ORIGINAL RESEARCH ARTICLE

Effects of a Multi-Ingredient Longevity Formulation (DoNotAge®) on Subjective Well-Being, Fatigue, and Gastrointestinal Tolerability: A 60-Day Randomised, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

BACKGROUND: Ageing is associated with progressive declines in subjective well-being, energy, and quality of life. Multi-ingredient longevity formulations targeting multiple hallmarks of ageing have gained scientific interest, yet few have been evaluated as finished products in human clinical trials. This study assessed the effects of DoNotAge®, a clinically formulated daily sachet combining 15 bioactive longevity ingredients including three proprietary compounds (SulforaBoost®, SIRT6Activator®, Nitralis®), on patient-reported well-being, fatigue, and gastrointestinal tolerability.

METHODS: A 60-day randomised, double-blind, placebo-controlled trial was conducted in Dubai with 30 participants (15 treatment, 15 placebo). Two placebo-arm participants withdrew, yielding 28 completers (15 treatment, 13 placebo). Primary outcomes were the WHO-5 Well-Being Index and the FACIT-Fatigue Scale, assessed at baseline (Day 0), midpoint (Day 30), and endpoint (Day 60). Secondary outcomes included the Gastrointestinal Symptom Rating Scale (GSRS), willingness to continue, and Patient Global Impression of Change (PGI-C). Between-group differences were evaluated using independent t-tests and Mann–Whitney U tests on change scores.

RESULTS: The treatment group demonstrated a mean WHO-5 percentage score improvement of +36.0 (SD 6.2) versus +9.8 (SD 11.6) in the placebo group (net difference: +26.2; $p < 0.0001$; Cohen's $d = 2.87$). FACIT-Fatigue total scores improved by +4.9 (SD 0.4) in the treatment group versus −0.1 (SD 0.3) in the placebo group (net difference: +4.9; $p < 0.0001$; Cohen's $d = 15.47$). Both primary endpoints exceeded their respective minimally clinically important differences (MCIDs). All GSRS domain scores remained unchanged in both groups, indicating no adverse gastrointestinal

effects. At Day 60, 100% of treatment participants were classified as responders on both primary endpoints, compared with 15% on WHO-5 and 0% on FACIT-Fatigue in the placebo group.

CONCLUSIONS: Daily supplementation with DoNotAge® for 60 days produced statistically significant and clinically meaningful improvements in subjective well-being and fatigue compared with placebo, with no gastrointestinal adverse effects. These findings support further investigation in larger confirmatory trials.

KEYWORDS: longevity; ageing; well-being; fatigue; NMN; resveratrol; sulforaphane; randomised controlled trial; dietary supplement; patient-reported outcomes

1. Introduction

Age-related declines in subjective well-being, energy levels, and overall vitality represent some of the most consistently reported concerns among ageing populations [1]. While the biological mechanisms of ageing are increasingly well characterised—encompassing mitochondrial dysfunction, NAD+ depletion, cellular senescence, epigenetic drift, and chronic low-grade inflammation [2]—translating this understanding into effective interventions that yield measurable improvements in how people *feel* remains a significant challenge.

A growing body of preclinical and early clinical evidence supports the potential of individual bioactive compounds to modulate specific hallmarks of ageing. Nicotinamide mononucleotide (NMN) has demonstrated NAD+ restoration and improvements in metabolic parameters in human trials [3,4]. Trans-resveratrol activates sirtuin pathways associated with cellular repair and longevity [5]. Sulforaphane, a potent activator of the Nrf2 antioxidant response pathway, has shown anti-inflammatory and cytoprotective effects [6]. Spermidine promotes autophagy and has been associated with improved cardiovascular and cognitive health in observational studies [7]. Calcium alpha-ketoglutarate (Ca-AKG) has been linked to reductions in biological age markers [8].

However, the vast majority of these compounds have been studied in isolation. The human body does not age through a single mechanism, and there is growing scientific interest in whether multi-ingredient formulations targeting multiple hallmarks simultaneously may produce synergistic or additive benefits that exceed those of individual compounds [9]. Despite this, very few multi-ingredient longevity formulations have been evaluated as *finished products* in randomised controlled trials—a critical distinction from the common industry practice of citing evidence for individual ingredients in isolation.

DoNotAge® is a daily sachet formulation containing 15 bioactive ingredients, including three proprietary compounds (SulforaBoost®, SIRT6Activator®, Nitralis®), designed to target multiple hallmarks of ageing within a single intervention. The present study represents the first randomised, double-blind, placebo-controlled trial to evaluate the effects of the complete DoNotAge® formulation on patient-reported outcomes in a healthy adult population.

The primary objective was to assess changes in subjective well-being (WHO-5 Well-Being Index) and fatigue (FACIT-Fatigue Scale) over a 60-day intervention period. Secondary objectives included gastrointestinal tolerability (GSRS), willingness to continue treatment, and global impression of change.

2. Materials and Methods

2.1. Study Design

This was a 60-day, single-centre, randomised, double-blind, placebo-controlled, parallel-group trial conducted at a clinical site in Dubai, United Arab Emirates. Participants were randomly allocated in a 1:1 ratio to receive either DoNotAge® or a matched placebo. Assessments were conducted at three timepoints: baseline (Day 0), midpoint (Day 30), and endpoint (Day 60). The trial protocol was designed in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants prior to enrolment. [Ethics committee approval: to be confirmed.]

2.2. Participants

Thirty generally healthy adults were enrolled. Inclusion criteria required participants to be aged 30–65 years and in self-reported good general health. Exclusion criteria included current use of prescription medications for chronic conditions, known gastrointestinal disorders, current supplementation with any of the study ingredients, pregnancy or breastfeeding, and any condition that, in the investigator's judgement, could confound the assessment of patient-reported outcomes.

Two participants in the placebo arm withdrew during the study period, yielding 28 completers (15 treatment, 13 placebo). Per-protocol analysis was conducted on all completers.

2.3. Intervention

Participants in the treatment group received one daily sachet of DoNotAge®, a multi-ingredient longevity formulation. Participants in the placebo group received a

visually and organoleptically matched placebo sachet. Both groups were instructed to take their sachet once daily with water, preferably in the morning.

The complete composition of the DoNotAge® formulation is presented in Table 1.

Table 1. Composition of DoNotAge® daily sachet.

INGREDIENT	DESCRIPTION / FORM
Glycine	*Amino acid*
SIRT6Activator®	*Fucoidan extract (proprietary)*
NMN	*β-Nicotinamide mononucleotide*
TMG	*Betaine anhydrous*
Ca-AKG	*Calcium alpha-ketoglutarate*
Trans-Resveratrol	*Trans-resveratrol*
Nitralis®	*Fermented beetroot, magnesium ascorbate, epimedium extract (proprietary)*
Quercetin	*Flavonoid*
Vitamin D3	*Vegan cholecalciferol*
Vitamin K2	*Menaquinone-7 (MK-7)*
Magnesium	*Magnesium bisglycinate*
SulforaBoost®	*Glucoraphanin from broccoli sprouts with myrosinase (proprietary)*
High Molecular Weight Hyaluronic Acid	*Oral hyaluronic acid*
CoQ10	*Ubiquinol form*
Spermidine	*Polyamine*

Three proprietary compounds developed by DoNotAge.org are indicated. Exact doses per sachet are proprietary.

2.4. Outcome Measures

Primary outcomes. The WHO-5 Well-Being Index [10] was used to assess subjective psychological well-being. The WHO-5 comprises five positively worded items rated on a 6-point Likert scale (0–5), yielding a raw score of 0–25, converted to a percentage score (0–100) by multiplying by 4. Higher scores indicate greater well-being. A percentage score change of ≥10 points is considered the minimally clinically important difference (MCID) [11]. Recall period: past two weeks.

The Functional Assessment of Chronic Illness Therapy—Fatigue Scale (FACIT-Fatigue, Version 4) [12] was used to assess fatigue. The FACIT-Fatigue comprises 13 items rated on a 5-point Likert scale (0–4), with two items reverse-scored (items 7

and 8). Total scores range from 0 to 52, with higher scores indicating less fatigue. The established MCID is 3–4 points [13]. Recall period: past seven days.

Secondary outcomes. The Gastrointestinal Symptom Rating Scale (GSRS) [14] was used to assess GI tolerability. The GSRS comprises 15 items rated on a 7-point Likert scale (1–7), yielding five domain scores (abdominal pain, reflux, indigestion, diarrhoea, constipation) calculated as means, plus a standalone nausea item. Lower scores indicate fewer symptoms. Recall period: past one week.

Two additional endpoint questions were administered at Day 60 only: (1) willingness to continue ("Would you continue taking this product if given the opportunity?"; 5-point scale from "Definitely not" to "Definitely yes") and (2) a Patient Global Impression of Change (PGI-C) item ("Compared to when you started this trial, how would you rate your overall health and well-being?"; 5-point scale from "Much worse" to "Much better").

2.5. Statistical Analysis

Between-group comparisons were conducted on change scores (Day 60 minus Day 0) using independent-samples *t*-tests. Mann–Whitney *U* tests were used as non-parametric confirmatory analyses. Effect sizes were calculated as Cohen's *d*. Baseline balance was assessed using independent *t*-tests. Responder analyses used MCID thresholds: ≥10 percentage points for WHO-5 and ≥4 points for FACIT-Fatigue. Statistical significance was set at $p < 0.05$ (two-tailed). All analyses were conducted per protocol on the completer population.

3. Results

3.1. Participant Flow and Baseline Characteristics

Of 30 enrolled participants, 28 completed the trial (15 treatment, 13 placebo). Two placebo-arm participants withdrew prior to Day 60.

Baseline characteristics were well balanced between groups for the primary endpoints. WHO-5 percentage scores were 34.4 (SD 4.5) in the treatment group and 33.8 (SD 3.9) in the placebo group ($p = 0.73$). FACIT-Fatigue total scores were 26.0 (SD 1.3) and 26.0 (SD 1.2), respectively ($p = 1.00$). Minor baseline imbalances were observed in three GSRS domains (reflux, diarrhoea, constipation; $p < 0.05$), though these did not affect the primary analyses.

3.2. Primary Outcomes

Results for the primary endpoints are summarised in Table 2 and Table 3.

Table 2. WHO-5 Well-Being Index percentage scores by group and visit.

TIMEPOINT	TREATMENT (N = 15) MEAN (SD)	PLACEBO (N = 13) MEAN (SD)	BETWEEN-GROUP DIFFERENCE
Day 0 (Baseline)	34.4 (4.5)	33.8 (3.9)	+0.6
Day 30 (Midpoint)	53.3 (6.7)	42.2 (2.1)	+11.2
Day 60 (Endpoint)	70.4 (7.1)	43.7 (11.7)	**+26.7**
Change (Day 0 → 60)	**+36.0 (6.2)**	+9.8 (11.6)	**+26.2 *****

**** p < 0.0001 (independent t-test on change scores). Mann–Whitney U p = 0.0002. Cohen's d = 2.87 (large effect). MCID = 10 percentage points; treatment change exceeds MCID.*

The treatment group demonstrated a progressive increase in WHO-5 percentage scores from 34.4 at baseline to 53.3 at Day 30 and 70.4 at Day 60, representing a mean improvement of +36.0 points (SD 6.2). The placebo group showed a mean increase of +9.8 points (SD 11.6), though this was driven largely by substantial variability including one outlier participant who showed an atypically large placebo response. The between-group difference in change scores was +26.2 ($p < 0.0001$; Cohen's $d = 2.87$). The Mann–Whitney U test confirmed this finding ($p = 0.0002$).

Table 3. FACIT-Fatigue total scores by group and visit.

TIMEPOINT	TREATMENT (N = 15) MEAN (SD)	PLACEBO (N = 13) MEAN (SD)	BETWEEN-GROUP DIFFERENCE
Day 0 (Baseline)	26.0 (1.3)	26.0 (1.2)	0.0
Day 30 (Midpoint)	28.1 (1.4)	26.9 (1.1)	+1.2
Day 60 (Endpoint)	30.9 (1.3)	25.9 (1.1)	**+4.9**
Change (Day 0 → 60)	**+4.9 (0.4)**	−0.1 (0.3)	**+4.9 *****

**** p < 0.0001 (independent t-test on change scores). Cohen's d = 15.47 (large effect). MCID = 3–4 points; treatment change exceeds MCID. Higher scores indicate less fatigue.*

FACIT-Fatigue total scores increased by +4.9 points (SD 0.4) in the treatment group, indicating reduced fatigue, compared with a change of −0.1 (SD 0.3) in the placebo group. The between-group difference was +4.9 ($p < 0.0001$; Cohen's $d = 15.47$). This improvement exceeded the MCID of 3–4 points.

3.3. Responder Analysis

Using pre-specified MCID thresholds, 100% (15/15) of treatment-group participants were classified as WHO-5 responders (change ≥10 percentage points), compared with 15% (2/13) in the placebo group. For FACIT-Fatigue (change ≥4 points), 100%

(15/15) of treatment participants met the responder threshold, compared with 0% (0/13) in the placebo group.

3.4. Gastrointestinal Tolerability

GSRS domain scores are presented in Table 4. No clinically meaningful changes were observed in any GSRS domain in either group over the 60-day study period. All domain score changes were 0.0 in both arms, indicating that DoNotAge® was well tolerated with no adverse gastrointestinal effects.

Table 4. GSRS domain scores at baseline and Day 60.

DOMAIN	TX BASELINE	TX DAY 60	TX Δ	PL BASELINE	PL DAY 60	PL Δ
Abdominal Pain	2.8	2.8	0.0	2.9	2.9	0.0
Reflux	2.4	2.4	0.0	2.7	2.7	0.0
Indigestion	3.1	3.1	0.0	3.2	3.2	0.0
Diarrhoea	2.6	2.6	0.0	2.8	2.8	0.0
Constipation	2.4	2.4	0.0	2.7	2.7	0.0
Nausea	2.4	2.4	0.0	2.5	2.5	0.0

Tx = Treatment; Pl = Placebo; Δ = change from baseline. Scale: 1 (no discomfort) to 7 (very severe). All between-group differences non-significant.

3.5. Endpoint Assessments

At Day 60, treatment-group participants reported a mean willingness-to-continue score of 4.5 (SD 0.5) compared with 2.8 (SD 0.8) in the placebo group ($p < 0.0001$; Cohen's $d = 2.55$). In the treatment group, 53% selected "Definitely yes" and 47% selected "Probably yes"; no treatment participant expressed unwillingness to continue. In the placebo group, the modal response was "Not sure" (62%).

PGI-C scores were 4.5 (SD 0.6) in the treatment group versus 2.9 (SD 1.0) in the placebo group ($p < 0.0001$; Cohen's $d = 1.93$). In the treatment group, 53% reported feeling "Much better" and 40% reported "Somewhat better". In the placebo group, 62% reported "About the same".

Table 5. Endpoint questions at Day 60.

MEASURE	TREATMENT (N = 15) MEAN (SD)	PLACEBO (N = 13) MEAN (SD)	*P*-VALUE	COHEN'S *D*
Willingness to Continue	**4.5 (0.5)**	2.8 (0.8)	**< 0.0001**	2.55
Global Impression of Change	**4.5 (0.6)**	2.9 (1.0)	**< 0.0001**	1.93

Willingness to Continue: 1 = Definitely not, 5 = Definitely yes. Global Impression of Change: 1 = Much worse, 5 = Much better.

4. Discussion

This randomised, double-blind, placebo-controlled trial demonstrates that 60 days of daily supplementation with DoNotAge® produced statistically significant and clinically meaningful improvements in subjective well-being and fatigue compared with placebo, with no adverse gastrointestinal effects.

The WHO-5 findings are particularly notable. The treatment group's mean score improved from 34.4% at baseline—a level suggestive of low mood warranting further assessment [11]—to 70.4% at Day 60, representing a shift into the "good well-being" range. The between-group difference of +26.2 percentage points substantially exceeded the MCID of 10 points, with a large effect size (Cohen's d = 2.87). Importantly, the improvement was progressive, with gains observed at both Day 30 and Day 60, suggesting a sustained rather than transient effect. The placebo group showed a modest mean increase of +9.8 points, though this was characterised by high variability (SD 11.6) driven by one atypical responder; the majority of placebo participants showed minimal change.

FACIT-Fatigue scores showed a similar pattern, with a treatment-group improvement of +4.9 points exceeding the MCID of 3–4 points. This is clinically relevant: the FACIT-Fatigue scale was originally developed and validated in chronic illness populations [12], and the observed improvement indicates a meaningful reduction in daily fatigue burden.

The 100% responder rate in the treatment group on both primary endpoints is striking. On the WHO-5, 15% of placebo participants (2/13) also crossed the MCID threshold, while no placebo participant met the FACIT-Fatigue threshold. The clear separation between treatment and placebo responder rates reinforces the consistency of the treatment effect. The endpoint assessments corroborate these findings: treatment participants overwhelmingly expressed willingness to continue (100% "Probably yes" or "Definitely yes") and perceived meaningful health improvements (93% "Somewhat better" or "Much better").

The null GSRS result is informative from two perspectives. First, it provides reassurance that the multi-ingredient formulation does not produce gastrointestinal adverse effects—a common concern with complex supplements containing multiple bioactive compounds at meaningful doses. Second, it indicates that the product's primary mechanism of benefit likely operates through systemic pathways (e.g., NAD+

restoration, sirtuin activation, mitochondrial support, antioxidant response) rather than through direct gut modulation.

The biological plausibility of the observed effects is supported by the formulation's composition. NMN restores NAD+ levels, which decline with age and are critical for cellular energy metabolism [3]. Trans-resveratrol and SIRT6Activator® activate sirtuin pathways involved in DNA repair, inflammation regulation, and metabolic homeostasis [5,15]. SulforaBoost® provides glucoraphanin with myrosinase for endogenous sulforaphane production, activating the Nrf2 cytoprotective pathway [6]. Spermidine promotes autophagy, the cellular recycling process that declines with age [7]. Ca-AKG, glycine, TMG, and CoQ10 support methylation, mitochondrial function, and cellular energy production. Nitralis® provides nitric oxide support through fermented beetroot combined with magnesium ascorbate and epimedium extract. The synergistic potential of these compounds acting on multiple ageing pathways simultaneously may account for the magnitude of the observed effects.

Limitations

Several limitations should be considered. First, the sample size (n = 28 completers) is small, and the results should be interpreted as hypothesis-generating. A larger confirmatory trial with greater statistical power is warranted. Second, the 15:13 imbalance resulting from two placebo-arm dropouts, while minor, should be noted. Third, minor baseline imbalances in three GSRS domains (reflux, diarrhoea, constipation) were observed, though these did not affect the primary endpoints. Fourth, the 60-day duration, while adequate for detecting subjective changes, does not address longer-term effects or durability of response. Fifth, all outcomes were patient-reported; future trials should incorporate objective biomarkers of ageing and health. Finally, exact ingredient doses are proprietary, which limits full reproducibility.

5. Conclusions

Daily supplementation with DoNotAge® for 60 days significantly improved subjective well-being and reduced fatigue compared with placebo in a randomised, double-blind trial. Both primary endpoints exceeded their respective minimally clinically important differences, with 100% of treatment participants classified as responders. The formulation was well tolerated with no gastrointestinal adverse effects. Treatment participants overwhelmingly reported willingness to continue and perceived meaningful improvements in their overall health.

These findings provide the first clinical evidence for DoNotAge® as a complete formulation and support its further evaluation in larger, longer-duration trials incorporating objective biomarkers of ageing.

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