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Preparation of Low-Sugar Herbal Buccal Tablet and its Antioxidant Activity

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Abstract: In this study, to prepare a low-sugar Herbal Buccal Tablet (HBT), Response Surface Methodology (RSM) was used to optimize the formula of HBT. HBT was prepared by wet granulation and tableting process based on formula optimization. The in vitro antioxidant activity, glycemic index, and particle microstructure of HBT were evaluated. The results showed that the optimal formula for HBT was *Siraitia grosvenorii* fruit powder of 15%, *canarium album* fruit powder of 16%, lily bulb powder of 7.1%, erythritol of 55%, and citric acid of 0.45%. HBT was prepared by adding 0.3% x glycosides, 5% Arabic gum, 1% magnesium stearate, and 0.15% menthol based on the optimal formula. Under the optimal formula, the content of total flavonoids and saponins in HBT was 10.08±0.05 mg/g and 11.28±0.03 mg/g, respectively. HBT had an advantage over Commercial Sugar-Sweetened Confectionery (CSC) because of its higher antioxidant activity. The results showed that HBT may have the potential to become a traditional candy substitute in the food industry due to its high content of active ingredients, low sugar content, and good antioxidant activity in the future.

Keywords: *Siraitia grosvenorii* Fruit, *Canarium Album* Fruit, Lily Bulb, Herbal Buccal Tablet (HBT), Antioxidant Activity

Introduction

The incidence of obesity, dental caries, hypertension, hyperglycemia, hyperlipidemia, and other diseases is on the rise due to excessive intake of high-sugar foods. However, candy has always been a popular traditional food due to people's fascination with sweets for thousands of years. In recent years, low-sugar candies, especially those favored by health benefits are gradually replacing high-sugar candies under the background of advocating a healthy diet (Liu, 2008). Among them, raw material powder pressed candy is more beneficial to the protection, absorption, and sustained release of functional factors (Liu, 2018; Liu *et al*., 2019). Compared with the heat-boiled candies, low-sugar functional tablet candy is one of the most important concerning issues in the food and healthcare industry and also has bright prospects for the development of the candy industry.

Excessive accumulation of oxygen free radicals can damage the structure and function of cells which leads to the occurrence and development of many diseases (Burlaka *et al*., 2019). Excessive production of oxygen-centered free radicals (also known as Reactive Oxygen Species-ROS) and the imbalance of antioxidant protection may induce oxidative stress, inhibit the normal functions of cell lipids, proteins, DNA, and RNA (Gülcin, 2012) and participate in the pathological process of more than 100 diseases (such as chronic inflammation, atherosclerosis, diabetes and some types of cancer, etc.,) (Valko *et al*., 2006). Antioxidants may remove excess reactive oxygen free radicals and alleviate their damage to targeted tissue (Valko *et al*., 2006), inhibit the production and activity of inflammatory mediators (Benavente-Garcia and Castillo, 2008), and directly reduce the gene expression pattern of pro-inflammatory cytokines (TNF-a and IL-1b) (Sridharan *et al*., 2016), thereby reducing the incidence of related diseases. As a result, an antioxidant function is the backbone of the treatment of inflammation, tumors, and other diseases (Gülcin, 2012). Compared with chemically derived antioxidants, plant-derived antioxidants are gradually attracting people's attention because of their unique effects and good safety (Ferlazzo *et al*., 2015).

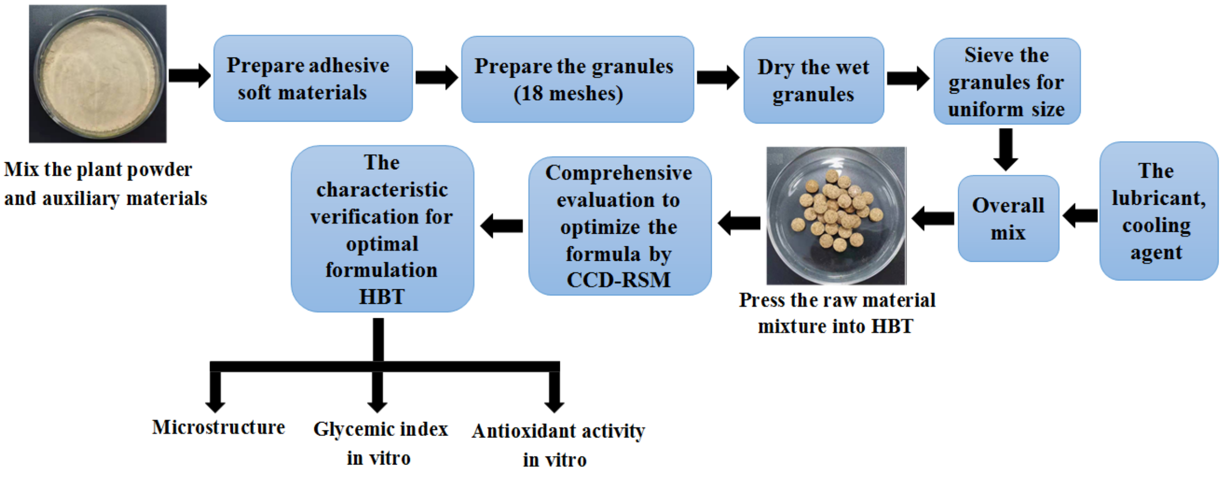

Fig. 1: The research flowchart of this study

Compound products of multiple ingredients can often get synergistic effects. The formula design based on traditional and modern evidence-based medicine is expected to achieve a better raw material ratio in terms of functionality and safety, inspiring the design and development of plant-derived antioxidant low-sugar tablet candy.

Some natural biologically active substances such as total flavonoids and total saponins are recognized as antioxidant substances in plants (Wang *et al*., 2018; Yi *et al*., 2017), which constitute the main component of antioxidant plant raw materials such as *Siraitia grosvenorii* fruit (Tang, 2020; Zhang, 2014), *Canarium album* Fruit (He *et al*., 2006) and Lily bulb (Lei *et al*., 2015). The above plant materials are listed in the classical prescription of Traditional Chinese Medicine (TCM) as throat-moistening, cough-relieving, heat-clearing, and anti-inflammatory drugs (Gao *et al*., 2015). They have been identified as raw materials for both medicine and food which has good safety by national departments and experts recently (Yu, 2017). However, to the best of our knowledge, there is little information on pressed candy with these raw materials power for both medicine and food.

Therefore, in the present study, the powder of *Siraitia grosvenorii* fruit, *Canarium album* fruit, and a lily bulb were used as the main raw materials. Response Surface Methodology (RSM) was used to optimize the formula of HBT. HBT was prepared by wet granulation and tableting process based on formula optimization. The antioxidant activity in vitro, glycemic index, and particle microstructure of HBT were also investigated to reveal the effect of formulation technology on its function (Fig. 1). The present study may open up a new way for the development of low-sugar health food from the above-mentioned medicinal and edible raw materials, which may prevent inflammation such as pharyngitis caused by free radicals. HBT may have the potential to become a traditional candy substitute in the future.

Materials and Methods

Materials and Reagents

The dried powder of lily bulb was purchased from Jiangxi Wanzai Qiannian Food Co., Ltd (Jiangxi, China). The dried powder of *Siraitia grosvenorii* fruit was purchased from Shanghai Jinliang Food Technology Co., Ltd (Shanghai, China). The dried powder of *Canarium album* fruit was purchased from Tao Jia Xiang Electronic Commerce Co., Ltd (Chongqing, China). The menthol was purchased from Henan Junheng Biological Technology Co., Ltd (Henan, China), and the steviol glycosides were purchased from Shenzhen Xingmu Biological Engineering Co., Ltd (Guangdong, China). The erythritol, citric acid, Arabic gum, and magnesium stearate were all purchased from Shangqiu Jianing Trading Co., Ltd (Henan, China). The above raw materials were food-grade and were sheared, sieved to 80-mesh, and then sealed at low temperature before the experiment began.

Ginsenoside standard substance, rutin standard substance, vanillin, and other reagents involved were of analytical grades and purchased from Shanghai Tengzhun Biotechnology Co., Ltd (Shanghai, China).

Preparation Method and Evaluation Index of HBT

HBT was prepared according to the reported method with minor modifications (Yu *et al*., 2020). The key raw materials (*Siraitia grosvenori* fruit powder, *Canarium album* fruit powder, erythritol, and citric acid were weighed according to the designed composition ratio. The auxiliary materials were 5% of Arabic gum, 0.3% of steviol glycosides, 1% of lubricant (magnesium stearate), and 0.15% cooling agent (menthol). The rest was the amount of lily bulb powder (the total amount was 100%). The weighed raw and auxiliary materials were mixed evenly and sprayed with 75% ethanol solution to prepare the soft material. The soft material was kneaded into a dough by hand. After kneading, the dispersion was good and the prepared soft material was granulated through an 18-mesh sieve. After granulating, the wet granules were dried at 50℃ until the moisture was less than 3%. Then the dried granules were sieved through 18-mesh and 80-mesh successively to make the particle size uniformly. Than 1% lubricant was added evenly to the particles under the sieve. The refreshing agent (menthol-ethanol mixed solution) (0.15%) was sprayed on the particles by atomization, finally mixed evenly, and pressed for HBT. Each group of HBT was vacuum packaged to evaluate the total flavonoids, total saponins, sensory score, and synthesis score.

Determination of Total Saponins

The content of saponin was determined by the perchloric acid-vanillin color method described by Lin *et al*. (2009). Methanol was used to dissolve the ginsenoside standard product to a final concentration of 2 mg/mL. Standard solutions (0, 25, 50, 75, 100, 125 μL) were placed in 10 mL test tubes, respectively. The solvent was evaporated under a vacuum to constant weight. 0.2 mL vanillin-glacial acetic acid solution (5%) and 0.8 mL perchloric acid were added into tubes and mixed in the water bath at 60℃ for 15 min. After cooling to room temperature, 5 mL glacial acetic acid was added to tubes, mixed well, and stood for 10 min (Lei *et al*., 2015). The standard solution was used as blank. The standard curve was obtained by measuring the absorbance of standard solutions at 560 nm. The amount of ginsenoside (m) was used as abscissa. The absorbance value (A) was used as ordinate. The following regression equation was obtained as follows:

$$A = 3.5177m - 0.041\left(R^2 = 0.9911, 0 \sim 0.25mg\right) \quad (1)$$

The samples were ground into powder according to the method of the NPC (2005). 1 g powder was dissolved in 50 mL methanol. The absorbance of 1 mL supernatant was measured based on the method described above. The average value of three replicates was substituted into the above Eq. (1) to calculate the content of total saponins in the *HBT* according to the following formula:

$$TSC\ (mg/g) = \frac{m \div v \times V}{M} \quad (2)$$

where *TSC* was total saponins content in the sample. *m* was the content of saponin in colorimetric solution (mg). *v* was the amount of reaction solution (1 mL). *V* was 50 mL. *M* was the sample powder weight (1 g).

Determination of Total Flavonoid Content

Total flavonoid was measured according to the method of Peñarrieta *et al*. (2007) with slight modifications. The standard curve was drawn before the samples test. Rutin standard solution with a concentration of 0.14 mg/mL was prepared. 0.3 mL $NaNO_2$ (5%) was mixed with 0, 1, 2, 3, 4, 5 and 6 mL standard solution and stood for 6 min, respectively. Then 0.3 mL 10% Al $(NO_3)_3$ solution was added to the mixture and stood for 6 min.

2 mL NaOH solution (1 mol/L) was added to the volumetric flask and made up to volume with 60% methanol. The mixture was blended and stood for 15 min. The standard solution was used to zero setting at the absorbance of 510 nm. The standard curve was drawn using rutin Concentration (C) and Absorbance (A). The regression equation was obtained as follows:

$$A = 6.6046C + 0.014\left(R^2 = 0.9932,\ 0 \sim 0.15mg/mL\right) \quad (3)$$

1 g sample powder was dissolved in 10 mL ethanol (60%). Then, 1 mL supernatant was used for absorbance determination based on the above method. The measurement was replicated three times. The content of total flavonoid in *HBT* was calculated based on Eq. (3) and formula (4).

$$HBT - TFC(mg/g) = \frac{c \times n \times V}{m} \quad (4)$$

where *TFC* is total flavonoid content in samples. *C* is the concentration of total flavonoids in the sample reaction liquid (mg/mL). *n* is diluted multiple (10). *V* is a sample raw liquid to accumulate volume (10 mL). *m* is sample powder weight (1 g).

Sensory Evaluation

Sensory evaluation was conducted according to the method of (Zeeshan *et al*., 2017) with slight modifications. The specific evaluation standard was listed in Table 1. Ten evaluators were selected to evaluate the sensory qualities of HBT in optimization tests from flavor, appearance, and taste. Among them, 40 points were assigned to flavor. 30 points were assigned to appearance. The remaining 30 points were given to taste. The product was scored with the average score after the removal of the highest score and the minimum score.

Comprehensive Evaluation Score

The comprehensive evaluation score of tablets was calculated based on the formula:

$$Y = (Gi / Gmax) \times 0.40 + (Hi / Hmax) \times 0.30 + (Zi / Zmax) \times 0.30 \quad (5)$$

where *Y* was the synthesis score. *Gi* was each group of sensory evaluation. *Gmax* was CCD design maximum value rating in 30 groups; *Hi* was the total flavonoid content measurement value per group. *Hmax* was the CCD design maximum value of total flavonoid content in 30 groups. *Zi* was the total saponin content measurement value per group. *Zmax* was the CCD design maximum value of total saponin content in 30 groups.

Experimental Design for Response Surface Optimization

Functional ingredients and flavoring agents are important factors that affect the nutritional and flavor quality of HBT (Shen *et al*., 2019). Therefore, in this study, the synthesis score of the total saponins content, total flavonoids content, and the sensory score was the response value. The addition ratio of *Siraitia grosvenorii* fruit powder (X_1), *Canarium album* fruit powder (X_2), erythritol (X_3), and citric acid (X_4) was chosen as key independent variables to optimize the formula of HBT using a four-factor and five-level Central Combination Design (CCD). The experimental scheme is shown in Table 2.

Verification Indicator: In Vitro Antioxidant Activity, Glycemic Index, Sem of Microstructure

In vitro Antioxidant Activity of HBT

DPPH Radical Scavenging Capacity

The DPPH free radical cleaning ability of samples was measured according to the method of (Pío-León *et al*., 2018) with slight modifications. The optimized HBT was ground into powder and dissolved in 60% ethanol to obtain a sample solution with different concentrations (0.05, 0.50, 1.00 mg/mL). 2.0 mL sample solutions and 2.0 mL DDPH (0.1 mmol/L, dissolved in 95% ethanol) were mixed and reacted for 30 min in dark. Then, the mixture was centrifugated at 8000 r/min for 10 min. The absorbance A_1 of the supernatant was determined at 517 nm. At the same time, the absorbance A_2 was detected for the reaction system of 95% ethanol solution (2 mL) and sample solution (2 mL). The absorbance A_0 was detected for the reaction system of DPPH solution (2 mL) and sample solvent (2 mL).

Vc and sugar-Sweetened Confectionery (CSC) solutions with different concentrations (0.05, 0.5, 1.0 mg/mL) were used as the control. Each test was repeated 3 times. The average value was used to calculate the scavenging rate on DPPH as well as the half Inhibitory Concentration (IC_{50}) of the samples. DPPH scavenging rate was calculated as follows.

$$DPPH\ scavenging\,\text{rate}\ (\%) = \left[1 - \frac{A_1 - A_2}{A_0}\right] \times 100 \quad (6)$$

Hydroxyl Radical (•OH) Scavenging Capacity

The measurement was conducted according to the method of Li (2013) with slight modifications. 2 mL sample solutions (0.05, 0.50, 1.00 mg/mL) were added to the test tube, respectively. 2 mL H_2O_2 solution (6 mmol/L) and 2 mL $FeSO_4$ solution (6 mmol/ L) were added to 2 mL sample solutions. The mixture was blended and stood for 10 min. 2 mL of salicylic acid (6 mmol/ L) was added to the mixture and kept at 37°C for 30 min. After that, the mixture was centrifuged at 5000 r/min for 5 min. The supernatant was used to determine the absorbance at 510 nm, which was A1. The sample solution was replaced with 2 mL 60% ethanol (sample solvent) and its Absorbance (A0) was determined. Finally, the salicylic acid solution was replaced with 2 mL anhydrous ethanol (salicylic acid solvent) and its absorbance (A_2) was determined.

Different concentrations of Vc solutions (0.05, 0.5 and 1.0 mg/mL) and different concentrations of CSC solutions (0.05, 0.5 and 1.0 mg/mL) were used as the control. The experiment was replicated three times. The hydroxyl free radical scavenging rate was calculated by the following formula:

$$Hydroxy\ scavenging\,\text{rate}\ (\%) = \left[\frac{A_0 (A_1 - A_2)}{A_0}\right] \times 100 \quad (7)$$

Determination of Total Reducing Capacity

The total reducing capacity of samples was determined based on the method of Wang (Wang *et al*., 2021). 1 mL sample solutions with different concentrations (0.05, 0.50 and 1.00 mg/mL), 2.5 mL phosphate buffer (0.2 mol/L, pH 6.6) and 2.5 mL potassium ferricyanide solution (1%, w/v) were mixed and incubated at 50°Cfor 20 min. Then, 2.5 ml trichloroacetic acid solution (10%, w/v) was added to the test tube and centrifuged at 3000 r/min for 10 min. 5 mL supernatant, 5 mL distilled water and 1 mL ferric trichloride solution (0.1%, w/v) were mixed and blended. After standing for 10 min, the absorbance (OD) value of homogenate was determined at 700 nm. The larger the OD value, the stronger the total weight of the reaction measurement. Vc solutions (0.05, 0.5, 1.0 mg/mL) and CSC solutions (0.05, 0.5, 1.0 mg/mL) acted as the controls. Each sample was repeated three times for analysis.

Glycemic Index of HBT in vitro

The Glycemic index was measured according to a method described by Englyst *et al*. (1999) and Goñi *et al*. (1997) with slight modifications. The digestion rate of starch in low-sugar Buccal Tablets (HBT) was measured by hydrolysis in vitro with complex enzymes to predict the glycemic index. The hydrolysis rate of HBT was calculated based on the following formula:

$$HBT\,(or\ RFWB)\ starch\ hydrolysis\ rate(\%) \\ = [Sampling\ time\ point\ hydrolyzed\ glucose\ amount \times 0.90] \\ /Total\ quality\ of\ samples \quad (8)$$

In this experiment, CSC with sucrose acted as the control. Digestibility of sucrose in vitro by hydrochloric acid hydrolysis was determined to predict the glycemic index. (CNSMC, 2016). The polysaccharide hydrate rate of CSC was calculated according to the following formula:

$$Hydrolysis\ rate(\%) \\ = [Sampling\ time\ point\ hydrolyzed\ glucose\ amount \times 0.95] \\ /\ Total\ quality\ of\ control\ samples \quad (9)$$

The Hydrolysis Index (HI) of a sample (HBT and CSC) was calculated based on the following formula:

$$HI = the\ AUC\ of\ sample\,/\,the\ AUC \\ of\ reference\ food\ (white\ bread) \quad (10)$$

where the AUC are the areas under hydrolysis curves (0-180 min) for all products (HBT, CSC, and white bread) respectively.

The Glycemic Index (GI) of HBT and CSC was calculated based on the following equation (Xue *et al*., 2018):

$$GI = 39.71 + 0.549\,HI \quad (11)$$

where HI was the hydrolysis index of the HBT and CSC respectively.

Microstructure Scanning of HBT

The microscopic morphology of HBT was performed by Scanning Electron Microscopy (SEM) (Correia *et al*., 2013). The HBT was crushed into powder and dried at 40°C for 12 h. The powder was evenly coated on the dissociated mica slide sprayed with metal and observed by SEM.

Statistical Analysis

Data Analysis was performed according to the reported method (Umana *et al*., 2020). The software of Design Expert V 8.0.6 was used to optimize and analyze the variance of the results. Each group of experiments was repeated 3 times and the average value was taken for further analysis. The results were expressed as the mean ± SD (standard deviation). Significant differences among samples were determined at p<0.05 (Olaoye *et al*., 2022).

Table 1: The sensory evaluation criteria of herbal buccal tablet

Scores	Flavor	Appearance	Taste
31-40	Suitable sourness and sweetness, no bitterness and astringency	Complete and smooth surface, natural and uniform color	Smooth, delicate and ungranular
21-30	Comparative suitable sourness and sweetness, mild astringency or bitterness	Complete without imperfection, smooth surface, natural and uniform color	smooth, delicate and ungranular
11-20	More acidic, heavier bitterness and astringency	Disability and rough surface, slightly uneven color	Smooth, slightly rough, slightly grainy
0-10	More acidic, bitterness and astringency are heavier	Serious lack of block, uneven surface, the color is very uneven	Too crisp, rough and grainy

Table 2: Levels and codes of four factors in central composite design

	Independent variables			
Level	Addition ratio of *Siraitia grosvenorii* (w/w, %)	Addition ratio of *Canarium album* (w/w, %)	Addition ratio of erythritol (w/w, %)	Addition ratio of citric acid (w/w, %)
2	19	20	60	0.60
1	15	16	55	0.55
0	11	12	50	0.50
-1	7	8	45	0.45
-2	3	4	40	0.40

Results

Statistical Analysis and the Model Building

A four-factor five-level test was carried out per the CCD-RSM. The result was shown in Table 3. Multiple regression fitting on the response values and each factor was performed using Design-Expert 8.0.6.1 software. The quadratic polynomial regression equation was obtained as follows:

$$Y = 0.70 + 0.036X_1 + 0.072X_2 + 0.008X_3 - 0.023X_4 + 0.011X_1X_2$$
$$-0.001X_1X_3 + 0.021X_1X_4 - 0.003X_2X_3 - 0.013X_2X_4$$
$$-0.032X_3X_4 + 0.021X_1^2 - 0.004X_2^2 + 0.007X_3^2 + 0.021X_4^2$$

where, Y is the synthesis score of the total saponins content, total flavonoids content, and sensory score. X_1, X_2, X_3, and X_4 are the addition ratio of *Siraitia grosvenorii* fruit powder, *Canarium album* fruit powder, erythritol, and citric acid (%), respectively.

The Analysis of Variance (ANOVA) was performed for the regression model according to the method (Sunday 2020; Eissa *et al*., 2022), which was shown in Table 4. The F test showed that the regression model had a high F value (F = 4.84) and a low P-value ($P = 0.0022$), indicating that the model was highly significant ($P<0.01$). The lack of fit of the equation was not significant ($P>0.05$), indicating that the established regression quadratic model could be used to analyze the formula optimization of HBT.

Optimization of Formula HBT and Validation of the Model

As shown in Table 4, the coefficient evaluation and significance test of the regression model showed that the interaction parameters X_3X_4 were significant ($P<0.05$), suggesting that the interaction between erythritol and citric acid significantly affected the synthesis score of HBT. According to the above-established model, the optimal formula for HBT principal component was obtained (15% *Siraitia grosvenorii* fruit powder, 16% *Canarium album* fruit powder, 55% erythritol, 0.45%citric acid). The comprehensive evaluation score of total flavonoids, total saponins content, and sensory value was 0.9175. Validation tests were carried out under these conditions. The above formula ingredients and other ingredients (0.3% stevia glycoside, 5% Arabic gum, and 7.1% lily bulb powder) were mixed evenly to prepare soft material and then the soft material was sieved into particles (18 mesh). The particles were dried at 50°C until moisture was less than or equal to 3%. The dried particles were added into 1% magnesium stearate and 0.15% menthol. Finally, HBT was prepared by pressing the above ingredients into tablets. The actual total flavonoid content of HBT was 10.08±0.05 mg/g. The total saponins content was 11.28±0.03 mg/g. The sensory score was 87 points and the synthesis score was 0.9319 points. The actual result was a 1.57% deviation compared with the predicted data by the regression model. These results indicated that the model had reliable predictability in optimizing the formula parameters of HBT. The microcapsule powder of xanthyl ester, blueberry powder, isomaltitol, sorbitol, and other auxiliary materials was mixed to prepare pressed candy by tableting technology. The optimum formula was determined using RSM as follows: Blueberry powder was 3.19%, peppermint essence was 4.26%, sucralose taste was 0.19%, lutein ester microcapsule powder was 9%, isomaltose ketositol was 55%, sorbitol was 30%, magnesium stearate was 1% and Arabic gum was 0.75%. After wet granulation, drying, sizing, blending, and tableting. Smooth tableted candy was obtained (Liu *et al*., 2019).

In Vitro Antioxidant Analysis of HBT

In vitro, the antioxidant activity of HBT was seen in Fig. 2. As shown in Fig. 2(A), the scavenging capacities of different samples on DPPH free radicals increased when the concentration increased gradually. The scavenging capacities of HBT against DPPH free radicals were lower than the positive control Vc at the same concentration but higher than CSC significantly($P<0.05$). The half inhibitory concentration (IC_{50}) values of HBT, CSC, and Vc against DPPH were 0.4398, 1.108, and 0.1131 mg/mL, respectively. Lower IC_{50} values mean a higher antioxidant activity. These results indicated that the effect of HBT on DDPH free radicals was always larger than CSC, although it was smaller than positive control Vc.

As shown in Fig. 2(B), the samples with different concentrations had the effect of scavenging hydroxyl free radicals (·OH). The scavenging rate of HBT, CSC, and Vc had an obvious dose-effect relationship in the concentration range from 0.05 to 1.00 mg/mL. The IC_{50} of HBT, CSC, and Vc against ·OH were 0.3856, 1.7121, and 0.1650 mg/mL, respectively. The ·OH scavenging rate of HBT was superior to CSC significantly(P<0.05), lower than positive control Vc overall. The ·OH scavenging rate of HBT was closer to that of Vc and the scavenging rate reached 90.41% when the concentration was 1.00 mg/mL.

The reducing force of antioxidants is often measured by the capacity of reducing potassium ferricyanide (Fe3+to Fe2+). The absorbance at 700 nm was determined to calculate the reducing force (Han *et al*., 2019). As shown in Fig. 2(C), the reducing power of HBT was lower than that of the positive control Vc but was larger than that of CSC at the same concentration significantly (P<0.05). As the concentration increased, the reducing power of all samples generally improved in a dose-effect manner within the concentrations of 0.05~1.00 mg/mL. The median Effect Concentration (EC50) of HBT, CSC and Vc was 0.661, 1.494 and 0.454 mg/mL, respectively. The results showed that the total reducing power of HBT was larger than that of

CSC. Based on the formula of the HBT principal component, HBT contained the man component of *Siraitia grosvenorii* and *Canarium album*. *S. grosvenorii* is a Chinese perennial that grows in southern China (Li *et al*., 2009). For the past two centuries, its fruit has been used to treat dry coughs, sore throats, and severe thirst (Lu *et al*., 2012), which contains mogrosides, polysaccharides, and polyphenols, vitamins, etc. (Abdel-Hamid *et al*., 2020). *S. grosvenorii* has antitussive, anti-asthmatic, antioxidant, and anti-diabetic activities (Liu *et al*., 2018). In China, the ripe fruit of *C. album* is also used as food and traditional medicine to treat swelling and sore throat, polydipsia, cough, etc., with antioxidant activity (Chang *et al*., 2017). The results of the antioxidant analysis revealed that HBT had higher antioxidant activity than CSC, which may be due to the antioxidant components of *S. grosvenorii* and *C. album i*n HBT.

In Vitro Glycemic Index Evaluation of Hbt

In Vitro Total Sugar Hydrolysis Rate

The rate of total sugar digestion such as starch or sucrose, etc., was expressed as the percentage of total sugar hydrolyzed in the product at different times (30, 60, 90, 120, and 180 min) (Goñi *et al*., 1997). The curve was shown in Fig. 3. White bread was used as the reference food. The in vitro hydrolysis rate of total sugar between groups of products increased from 0 to 90 min obviously and then reached a maximal plateau level from 90 to 180 min slowly. The hydrolysis value of total sugar for the Reference Food White Bread (RFWB) was 80.42% within 180 min. The hydrolysis value for CSC was 37.66%. Compared with these control groups, HBT generated the least percentage of hydrolysis, which was only 21.95%. The reason may be the different ingredient contents in HBT and CSC. Many factors affect starch digestion, such as the source and processing of starch, which can significantly affect the glycemic index of starch (Hu *et al*., 2004). HBT incorporated non-sugar sweetener (erythritol, stevia) in the hydrolysis to reduce the total sugar content and its digestibility compared with white bread with high starch content and CSC with sucrose as sweetener, resulting in the reduction of total sugar hydrolysis rate.

In Vitro Glycemic Index

The GI refers to the relative ability of sugary foods to raise blood glucose levels, compared to the postprandial blood glucose response of a reference food (glucose or white bread). The GI of hyperglycemic food is greater than or equal to 70. The GI of medium-glycemic food is in the range of 56-69 and the hypoglycemic food is less than or equal to 55 (Zhang *et al*., 2013). As shown in Table 5, the total sugar Hydrolysis Index (HI) for HBT was 22.50 and lower than the control CSC significantly ($P<0.05$) which was 88.45.

Table 3: Central composite design with response values for the formula for the optimization of HBT

	Independent variable							
run	X_1(%)	X_2(%)	X_3(%)	X_4(%)	Sensory score	Total flavonoids (mg/g)	Total saponins (mg/g)	Y (synthesis score)
1	-1	-1	-1	-1	72	7.61	6.23	0.67
2	1	-1	-1	-1	47	9.01	8.17	0.65
3	-1	1	-1	-1	69	10.79	9.27	0.82
4	1	1	-1	-1	69	11.80	10.63	0.89
5	-1	-1	1	-1	80	8.80	5.70	0.72
6	1	-1	1	-1	78	8.00	8.76	0.77
7	-1	1	1	-1	94	10.40	9.99	0.93
8	1	1	1	-1	89	11.29	11.08	0.97
9	-1	-1	-1	1	67	6.18	6.34	0.61
10	1	-1	-1	1	67	7.25	7.69	0.68
11	-1	1	-1	1	66	7.47	8.83	0.71
12	1	1	-1	1	84	10.20	10.90	0.91
13	-1	-1	1	1	51	5.85	7.67	0.57
14	1	-1	1	1	75	6.44	7.63	0.69
15	-1	1	1	1	68	7.57	8.52	0.71
16	1	1	1	1	72	8.87	9.95	0.80
17	-2	0	0	0	86	5.86	7.10	0.71
18	2	0	0	0	73	10.28	9.90	0.84
19	0	-2	0	0	56	6.03	7.16	0.59
20	0	2	0	0	59	9.12	10.15	0.76
21	0	0	-2	0	71	7.81	8.35	0.73
22	0	0	2	0	71	7.67	7.75	0.71
23	0	0	0	-2	64	9.53	8.10	0.73
24	0	0	0	2	77	9.84	8.76	0.82
25	0	0	0	0	62	9.41	8.44	0.73
26	0	0	0	0	67	7.75	8.17	0.70
27	0	0	0	0	69	7.58	7.95	0.70
28	0	0	0	0	76	7.98	8.08	0.75
29	0	0	0	0	70	6.55	8.16	0.69
30	0	0	0	0	65	6.16	8.12	0.65

Table 4: Analysis of variance for the fitted quadratic polynomial model

Variance source	Sum of square	Degree of freedom	Mean square	F-value	P-value	Significant test
Model	0.22	14	0.016	4.84	0.0022	**
X_1	0.031	1	0.031	9.56	0.0074	**
X_2	0.12	1	0.12	37.58	<0.0001	**
X_3	1.609×10^{-3}	1	1.609×10^{-3}	0.49	0.4935	n.s.
X_4	0.013	1	0.013	3.98	0.0646	n.s.
X_1X_2	1.770×10^{-3}	1	1.770×10^{-3}	0.54	0.473	n.s.
X_1X_3	2.627×10^{-5}	1	2.627×10^{-5}	8.042×10^{-3}	0.9297	n.s.
X_1X_4	7.332×10^{-3}	1	7.332×10^{-3}	2.24	0.1548	n.s.
X_2X_3	1.607×10^{-4}	1	1.607×10^{-4}	0.049	0.8275	n.s.
X_2X_4	2.759×10^{-3}	1	2.759×10^{-3}	0.84	0.3726	n.s.
X_3X_4	0.016	1	0.016	4.95	0.0419	*
X_1^2	0.012	1	0.012	3.80	0.0703	n.s.
X_2^2	4.947×10^{-4}	1	4.947×10^{-4}	0.15	0.7026	n.s.
X_3^2	1.369×10^{-3}	1	1.369×10^{-3}	0.42	0.5271	n.s.
X_4^2	0.013	1	0.013	3.87	0.0680	n.s.
Residual	0.049	15	3.266×10^{-3}			
Lack of Fit	0.044	10	4.358×10^{-3}	4.03	0.0687	n.s.
Pure Error	5.409×10^{-3}	5	1.082×10^{-3}			
Cor Total	0.27	29				

Table 5: Hydrolysis Index (HI) and glycemic index of different buccal tablets

Different groups of products	HI	GI
CSC	88.45 ± 0.72^{a}	88.26 ± 0.65^{a}
HBT	22.50 ± 0.61^{b}	52.06 ± 0.252^{b}

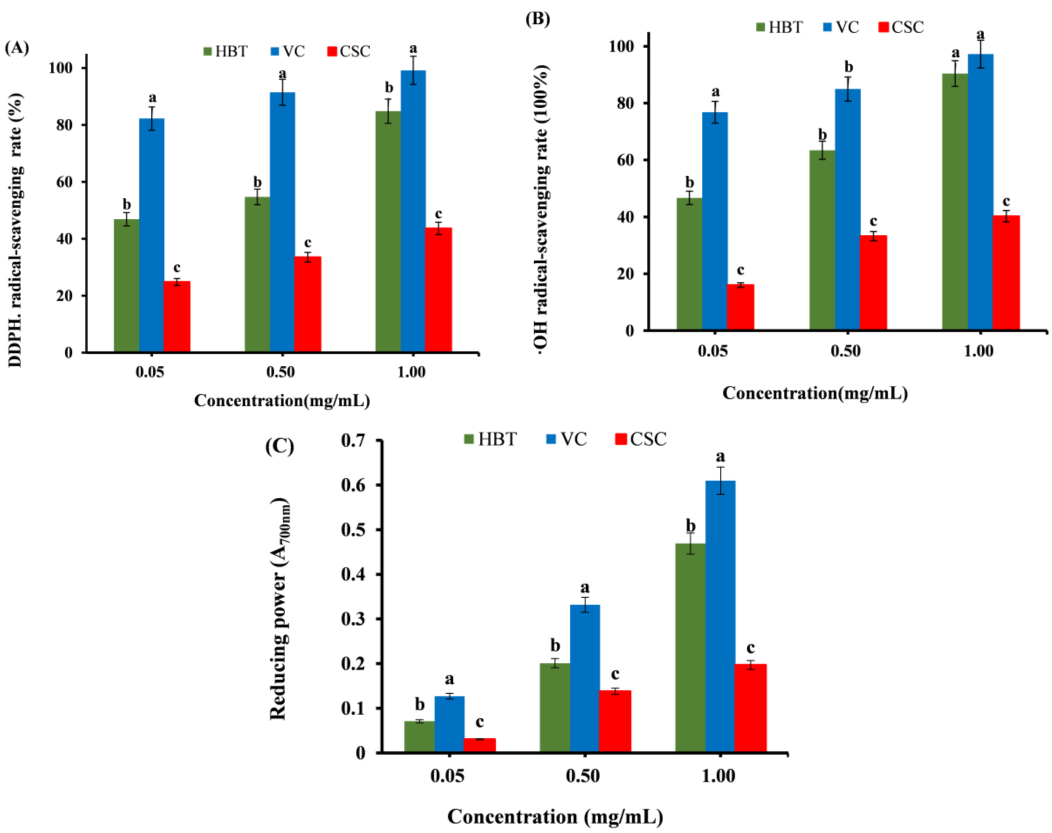

Fig. 2: The in vitro antioxidant activities of HBT and CSC using Vc as the positive control. (A) DPPH· scavenging capabilities; (B) ·OH scavenging capabilities; (C) Reducing power. Different lower-case letters for the same concentration represented signs if

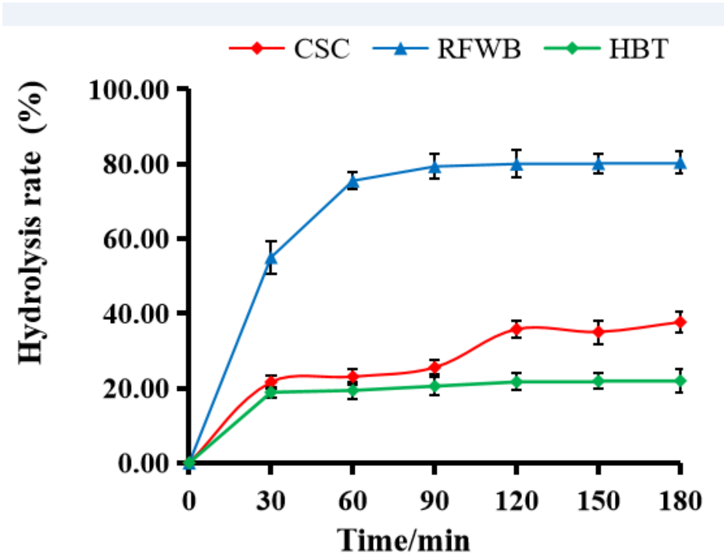

Fig. 3: Total sugar hydrolysis rate of different products in vitro

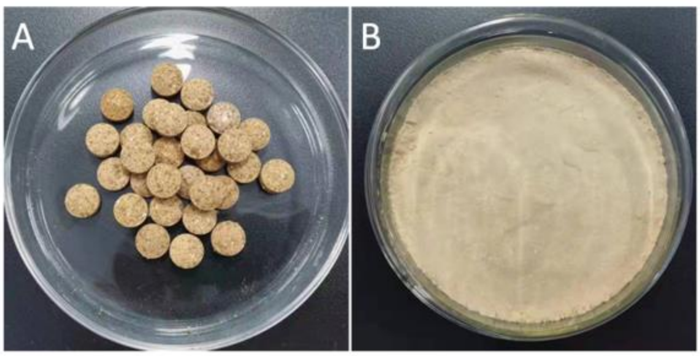

Fig.4: The image of HBT and raw material mixed powder (A is HBT, B is a raw material mixed powder)

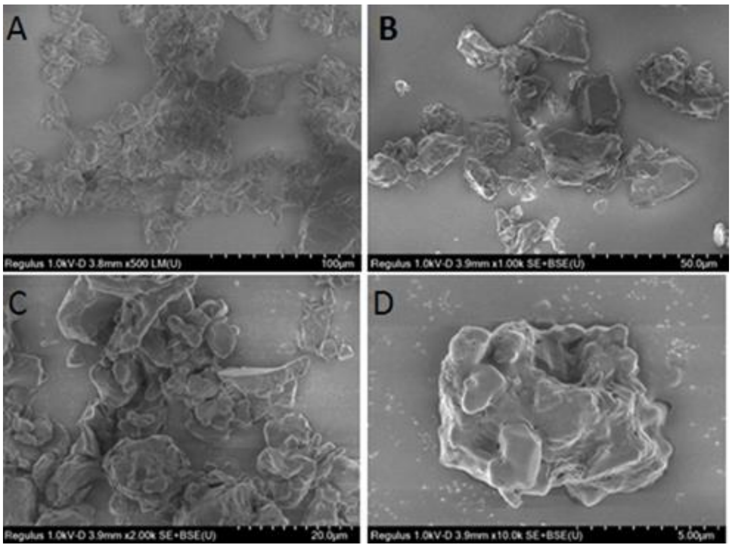

Fig.5: SEM images of microstructure of HBT (A: 500 times; B: 1000 times; C: 2000 times; D:10000 times)

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The predictive GI for HBT was 52.06 by Eq. (11), which may be classified as a portion of food with a low-glycemic index (GI≤55), also lower than CSC by 41.01% significantly (P<0.05). The GI value of CSC was as high as 88.26, which belonged to hyperglycemic food (GI>75). (Zhang *et al*., 2013) found that the hydrolysis index and glycemic index of resistant starch biscuits were 49.19 and 66.72, respectively. Meanwhile, the resistant starch biscuits had the advantages of uniform color and intact appearance with a moderate glycemic index (Zhang *et al*., 2013). Our results suggested that HBT belonged to food with a low-glycemic index, which was different from the resistant starch biscuits (Zhang *et al*. 2013). The main reason may be that the type and content of starch were different. The results indicated that HBT may be suitable for people with diabetes and those who want to control blood sugar.

Evaluation of the Appearance and Microstructure

Four kinds of spray-dried fruit powder (pineapple, dragon fruit, guava, and mango), maltodextrin, and stevia were mixed to prepare mixed fruit and vegetable powder tablet by tableting technology. SEM image showed an irregular particle shape on the surface of the fruit powder tablet (Saifullah *et al*., 2014). The HBT obtained by the plant powder tableting process was light yellow, which was closer to white with a smooth surface (Fig. 4A). It matched the color of the raw mixed material powder before processing (Fig. 4B), which was mainly composed of white lily bulb powder, a small amount of brown *Siraitia grosvenorii* fruit powder, and *Canarium album* fruit powder. The result showed that the plant powder tableting process had a better color protection effect on candy products.

SEM image of microstructure of HBT powder was shown in Figure under SEM magnified 500-10000 times. As shown in Fig. 5, the microscopic particle is irregular in shape and varies in size. Most of the small particles (except for a few scattered) are attached to the large particles, indicating that HBT by plant powder tableting process was rich in components, easy to interact and cross-link between molecules, which made the particles easy to bond.

Discussion

In this study, four factors that have a greater impact on the efficacy ingredients and taste of HBT components were selected, including *Siraitia grosvenorii* fruit powder, *Canarium album* fruit powder, erythritol, and citric acid, which act as independent variables. The CCD-RSM was used for a four-factor five-level test to optimize the optimal HBT formula based on the comprehensive evaluation of the content of functional ingredients (total saponins, total flavonoids) and sensory scores. Under the predicted formula conditions, the actual comprehensive scores of total flavonoids, saponins content, and sensory scores in HBT were almost equivalent to the predicted values, indicating that the CCD-RSM could be a feasible way to optimize the formula parameters of HBT.

The results showed that the antioxidant capacity of the optimized HBT formula was higher than that of CSC and lower than the positive control VC (Fig. 1). When the mass concentration of HBT increased to 1 mg/mL, its scavenging rate against •OH was close to VC (Fig. 1(B)), which was probably due to the combination of Vc at the high concentration of •OH electrons was close to saturation. •OH was in equilibrium, so the radicals scavenging rate was difficult to improve and close to HBT at the same concentration (Akinmoladun *et al*., 2007). The antioxidant capacity of HBT was higher than that of CSC, which was due to the strong antioxidant activity of total saponins and flavonoids in *Virginia grosvenorii* fruit (Qi *et al*., 2006; Shao *et al*., 2019), *canarium album* fruit (Xu *et al*., 2017) and lily bulb powder (Su et al., 2021; Lei *et al*., 2015). The verification test showed that the content of total flavonoids and total saponins in HBT reached 10.08±0.05 mg/g and 11.28±0.03 mg/g respectively. These ingredients may serve as the material basis of HBT antioxidant function. Precise structural analysis is necessary to investigate in further study.

The in vitro hydrolysis rate of total sugar and predictive glycemic index in HBT were lower than those of CSC (Fig. 2 and Table 5), suggesting that non-sugar sweeteners (erythritol, stevioside) instead of traditional sugars (such as sucrose) used in HBT could effectively reduce the sugar content and glycemic index. In summary, the HBT prepared may be a foodstuff suitable for obese and diabetic people.

Conclusion

In the present work, formula optimization, in vitro antioxidant capacity, and glycemic index of HBT were investigated. The optimal formula of HBT by RSM was obtained. The HBT prepared by optimal formula had a cool taste with a suitable sweet and sour taste. HBT had higher antioxidant activity than the control CSC. In addition, the GI of HBT was lower than that of CSC. HBT was more suitable for people suffering from inflammation caused by free radicals such as pharyngitis as well as high blood sugar.

The present study might provide a reference for the development of low-sugar health foods. In the future, other bioactive components involved in antioxidant function in HBT still need to be further identified. Meanwhile, precise structural analysis of antioxidant functional components in HBT and their structure-activity relationship need to be further investigated.

Nomenclature

HBT Low-sugar Herbal Buccal Tablet
RSM Response Surface Methodology
CSC Commercial Sugar-sweetened Confectionery
TCM Traditional Chinese Medicine

TSC	Total Saponins Content
TFC	Total Flavonoids Content
CCD	Central Combination Design
DPPH	1,1-Diphenyl-2-Picrylhydrazyl
Vc	Vitamin C
IC_{50}	Half Inhibitory Concentration
AUC	Areas Under hydrolysis Curves
SEM	Scanning Electron Microscopy

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Author's Contributions

Yuqing Wang, Mingjie Sun, Rui Xu, and Xuan Hu: Performed the preparation, Antioxidant, and Glycemic Index Evaluation of HBT.

Yao Chen, Jieru Zhang, and Gaixia QU: Carried out the formulation optimization of HBT based on the comprehensive evaluation of total saponins, total flavonoids, and sensory scores.

Yang Zhang, Hongfang Cai: Took Photographs of product appearance and electron microscope scanning of microstructure.

Hongfang Cai and Xinyi Chen: Revised and polish the manuscript.

Dongxing Zhu: Designed the experiments, and wrote and polish the manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

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