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The enhancing effects of Biobran/MGN-3, an arabinoxylan rice bran, on healthy old adults' health-related quality of life: a randomized, double-blind, placebo-controlled clinical trial

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Abstract

Purpose The world's older population is growing rapidly and the need to find measures to combat age-associated decline of physical, mental, and cognitive functions and improve their health-related quality of life (HRQOL) is escalating. Biobran/MGN-3, an arabinoxylan rice bran, has been previously reported to improve the quality of life in cancer patients. The objective of the current study was to examine the effect of a low dose of Biobran/MGN-3 supplementation on the HRQOL in a healthy older adult population.

Methods Sixty apparently healthy subjects, 40 males and 20 females, over 56 years old were recruited and blindly randomized into two group receiving either placebo or Biobran/MGN-3 (250 mg/day for 3 months). Participants did not take any vitamins or medications during the study and their health was closely monitored. HRQOL was assessed at the initiation and termination of the study using the previously validated Arabic version of SF-12v2 questionnaire.

Results For all measured HRQOL domains, there was no statistically significant difference in baseline scores between the two groups. Compared to baseline values and placebo-treated subjects, Biobran/MGN-3 supplementation significantly enhanced the levels of physical and mental component summary scores as well as role-physical, bodily pain, vitality, and social functioning subdomain scores.

Conclusion These results show that Biobran/MGN-3 is a promising psychoneuroimmune modulatory agent that could improve the HRQOL in healthy old adults.

Keywords Biobran/MGN-3 · Older adults · Health-related quality of life · Social behavior · Cognitive activity

Abbreviations

HRQOL	Health-related Quality of Life
PCS	Physical Component Summary
MCS	Mental Component Summary
PF	Physical Functioning
RP	Role-Physical
RE	Role Emotion
BP	Bodily Pain
MH	Mental Health
VT	Vitality
SF	Social Functioning
WHO	World Health Organization
QOL	Quality of Life
GH	General Health
PA	Physical Activity

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Introduction

Population aging is rapidly emerging as a major public health challenge with projected serious implications in almost all life aspects including social, labor, financial, and health care and all civil services [1]. The global population aged more than 60 years reached 962 million in 2017, which was more than twice as large as the number in 1980 [2]. This number is expected to double again by 2050 to reach nearly 2.1 billion [2]. Defining old age is a complicated process that depends not only on chronological age but also on the cultural norms by which each society makes sense of old age. While the United Nations generally use 60 years to define older population [3], most developed countries use a chronological age of 65 years to define old age. In African nations, the World Health Organization (WHO) suggests a cut-off chronological age somewhere between 50 and 55 years to define old age [3]. Aging is typically associated with significant increase in the risk of developing chronic diseases and often results in decline of health-related quality of life (HRQOL), which involves physical, mental and psychological health [4]. Developing interventions that foster healthy aging and counteract age-related decline of HRQOL was at the frontier of medical research recommended by the WHO comprehensive action plan to meet the population aging challenge [1].

HRQOL is a broad concept that encompasses the concepts of both health and quality of life (QOL), which by definition are very broad concepts. Health was defined by the WHO as a state of complete physical, mental, and social health and not merely absence of disease or infirmity [5]. The WHO defines the QOL as the "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [6]. The integration of the concepts of health and QOL is reflected in the HRQOL definition, which assesses how well a person functions in his/her life and his/her perceived well-being in physical, mental, and social domains of health [7]. HRQOL is being increasingly used as a health outcome. It has been used to evaluate the impact of illness, treatment intervention, clinical trial intervention, and provided health services [8, 9].

Several instruments have been developed to evaluate HRQOL. One of the most investigated instruments is the 12-item short form health survey version 2 (SF-12v2) (Quality Metric Inc., Lincoln, RI, USA). SF-12v2 is a multipurpose generic questionnaire that was developed in the United States from the first version SF-12v1. The short versions were developed as short substitutes to the 36-item SF36. The SF-12v2 was demonstrated to provide a valid and reliable assessment that was comparable to that of SF36 while having the advantage of being easier and quicker to complete [10, 11]. Therefore, SF-12v2 has been used by several health care delivery organizations such as the National Commission on Quality Assurance (NCQA) and Pacific Business Group to conduct the annual member health care survey and to monitor treatment outcomes, respectively [12]. In addition, the SF-12v2 became the instrument of choice for use in population health surveys and large scale clinical studies. The instrument has been validated for several chronic diseases and conditions as well as in the general population of various ethnic groups [10, 13–16].

The SF-12v2 assesses the subject's rating of eight HRQOL domains encompassing physical functioning (PF), role-physical (RP, limitations due to physical functioning), bodily pain (BP), general health (GH) perceptions, vitality (VT), social functioning (SF), role emotion (RE, role limitations due to emotional problems), and mental health (MH). In addition, two summary scores, physical component summary (PCS) and mental component summary (MCS) scale scores, could be derived from the eight domain scores [10, 17]. The PCS and MCS are computed using principle component analysis (PCA). Weighting coefficients gained by PCA have been gathered for data from the US general population [17]. These weighting coefficients have been suggested to be applied for different countries and ethnic groups to facilitate comparison across different studies [17]. This approach offers a great advantage when applied in countries where no large scale normative data are available. Several studies have demonstrated that SF-12v2 summary scores do not necessarily reflect individual SF-12v2 domain scores. Therefore, it is also important that all SF-12v2 domain scores be reported and interpreted alongside the summary scores [18].

Psychoneuroimmunology research provides solid evidence for the reciprocal interaction between the immune system and psychosocial and cognitive functions in humans [19–21]. Chronic psychosocial stress, depression, and aging were found to exhibit abnormal pro-inflammatory cytokine levels, decreased lymphocyte proliferation and reactivity, decreased natural killer cell activity, and decreased cell mediated immunity [22, 23]. Conversely, therapeutic modulation of immune functions was reported to impact physiological, psychosocial, and cognitive functions [24, 25]. For example, reducing pro-inflammatory cytokines could relieve mode disorders and depressive symptoms of treatment-resistant depression [25, 26].

Biobran/MGN-3, a rice bran-derived nutritional supplement, has previously been proven to be a potent immunomodulatory agent with compelling anticancer activity in both animal models and cancer patients [27, 28]. Biobran/MGN-3 has also been shown to improve HRQOL in cancer

patients [29–31]. Immune enhancement could be the underlying mechanism of both Biobran/MGN-3's anticancer effect and its ability to improve HRQOL in cancer patients. In the current study we hypothesize that Biobran/MGN-3, by virtue of its known potent immune enhancement effect, could induce psychoneuroimmuno-modulatory effects that could be detected and measured via HRQOL scores in old adults.

Subjects and methods

Biobran/MGN-3

Biobran/MGN-3 is a denatured hemicellulose that is obtained by reacting rice bran hemicellulose with multiple carbohydrate hydrolyzing enzymes from Shiitake mushrooms. It is an arabinoxylan with a xylose in its main chain and an arabinose polymer in its side chain [32]. Subjects were treated with Biobran/MGN-3 at a dose of 250 mg/day aliquoted in sachets that were taken orally with meals for 3 months. Biobran/MGN-3 was provided by Daiwa Pharmaceutical Co. Ltd., Tokyo, Japan.

Study design

Sixty apparently healthy older adults subjects (≥ 56 years old) of both sexes (40 males and 20 females) were recruited from local residents visiting outpatient clinics at Zagazig University Hospital, Zagazig, Egypt, using a systematic random sampling technique (random selection of first person, followed by selection of every fourth person). Age ≥ 56 years was used because the WHO suggests a cut-off chronological age somewhere between 50 and 55 years to define old age in African nations [3]. Males and females were randomly assigned to either the Biobran/MGN-3 group ($n = 30$, 20 males and 10 females, 250 mg/day orally for 3 months) or the placebo control group ($n = 30$, 20 males and 10 females, 250 mg/day orally for 3 months). Blinding was ensured at all study levels, including during the randomization process, study participants' and physician's involvement, and statistical analysis. Informed consents were obtained from willing participants after explaining the study purpose and design. During the study, the enrolled subjects were instructed not to take any over the counter drugs including vitamins without consulting the study principle investigator. Each participant was asked to report the occurrence of any adverse effects. When reported, clinical verification of the condition was made via a thorough clinical examination with consultation of a specialist if needed. After verification of the condition, a decision was made to either interrupt Biobran/MGN-3 supplementation or continue with the necessary therapy at home without interruption of Biobran/MGN-3 supplementation. Follow-up was continued until the condition was completely alleviated or further treatment was offered. Assessment of the participants' HRQOL was made at the initiation and termination of the study (3 months post intervention) using the previously validated Arabic version of the SF-12v2 survey (www.optum.com).

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by Institutional Review Board (IRB approval no. 1507, June 2018), Zagazig University Hospital, Faculty of Medicine.

Inclusion criteria

Subjects 56 years or older who were willing to provide written consent to participate voluntarily in the study were included in the study.

Exclusion criteria

We excluded subjects with current or a history of infections or malignancies, autoimmune disorders, marked portal hypertension and pancytopenia, or major psychological insult. We also excluded those who were using antiviral therapy, vitamin or antibiotic supplements, and patients receiving other antiviral or anticancer therapies (radiation, chemotherapy).

Instrument and score calculation

The validated Arabic version of the health-related quality of life SF-12v2 health questionnaire was used. The questionnaire yields two summary scores (physical and mental component) and eight health-related domain scores (GH, PF, RP, RE, BP, MH, VT, and SF). The scores were calculated as described by the developer [10]. Briefly, after data entry, any out of range scores that were erroneously entered either as lower than or higher than the minimum or maximum pre-coded values, respectively, were recoded as missing. The scores of general health (Q1), bodily pain (Q5), vitality (Q6b), and mental calmness/peacefulness (Q6a) were reverse-coded so that higher scores reflected better health status (Labels starting with Q refer to specific question numbers and parts on the SF-12v2 questionnaire). The general health code, from excellent to poor, was recalibrated to values of 5.0, 4.4, 3.4, 2.0, and 1.0, which has been reported to achieve a better linear fit to the underlying measured health response. The eight health domain components were constructed as follows: GH = Q1, PF = Q2a + Q2b, RP = Q3a + Q3b, RE = Q4a + Q4b, BP = Q5, MH = Q6a + Q6c, VT = Q6b, and SF = Q7. Raw scores of each health domain were computed by algebraic summation of item scores in the same domain and then transformed to the 0–100 scale using the following equation: transformed score = ((actual raw

score − lowest possible raw score)/(possible raw score range) × 100). The normalized-based score (*Z*-score) of each health component domain was obtained using the mean and standard deviation (SD) of the U.S. health population. This approach could be applied for different countries and was recommended to facilitate comparison of different health score domains and cross-cultural comparisons of results [33]. The aggregate physical (AGGPHYS) and mental (AGGMENT) summary scores were calculated using linear addition of the eight health component Z-scores after being multiplied by their respective coefficient factor derived from principle component analysis with orthogonal rotation of the 1990 general U.S. population data as follows: AGGPHYS = (PF *Z*-score × 0.42402) + (RP *Z*-score × 0.35119) + (BP *Z*-score × 0.31754) + (GH *Z*-score × 0.24954) + (VT *Z*-score × 0.02877) + (SF *Z*-score × − 0.00753) + (RE *Z*-score × − 0.19206) + (MH *Z*-score × − 0.22069); and AGGMENT = (PF *Z*-score × − 0.22999) + (RP *Z*-score × − 0.12329) + (BP *Z*-score × − 0.09731) + (GH *Z*-score × − 0.01571) + (VT *Z*-score × 0.23534) + (SF *Z*-score × 0.26876) + (RE *Z*-score × 0.43407) + (MH *Z*-score × 0.48581). Finally, the normalized-based T-scores of physical and mental component scores together with the eight health domain *Z*-scores were obtained by subjecting them to a linear transformation operation consisting of multiplication by ten followed by addition of 50, which had achieved a mean of 50 and SD of 10 in the 1998 U.S. general population.

Statistical analysis

Continuous variables were expressed as mean ± SD and categorical variables were presented as number and percent. Two-tailed student *t*-test for continuous variables that were normally distributed or Fisher exact test for categorical sparse data were used to compare the intervention and the placebo groups, whereas two-tailed paired t-test was used to examine the effect of treatment intervention within a group (i.e., compare post-treatment level with the pre-treatment level) for each group. For non-normally distributed data, we used non-parametric Wilcoxon-Signed Rank test for paired data to examine the effect of treatment within groups. We used non-parametric analysis of covariance (RANCOVA) in order to compare the 3 months post-treatment HRQOL domain scores between the Biobran/MGN-3 and placebo groups. In order to adjust for differences in the baseline score levels, the baseline values were used as covariate. p values < 0.05 were considered statistically significant. To produce graphs, the mean ± SD was used. SPSS version 22 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA) were used for statistical analysis.

Sample size

A power analysis using an effect size of 0.4 for a repeated measure analysis of variance with two measurements in two groups, taking into consideration the possibility of within (between two time points) and between (Biobran/MGN-3 and time) interactions, was performed using G*Power software package (Version 3.1.9.2; Franz Faul, Germany). The effect size of 0.4 was chosen based on our hypothesized positive correlation between Biobran/MGN-3-induced immune enhancement and improvement of HRQOL. An effect size of 0.4 was related to, but considerably lower than, 0.8, which we previously found suitable to detect the immunomodulatory effect of Biobran/MGN-3 [34]. With the criterion of significance (α) set at 0.05, a sample size of 30 subjects per group (total of 60 subjects) results in a power of more than 0.95 to yield statistically significant results.

Results

Results of this study summarize the HRQOL changes among older adults post-exposure to Biobran/MGN-3 at 250 mg/day for 3 months. Results were compared with the baseline values as well as with a placebo group.

HRQOL domain scores were not different between the groups at the initiation of the study

Table 1 shows the median and quartile baseline parameter values for the two groups in the study. There was no measurable statistically significant difference in baseline values between subjects in the placebo- versus Biobran/MGN-3-treated group.

Placebo supplementation did not induce any change in HRQOL scores

The effects of placebo supplementation for 3 months on different parameters of HRQOL are shown in Table 2 and Fig. 1. Placebo supplementation did not change any of the HRQOL parameters under investigation as compared to baseline values.

Biobran/MGN-3 supplementation enhanced HRQOL domain scores

The effects of Biobran/MGN-3 supplementation for 3 months on HRQOL domains are shown in Table 3 and Fig. 2. With the exceptions of physical functioning and

Table 1 Comparison of the initial HRQOL domain scores for Biobran/MGN-3 and placebo groups

HRQOL domain[a]	Placebo[b]	Biobran/MGN-3[b]	*p* Value[c]
Physical component summary	48.3 (38.7–52.8)	44.7 (40.0–48.0)	0.487
Mental component summary	40.2 (32.4–47.3)	40.3 (29.8–52.1)	1.000
Physical functioning	47.9 (47.9–56.5)	47.9 (39.3–47.9)	0.404
Role-physical	43.4 (29.5–52.6)	38.7 (34.1–48.0)	0.659
Bodily pain	47.3 (37.1–47.3)	37.1 (37.1–47.3)	0.489
General health	44.7 (29.6–44.7)	44.7 (29.7–44.7)	0.651
Vitality score	47.7 (37.7–57.8)	47.7 (27.6–57.8)	0.777
Social functioning	36.4 (26.3–46.5)	41.4 (26.3–56.6)	0.404
Role-emotional	39.3 (33.7–44.9)	33.7 (28.1–44.9)	0.289
Mental health	43.2 (34.1–52.3)	46.3 (34.1–52.3)	0.994

[a]Both baseline and termination data or one of them were not-normally distributed as suggested by Shapiro–Wilk and Kolmogorov–Smirnov tests

[b]Median value (lower quartile–upper quartile)

[c]Determined with Mann–Whitney test

Table 2 Placebo supplementation (250 mg/day) for 3 months did not affect any of the SF-12v2 HRQOL domains

HRQOL domain[a]	Baseline[b]	Placebo supplementation[b]	*p* Value[c]
Physical component summary	48.3 (38.7–52.8)	44.0 (38.9–50.8)	.441
Mental component summary	40.2 (32.4–47.3)	39.6 (32.7–49.8)	.813
Physical functioning	47.9 (47.9–56.5)	47.9 (47.9–56.5)	.857
Role-physical	43.4 (29.5–52.6)	38.7 (29.5–48.0)	.539
Bodily pain	47.3 (37.1–47.3)	37.1 (26.9–47.3)	.134
General health	44.7 (29.6–44.7)	44.7 (29.6–44.7)	.97
Vitality score	47.7 (37.7–57.8)	37.7 (37.7–47.7)	.345
Social functioning	36.4 (26.3–46.5)	36.4 (26.3–36.4)	.38
Role-emotional	39.3 (33.7–44.9)	39.3 (33.7–44.9)	.969
Mental health	43.2 (34.1–52.3)	40.2 (34.1–52.3)	.818

[a]Either both of the baseline and termination data or one of them were not-normally distributed as determined by Shapiro–Wilk and Kolmogorov–Smirnov tests

[b]Median (lower quartile–upper quartile)

[c]Determined with Wilcoxon-signed rank test

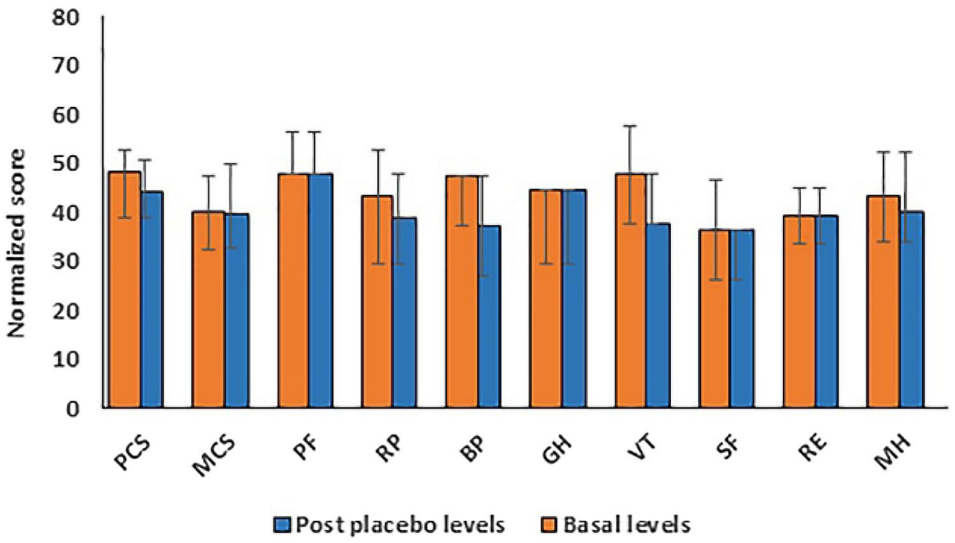

Fig. 1 Effect of placebo on older adults HRQOL domains assessed by SF-12v2. Placebo supplementation (250 mg/day, 3 months) did not improve any HRQOL domains ($N = 30$). The bars and error bars represent medians and inter-quartile ranges, respectively. PCS—physical component summary, MCS—mental component summary, PF—physical functioning, RP—role-physical, BP—bodily pain, GH—general health, VT—vitality, SF—social functioning, RE—role emotion, MH—mental health

Table 3 Biobran/MGN-3 supplementation (250 mg/day) for 3 months significantly improved most of SF-12v2 older adults HRQOL domains

HRQOL domain[a]	Baseline[b]	Biobran/MGN-3 supplementation[b]	*p* Value[c]
Physical component summary	44.7 (40.0–48.0)	49.21 (38.5–57.7)	.047*
Mental component summary	40.3 (29.8–52.1)	46.6 (43.6–52.1)	.003*
Physical functioning	47.9 (39.3–47.9)	47.9 (39.3–56.5)	.660
Role-physical	38.7 (34.1–48.0)	48.0 (38.7–57.2)	.002*
Bodily pain	37.1 (37.1–47.3)	47.3 (37.1–57.4)	.006*
General health	44.7 (29.7–44.7)	44.7 (29.6–55.5)	.083
Vitality score	47.7 (27.6–57.8)	57.8 (47.7–57.8)	.001*
Social functioning	41.4 (26.3–56.6)	46.5 (36.4–56.6)	.012*
Role-emotional	33.7 (28.1–44.9)	42.1 (39.3–44.9)	.003*
Mental health	46.3 (34.1–52.3)	52.3 (40.2–52.3)	.002*

*Significant at $p \leq 0.05$

[a]Both baseline and termination data or one of them were non-normally distributed as suggested by Shapiro–Wilk and Kolmogorov–Smirnov tests

[b]Median values (lower quartile–upper quartile)

[c]Determined with Wilcoxon-signed rank test

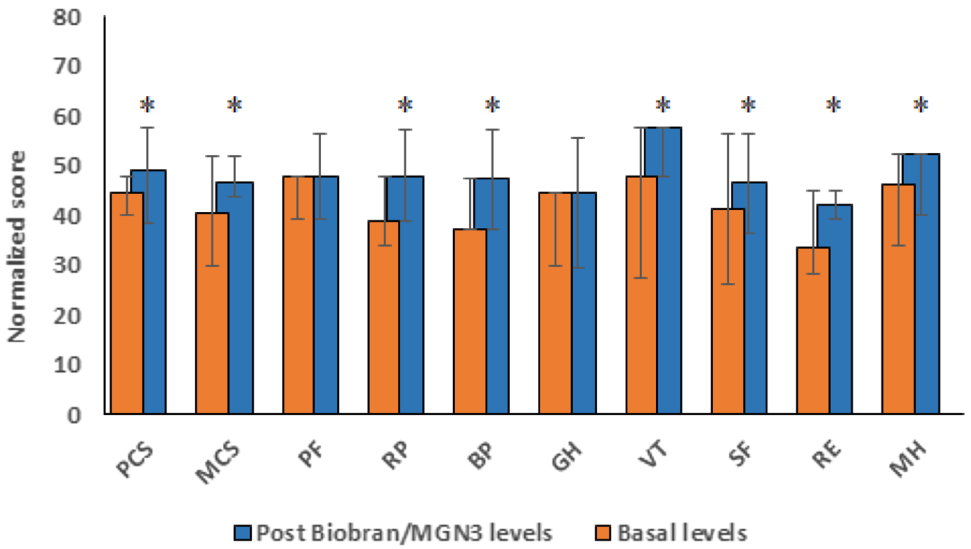

Fig. 2 Effect of Biobran/MGN-3 on older adults HRQOL domains assessed by SF-12v2. Biobran/MGN-3 supplementation (250 mg/day, 3 months) has significantly improved many HRQOL domains ($N = 30$). The bars and error bars represent medians and inter-quartile ranges, respectively. PCS—Physical component summary, MCS—Mental component summary, PF—physical functioning, RP—role-physical, BP—bodily pain, GH—general health, VT—vitality, SF—social functioning, RE—role emotion, MH—mental health. *Significantly different from baseline value of Biobran/MGN-3 treated group at $p < 0.05$ levels

general health domains, older adults who received Biobran/MGN-3 showed significant improvement across HRQOL domains as compared to baseline values ($p < 0.05$).

Comparison of Placebo with Biobran/MGN-3

The difference in HRQOL domains 3 months post treatment for subjects receiving placebo versus Biobran/MGN-3 are illustrated in Table 4. Results showed statistically significant differences in post-treatment HRQOL domain scores for 6 out of 10 parameters ($p < 0.05$). The noticeable improvements gained by subjects supplemented with Biobran/MGN-3 included physical component summary and role-physical, mental health, bodily pain, social functioning, and vitality scores. Our results indicate that Biobran/MGN-3 supplementation for 3 months significantly improved these parameters of healthy older adults as compared to the placebo group at 3 months.

Table 4 Comparison of HRQOL domain scores after supplementation of Biobran/MGN-3 and placebo groups using non-parametric ranked analysis of covariance (RANCOVA)

HRQOL domain[a]	Post Placebo supplementation[b]	Post Biobran/MGN-3 supplementation[b]	F-test (Quade's test)	*p* Value
Physical component summary	44.0 (38.9–50.8)	49.21 (38.5–57.7)	4.57	0.037*
Mental component summary	39.6 (32.7–49.8)	46.6 (43.6–52.1)	6.68	0.012*
Physical functioning	47.9 (47.9–56.5)	47.9 (39.3–56.5)	0.23	0.645
Role-physical	38.7 (29.5–48.0)	48.0 (38.7–57.2)	8.01	0.006*
Bodily pain	37.1 (26.9–47.3)	47.3 (37.1–57.4)	12.49	0.001*
General health	44.7 (29.6–44.7)	44.7 (29.6–55.5)	0.363	0.549
Vitality score	37.7 (37.7–47.7)	57.8 (47.7–57.8)	21.15	0.000*
Social functioning	36.4 (26.3–36.4)	46.5 (36.4–56.6)	12.96	0.001*
Role-emotional	39.3 (33.7–44.9)	42.1 (39.3–44.9)	0.55	0.462
Mental health	40.2 (34.1–52.3)	52.3 (40.2–52.3)	3.42	0.070

Ranks of basal score levels were used as covariate

*Significant at $p \leq 0.05$

[a]Both baseline and termination data or one of them were not-normally distributed as suggested by Shapiro–Wilk and Kolmogorov–Smirnov tests

[b]Median value (lower quartile–upper quartile)

Discussion

The results of the current study demonstrate that Biobran/MGN-3 at a low dose of 250 mg/day for 3 months can improve HRQOL in several key life domains including role-physical, bodily pain, vitality, and social functioning. Biobran/MGN-3 has previously been proven to be a potent anticancer agent, with extensive studies showing its ability to exert anticancer effects in animals bearing tumor [27, 28] and in cancer patients [35]. Biobran/MGN-3's ability to improve the HRQOL in cancer patients has also been studied. In a major clinical trial involving 152 patients with progressive and partially metastasized cancer with different types of malignancies (96 patients in the Biobran/MGN-3 group and 56 in the control group), patients that were treated with Biobran/MGN-3 plus conventional therapy (CT) recorded marked improvement in appetite as compared with CT alone [29]. In another study that involved 35 patients with various cancer types, treatment with mistletoe lectin and Biobran/MGN-3 resulted in significant improvements to HRQOL parameters, including decreased pain, improvement of anxiety, increase of physical activity, improvement of appetite, improvement of sleep, improvement of digestion, and decrease of side effects during oncotherapy [30]. Improved HRQOL was also reported in one case report, a 64-year-old female with terminal cancer and an extremely poor prognosis (umbilical metastasis of recurrent colorectal cancer) who was treated with a combination of chemotherapy and Biobran/MGN-3 which led to a prolongation of lifespan (2 years) and maintenance of HRQOL [31].

The observation of HRQOL enhancements in the current study stems from improvement of several key areas of healthy older adults subjects' lives, including their levels of physical activity, vitality, mental health, cognitive activity, pain, and social functioning. Evidence that an improvement in physical activity (PA) is associated with improvements in psychological, cognitive, and functional health has been reported in many studies [36–38]. Furthermore, restricted PA is associated with decreased HRQOL and higher rates of morbidity and mortality [39]. In line with these observations, guidelines for Americans established in 2008 recommend that all older adults should engage in regular PA [40, 41], and the WHO recommends a weekly moderate exercise time of 150 min per week for older adults to obtain health benefits [42]. Results of the current study showed that Biobran/MGN-3 supplementation for 3 months helped older adults to achieve significant improvements in PA as compared to the placebo group and baseline values, suggesting that it could promote their ability to engage in regular physical activity. This finding is of particular interest given the wide variability in PA levels that have been seen in studies of older adults. In a systematic review of 53 studies by Sun and colleagues, 45 studies reported that only 20–60% of the older adults met the recommendations for PA levels [43].

In SF-12v2, role-physical (RP) measures subjects' perceived limitations in functioning due to physical problems, and the RP score combines the perceived personal satisfaction with accomplished activities and the abandonment of desired activities due to physical limitation. As such, it could be envisioned that enhancement of RP scale could be achieved by improving bodily functions, alleviating physical limitation, or elevating a person's satisfaction with performance of accomplished activities. We did not detect significant improvement in the physical functioning (PF) or general health (GH) domains in the Biobran/MGN-3 group in comparison to either the baseline values or the placebo

group. Since PF measures ability limitations in performing moderately vigorous daily activities such as moving a table or pushing a vacuum cleaner, the lack of a positive effect of Biobran/MGN-3 on PF is not unexpected given the heterogeneous causes of physical limitation if present. GH is a general assessment of the subject's physical and mental health, and the lack of PF improvement could lead to the observed GH lack of improvement. While it may be puzzling at first that Biobran/MGN-3 could significantly improve RP without parallel improvements in PF and GH, one explanation can be drawn from the fact that Biobran/MGN-3 supplementation also induced improvements in vitality, mental health, social functioning, and role emotion scores.

The vitality scale measures the subjective feeling of energy/enthusiasm, and the resulting positive energy would enforce role emotion, social functioning, mental health, and role-physical, all of which are psychologically inter-related. Synergistic improvement in these domains could enhance the subject's positive mood and ability for better planning and recruiting social support to execute the desired activity. Successful application of these functions to perform the desired activity could increase personal satisfaction of his or her abilities and, as such, the role function score. Collectively, the SF-12v2 yielded two summary scores, namely, physical and mental component summary scores. Each summary score was calculated from all eight subdomains by principle component analysis with varimax rotation, and our study showed that Biobran/MGN-3 supplementation significantly improved both.

HRQOL is very sensitive to pain. Biobran/MGN-3 supplementation significantly reduced perceived bodily pain in the treatment group compared to the initial levels and to the placebo group. Several studies of HRQOL in the older population have examined its association with pain severity. A considerable percentage of older adults often suffer from pain and discomfort, including low back pain (LBP), as compared with younger groups [44, 45]. In addition, the manifestations of pain can compound with each other and with other HRQOL factors to lower overall HRQOL scores. LBP plus leg pain results in worse HRQOL as compared with LBP only [46], and pain is associated with psychological difficulties and social restrictions which impair HRQOL. New and safe treatments that overcome pain are urgently needed, and the ability of Biobran/MGN-3 to decrease the pain severity in healthy older adults shown here is of particular interest.

Finally, social active participation has been shown to play an important role in the emotional well-being of older population and is a pivotal factor in HRQOL. The capacity of people to share positive emotions with others has been shown to have a positive effect in maintaining successful social relationships and to improve personal well-being [47]. The breakdown in the social self, known as loneliness, has a profound impact on HRQOL as it is usually associated with cognitive decline, depression, and dementia that leads to more social isolation [48, 49]. Lonely older age subjects have demonstrated an upregulation of pro-inflammatory nuclear factor-kappa B (NF-κB) and downregulation of anti-inflammatory glucocorticoid receptor as compared with non-lonely subjects [50, 51]. Successful social relationships has been rated as the most important aspect associated with high HRQOL [52, 53]. Results of the current study reveal that healthy older adults supplemented with Biobran/MGN-3 at a low dose of 250 mg/day for 3 months have significant improvements in their social behavior.

The mechanisms underlying Biobran/MGN-3's effect on HRQOL parameters may be due in part to Biobran/MGN-3's action on the immune system. With regard to cognitive function and mental health, psychoneuroimmunology studies have revealed comprehensive reciprocal crosstalk between the nervous and immune systems [54–56]. Peripheral inflammation can influence mood and psychological status. Pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) have been proposed to act as neuromodulators involved in the mediation of the behavioral and neurochemical features of depressive disorders [57, 58], with strong evidence coming from the finding that anti-inflammatory drugs can alleviate depression [59].

The peripheral immune system and the central nervous system may share some of the same key signaling molecules, such as the receptors for the classic neurotransmitters acetylcholine and dopamine [60, 61]. Effects of psychological stress on immune functions have been examined in several studies. Downregulation of NK cell activity and reduction in their absolute numbers has been reported in human subjects after exposure to stressors such as hip fracture-induced depression [62], threatening life events among hospitalized depressed patients [63], temporally confined naturalistic stressor (academic stress) [64], and examination stress among medical students [65, 66]. Other studies reported decreased percentages of helper T-cells and cytotoxic T-cells among medical students [67]. Chronic stress reduces T cell mediated immunity, including a decrease of T cell response to mitogens, cytokine production and CD4+ T-lymphocytes [68], and the low percentages of total T-lymphocytes (OKT-3+) and helper T-cells (OKT-4 +) among family caregivers of Alzheimer's disease victims [69]. Biobran/MGN-3 has been shown to be a potent immunomodulator that has the ability to enhance human NK cell activity [34, 70] and CD4+ and CD8+ T-cell responses to mitogens [32]. This suggests that the cognitive improvement of older adults in the current study may be attributed to increased immune cell functioning post treatment with Biobran/MGN-3.

Older adults are known to be susceptible to viral infection and cancer, and in this context, Biobran/MGN-3's

immunomodulatory capabilities can activate dendritic cells (DCs) [71, 72] and enhance human NK cell activity in young adults [70] and in older adults [34]. We believe that the improvement in social behavior is due to augmentory effects of Biobran/MGN-3 on different arms of the immune system, based on the fact that NK cells play a critical role in host immune defense against viral infections and tumors [73] and DC cells exhibit potent anticancer effect [74, 75]. It is also of interest to note that chronic fatigue syndrome (CFS), a disease that is characterized by fatigue, cognitive difficulties, and impaired memory, is associated with a decrease of NK cell activity and a reduced response of T-cells to mitogens and other specific antigens. These immune abnormalities may result in alterations to the central nervous system functioning in people with CFS [76]. Given that Biobran/MGN-3 induces NK activation [34, 70] and T cell response to mitogens [32], Biobran/MGN-3 may be helpful in increasing cognitive performance in people with CFS.

The strength of our study stems from the use of a randomized double-blind placebo-controlled study design. The placebo supplement (provided by the manufacturer, Daiwa Pharmaceutical Co. Ltd., Tokyo, Japan) was impossible to distinguish from Biobran/MGN-3 except by the provided code. Limitations in the study, namely the use of a small sample size (30 subjects/group) and the lack of assessment of immunological changes induced by Biobran/MGN-3 due to cost limitations, prohibited us from making stronger claims about correlations between HRQOL improvement and immunological modulations.

We conclude that ingestion of Biobran/MGN-3 at a low dose (250 mg/day) for 3 months can improve HRQOL in healthy older adults. Biobran/MGN-3 is a safe and nontoxic agent, and its effect on HRQOL in older adults should be studied further.

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Compliance with ethical standards

Conflict of interest Dr. Elsaid, Dr. Fahmi, and Dr. Shaheen have nothing to disclose; Dr. Ghoneum has received grants from Daiwa Pharmaceutical Co., Ltd., Japan, outside the submitted work.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Zagazig University Hospital, Faculty of Medicine, IRB approval no. 1507, June 2018) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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