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

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ANNOUNCEMENT

- The 2019 International Conference on Quality of Life was held at Kyoto Pharmaceutical University from Sept 28-29, 2019. Further information can be found at http://as4qol.org/icqol/2019/
- We have moved to continuous publication. Beginning January 2019 the editing committee has decided to adopt a continuous publishing model for Journal publication. Individual articles will be released online as they become ready, allowing a steady stream of informative quality articles. We will also be moving to a calendar year issue cycle. In traditional terms, each volume will encompass a single year and consist of a single issue. Publishing on a just-in-time basis allows authors to present their results in a timely fashion, and our readers, students, and colleagues to access our content and cite articles more quickly and free from the restrictions of a predefined timetable. As a result of these changes, the look and style, as well as the function, of the Journal will be different, and hopefully improved.
- The 2019 International Meeting on Quality of Life was held recently. Proceedings as well as photos and other information can be found at http://as4qol.org/icqol/

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Full Paper

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Abstract

The present study reaffirmed that single-use of disorder-orientated functional foods may not be effective in resolving certain muscle- and orientation-relevant health problems**.** A male diabetic patient P on a functional food A (a product for blood pressure control) intake for more than 10 yr suffered from certain physical symptoms (PSs) such as forearm Grip-holding (FGH) muscular strength (PS-1), hindlimb joints (HJs) discomfort (PS-2), physical balance or orientation on one-legged standing (PS-3), and urination flow onset-latency and duration of complete emptying (PS-4) as well as poor metabolic indexes such as high levels of total cholesterols (T-Cho), low-density lipoprotein-cholesterols (LDL-C), triglycerides (TG), and HbA1C. When intake of A was complemented with daily product B, intake all PSs improved in a time-dependent manner; with different PS improvements requiring different intake duration: shorter intake duration for PS-1 (3-wk intake and thereafter), and longer intake durations for other PSs (at least more than 3-month intake). Additionally, high levels of T-Cho and relevant indexes were also improved over time with different intake durations, although the blood sugar levels (HbA1c) were unaffected. T-Cho (3-month intake), LDL-C (3-month intake), TG (after 6-month intake) were restored after different intake durations; however, blood sugar levels (HbA1c) were unaffected despite mulberry leaf extract having been documented to reduce blood sugar levels. Improvements of PSs and metabolic indexes were probably due to complementary effects of B whose effects in combination with A improved metabolic activity, nutritional, blood circulation and neurological effects and may have contributed to the favorable outcomes in this study.

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

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1. Background

The Ministry of Health, Labor and Welfare of Japan refers to functional foods as food for specified health uses (FOSHU) as foods containing ingredients with functions for health and officially approved to claim its physiological effects on the human body which FOSHU is intended to be consumed for the maintenance/promotion of health or special health uses by people who wish to control health conditions, including blood pressure or blood cholesterol. (www.mhlw.go.jp). Additionally, According to Zeratsky of the Mayo Clinic,[1] functional foods are foods that have a potentially positive effect on health beyond basic nutrition. Proponents of functional foods say they promote optimal health and help reduce the risk of disease. Numerous publications[2,3,4] of functional foods have demonstrated that these foods are taken as choices for health maintenance and prevention of various diseases in humans. Although some functional foods do not have the claimed effects (due to plant source, extration process, manufcturer, etc.), some may provide preventive effects when taken in proper doses and followed in a faithful intake regimen with appropriate ingredient factors in place.[5,6,7] To ensure consumers benefit from foods with specific actions for health maintenance and promotion, the Japanese government requires assessment for safety of the food and effectiveness of the functions for health, and the claims must be approved by the Ministry of Health, Labor and Welfare (www.mhlw.go.jp).

However, because they are plant-based products, the effects are slow and gradual, and persistent use at the proper dosage and with a faithful regimen is required to produce useful effects, if any.[7] In general, an appropriate intake period of 2-3 weeks or more is required to yield positive signs or significant effects, depending on the product and target-treatment. The purpose of this study was to demonstrate that (I) single-use of disorder-oriented functional foods might not be effective in resolving aging-derived muscle- and orientation-relevant health problems, even though effects documented on the product might seem applicable; and (II) ineffective use of a single-product (A) for certain disorders can be effectively complemented by the use of another product (B).

Because diabetic patient P (male; age: 67) was previously hypertensive (systolic blood pressure (SBP) range/diastolic blood pressure (DBP) range vs 140-165/90-110 mmHg), he has been taking functional food A (a product for blood pressure control) for more than 10 yr; he therefore has maintained normal SBP/DBP range values of 125-128/72-78 mmHg without the use of antihypertensive medication since the time he started taking functional food A. Patient P was not taking any medications other than a prescribed antidiabetic (metformin HCl: Metogluco™ 250) for type-2 diabetes, which he had been taking for more than 10 yr. However, he recently experienced poor physical symptoms (PSs) such as: 1) poor forelimb grip-holding (FGH) strength; 2) joint discomfort/pain of hindlimb on walking, especially when climbing staircases; 3) poor balance/orientation on standing; and 4) deficient urination flow, and 5) unfavorable metabolic indexes registering unwanted levels in: a) total cholesterols (T-CHO); b) low-density lipoprotein cholesterols (LDL-C); c) triglycerides (TG); and d) glycemated hemoglobin (HbA1c). His poor PSs and metabolic indexes did not improve despite taking prescribed medication and consuming A faithfully for more than 6 months. Incidentally, functional food A (3eplus) contained major ingredients such as tocotrienols (3e), decohexanoic acid (DHA), eisosapentaenoic acid (EPA), etc. manufactured by company X).

In other words, (I) we attempted to confirm the effects of exclusive use of functional food A on the aforementioned physical symptoms and metabolic indexes; and (II) further pursued to study the effects of combined intake of product A and B on those PSs and metabolic indexes. Product B contained mulberry leaf extract (0.2%) powder, cyanobacteria extract, and moringa leaf extract manufactured by company Y.

2. Methods

Patient P has been taking functional food A at 3 capsules per day (1 capsule before each meal or 2 hr after each meal) from the year 2010 faithfully, and took the same dosage and followed a faithful regimen for the entire duration of present study, starting from December 21, 2018. Measurements of PS (Table 1) and metabolic (Table 2) indexes were monitored accordingly (see below for details). Product B was initiated on March 22, 2019 [3 months after B intake, or after the last recording of relevant data using A (December 21, 2018), and continued to monitor the relevant readings subsequently at 3-month intervals (i.e. 6 months after initial B intake)].

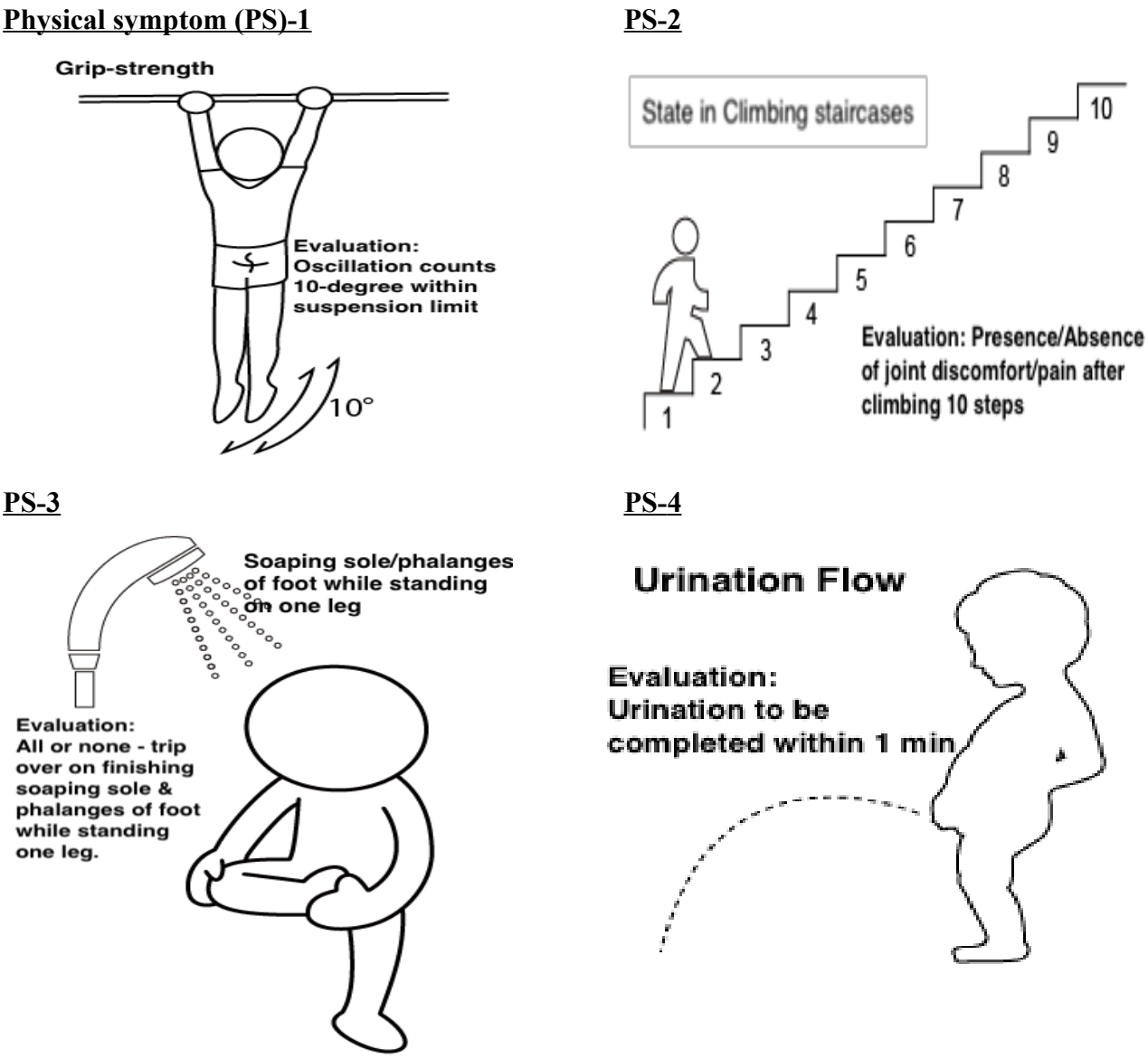

Fig. 1: Physical symptoms (PSs) 1 – 4 were monitored accordingly: PS-1 (forearm grip-holding (FGH) muscular strength on 2 weekend days per week); PS-2 (hindlimb joints (HJs) discomfort (HJ) on 10-step stairs climbing on test-day); PS-3 (balance or orientation on standing on test-day); and PS-4 (Urination flow onset or latency and complete emptying duration or flow time: daily).

2.1 Forearm Grip-holding (FGH) muscular strength: physical symptom (PS)-1 (Fig. 1)

To monitor forelimb muscular strength, we used the FGH strength while hanging on a monkey-bar with ca. 12- to 15-degree oscillations of lower limbs: Patient P registered ca. 9-10 counts for 2 trials in each session before intake (as controls), and this index (or counts) was monitored for only 2 days (i.e. on the weekend) at weeks (wk) 1, 3 and months 3 and 6 after intake. The average value of 2 trials per day for the 2 weekend days was taken for comparisons (Fig. 1).

2.2 Discomfort of hindlimb joints (HJs) on climbing staircases: PS-2 (Fig. 1)

Comfort of HJs was monitored using staircase-climbing. Normally, Patient P uses elevators to go to office (on first floor) daily; however, in this study, he was instructed to climb a 10-step staircase (step 1 starting on the ground floor) to enter office on the test-days (i.e. last day of evaluation). Controls were taken twice at 3-day intervals within the wk before starting daily intake of functional food B until end of study. On ordinary days of no testing, he was asked to use the elevator. Additionally, patient was asked to note down the presence/absence of joint discomfort and/or pain (if any) after climbing the 10-step staircase on test-days. After climbing the 10-step staircase, joint-discomfort rankings of hind-limbs at wk 1 and 3, as well as months 3 and 6 after intake were rated in an all-or-none fashion: 'Yes' when discomfort/pain was felt and 'No' for absence of discomfort/pain. Each test was taken on the last day of indicated time of in-

take: i.e. on day 7 for 1-wk after intake, day 21 on 3-wk after intake, and so on.

2.3 Balance or orientation stability on one-legged standing (PS-3: Fig. 1)

Many Asians commonly soap the soles of their feet standing on one leg while having showers. The time they can keep their balance on one-leg standing decreases with aging or poor physical balancing ability. In PS-3, we had the patient evaluate his balance in the one-leg standing position. The patient was asked at random to measure the duration before falling due to loss of balance of being able to stand on one leg while soaping the sole of their foot in the shower. A non-event would require 9-10 sec (previous personal record) for complete soaping of the sole and phalanges of the foot, thought in the present study - due to aging - the patient always lost balance after 3-4 sec. This index was measured in an all-or-none manner (cut-off time:10 sec), where answers included 'Yes' (falling in <10 sec) or 'No' (standing without falling in >10 sec), on the day tested at wk 1 and 3, and at months 3 and 6 after intake to mark the post-intake outcome (Fig. 1).

2.4 Urination flow onset-latency and duration of complete emptying (PS-4: Fig. 1)

Normal attempts of healthy adults take <10 sec and <1 min to start urination (onset-latency) and completely emptying of the bladder (flow time or duration: from onset to termination of the urination event), respectively. However, in the case of patient P in this study, an onset time of >10 sec and a duration of >1.5 min to completely empty the bladder (probably due to aging) were required. Urination was measured in a poor-or-good (all-or-none) fashion. Patient P was asked to judge each attempt as poor (>10 sec) or good (<10 sec) and poor (>1.0 min) or good (<1.0 min) for urination onset and duration respectively at wk 1 and 3 as well as months 3 and 6 after intake: cut-off times for urination latency and duration were designated as 10 sec and 1.5 min, respectively.

2.5 Metabolic indexes

The following metabolic indexes were measured on patients' scheduled regular visits to the hospital: a) total cholesterols (T-CHO); b) low-density lipoprotein cholesterols (LDL-C); c) triglycerides (TG); and d) glycemated hemoglobin (HbA1c) were measured at 3-month intervals at a regularly visited hospital, starting from December 21, 2018, 3 months (March 22, 2019) and 6 months (June 22, 2019) after intake, accordingly (Table 2). Other blood indexes irrelevant to the study were omitted from our investigation.

3. Results

Note that the level of intake of product A was routinely maintained at 3 capsules daily without resting. The FGH muscular strengths (PS-1) were determined on the 2 weekend days; 2 trials were taken each day, and a total of 4 trials for the 2 days were recorded for comparison. Daily monitoring indexes such as ease of walking and comfort/pain on climbing staircases (PS-2), coordination standing (balancing act) on one leg while showering (PS-3), and urination flow onset-latency and duration were measured (PS-4). Marked

Table 1 Deficient physical symptoms (PS-1 to -4) improved when functional food A was complemented with functional food B.

Before intake	(After intake)	1-week	3-week	3-month	6-month
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' or 'No' 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-on-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)

Table 2: Clinical Examination Report monitored at 3-month intervals

Item	Units (IS*)	Std range (IS*)	12. 21, 2018	3. 22, 2019	6. 21, 2019
SBP/DBP	mmHg	120/80	124/80	127/75	124/70
HbA1c	%	7.0 – 8.0*	8.0	8.1	8.0
T-Cho	mg/dL (mmol/L)	120-220 **(3.08-5.64)**	**H 225 (5.77)**	**201 (5.15)**	**179 (4.59)**
TG	mg/dL (mmol/L)	50-150 **(0.56-1.69)**	**H 251 (2.82)**	**H 306 (3.44)**	**129 (1.45)**
HDL-C	mg/dL (mmol/L)	35-60 **(0.90-1.54)**	**42 (1.08)**	**38 (0.97)**	**39 (1.00)**
LDL-C	mg/dL (mmol/L)	65-139 **(1.67-3.56)**	**H 152 (3.90)**	**131 (3.36)**	**117 (3.00)**

Note: Post-intake of A: Dec 21, 2018 + Intake of B initiated (from Mar 22, 2019)

*SBP/DBP: systolic blood pressure/diastolic blood pressure; HbA1c: glycemated hemoglobin; T-Cho: Total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein-cholesterols; LDL-C: low-density lipoprotein-cholesterols. **Standard range for diabetics considered 'good': 7.0-8.0 (for normal healthy humans: 4.0-5.6) ; H: higher than normal range values.*

improvements were achieved in all indexes tested after 3-months of intake, although PS-1 improved by ca. 50% 3-wk after intake. Three months after intake and thereafter all parameters continued to improve in a time-dependent manner using the same daily dosages. Each PS was pursued as follows:

1) PS-1: The FGH muscular strength of patients P on oscillating on a monkey-bar showed no improvement 1-w after intake; however, counts were improved by ca. 1.5, 2.0 and 3.0 times at 3 wk, 3 months and 6 months after intake respectively (Table 1) in a time-dependent fashion, indicating that daily intake of product B elicited useful effects on FGH muscular strength.

2) PS-2: HJ discomfort of patient P improved in a time-dependent manner similar to PS-1. Although discomfort and pain were felt 1- and 3-wk after intake, the symptoms started to show relief 3 months after intake, and continued to improve up to 6 months after intake.

3) PS-3: As for balance on a one-legged standing during soaping of the foot-sole, physical balance was markedly improved 3 months after intake, and the stable physical balance continued through to 6 months after intake, although 1- and 3-wk regimens were not long enough to improve the physical balance.

4) PS-4: The urination onset-latency and duration values resembled those of PS-2 and PS-3: improvement in the two indexes from poor to good with shorter time-lengths, yielding relief to patients in urination 3 and 6 months after intake of product B.

5) Metabolic indexes (Table 2): Similarly, T-CHO, LDL-C and TG decreased with intake in a time-dependent manner, reaching levels within normal ranges for T-CHO and LDL-C 3 months after intake, while TG was eventually normalized to its normal range 6 months after intake. However, blood sugar levels did not improve, with HBA1C scoring levels ranging 8.0-8.1, indicating intake of products A and B was not beneficial to the diabetic conditions with reference to clinical data, although PSs were improved overall in a time-dependent manner, starting from 3-wk after intake for PS-1, noted 6-wk after intake for PS-2 and PS-3, and observed 3-month after intake and thereafter for PS-4.

4. Discussion

Functional foods or food ingredients with biological activities furnish functional (beneficial) effects to the body systems from the cellular level all the way up to the living system as a whole.[1-7] With aging (Park; time.com: human-brain starts from age 24 yr), humans tend to eat less (in quantity and therefore quality) and body mechanisms slow down to accommodate lower cellular, organic, and systemic deficiencies. As a result, the body system suffers inadequacies and incompetence against hostile and damaging factors from within and outside the body system. Therefore, supplements or functional foods - taken faithfully on a regimened basis - will replenish the lack for nutritional supplies to body functions and living system needs derived from reduced daily food intake, especially in the elderly.

Based on ingredient biological/nutraceutical effects of 3e,[6-8] and DHA/EP[9-12] documented in literature, functional food 3eplus (A) well-maintained the SBP/DBP values well within upper/lower limits of the normal blood pressure range (120/80 mmHg): e.g. 124/80 – 124/70 mmHg registered in patient P. However, single-intake of functional food (A) could not solve all the problems encountered by the diabetic patient (probably due to inadequate optimal intake), despite certain individual ingredients contained in A being re-

ported to provide certain useful effects for PS-1 to PS-4 (Table 1) and metabolic indexes[6-12] (Table 2) monitored in the present study. Therefore, product B was added to attempt to normalize the affected indexes (with consistent intake of product A), and the results showed recovery of most (3-month B intake) and all (6-month B intake) the monitored metabolic indexes (LDL-C, TCho, TG) after complementary intake of product B (Table 2). HDL-C was normal and remained stable since the monitoring was initiated.

In the present case study, the following established outcomes were probably due to the documented biological/nutraceutical activity of the ingredients complementing those of product A: viz., mulberry leaf extract, moringa leaf extract and cyanobacteria biomass. Mulberry (Morus Alba L.) leaf extract has been known to control blood sugar levels,[13-19] suppress inflammatory mediators and oxidative stress,[20,21] protect the pancreatic β-cells,[21] and modulate glucose metabolism in diabetic rats,[13] as well as provide various other useful effects.[13-21] Apart from the many important vitamins, minerals and minerals, the amino acids contained in moringa *oleifera* help muscle-building in the body. Additionally, moringa *oleifera* contains various antioxidants (substances that can protect cells from damage and may boost the immunosystem).[22,23] Furthermore, some of these antioxidants may lower blood pressure and reduce fat in the blood and initiate anti-inflammatory activity in bodily tissues.[24,25] As for the cyanobacteria biomass (spironila *Arthrospira*), a blue-gr een microalgae, it is used as a dietary supplement or whole food[25] and as a feed supplement in the aquaculture and poultry industries.[27]

Each individual natural ingredient offers mild effects, and requires a long period (at least more than 2-3 weeks) for consumers to experience its health benefits, if any. To reassure definite effects are established, a combination of the aforementioned ingredients was used in the present study. The study was attempted in anticipation of additional and/or synergistic effects from various different individual ingredients, where an ingredient which did not elicit effective enough activity on an individual basis would yield significantly useful effects in combination with other ingredients, if taken on a regular regimen or daily basis for a certain period. Moreover, since clinical studies on the combination of aforementioned ingredients have not been endeavored, the present study employed the combined use of mulberry leaf extract, moringa leaf extract, and spirolina to complement product A ingredients as a functional food to elucidate the effects on various symptoms in a case study involving type-2 diabetes. The results revealed that useful effects of a single-product (A) with multiple biologically active ingredients were complemented by the use of another product (B) with ingredients with different nutraceutical effects, implying that there is such thing as a magic bullet in functional food intake for health maintenance and quality-of-life (QoL) promotion. This study would offer first-hand insight into the useful effects of combined use of extract-ingredients on the following symptoms with relevant explanations for beneficial effects achieved:

4.1 Effects on PSs (Table 1)

1) **PS-1:** Intake of B with A improved FGH muscular strength of patient P, indicating B may have improved muscular activity via its rich natural nutritional provision, as product A per se could not attenuate the uncomfortable symptoms and deficient strength felt by patient P. Although mulberry (Morus Alba L.) leaf extract has been known to control blood sugar levels, suppress inflammatory mediators and oxidative stress, protect pancreatic β-cells. and modulate glucose metabolism in rats with diabetes and other health problems,[13--21] the present study did not show any anti-diabetic effect: viz., HbA1c remained unchanged (Table 1). As mulberry leaf extract furnishes an ingredient useful in improving skeletal muscle,[15] moringa leaf extract provides multiple vitamins, minerals and amino acids,[22-25] and cyanobacteria extract (spirolina) is rich in amino acids and minerals[26,27] (i.e. nutritional needs for muscles and muscular activity), PS-1 of the patient improved using the functional food benefits of the ingredients consumed. It is possible that the glycemia-effective ingredients in Mulberry leaf extract were inadequate or the manufacturer source X was not providing an extract with high enough levels of the useful ingredients such as 1-deoxynojirimycin (DNJ)[14,15] and/or fagomine[18] contents and others[13,17] in the extract.[17,19-21]

2) **PS-2:** In addition to nutritional effects described in 1), moringa (in product B) may have provided anti-inflammatory effects[23] useful in attenuating discomfort/pain when muscular exertions/constructions were exerted on hindlimbs,[7,8] and product A may have improved blood circulation to provide combined relief in staircase-climbing.[10-12]

3) **PS-3:** In addition to providing nutritional benefits to muscles (by product B),[22,23] improvement of pe-

ripheral blood microcirculation, brain blood flow and neurological functions by product A[10-12] (which could not be effective enough when used alone) may have contributed to better balance during the act of soaping the sole of the foot by patient P. The compensatory effect of product B in improving PS-3 was clearly demonstrated by the combined use of products A and B.

4) **PS-4:** Urination latency/onset and duration were definitely improved by the complementary action of product B intake[7,10,23], since product A alone showed poor urination indexes (urination onset and urination duration). It is possible that useful effects on the prostrate gland may have contributed to these 2 indexes (the prostrate gland status of patent P was not examined before or after the study).

4.2 Effects on metabolic indexes (Table 2)

1) Exclusive use of product A (3 capsules/day; designed for blood pressure, liver protection, metabolic disorders, etc.) persistently maintained normal healthy blood pressure readings, confirming the effects of 3e[6-8] and DHA/EPA.[9-12]

2) Although documented to be effective for certain metabolic disorders,[6-8] exclusive use and/or dosages of product A consumed were probably inadequate for restoring unhealthy levels of T-Cho, LDL-C, and TG to normal ranges, even though faithful consumption of A persisted for more than 8 yr.

3) Complementary use of product B markedly reduced metabolic disorders to regain normal range-levels: T-Cho and TG levels were normalized after 3-month, while LDL-C levels were improved 6 months after intake. These indicate that B improved certain metabolic activities or functions to directly and indirectly restore the abnormal levels of these indexes.[13-25]

4) Hyperglycemia was unaffected (Table 2).

Although mulberry leaf extract contains DNJ (1-deoxynojirimycin),[14,15] which has been shown to reduce glucose absorption by inhibiting alpha-glycosidases,[13-16] and compounds, such as fagomine, which induce insulin secretion,[19] and antioxidants that putatively reduce lipid peroxidation,[20-22] the HBA1c values showed no effects from the mulberry leaf extract.

Our findings confirmed that product A per se was able to control and maintain normal blood pressure readings; however, patient P still suffered from PS1-4 with abnormal metabolic indexes, demonstrating the ineffectiveness of A on these physical and biochemical data. Combined use of A and B definitely improved the above-mentioned PSs (Table 1), and metabolic indexes such as T-Cho, TG and LDL-C (Table 2) probably via the complementary biological and nutraceutical effects of product B, although HbA1c values did not improve. Product B contains mulberry leaf extract that supposedly would have improved blood sugar readings. The fact that HbA1c values remained unchanged and unfavorable implies that the extract may not contain adequate levels/amounts of the active ingredients responsible for lowering blood sugar. As such, a further study using mulberry leaf extract from another source (where the active ingredient is present in higher concentrations) is warranted to actually elucidate if the active ingredients (DNJ, fagomine) would yield a more favorable result on blood sugar levels.

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