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A Case Study on Functional Food Intake in a Diabetic Patient: No Such Thing as a Magic Bullet Part-II

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Full Paper

A Case Study on Functional Food Intake in a Diabetic Patient: No Such Thing as a Magic Bullet Part-II

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Abstract

BACKGROUND: Useful ingredients in functional foods A and B previously improved certain physical symptoms (PSs) deficits due to ageing; however, blood sugar levels (monitored as glycemated hemoglobin or HbA1C) of a type-2 diabetic were unsatisfactory. We investigated the probable factors by focusing on the supply source, types and concentrates of sugar-regulating substances in ingredient mulberry leaf extract (MLE) as the extract was previously not well-defined. The revised functional food C (replaced previously known B), where all ingredients remained the same in quantity and supply sources, except MLE where the useful ingredient 1.2% 1-deoxynojirimycin (DNJ) was defined and obtained from a new supplier Z. **METHODS:** Volunteer patient P, who led a sedentary lifestyle, had continued intake of functional food A and complemented A with C after 2 control readings had been taken. Controls and blood analytical data were respectively monitored before and after combined A+C intake at 3-month (3-mo) intervals. Blood pressure (BP), body mass index (BMI), and other metabolic indexes were taken before (A alone) and after combined A+C intake. P led his usual normal life without dietary restrictions. PSs were also monitored before and after combined A+C intake. **RESULTS:** Blood pressure (BP) was normal, with slight improvement in BMI values. Total cholesterol (T-Cho), triglycerides (TG) levels varied in a similar pattern, which eventually registered normal after 9-mo combined A+C intake. HbA1c levels scored impressive improvements in

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a time-dependent manner: i.e. decreasing from 8.0 and 9 (controls) to 7.5, 6.9, and 6.8 at 3-, 6- and 9-mo combined A+C intakes, respectively. Improved PSs were well maintained. **DISCUSSION:** The BMI improved from overweight to normal status. Rebounds in T-Cho (3-, 6-mo) and TG (6-mo) levels were probably associated with high-calorie sweets taken in August. The most impressive finding in this study is the marked improvement in HbA1c findings. Replacement of MLE from a new source Z with defined 1-deoxynojirimycin (DNJ) concentrate made all the difference: the alpha-glucosidases-inhibiting DNJ, fagomine, and other active sugar-regulating components in MLE may have lowered blood sugar levels, thus improving Hb_{A1c} values. Functional foods comprising effective ingredients would most likely elicit useful effects, if the active ingredient with a defined concentrate was used.

Keywords: single-product, complementary product, physical symptoms, glycemic index, metabolic indexes.

1. Background

Our previous manuscript described the usefulness of food ingredients when used in a combination of functional foods A and B that indications show had potentially positive effects on health via the purported effects of the ingredients[1-4] in a patient with preexisting conditions.[5] Although some the functional foods do not show the purported effects, some may provide preventive effects when taken in proper doses over certain threshold intake periods: A faithful intake regimen with appropriate ingredient factors in place at the appropriate dosages for a long-enough intake period are the basic conditions for eliciting the best outcomes.[6-8] In our previous study,[5] the ingredients were significantly useful in improving certain deficit physical symptoms (PSs) due to ageing; however, the analytical blood parameters of the type-2 diabetic patient were not all favorable: the blood sugar levels monitored as glycemated hemoglobin (HbA1C) were especially unsatisfactory. The reasons were probably attributable to the supply sources, types and concentrations of sugar-regulating ingredients in mulberry leaf extract (MLE), moringa extract and cyanobacteria extract used. We investigated MLE in this study as it is most related to the sugar-regulatory role.

The purpose of the study was to investigate the type, supply source and concentrate of ingredients in previously used functional food B[5] (known as C in the present study) supposedly associated with blood sugar levels. As the effects of ingredients used were well-accounted for in the outcomes in a previous study,[5] only ingredients suspected of not providing the desired effects were scrutinized for change in the present study: we started with MLE. As demonstrated in the previous study,[5] ingredients in functional food B were anticipated to be effective in producing certain favorable body aspects, and were therefore kept unchanged as valid ingredients in this follow-up study, except for making a note on the supply source and concentrate of the potent sugar-regulating MLE. We called the revised functional food C (previously known as B), where all ingredients remain the same as to quantity and supply source. MLE was analyzed to contain not less than 1.2% of the sugar-regulating compound, 1-deoxynojirimycin (DNJ), from a new supply source (W). Fresh ML powder was used in the previous study without analysis of its DNJ content.

Our observations of blood sugar levels and HbA1c in a type-2 diabetic P (male; age: 69) using functional food A (3eMulti: a product for blood pressure (BP) control) for more than 10 yr were as follows: he has maintained a healthy and normal systolic BP (SBP)/diastolic BP (DBP) ranges of 125-128/72-78 mmHg without the use of antihypertensive medication since having started taking functional food A (pre-intake SBP/DBP values before 2008: 135-145/90-96 mmHg). His HbA1c values were poor (8.0-9.0%). Other than taking a prescribed antidiabetic (Metogluco™ 250) for type-2 diabetes for more than 10 yr, patient P was not taking other medications. In this study, function food C (G-Max Mulberry Plus, or GMP, containing MLE powder (from a new supply source Z, cyanobacteria extract, and moringa leaf extract from previous source Y) was administered. Intake of functional food A as well as combined A + C was monitored at 3-mo intervals.

Since his poor physical symptoms (PSs) – poor forelimb muscular (grip-holding) strength, hindlimb joint discomfort/pain on walking/climbing stairs, balance/orientation on standing, and deficient urination flow – have improved using A + B combined,[5] we continued to follow the status of PSs-1 to -4 in the

present study using functional food A+C combined. We focused especially on metabolic/blood indexes (especially blood sugar levels and Hb_{A1c} (since the subject was a type-2 diabetic) while observing the PSs at 3-mo intervals. The ingredients in B and C were similar, except for MLE in C where the DNJ had defined concentrates of ≧1.2% in this study. The results using C revealed that favorable outcomes on blood sugar (HbA1c) were established and reconfirmed the favorable outcomes of other metabolic readings including total cholesterols (T-Cho), triglycerides (TG), and low-density lipoprotein cholesterols (LDL-C) when compared to data from the previous study.[5]

2. Materials and Methods

2.1 Materials

Functional food A (3eMulti), which contained tocotrienols, decosahexanoic acid (DHA), etc., was similarly manufactured and used at the same dosage and a regimen similar to the previous study.[5] Functional food C contained ingredients similar (MLE, moringa leaf extract, cyanobacteria extract, etc.) to B, except MLE in functional food C was obtained from a different supply source (Z) to replace the previous ML extract (with undefined NDJ concentration in B: viz., C indicated the defined NDJ concentration).

2.2 Patient

Patient P (male, 69 yr old), who had a more than 10 yr clinical history of type-2 diabetes, volunteered for the present study. He led a sedentary lifestyle with limited physical activity, and had been visiting a nearby clinic on a regular 3-month basis for medical monitoring. Although he has continued intake of functional food A (2 softgels before meals or with empty stomach; 4 softgels daily) since 2008 and underwent a previous case-study,[5] patient P had a 6-month washout period of functional food B usage as described in the previous study.

2.3 Study Protocol

The present study started on Dec 16, 2019, and two controls (Dec 16, 2019 and March 23, 2020) were measured, followed by functional food C intake as a follow-up complementary intake of function food A. Therefore intake of C was combined with A from March 24, 2020 (day 0 of combined A+C intake). Briefly, the post-intake were monitored at ca. 3-month (mo) regular intervals: viz., 3 (June 12, 2020), 6 (September 4, 2020) and 9 (November 27, 2020) mo after the combined A+C intake.

2.4 Investigation Indexes

Blood pressure (BP) and the following metabolic indexes were measured at 3-mo intervals: body mass index (BMI)-related body weight (kg) and height (m), levels of glycemated hemoglobin (HbA1c), total cholesterols (T-Cho), triglycerides (TG), high-density lipoprotein-cholesterols (HDL-C), and low-density lipoprotein-cholesterols (LDL-C), were all measured on December 16, 2019 and March 23, 2020 as control values before complementary functional food C (GMP) intake. GMP intake was initiated on March 24, 2020 (day 1 after recording 2 control values).

2.5 Food Habits

Patient ate meals prepared in a variety of cooking styles with different foods in usual ways without calorie restrictions. However, he ate high-fat high-sugar durians (fruiting season: May-August) and rather high-fat high-calorie lard-laden portions (one-half of cake daily) of festival mooncakes (on-sale season: August-September) received from his siblings residing overseas in August (these sweets are made and eaten before and after the moon-cake festival in East and Southeast Asia: from early August to end of September each year).

2.6 Physical Symptoms (PSs)

Since attenuated physical symptoms (PS) of patient P improved markedly using combined use of functional foods A+B in a previous study,[5] we continued to monitor the previously tested PSs (grip-strength, walking and climbing staircases, standing on one-foot in shower, urination flow) over time in a similar regimen as previously described[5] to gauge if the formula with a defined MLE concentration would work as effectively.

Table 1: Clinical Examination Report monitored at 3-month intervals: Consistent intake of A before 2019 + Intake of C initiated (from March 24, 2020). Functional food C was combined with A from March 24, 2020. Note that controls were taken twice (December 16, 2019 and March 23, 2020) before combined A+C intake.

Clinical findings			**3eMulti** intake alone↓		*3eMulti + GMP intake*		
Items	Units (IS*)	Standard Range (IS*)	16-Dec-19	23-Mar-20	*12-Jun-20*	*04-Sep-20*	*27-Nov-20*
BMI**	kg/m^2 (m sq)	60-150	25.2	25.3	25.2	24.9	24.9
HbA1c[#]	%	7.0-8.0***	**H 8.0**	**H 9.1**	**H 7.5**	***6.9***	***6.8***
T-Cho	mg/dL (**mmol/L**)	120-220 (**3.08-5.64**)	212 (**5.43**)	198 (**5.08**)	**H** 240 (**6.15**)	**H** 230 (**5.89**)	213 (**5.46**)
TG	mg/dL (**mmol/L**)	50-150 (**0.56-1.69**)	**H 188** **(2.11)**	**117** (1.31)	**148** (**1.66**)	**H 194** **(2.18)**	**121** **(1.35)**
HDL-C	mg/dL (**mmol/L**)	35-60 (**0.90-1.54**)	43 (**1.10**)	45 (1.15)	45 (**1.15**)	39 (**1.00**)	39 (**1.00**)
LDL-C[$]	mg/dL (**mmol/L**)	65-139 (**1.67-3.56**)	**H** 145 (**3.72**)	**H 141 (3.62)**	**127** (**3.25**)	**H 160** (**4.10**)	**120** (**3.08**)
BP[##]	mmHg	90-139/60-89	128/80	124/74	124/70	122/76	122/76

*IS: international standard unit; G-Max Mulberry Plus (GMP) in tablet formula.
**BMI: normal (18.5 - <25), overweight (≧25 - <30), obese (≧30)
***Standard range for diabetics: 7.0-8.0; for normal healthy humans: 4.0-5.6)
[#]Glycemated hemoglobin: range considered 'good' for diabetics: 7.0-8.0 (normal range: 4.0-5.6)
[##]BP blood pressure expressed as SBP/DBP values in mmHg (normal – prehypertension levels)
H: higher than normal range values
[$]LDL-C: (Note: A https//my.clevelandclinic.org)[15] Near-optimal – above-optimal: 100-129 mg/dL (2.56-3.30 mmol/L); borderline high: 130-159 mg/dL (3.33-4.08 mmol/L);

3. Results

3.1 Blood Analysis and Metabolic Indexes (Table 1)

After taking functional food A for more than 10 yr, patient has consistently maintained BP values (SBP/DBP values of 125-128/72-78 mmHg) which were within the normal pre-hypertensive SBP/DBP upper/lower ranges (90-139/60-89 mmHg) without the use of antihypertensive medication. However, the SBP/DBP values registered 135-145/90-96 mmHg before functional food A (i.e. before 2008). The improved PSs were well maintained before from the previous study, and continued to remained favorable after 3-mo combined A + C intake and thereafter (until 9-mo intake).

Based on international standardization, body mass index (BMI) values imply the following categories: normal (18.5 - <25 kg/m^2), overweight (≧25 - <30 kg/m^2), and obese (>30 kg/m^2). In our study, BMI values for the patient in the normal (24.9 kg/m^2) range were achieved, and improved from overweight category (25.2-25.3 kg/m^2), after 6-mo intake of combined A+C. In our previous study,[5] the BMI values with either only functional food A alone (25.0 - 25.2 kg/m^2) or combined A+B intake did not change (data not shown). Patient P did not change his dietary habits and just carried on with his usual eating habits and lifestyle. In fact, he devoured substantial amounts of high-fat high-sugar fruit/sweets (durians/mooncakes) in July-August period.

The T-Cho levels (normal range in control readings) fluctuated in the high-range values after 3-mo (6.15 mml/L) and 6-mo (5.89 mmol/L) intake to eventually improve to normal (5.46 mmol/L) values after 9-mo combined A+C intake. In the case of TG, the fluctuating values improved with faithful and continuous intake of A+C after 3-mo (1.66 mmol/L) and 9-mo (1.35 mmol/L) intake, although a rebound was observed on September 4, 2020 (6-mo intake) after combined A+C intake. HDL-C values (the higher the better) remained rather consistent throughout the study (1.0 – 1.15 mmol/L): i.e. values varied within normal healthy lower-range values (not registering below the unhealthy threshold of 0.90 mmol/L or 35 mg/dL). LDL-C is a stubborn index that responded favorably after 3-mo intake (3.25 mmol/L or 127 md/dL) and terminated at an even more impressive level (3.08 mmol/L or 120 mg/dL) after 9-mo intake. All in, the useful effects of combined A+C intake in restoring normal healthy threshold values on three cholesterol types (T-Cho, HDL-C, LDL-C) and TG were established.

Apart from the normal range-values of BP, the HbA1c (%) scored impressive improvements in a time-

Table 2: Improved physical symptoms (PSs) were well maintained after intake of functional food A, and remained favorable after A was complemented with C. Refer to Table 3 for details of PS-1 to -4.

		..... *After 3eMulti + GMP intake*		
	March 23, 2020	**Jun 12 (3 mo)**	**Sept 4 (6 mo)**	**Nov 17 (9 mo)**
FGH strength[1]	28-30	28-31	28-29	29-30
Climbing staircases[2]	No	No	No	No
Balance Coordination[3]	No	No	No	No
Urination flow[4]				
Onset/latency	Good	Good	Good	Good
Duration	Good	Good	Good	Good

[1]PS-1; [2]PS-2; [3]PS-3; [4]PS-4

dependent manner. This trend indicated decreasing values of HbA1c from 8.0 and 9.1 (before combined A+C intake) to after combined A+C intake values of 7.5% (3-mo), 6.9% (6-mo), and 6.8% (9-mo).

3.2 Physical Symptoms

Based on our observations, data on the general outcomes in PSs were persistently maintaining favorable states (Table 2) using function food C were analogous to data of a previous study using functional B (Table 3).[5] Intake of GMP showed the same beneficial effect on forearm grip-hold (FGH) strength after 3-m intake and thereafter: Note that MLE was now defined as a percentage of mulberry extract of not less than 1.2%. In a similar way, lack of pain (yes/no) in climbing stairs, maintenance of balance and coordination (yes/no) during showers, and urination flow onset/frequency (poor/good) were well maintained after 3-mo intake and thereafter.

4. Discussion

Functional foods or food ingredients with biological activities have beneficial effects on the body system from the cellular level all the way up to the living system as a whole.[1-10] The useful effects of combined A+C intake reconfirmed the buffering actions on physical symptom (PS) deficits studied previously.[5] With regard to blood pressure (BP), the present findings confirmed the usefulness of functional food A:

Table 3: Painful physical symptoms (PS-1 to -4) improved when functional food A was complemented with functional food B.[5]

	Before intake	**After intake**			
		1-week	**3-week**	**3-mo**	**6-mo**
FGH strength[1]	9-10	9-10	15-16	19-20	29-30
Climbing staircases[2]	Yes	Yes	Yes	No	No
Balance Coordination[3]	Yes	Yes	Yes	No	No
Urination flow[4]					
Onset/latency	Poor	Poor	Poor	Good	Good
Duration	Poor	Poor	Poor	Good	Good

[1]: *PS-1. FGH muscular strength (best average 10-degree oscillation counts while being suspended)*

[2]: *PS-2. Climbing 10-step staircases: (joint discomfort/pain after climbing 10-step staircase: 'Yes' with pain or discomfort, or 'No' without any discomfort or pain was recorded on an all-or-none basis)*

[3]: *PS-3. Balance Coordination: (fell/tripped over at less or more than 10-sec duration while soaping foot-sole based on an all-or-none evaluation)*

[4]: *PS-4. Urination flow onset/latency (poor: >10 sec, good: <10 sec); duration (poor: > 1 min; good: < 1 min based on cut-off times of 10 sec for urination latency/onset, and 1 min for urination duration)*

viz., lowest-highest SBP/DBP ranges registered 122-128/70-80 mmHg throughout the study, values which are analogous to mean values of previous 10-yr readings (data not shown). As has been documented in the previous study,[5] ingredients such as tocotrienols (3e),[7-11, 14] and DHA/EPA (eicosapentaenoic acid),[10-14,18] etc. were useful in keeping the BP consistent. Data measured in the present study reconfirmed the useful contribution of A in maintaining continuous normotensive effects without tolerance or resistance over long-term use of functional food A in the patient.

The body mass index (BMI) did not show a markedly favorable effect with functional food A intake alone; however, combined A+C intake improved to a more favorable category from overweight (>25 or 25.3 kg/m^2) to normal (<25 or 24.9 kg/m^2) status, implying that the body weight was measurably reduced. As expected, given major functionally active ingredients in both A and C are believed to have induced attenuation of body weight,[13-16] restoration of the normal BMI status was demonstrated, albeit the weight-reducing effect might have been camouflaged by the eating of high-fat high-calorie sweets (moon-cakes) in August. The data could suggest that it might have been worse had he not taken combined A+C compared to values before and after the combined A+C intake: viz., the observed rebounds in T-Cho (3-, 6-mo) and TG (6-mo) levels. The BMI might have been improved with more physical activity and healthy dietary habits, as patient led a sedentary lifestyle despite his hefty appetite leading to 2-3 weeks (or more) of continuous daily consumption of high-fat high-sugar festive tidbits in August 2020. Notice that the increased TG levels coincided with this T-Cho increase monitored in September; these were probably closely associated with dietary habit as described in 'Materials and Methods' (food habits: 2.5). However, further tests are warranted to confirm the outcomes.

Food A alone is documented to be effective on certain metabolic disorders, and single-use and/or dosages of functional food A alone maintained normal T-Cho levels (as shown in the 2 control readings: 198-212 mg/dL or 5.08-5.43 mmol/L respectively); however, the levels increased to 6.15 mmol/L (or 240 mg/dL) at 3 mo and 5.89 mmol/L (or 230 mg/dL) at 6 mo after combined A+C intake: readings higher than normal upper range of 5.64 mmol/L (220 mg/dL). The increased T-Cho values at 3-mo (6.15 mmol/L or 240 mg/dL) and 6-mo (5.89 mmol/L or 230 mg/dL) after combined A+C intake could have been attributable to intake of durians (season May-June) and festival mooncake sweets (August-September). This excessive intake of high-sugar high-calorie fruit/sweets in May-June and August-September could also account for the increased TG levels (coinciding with increased T-Cho value) 6 mo after combined A+C intake. All in all, T-Cho and TG levels were restored to normal levels after 9-mo continuous combined A+C intake. Increased LDL-C levels were normalized after 9-mo combined A+C intake. Functional food A alone was not effective either in lowering LDL-C levels after more than 10-yr intake. The food formula, dosages, and intake frequency may be factors at play; intakes of higher doses with higher frequency and additional ingredients may produce useful results. Further studies are warranted to realize lowering these generally intractable stubborn unwanted metabolites. These time-related LDL-C variations of pre-intake and post-intake levels under combined use of A+C were analogous to T-Cho and TG changes, although the pre-intake control LDL-C values were categorized as borderline high values, defined as 100-129 mg/dL (2.56-3.30 mmol/L), when compared to the IS values of 65-139 mg/dL (1.67-3.56 mmol/L).

The most impressive finding in this study is the marked improvement in Hb$_{A1c}$ levels. Replacement of previous mulberry leaf extract (MLE) from supplier Y in the previous study with the present-study MLE (with defined 1-deoxynojirimycin or DNJ concentrate) from another supplier (Z) made all the difference. As documented extensively, MLE[19-30] contains 1-deoxynojirimycin (DNJ), one of the main functional component in MLE[25] and fermented soybeans[21] which has been shown to inhibit digestion and reduce glucose absorption by inhibiting alpha-glucosidases (sucrase, maltase, glucoamylase),[21,22] as a competitive inhibitor.[29,30] and compounds, such as fagomine,[24] which induces insulin secretion in lowering blood glucose[23] levels, and antioxidants that putatively reduce lipid peroxidation in promoting heart functions.[26-30] Active components in MLE modulate hepatic glucose metabolism in alloxan-induced diabetic mice involving up- and down-regulation of mRNA expression of rate-limiting enzymes in influencing blood sugar levels.[22,27] Although the BMI data showed an improvement from overweight (control conditions) to normal only after 6 and 9 mo intake using combined A+C, the difference was of the highest reduction of 0.3 (25.2 to 24.9) kg/m^2 in this study. Note that the effective BMI improvement required at least 6-mo combined A+C intake to realize a 0.3-kg/m^2 reduction in the present subject. However, considering the intake of high-calorie sweets in August, the findings at 6-mo post-combined A+C intake could have achieved a greater margin than the data shown if lower-calorie food intake was practiced. In other words, combined

A+C intake may also serve as functional food for reducing weight, as MLE[16] and moringa[15,30] extract have been implicated in certain studies. Furthermore, *Spirulina fusiformis* may have potentiated the anti-hyperglycemic effect[15,30] of the two aforesaid ingredients. However, the only ingredient altered in this study (with reference to a previous study[5]) was MLE with change in supply source but without altering intake dosages. Therefore, the potent anti-hyperglycemic effect observed in the present was most likely attributable to MLE, although the hypoglycemic effect could have potentiated by moringa extract[28] and cyanobacteria extract (spirulina).[31]

The present study was limited by uncontrolled dietary habits of patient. It is difficult and impractical for patients to follow a strictly regulated diet throughout a period of more than 9 calendar mo or more. Since the results were remarkable and apparent in exhibiting marked improvements of disease-related parameters or indexes despite non-restricted dietary intake, the intake of designated functional foods was useful and should be encouraged for the benefits of patients in taking function-relevant products. The important observations in the previous[5] and present studies substantiate the importance of the supply source and of a known concentration of active ingredients (DNJ in this case).

In conclusion, functional foods comprising an effective single-ingredient might elicit potent and useful effects, even if the active ingredient with known concentration was from a reliable supply source. Use of sub-effective dose in combination with other complementary ingredient may help to realize documented clinical outcomes via either additional or synergistic effects. Different from drugs, a combination of functional ingredients with defined concentrate for each ingredient and mutually useful combination, at appropriate dosages, with complementary and continuously faithful intake are – all in all – essential for products to yield apparently health-related useful effects over a long-enough intake period of at least 3-6 mo.

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