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Optimizing flavonoid-rich Quranic Mixed Food (QMF) formulation with simplex-centroid mixture design

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Abstract

Quranic food, which defines as the food mentioned in the Holy Quran has gain attention as a functional food to prevent disease in the current era. The food had high potential as an excellent ingredient for the development of nutraceutical products. Flavonoid is one of the phytochemicals in Quranic food that contribute to their therapeutic properties. Unfortunately, there is less study on the health properties of Quranic food mixture that lead to misunderstanding of the mixture of Quranic food. A paramount concern regarding the addition of multiple bioactive ingredients into a product is the possibility of interaction among elements may result in degradation of the ingredient, and the functionality could be reduced or improved. Therefore, this study was aimed to optimize the flavonoid content of Quranic Mixed Food (QMF) containing dates, raisins, pomegranates, figs, and honey. Consequently, the special cubic model of simplex centroid design was employed as it was the most reliable and can be utilized in the optimization process as the *p*-value was significant, and the lack of fits was not substantial. The simplex centroid method had successfully optimized the QMF formulation. To conclude, the optimized formulation of flavonoid-rich QMF containing 42.88% raisins, 42.88% pomegranates, 13.97% honey, 0.17% dates, and 0.11% figs.

1. Introduction

Health and wellness are among the core segments of the fast-moving consumer good, with the ever-increasing health consciousness among consumers around the world (Nazir *et al.*, 2019). At present, nature-based nutraceutical food products with targeted physiological functions are the heart of research and development activities (De Vries *et al.*, 2018). In conjunctions to those matters, there were several studies conducted on exploring the unique medicinal properties and chemical constitution of food mentioned in the Holy Quran which is known as Quranic food (Sheikh and Dixit, 2015). It cannot be denied that Quranic food had therapeutic effects and used in preventive medicine for decades (Western et *al.*, 2009). The popular Quranic food and known to had benefits to health are dates, raisins, honey, pomegranates, and figs (Muhammed and Shamsi, 2016; Al-Habsi and Al-Khusaibi, 2018). Flavonoid is the polyphenol in those mentioned foods reported to have the ability to be a biological modifier that gives health benefits to consumers (Rahmani *et al.*, 2014; Asaduzzaman *et al.*, 2015; Azahar *et al.*, 2017). Unfortunately, there is less study on the health properties of Quranic food mixture that lead to misunderstanding of the mixture of Quranic food (Muhammed and Shamsi, 2016). Significant concern regarding the addition of multiple bioactive ingredients into a product is the possibility of interaction among ingredients may result in degradation of the ingredient, and the functionality could be reduced or improved (Sun-Waterhouse, 2011). Hence, the systematic optimization method on multiple natural ingredient interaction research concerning certain food content will help to enlighten the understanding of those matters.

Optimization of the formulation can be conducted by any design expert software (Wass, 2001), as it involves

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three main steps which are analyzing to select of the fitted model, optimization (Adiba *et al*., 2011; Salem *et al*., 2011; Bose *et al*., 2013; Saifullah *et al*., 2016; Azahar *et al*., 2017) and validation (Banala *et al*., 2013; Rahim *et al*., 2018). The simplex centroid method is a collection of statistical and mathematical techniques that useful in developing, improving, and optimizing the mixture (Patel *et al*., 2017). Understanding the effects of independent variables and the interactions between variables and response can be achieved through analysis of variance (ANOVA) of the mix (Amalina *et al*., 2018). In the optimization technique, selecting the best model is the primary procedure to determine the desirability function of multiple responses. The desirability of the model can be determined by analyzed the F value, lack of fits test, F statistics, multiple correlation coefficient (R^2) test and desirability value (Marasini *et al*., 2012).

In accordance with the development of the Quranic Mixed Food (QMF) product, there is less available research on the flavonoid content of that Quranic food when mixed. On the other hand, the selection of functional ingredients that had specific phytochemical properties is the primary challenge being faced in formulating nutraceutical products as the results of increasing demand from the consumer for more variety and optimize the benefits of food (Ververidis *et al*., 2007). Therefore, the simplex centroid design method can be utilized in this study to develop the optimized formulation. Our study aimed to employ the simplex centroid design of Design Expert in optimizing the formulation of QMF. The optimization goal was to develop the formulation of QMF with an optimized total flavonoid content (TFC). The optimized formulation will be utilized as an ingredient in nutraceutical food development in the future.

2. Materials and methods

2.1 Chemical and instrument

Aluminium chloride ($AlCl_3$), methanol (CH_3OH), potassium acetate (CH_3CO_2K), and quercetin ($C_{15}H_{10}O_7$) were purchased from Merck Germany. The instrument used was Ultraviolet-visible (UV-Vis) spectrophotometer (T60 U, PerkinElmer, USA), laboratory juice maker (KEA0236, Alpha, China), and vacuum oven (VD 23, Binder, Canada).

2.2 Collection and preparation of food powder

All raw materials, dried dates, dried raisins, pomegranate fruit, dried fig, and honey, were purchased from the local market in Johor, Malaysia. Pomegranate fruit was washed and peel then juice was collected by juice maker. All dried fruit (fig, date, and raisin) were soaked in distilled water in ratio 1:1 for 24 hrs at 4±2°C before processed by the following method by Pourghayoumi *et al.* (2016). All the juices were filtered using sterile Whatman No. 1 filter paper to get a clear juice. Consequently, fruit juice was mixed as the proportion suggested by experimental design (Table 1) and dried at 35±2°C for 16 hrs to produce powder (Ramamoorthy and Bono 2007) and stored at -15±2°C before further analysis.

2.3 Experimental design

The optimization process was conducted by following the method of Rahim *et al.* (2018) with modification. The simplex centroid design was used as the experimental design. The percentage of dates, raisins, pomegranates, figs, and honey is chosen as independent variables while total flavonoid content was assigned as the dependent variable. The optimization process is conducting by changing the percentage of independent variables concurrently and keeping their total percentage constant (100). The simplex-centroid mixture design was chosen for the experiments due to the independent variables have an equal variety, which between 0 – 100, and there had been no constraints on the design space. The simplex refers to the geometry shape of a triangle in two-dimensions while tetrahedron in three-dimensions. The simplex-centroid is extra uniformly allotted within the indoors of the triangle and helps to come across the curvature of the reaction surface. All proportions of all independent variables in each mixture were sum to 100% for a mixture load of the desired amount.

2.4 Response analysis

The response of this study was total flavonoid content (TFC) that was determined spectrophotometrically according to the Dowd method describe by Ramamoorthy and Bono (2007) with a slight modification. The 1 mL of sample solution (0.4 mg/mL) was taken and mixed well with 3 mL of methanol. Then, 0.2 mL of 10% $AlCl_3$ and 0.2 mL of CH_3CO_2K in 1 M were added to the mixture. The solution was held at the dark condition for 30 mins before absorption readings were taken at 420 nm against the blank. The TFC was determined using a standard curve with quercetin (0, 10, 50, 100, and 200 µg/mL) as the standard. TFC was express as mg of quercetin equivalents (QE)/mg of sample.

2.5 Statistical analysis and optimization

Optimization and statistical analysis were constructed by using a Simplex Centroid design of Design-Expert Software 6.0.3 models. The data were analyzed by analysis of variance (ANOVA), followed by

Table 1. Design layout and experimental results for TFC

RUN	Independence Variable Proportion (%)					Response
	Date	Raisin	Pomegranate	Fig	Honey	TFC (µg QE/ mg)
1	25	25	25	25	0	11.05 ± 0.4^{ghijkl}
2	0	0	0	100	0	8.06 ± 0.6^{klmn}
3	0	0	50	50	0	13.04 ± 0.9^{cdefghi}
4	0	33.33	0	33.33	33.33	4.86 ± 0.3^{nop}
5	0	50	50	0	0	22.38 ± 2.5^{a}
6	33.33	0	33.33	0	33.33	9.45 ± 2.0^{ijklmn}
7	0	0	50	50	0	13.04 ± 0.9^{cdefghi}
8	100	0	0	0	0	13.21 ± 0.9^{cdefghi}
9	0	0	100	0	0	17.08 ± 0.3^{bc}
10	20	20	20	20	20	11.11 ± 1.8^{ghijkl}
11	33.33	0	33.33	33.33	0	16.63 ± 1.5^{cde}
12	10	10	60	10	10	11.99 ± 1.5^{defghij}
13	50	50	0	0	0	16.69 ± 1.0^{cd}
14	33.33	33.33	33.33	0	0	9.45 ± 2.0^{ijklmn}
15	10	60	10	10	10	11.94 ± 2.3^{defghij}
16	0	50	0	0	50	8.51 ± 2.4^{jklmno}
17	0	50	0	50	0	9.45 ± 2.0^{ijklmn}
18	25	0	25	25	25	14.31 ± 0.2^{cdefgh}
19	0	50	0	0	50	6.96 ± 2.4^{lmnop}
20	50	50	0	0	0	14.42 ± 1.2^{cdefg}
21	33.33	0	0	33.33	33.33	11.11 ± 1.8^{ghijkl}
22	25	25	25	0	25	11.66 ± 1.1^{fghijk}
23	50	0	50	0	0	11.16 ± 0.9^{fghijkl}
24	33.33	33.33	0	33.33	0	12.60 ± 1.5^{cdefghij}
25	10	10	10	10	60	4.80 ± 1.5^{nop}
26	0	0	0	0	100	4.19 ± 0.7^{op}
27	0	0	50	0	50	6.52 ± 1.3^{mnop}
28	10	10	10	60	10	10.39 ± 1.7^{ghijkl}
29	50	0	0	0	50	6.96 ± 2.0^{lmnop}
30	0	0	0	50	50	2.04 ± 1.9^{p}
31	60	10	10	10	10	15.58 ± 2.0^{bcdef}
32	0	0	33.33	33.33	33.33	3.80 ± 1.3^{op}
33	0	33.33	33.33	0	33.33	19.62 ± 2.8^{ab}
34	33.33	33.33	0	0	33.33	11.71 ± 1.6^{efghijk}
35	0	0	50	0	50	6.52 ± 1.3^{mnop}
36	50	0	0	50	0	19.67 ± 2.0^{ab}
37	25	25	0	25	25	8.51 ± 0.5^{jklmno}
38	0	100	0	0	0	13.98 ± 0.4^{cdefghi}
39	0	33.33	33.33	33.33	0	9.56 ± 0.3^{ghijklm}
40	0	25	25	25	25	11.60 ± 0.4^{fighijk}
41	50	0	0	50	0	16.08 ± 0.7^{cdef}

Values are expressed as mean±SD. Values with different superscripts within the column are significantly different from each other ($p\leq0.05$)

optimization through a linear, quadratic and special cubic models were used for a variety of response as a function of significant interaction effect ($p<0.05$) between the proportion with acceptable determination coefficients ($R^2>0.90$). The differences were determined by the Turkey LSD test and defined as statistically significant at $p<0.05$.

3. Results and discussion

Model fitting and performance analysis statistical result discussed how the best model could be selected while content modelling, proportion optimization, and validation process explain the details of optimized QMF.

3.1 Analysis of response

Table 1 shows the TFC of all formulation of QMF generated by Design-Expert software (version 6, USA, 2000). The TFC was express as mg of quercetin equivalents (QE)/mg of sample. It is determined quantitatively with quercetin standard curve (Figure 1) by the equation y = 2.0399x + 0.003, R^2 = 0.98. Quercetin was selected as standard as it is reported as the main type of flavonoids presented at high value in Quranic food (Slatnar *et al*., 2011; Marquez *et al*., 2012; Al-Habsi and Al-Khusaibi, 2018). The data shows that the highest (p<0.05) TFC content for the single component is 17.07±0.3 µg QE/mg (pomegranate), and the lowest (p<0.05) TFC content is 4.20±0.7 µg QE/mg (honey). Previous studies have demonstrated that pomegranates (Poyrazoğlu *et al.,* 2002) and raisins (Marquez *et al*., 2012) had high flavonoid content compared to dates (Harnly *et al*., 2006), figs (Slatnar *et al*., 2011) and honey (Khalil *et al*., 2011). Table 1 also showed that the TFC for the 5^{th} run (50% raisin: 50% pomegranate) exhibited the highest (p<0.05) TFC value (22.38±2.5 µg QE/mg). In contrast, the 30^{th} run (50% date: 50% honey) had the lowest (p<0.05) content of TFC (2.04±0.2 µg QE/mg). Previous research had reported that there was no scientific data on the relationship between QMF and TFC. The single most striking observation to emerge from the data comparison was the proportion of mixture with raisin and pomegranate might improve the flavonoid content of the mixture. In contra, the mixture with honey may not improve the flavonoid content of the mixture. These results support the idea of Hidalgo, Sánchez-Moreno and de Pascual-Teresa (2010) that flavonoid-flavonoid interaction may give synergic or antagonistic effect. The effect of variables on the flavonoid contents is further discussed in the modelling equation and mixture optimization.

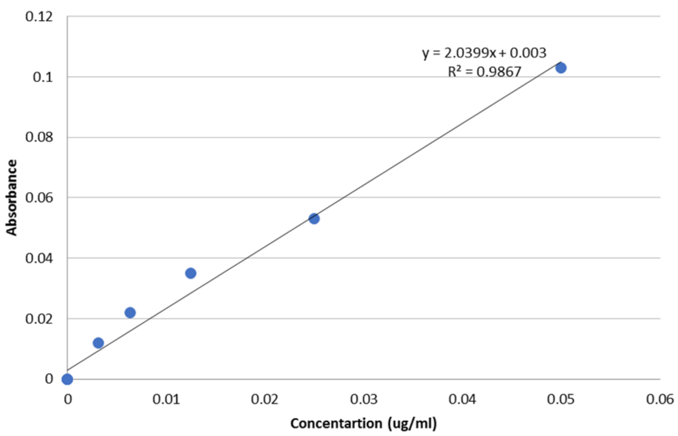

Figure 1. Calibration curve of Quercetin standard

3.2 Model fitting and performance analysis

Table 2 indicates the ANOVA analysis of the model, showing the responses were fitted to linear, quadratic, and special cubic models. The mixture model coefficients were validated by ANOVA of the response variable for linear, quadratic, and specific cubic models. The ANOVA results were calculated based on 95% confidence intervals. These findings were used to determine the best-fitted model for five independence variables (proportion of dates, raisins, pomegranates, figs, and honey). The performance of the model was evaluated by using variation within the samples (F-statistics), lack of fit test, and multiple correlation coefficient (R^2) tests. Based on the result, the large amount of model F-value implies there is less probability of different variations of result to occur. It showed that linear, quadratic, and special cubic model is highly significant when the probability value is low (p<0.0001) indicating that the model can be utilized in determining the interaction effect of variables and response.

Comparing the probability F value of lacks fit, the specific cubic model is the more desirable model to be selected as it is not significant. Furthermore, the performance of the models also checked by the determination of R^2, coefficient of variation (CV), and adequate precision. The R^2 value signifies the measure of the amount of variation around the mean explained by the model. From Table 2, the R^2 for the special cubic model is higher compared to linear and quadratic. According to Azahar *et al.* (2017), the closer the R^2 value to 1.0, the better and significant the model fits the actual data. The CV for special cubic shows the lowest value, which indicates better reliability of the model. Another important finding was the adequate precision to measure the signal to noise ratio. The adequate precision of the special cubic value was highest as stated in Table 2 (16.810) relative to other models; linear (12.977) and quadratic (10.929). This suggests that the most accurate model for use as an optimization process was the special cubic model.

3.3 Modelling of TFC content

The model fitting and performance analysis had identified that special cubic is the best model to be selected. The empirical regression of special cubic model of their relationship between responses and the five

Table 2. ANOVA Analysis Result

Model	F value	Prod > F value	Lack of fit-Prob > F value	R^2	CV	Adequate Precision
Linear	9.69	< 0.0001	0.0112	0.5186	31.56	12.977
Quadratic	5.93	< 0.0001	0.0243	0.7616	26.14	10.929
Special Cubic	14.18	< 0.0001	0.2422	0.9551	14.46	16.81

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variables for total flavonoid contents could be expressed as below:

$$TFC = 2.67*A + 2.65*B + 3.24*C + 1.57*D + 0.66*E + 2.46*A*B - 3.40*A*C + 5.46*A*D - 1.44*A*E + 5.44*B*C - 1.35*B*D - 0.97*B*E + 0.16*C*D - 3.26*C*E - 3.59*D*E - 43.41*A*B*C - 16.54*A*B*D - 1.65*A*B*E + 19.96*A*C*D + 15.96*A*C*E + 15.43*A*D*E - 25.25*B*C*D + 39.73*B*C*E - 2.38*B*D*E - 8.93*C*D*E \quad (1)$$

Where A is dates, B is raisin, C is pomegranate, D is fig, and E is honey. A positive sign in each equation represents a synergistic effect of the variables. On the other hand, a negative sign represents an antagonistic effect of the variables (Azahar *et al*., 2017). From Equation (1) identified that mixture of date-raisin, date-fig, raisin-pomegranate, pomegranate-fig, date-pomegranate-fig, date-pomegranate-honey, date-fig-honey, and raisin-pomegranate-honey show synergic effect. Contrarily, date-pomegranate, date-honey, raisin-fig, raisin-honey, pomegranate-honey, fig-honey, date-raisin-pomegranate, date-raisin-fig, date-raisin-honey, raisin-pomegranate-fig, raisin-fig-honey, and pomegranate-fig-honey show antagonistic effect. These results agree well with the argument by Sun-Waterhouse (2011), and Hidalgo *et al.* (2010) on there is the possibility of interaction among ingredients may result in degradation of the ingredient functional properties. This research is the first step towards a more profound understanding of the interaction of selected ingredients toward the functional properties.

3.4 Mixture proportion optimization

The desirability function was calculated based on the ratio in the range (0-100) of all factors (proportion of dates, raisins, pomegranates, figs, and honey) and the maximum output of response (TFC). It can be observed from the comparison of different scatter plot of the model (Figure 2), the maximum desirability value 1.0 achieved by the specific cubic model (a) followed by 0.91 for the quadratic model (b) and, lastly, 0.7 for the linear model (c). The desirability near 1.00 is the most acceptable (Arunkumar, 2009) for the optimization of the mixture.

This result further confirms that special cubic is the most acceptable model for optimization. Then, an exact depiction of the variables proportion and corresponding desirability of the optimized model was shown in Figure 3.

Referring to the contour plot, X1 (pomegranate), X2 (raisin), and X3 (date) are the most factors that influence the optimizing of TFC (Figure 3). It is evident from this study that the factors (date, raisin, pomegranate, fig, and honey) would interact with each other and, in turn, affect the flavonoids content differently. It identified that the pomegranate, raisin, and date were the most significant factors in determining the optimum flavonoid content compared to fig and honey. According to the previous report (Poyrazoğlu *et al*., 2002; Harnly *et al*., 2006; Khalil *et al.,* 2011; Slatnar *et al*., 2011; Marquez *et al*., 2012) which is also in line with this study, the flavonoid content of pomegranate, raisin, and date is higher as compared to fig and honey. In this study, all five factors

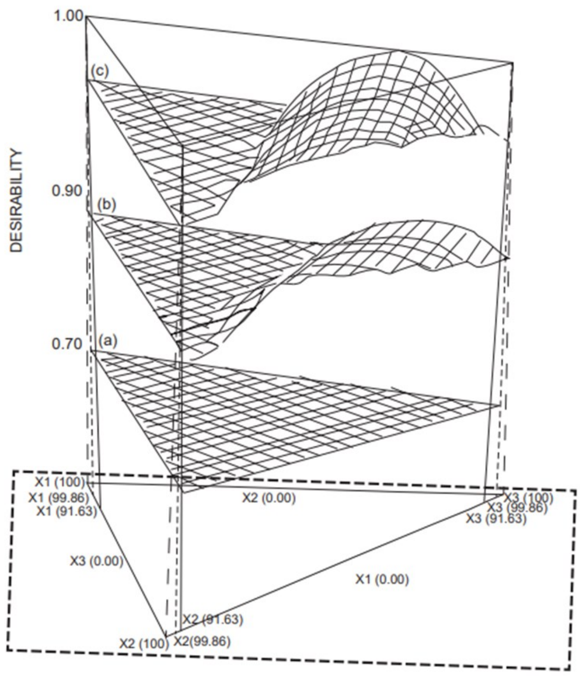

Figure 2. Comparable scatter plots of the desirability function for three different models; (a) specific cubic model, (b) quadratic model, and (c) linear model.

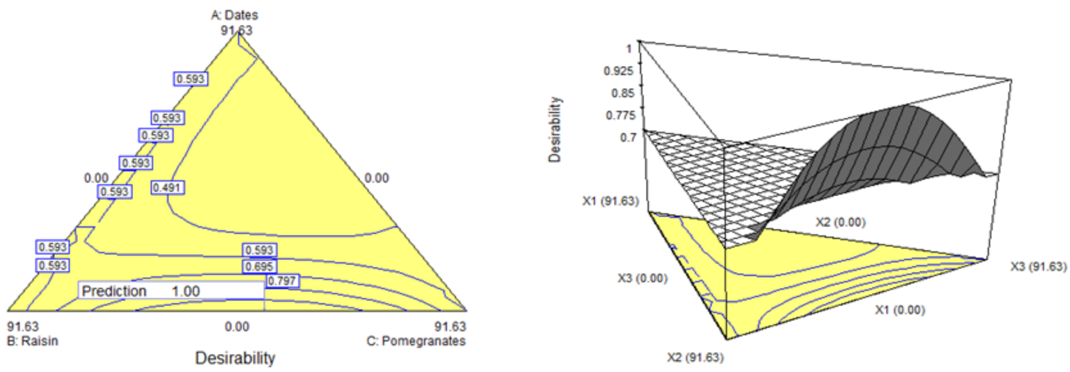

Figure 3. Mixture contour (left) and scatter (right) plots for TFC

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were selected due to their individual properties that high in flavonoid content (Slatnar *et al.,* 2011; Marquez *et al.*, 2012; Al-farsi *et al.*, 2018) which contribute to the therapeutic properties. Thus, increasing the proportion of pomegranate and raisin simultaneously, as shown in the contour plot, will help in optimizing the flavonoid content of QMF formulation, which shows the desirability value is one. A possible explanation for this is that individual pomegranate and raisin had high flavonoid content as compared to honey, then it shows a synergistic effect on the response.

3.5 Validation of model

Previously optimization analysis, ten mixture suggested for the specific cubic model obtained using Design-Expert software. However, only one mixture (0.17% date, 42.88% raisin, 42.88% pomegranate, 0.11% fig, and 13.97% honey) with the highest desirability (1.00) were selected for the validation process. Finally, to confirm the validity of the optimal factors and predicted response calculated, three batches of selected optimized formulation were prepared and analyzed. The predicted response value is 22.83 µg QE/mg while the experimental value is 23.87 µg QE/mg. The bias between the predicted and experimental value is 4.36%. The bias value is below than 10% which acceptable and confirms that the model is validated. Thus, indicating the success of simplex centroid design used to the optimization of the Flavonoid-rich Quranic Mixed Food formulation.

4. Conclusion

The special cubic model is selected as the best model for optimizing the flavonoid-rich QMF as it satisfied all tests conducted by software. The model had better fitness compared to the linear and quadratic models. In addition, the equation represents a more detailed interaction on their response relationship with the five variables for total flavonoid content. Also, the highest desirability (1.00) and the combination of all variables to get the maximum flavonoid content. The optimized flavonoid-rich QMF formulation consist of 42.88% raisins, 42.88% pomegranates, 13.97% honey, 0.17% dates, and 0.11% figs. The main factors that influence the flavonoid content of the mixture were pomegranates and raisins. Thus, the optimized formulation can be used as an ingredient in developing food or nutraceutical products in the future.

Conflict of interest

The authors declare no conflict of interest.

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