; 3.4 g lipids; 44.8 g carbohydrate; 8.2 g fixed mineral residue; 18.8 g dietary fiber.

[b] High-fat. Source: Brazilian Food Composition Table - TACO Version 4, contains the following composition: 34.55% standard chow, 8.13% sucrose, 13.32% lard, 32.55% powdered milk and 12.44% soybean oil.

[c] The kind of carbohydrates of the High-Fat diet: sucrose and lactose.

[d] The kind of lipids of High-Fat diet: polyunsaturated fatty acids and saturated fatty acids.

specifications. The TC, high-density lipoprotein (HDL) and TG were analysed by enzymatic method using commercial kits from Labtest (Labtest Diagnóstica S.A., Brazil). Samples of hepatic tissue, epididymal, retroperitoneal and brown adipose tissue were collected and weighed immediately.

2.6. Glucose tolerance test

Glucose tolerance test (GTT) was performed after 10—12 h fasting, two days before decapitation, as well as the first blood collection (time 0) by a cut at the caudal end of the animal. Subsequently, a glucose solution of 1 mg/g of animal's weight was injected intraperitoneally, according to the protocol developed by our research group. Blood sample collection was performed at times 0′, 30′, 60′, and 120′ [12]. Glucose concentrations were determined by the Accu-Chek glucometer (Accu-chek Performa Roche, Mannheim, Germany) according to the manufacturer's specifications. In addition, with GTT data was calculated the area under the curve (AUC).

2.7. Statistical analysis

Data are presented as means ± standard error. Normality test (Kolmogorov—Smirnov test) was followed by nonparametric Kruskal—Wallis and post-hoc Dunn test to identify differences between groups. Data analysis was performed using IBM SPSS v.22 software. Differences were considered significant at $p < 0.05$.

3. Results

3.1. Food intake and body weight

In Fig. 1A, it was observed that the standard diet groups behaved similarly over the weeks of treatment and the high-fat groups also, but had a higher food intake (grams). In Fig. 1C, it was noted that the groups started and ended the treatment with similar weights. It was observed that from week 2 to week 10, the standard diet groups had a reduction in weight compared to the high-fat groups, but without significant difference.

High-fat diet animals (HFD and HFDG) showed higher total food intake, approximately 97%, as compared with their standard diet groups (SD and SDG) (Fig. 1B). However, the higher amount of food intake in HFD and HFDG did not modify the weight gain as compared with SD and SGD groups (Fig. 1D).

3.2. Tissues weight

Retroperitoneal, epididymal and brown fat pads weights were similar in all groups (Figs. 2A, B and C). HFD provoked a significantly increase in liver weight, approximately 14%, as compared with SD (Fig. 2D). HFDG showed ~5% less liver weight compared with HFD, however, this difference did not achieve statistical significance.

3.3. Glucose tolerance test (GTT)

In respect of blood glucose concentrations during GTT, no significant difference was found between the groups (Fig. 3A). On the other hand, HFDG presented a marked increase on area under curve, approximately 79%, as compared with HFD (Fig. 3B).

3.4. Biochemical analysis

Blood measurements of glucose and lipid metabolism are shown in Table 2. The groups fed with high-fat diet (HFD and HFDG) presented significantly higher triglycerides concentration, but only HFD achieve statistical difference when compared with SD group. No statistical difference was observed between groups in other blood variables.
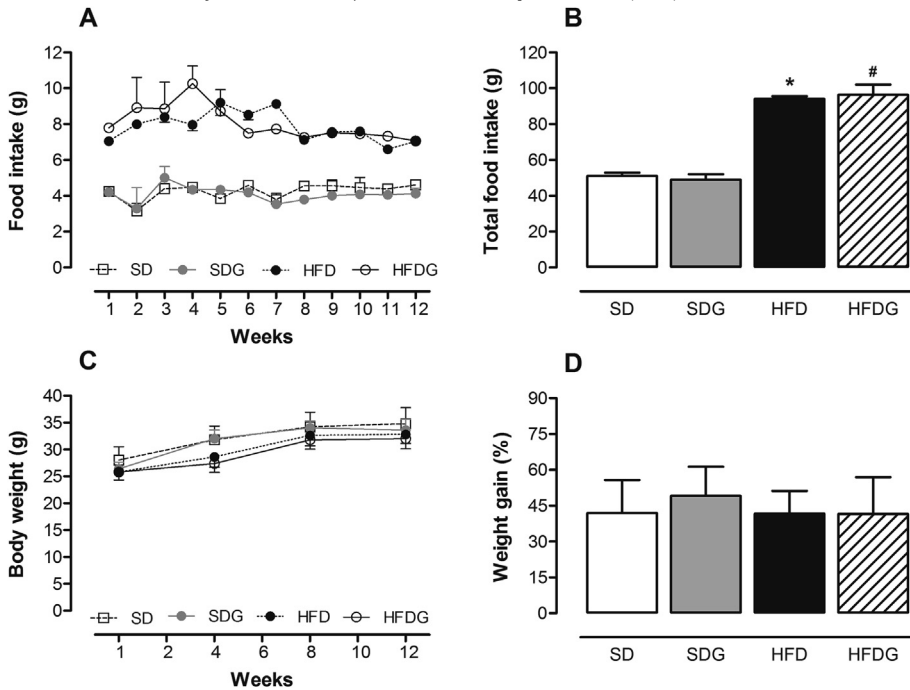
Fig. 1. Food intake and body weight. Panel A, food intake separated by weeks. Panel B, sum of all food consumed for 12 weeks. Panel C, body weight separated by weeks. Panel D, sum of all weight gain for 6 weeks. SD: standard diet; SDG: standard diet with gingerol; HFD: high-fat diet; HFDG: high-fat diet with gingerol. *different from SD; #different from SDG. Data are mean ± SD, Kruskal–Wallis and post-hoc Dunn test (p < 0.05), n = 10 each group.
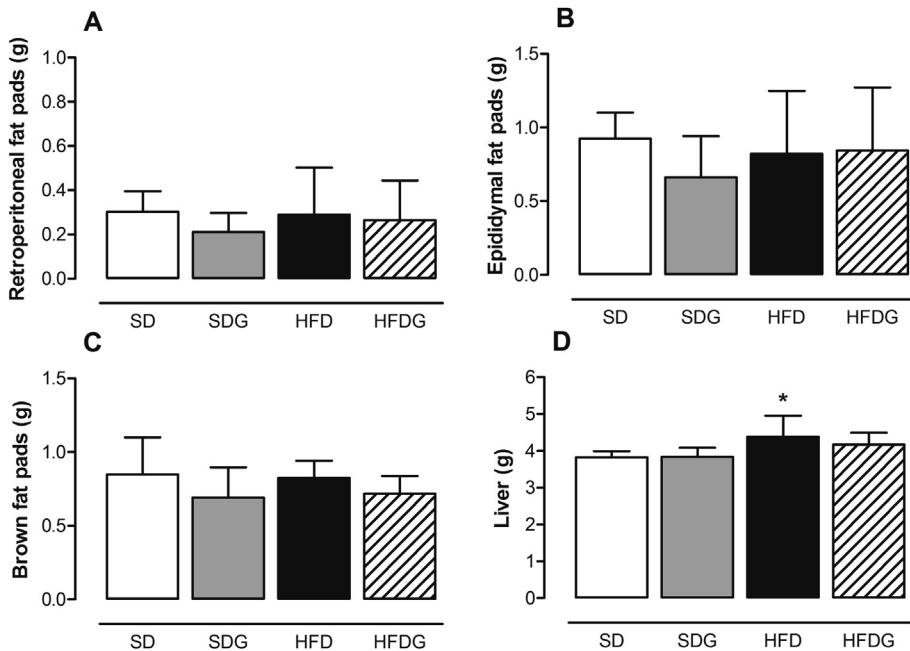

Fig. 2. Tissue weight. Panel A, retroperitoneal fat pads. Panel B, epididymal fat pads. Panel C, brown fat pads. Panel D, liver. SD: standard diet; SDG: standard diet with gingerol; HFD: high-fat diet; HFDG: high-fat diet with gingerol. *different from SD. Data are mean ± SD, Kruskal–Wallis with post-hoc Dunn test (p < 0.05), n = 10 each group.
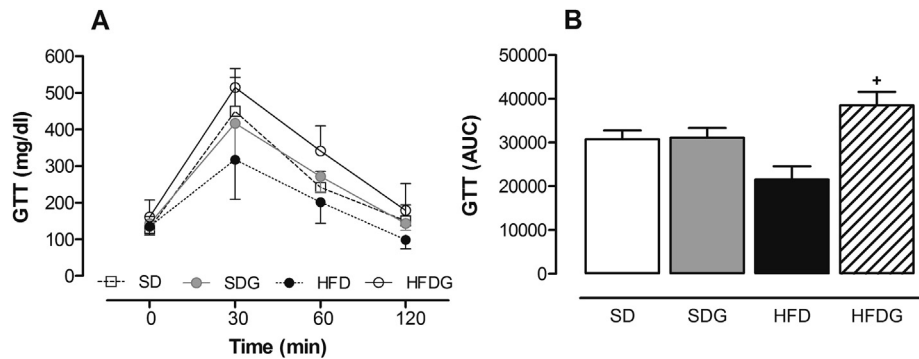
Fig. 3. Panel A, Glucose tolerance test (GTT); Panel B, Area Under the Curve (AUC) of GTT. SD: standard diet; SDG: standard diet with gingerol; HFD: high-fat diet; HFDG: high-fat diet with gingerol. +different from HFD. Data are mean ± SD, Kruskal–Wallis with post-hoc Dunn test (p < 0.05), n = 10 each group.

Table 2
Plasma biochemical profile of mice fed with standard and high-fat diet with and without gingerol (analysis at the end of study).

Variables	SD	SDG	HFD	HFDG
Glucose (mg/dL)	122.2 ± 32	136 ± 15.8	128 ± 22.4	146.6 ± 35
TG (mg/dL)	88 ± 26	96.2 ± 13.9	151.5 ± 31*	109 ± 34
TC (mg/dL)	118 ± 16.2	112.5 ± 16.4	126 ± 39.3	129 ± 21.8
HDL (mg/dL)	81 ± 17.9	82 ± 27	52.8 ± 23	63.9 ± 22.4

SD: standard diet; SDG: standard diet with gingerol; HFD: high-fat diet; HFDG: high-fat diet with gingerol; TG: triglycerides; TC: total cholesterol; HDL: high-density lipoprotein; *different from SD. Data are mean ± SD, Kruskal–Wallis with post-hoc Dunn test (p < 0.05), n = 10 each group.

4. Discussion

The main findings of the present study were that ginger supplementation had limited effects to prevent fat gain in mice fed a high-fat diet. Despite of HFD and HFDG groups present higher total food intake as compared with their standard diet groups (SD and SDG), the ginger supplementation did not affect the final body weight. Moreover, we found that ginger supplementation in HFDG did not prevent increases on area under curve in GTT test and did not change lipid profile.

Our results are similar of a previous study in which ginger supplementation (500 mg/kg) for 16 weeks, did not lead to significant difference in BW of the SD groups [11]. On the other hand, the authors found that HFD induced a significant increase in BW of the mice compared with the SD. In opposite to our results, ginger supplementation in HFDG group attenuated the increase in BW and inhibited the accumulation of body fat compared with HFD without supplementation [11]. It was suggested that ginger supplementation is able to modulate the composition of the gut microbiota, prevent triglyceride deposition and inhibit the differentiation of preadipocytes into adipocytes [11,13]. Those effects act against adiposity, however, our results did not show similar effectiveness.

Regarding total food intake, both HFD and HFDG groups showed a marked higher consume as compared with their standard diet groups. Similar food intake behavior is observed in Wang et al. [11]. It is known that a diet rich in fat is more palatable, have higher energy efficiency and calorie density in comparison to standard diets [14–17]. This is effective in encouraging mice to consume more of this type of diet and present adiposity. Despite that, our study did not show difference in weight gain. These analyses were controversial in previous studies which applied ginger supplementation in the same mice model fed with high-fat diet [11]. Further investigations are needed to elucidate those differences related to higher high-fat diet intake and final weigh gain in mice.

Regarding tissue weight, we did not observe gingerol effects in retroperitoneal, epididymal and brown fat pads as well as did not observe changes of liver weight in HFDG. Different results were found in Kim's et al. [18] study, which epididymal adipose tissue was lower in the ginger supplemented group than that in the SD group. It was suggested that gingerol inhibit body weight accumulation, because is effective to stimulate lipolysis in adipocytes and prevent adipogenesis by blocking the action of peroxisome proliferator-activated receptor-γ (PPAR-γ) and adipocyte protein 2. Both proteins are involved in fat accumulation by acting on lipid biosynthesis pathways [18−20].

Regarding liver weight, Leal et al. [21] provided for Wistar rats a cafeteria diet with ginger extract and did not observe significant changes on liver weight compared to the SD group. At the Kim's et al. [18] study, they found no significant changes on liver weight in HFDG either, similar to our study. On the other hand, Kim et al. [18] (2018) and Leal et al. [21] observed lower lipid accumulation and fat deposition on liver tissue. It was postulated that gingerol can regulate gene expression at the post-transcriptional level by lowering microRNAs (miRNAs), in particular microRNA-21 and microRNA-132 expression [18]. Also, it was observed that gingerol acts regulating early phase events of adipogenesis and triglyceride synthesis by activation of the $5'$-adenosine monophosphate-activated protein kinase (AMPK) pathway [18]. The AMPK is a serine/threonine protein kinase that acts as a cellular sensor, which restores energy homeostasis [22,23]. This protein regulates multiple metabolic pathways in different organs and it was suggested that AMPK have therapeutic importance on controlling inflammation, lipid metabolism, glucose homeostasis and treating obesity, insulin resistance, DM2, non-alcoholic fatty liver disease and cardiovascular disease [24]. In our study, although we did not evaluate protein expression like miRNA and/or AMPK, we assume that the variability on the fat pad and liver weight did not allow observing any effective changes induced by gingerol supplementation.

In respect of GTT test, we did not expect that HFDG group presented a marked increase on area under serum glucose curve. This result differs from Wang's et al. [11] study, which ginger supplementation reduced GTT AUC values on HFDG as compared with HFD without supplementation. Evidence has revealed that ginger had an antihyperglycemic effect and improved glucose homeostasis in HFD-fed mice, due to reduce of the PPAR-α/γ and factor nuclear kappa B [11,25].

We did not observe gingerol effects in biochemical profile. Similar to our results, Leal et al. [21] provided for a Wistar rats a cafeteria diet and ginger extract and they observed that the extract did not promote significant changes in glycemic and lipid profile compared to the control group. In opposite, Wang, et al. [10] which provided 500 mg/kg of ginger in HFD-fed mice for 16 weeks, found that ginger was effective in preventing HFD-induced increase in serum glucose, TC, TG and HDL, which differs from our results, since gingerol supplementation was not able to modulate these variables. It is suggested that ginger reduce intestinal cholesterol in animal models [26]. It is worth highlighting that an improvement in lipid metabolism depends on the decrease in body weight. We propose that, in order to observe any difference in the lipid and glycemic profile in our study, a decrease in body weight would be necessary. However, due to the complex composition of ginger and its bioactive substances, the precise mechanisms in regulating metabolic profile remain unknown. Thus, more studies are necessary to fully evaluate the ginger's compounds.

In Wang's et al. [11] experiment, they administered ginger orally by gavage at the same dosage of ginger as used in our study and found less increase on body weight gain, less accumulation of body fat and the fasting blood glucose was restored. Moreover, they provided ginger for 16 weeks and the time effect in our experiment could have affected the expected ginger responses.

Similar to our results, Leal et al. [21] provided cafeteria diet (also high in fat) and powdered ginger extract as an oral formulation at 15% concentration of the extract administered daily by gavage. They found that ginger extract did not promote significant changes in glycemic, lipid profile and liver weight when compared to the control group. Recent data [27] showed that mice who receive ginger in water (a by-product obtained during lyophilization, that contained chrysin and galangin) from ginger rhizomes at a rate of 25% and 50% (v/v), decreased significantly the body weight gain. In addition, TC and serum TG were also reduced in these groups. These data suggest this methodology can be adequate to obtain desired results. The authors propose that ginger in water acts by regulating lipid metabolism through the greater stimulation of lipolytic pathways and greater attenuation of lipogenic pathways. In addition, it seems ginger in water is useful to increase insulin sensitization and to facility the transport of glucose to liver cells.

Thus, regarding the limitations of the present study we can point out the time of supplementation and the dose of ginger administered and both were based on previous studies in the literature. We also suggest, that if ginger was administered by gavage and not mixed with the diet, the results could have been more favorable in improving glucose and lipid profile. On the other hand, even in experiment that administered ginger extract orally [21], it was not possible to obtain favorable results in reducing body and liver weight, TG, blood glucose and increasing HDL. Another possibility would be to increase the dosage as far as it does not cause toxicity to see the possible effect, or maybe to add the ginger in the water, since the results are promising.

The strength of our study is that to our knowledge it is one of the few studies in our country that investigated the ginger effects on animals fed with high-fat diet and it is also one of the few studies that found controversial data to those reported in the literature. Also, we used the ginger that is sold in the local market and administered it along with the diet, trying to approximate the reality what is done by the general population. According to our results, we concluded that gingerol supplementation had limited effects in preventing weight gain and improving lipid profile. Furthermore, gingerol did not affect glucose tolerance.

Ethics statements file

Authors followed the guidelines of the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978).

Author contributions

The authors responsibilities were as follows: **A.J.C.M.Z:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft, Project administration, Validation, Data Curation, Visualization, Project administration, Funding acquisition. **C.B.S:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft, Validation, Visualization. **A.G.J:** Software, Formal analysis, Writing - Original Draft, Visualization. **M.R:** Writing - Original Draft, Visualization. **C.D.M:** Writing - Original Draft, Visualization. **D. C:** Resources, Visualization. **M.C.F.F:** Conceptualization, Methodology, Investigation, Validation, Visualization. **V.M.M.S:** Conceptualization, Methodology, Investigation, Writing - Original Draft, Supervision, Validation, Visualization. All authors have read and approved the final manuscript.

Funding Source

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgements

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