scientific reports

Check for updates

OPEN

Effects of rice bran arabinoxylan compound on quality of life of cancer patients during active treatment: a randomised placebo-controlled pilot trial

Soo Liang Ooi[1], Peter S. Micalos[2], Robert Zielinski[3,4], Judith Lacey[5], Suzanne Grant[5,6], Steven Kao[5], Terry Golombick[7] & Sok Cheon Pak[1]✉

The effects of a plant-based immunomodulator, rice bran arabinoxylan compound (RBAC), on the quality of life (QoL) of cancer patients during active treatment are unclear. The RBAC-QoL study was a randomised, placebo-controlled, double-blind feasibility study to address the role of RBAC in cancer patients receiving systemic therapies. The primary outcome measure was patient-reported functional, symptom, and global QoL scores. Secondary and exploratory outcome measures included nutritional indices and cytokine changes. Adult patients ($n = 29$) with solid organ tumours (≥ stage II) undergoing systemic treatment were recruited from outpatient centres in New South Wales, Australia. Group allocation was assigned through stratified randomisation (RBAC = 12, placebo = 17). Interventions were either RBAC or matched placebo at 3 g/day for 24 weeks. The participants, oncologists, and data collectors were blinded. Data were collected from five study visits, 6 weeks apart. An intention-to-treat analysis was performed using repeated measure ANOVA with pairwise comparisons where statistical significance was observed. Data sets not conforming to normality were tested with nonparametric ANOVA-type statistics. The global QoL scores differed significantly between groups with a large effect size ($p = 0.031$, eta^2[g] = 0.147). Pairwise comparisons found significant differences favouring the RBAC group at week 6 ($p = 0.017$, Cohen's $d = 1.119$) and week 24 ($p = 0.041$, $d = 0.970$). Compared to the placebo group, the RBAC group showed significantly better role ($p < 0.001$) and social functioning ($p = 0.037$), while the cognitive functioning score difference was trending higher ($p = 0.055$). Regarding cancer symptoms, the placebo group reported significantly worse scores ($p < 0.05$) in fatigue, pain, dyspnoea, and appetite loss compared to the RBAC group. Significant elevations ($p < 0.05$) of cytokine interferon-γ, interleukin 1RA and 12p40, as well as total protein, were also detected in the RBAC group compared to placebo over time. These serum markers correlated positively with the global QoL scores, suggesting potential interactions of immune activity, nutritional status, and QoL. No intervention-related adverse events were reported in both groups. RBAC improves QoL beyond placebo during systemic cancer treatment, potentially through the immuno-nutritional pathway.

***Trial registration*: Prospective registration on the Australian New Zealand Clinical Trials Registry (ANZCTR Reg No: ACTRN12619000562178p, 10/04/2019).**

Keywords Biobran, Biological response modifier, Natural compound, Polysaccharide, Immunomodulator, Immunotherapy, Chemotherapy, Symptom management, Supportive care, Patient-reported outcome measures

Abbreviations

[1]School of Dentistry and Medical Sciences, Charles Sturt University, Panorama Avenue, Bathurst, NSW 2795, Australia. [2]School of Dentistry and Medical Sciences, Charles Sturt University, Port Macquarie, NSW 2444, Australia. [3]School of Medicine, Western Sydney University, Penrith, NSW 2751, Australia. [4]Central West Cancer Centre, Orange Health Service, Orange, NSW 2800, Australia. [5]Chris O'Brien Lifehouse, Camperdown, NSW 2050, Australia. [6]NICM Health Research Institute, Western Sydney University, Westmead, NSW 2145, Australia. [7]Southern Sydney Haematology, Kogarah, NSW 2217, Australia. ✉email: spak@csu.edu.au

AES	Australian eating survey
ANOVA	Analysis of variance
ANCOVA	Covariance analysis
ARFS	Australian recommended food score
BMI	Body mass index
CAMQ	Use of Complementary and Alternative Medicine Questionnaire
CONSORT	Consolidated Standards of Reporting Trials
Cr	Creatinine
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for the Research and Treatment of Cancer
HREC	Human Research Ethics Committee
IFN	Interferon
IL	Interleukin
INI	Inflammatory-nutritional index
IPAQ	International Physical Activity Questionnaire
mATS	Modified ANOVA-type statistic
MET	Metabolic equivalent of task
NK	Natural killer
NLR	Neutrophil-to-lymphocyte ratio
QL2	Global QoL scale
QLQ-C30	Core 30-item QoL questionnaire
QoL	Quality of life
RBAC	Rice bran arabinoxylan compound
RM	Repeated measures
RNA	Ribonucleic acid
RTE	Relative treatment effects
TNF	Tumour necrosis factor-alpha
TP	Total protein
WBC	White blood cell count

Background

Cancer is a global health concern. According to the Global Cancer Observatory data released by the International Agency for Research on Cancer, there were close to 20 million new cancer cases worldwide in 2022 and the disease caused approximately 9.7 million deaths[1]. At this rate, nearly one in five people in the world will develop cancer in their lifetime[2].

Survival is the primary outcome of concern in cancer therapies[3]. Cytotoxic agents, including newer targeted therapies and immunotherapies, surgery and radiotherapy, are routinely used to eradicate malignant cells[4]. Their administration also significantly affects healthy tissues and causes unwanted and common side effects such as nausea, vomiting, diarrhoea, appetite loss, peripheral neuropathy, fatigue and many others[5]. As a result, cancer treatment can be physically and emotionally challenging for the patients, affecting them socially and financially.

Cancer and its treatment could have long-term impacts on patients. With improvements in therapeutics coupled with early detection, people are now living longer after cancer diagnosis[6]. Hence, there is a growing focus on the importance of supportive care rather than merely on cancer cure. The quality of life (QoL) outcome of cancer patients becomes a crucial clinical consideration[3,7,8]. Improving the QoL of patients through complementary and supportive treatments has been suggested to enhance overall well-being and disease outcomes[9,10].

Rice bran arabinoxylan compound (RBAC) is a plant-based immunomodulator that has exhibited anticancer properties in research and demonstrated immune restorative function in cancer patients clinically by upregulating natural killer (NK) cell activity and enhancing inflammatory and cytotoxic responses[11]. Previous reviews by the lead author[11,12] found evidence showing RBAC as a complementary therapy used with conventional cancer treatment, which enhanced the immune profile, especially in boosting the NK cell activity, reduced treatment side effects, improved treatment outcomes and survival rates. RBAC was hypothesised to impact the QoL of cancer patients by improving immune function and lowering systemic inflammation, leading to reducing treatment toxicity, symptom severity, and behavioural comorbidities while enhancing the nutritional status and physical functioning[13]. However, there is a lack of well-designed clinical trials assessing the impact of RBAC supplementation on the QoL of cancer patients using validated QoL instruments[11,12].

The present pilot study was conducted to obtain preliminary data for informing the design of a future large-scale clinical trial. This study utilises an internationally validated questionnaire, the European Organisation for the Research and Treatment of Cancer (EORTC) core 30-item QoL questionnaire (QLQ-C30), to determine the potential effects of RBAC compared with placebo on the QoL of cancer patients undergoing active anticancer treatment of either chemotherapy or immunotherapy. Secondary objectives were to ascertain potential associations between RBAC intervention, nutritional, and immune markers as possible mechanisms influencing the QoL of the patients.

Methods

Trial design

The RBAC-QoL study was a randomised, placebo-controlled trial consisting of two parallel groups. The trial was approved by the Human Research Ethics Committee (HREC) of Concord Repatriation General Hospital, Sydney Local Health District (Application No. 2019/ ETH00489) and the Charles Sturt University HREC (Protocol No. H19244) and registered with the Australian New Zealand Clinical Trials Registry (ANZCTR Reg No: ACTRN12619000562178p; First registration on 10/04/2019).

The study protocol was available for open access[14]. A report documenting the approved protocol variations, statistical methods, and interim analysis has also been published[15]. A more detailed description of the study methodology can also be found in Supplementary S1. Readers are encouraged to refer to them for further details. All methods were carried out in accordance with the principles, regulations, governance and guidelines for conducting clinical trials based on the National Clinical Trial Governance Framework of Australia[16]. This report adheres to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines[17].

The trial included adult patients (≥ 18 years old) diagnosed with any solid organ cancer (≥ stage II) and undergoing chemotherapy or immunotherapy treatment, recruited from four outpatient cancer centres in New South Wales, Australia. The recruitment target was 50 participants, with equal distribution across two groups based on a priori calculations. Participants were randomly assigned to either the RBAC or placebo group using a computerised stratified algorithm with metastatic status (yes/no) and treatment (chemotherapy or immunotherapy) as inputs. The patient, the treating oncologist, and the study coordinator were blinded to the group allocation.

The participant took either RBAC or a placebo powder (dissolved in water) as an oral supplement (3 g/day) for 24 weeks. All intervention packs were manufactured by the same company and were identical in appearance, containing RBAC or placebo powder with similar colour, odour, and taste. All participants continued their oncological treatment during the trial and were required to attend five study visits, spaced 6 weeks apart, to provide data and undergo blood tests (total duration: 24 weeks).

Outcome measures

The primary outcome measure was self-reported QoL based on the QLQ-C30 completed either on paper or electronically. The scoring of QLQ-C30 followed the procedures stipulated by EORTC[18] with a global QoL scale, five functional scales (physical, role, emotional, cognitive, and social), and nine symptom-related measures (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea) plus a financial difficulties item.

The secondary outcome measures of this study included body composition parameters (body weight, body fat ratio, and muscle mass), body mass index (BMI), and biochemical indices for nutritional assessment based on immunological and inflammatory markers. These nutritional status indices were the neutrophil-to-lymphocyte ratio (NLR) and the inflammatory-nutritional index (INI = the ratio of C-reactive protein and albumin).

Fifteen human cytokine/chemokine markers, including granulocyte-macrophage colony-stimulating factor, interferon-gamma (IFN-γ), interleukin (IL)-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p40, IL-12p70, IL-13, monocyte chemoattractant protein-1, and tumour necrosis factor-alpha (TNF-α), were analysed using multiplex quantification via Luminex xMAP technology (Luminex, Austin, TX, USA) to explore the immunomodulating effects of RBAC. The multiplexing analysis was conducted by Eve Technologies Corp. (Calgary, AB, Canada).

Patient safety was assessed with routine blood tests during cancer treatment, including complete blood count, liver function, electrolytes, urea, creatinine, and prealbumin. Adverse events reported by participants during clinical visits throughout the trial were also tracked and documented based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Data on the participants' lifestyle factors were also collected using the Australian Eating Survey (AES) for dietary quality[19], the International Physical Activity Questionnaire (IPAQ) for physical activeness[20], and custom-designed Use of Complementary and Alternative Medicine Questionnaire (CAMQ) for usage and perceived value of complementary therapies[14].

Statistical methods

Datasets were analysed with RStudio version 2024.09.0 Build 375 (Posit, Boston, MA, USA), running R version 4.4.0. Data analysis was based on the intention-to-treat principle. Every data point collected from participants in the trial was used regardless of withdrawal. Between-group comparisons over different time points were analysed with RM ANOVA. Pairwise comparisons were conducted when statistical significance was observed with the false discovery rates applied to adjust the p-values for multiple comparisons. Pearson's correlation coefficient (r) was used to detect the strengths and directions of the relationships among the significant outcome variables.

Outcome measures with data not conforming to normality were tested using nonparametric tests with ANOVA-type statistics utilising the npartLD R software package[21].

Between-group comparisons were analysed for baseline characteristics and adverse events. Continuous variables were reported as mean ± standard deviation. The difference between any two means was analysed using two-sided Student's t-statistics. Fisher's exact test was used to determine if there were nonrandom associations between two categorical variables. A p-value of less than or equal to 0.05 was considered statistically significant.

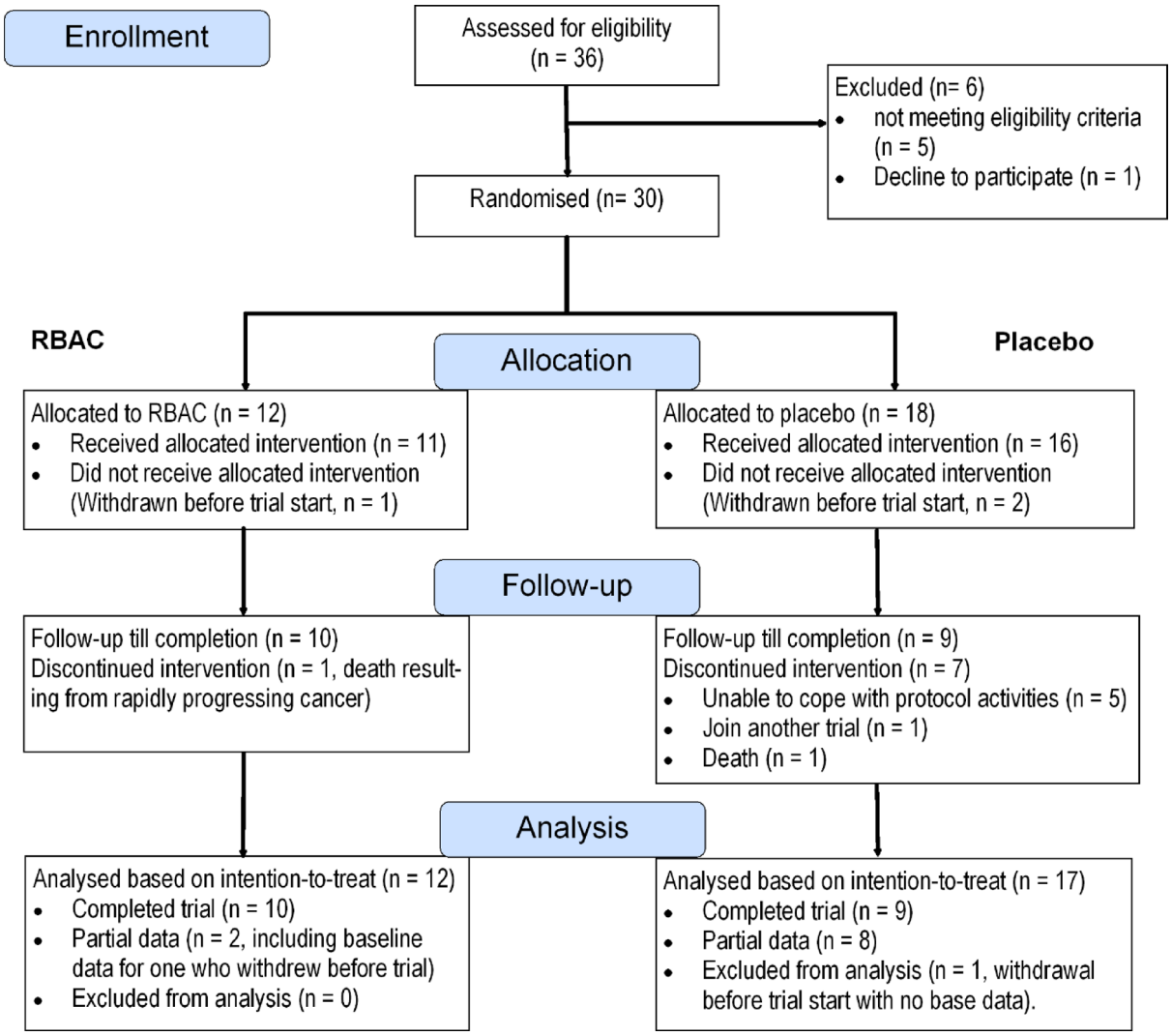

Fig. 1. The recruitment flow of the RBAC-QoL study in a CONSORT diagram.

Results

Recruitment flow

Recruitment was conducted from June 2020 to December 2023, with interruptions during the COVID-19 pandemic. Follow-up with the last participant was completed in April 2024. The trial concluded short of the recruitment target due to resource and financial constraints. The participant flow report is presented in a CONSORT flowchart[22], depicted in Fig. 1.

In summary, 30 eligible participants were randomly assigned to the two intervention groups (RBAC = 12, placebo = 18). Runs test for randomness (Wald-Wolfowitz test) on the allocation sequence yielded a p-value of 0.441, indicating that the group allocation was random. Eleven of them withdrew in various stages with only 19 completed the trial: 10 in the RBAC group and 9 in the placebo group. Overall, among those who completed the trial, the compliance rate was high, averaging 99%, indicating the ease of consuming the oral supplements.

All participants with at least some data collected were included in the intention-to-treat analysis. Only one participant from the placebo group was omitted, as the participant withdrew before providing any baseline data. Thus, data from 29 participants (RBAC = 12, placebo = 17) were analysed for the primary outcome.

Participant characteristics

The characteristics of both groups are shown in Table 1, comparing age, sex, body composition, cancer type, cancer stage, recurrence, metastasis, treatment type, lifestyle factors, and trial status. No significant differences were detected between the groups in baseline characteristics. Although the withdrawal rate appears higher in the placebo group (41.2%) than in the RBAC group (8.3%), the difference in frequency distribution did not reach statistical significance.

	RBAC	Placebo	*p* value
N (available for analysis)	12 (100%)	17 (100%)	
Age	68.8 ± 9.17	64.1 ± 7.35	$p = 0.152$
Sex			
Male	7 (58.3%)	14 (83.3%)	$p = 0.218$
Female	5 (41.7%)	3 (17.7%)	
Body composition			
Weight	79.0 ± 24.38	86.2 ± 18.26	$p = 0.381$
Body Mass Index	27.6 ± 7.79	27.6 ± 4.67	$p = 0.988$
Primary cancer			
Lung	2 (16.7%)	6 (35.3%)	$p = 0.268$
Melanoma	4 (33.4%)	2 (11.7%)	
Colon and Rectum	1 (8.3%)	4 (23.5%)	
Ovary and Uterus	3 (25.0%)	1 (5.9%)	
Bladder	1 (8.3%)	–	
Stomach	1 (8.3%)	–	
Breast	–	1 (5.9%)	
Oesophagus	–	1 (5.9%)	
Pleura	–	1 (5.9%)	
Kidney	–	1 (5.9%)	
Cancer stage			
II	1 (8.4%)	1 (5.9%)	$p = 0.847$
III	4 (33.3%)	8 (47.1%)	
IV	7 (58.3%)	8 (47.1%)	
Recurrence			
No	7 (58.3%)	11 (64.7%)	$p = 1.0$
Yes	5 (41.7%)	6 (32.3%)	
Metastasis			
No	2 (16.7%)	4 (23.5%)	$p = 1.0$
Yes	10 (83.3%)	13 (76.5%)	
Treatment			
Chemotherapy	7 (58.3%)	12 (70.6%)	$p = 0.694$
Immunotherapy	5 (41.7%)	5 (29.4%)	
Lifestyle factors			
Diet (ARFS)	30.7 ± 8.51	33.5 ± 8.74	$p = 0.456$
Physical activity (MET/week)	830.3 ± 601.7	706.5 ± 639.9	$p = 0.399$
CAMQ score	15.8 ± 12.74	11.1 ± 12.41	$p = 0.493$
Trial status			
Withdrawn	1 (8.3%)	7 (41.2%)	$p = 0.105$
Deceased	1 (8.3%)	1 (5.9%)	
Completed	10 (83.4%)	9 (52.9%)	

Table 1. Participant characteristics. All continuous variables are presented as mean ± standard deviation, and the hypothesis testing of two means was based on the two-sided Student's t-test. Significant testing of categorical variables was determined using Fisher's exact test. ARFS = Australian recommended food score; CAMQ = Use of complementary and alternative medicine questionnaire; MET = metabolic equivalent of task; RBAC = rice bran arabinoxylan compound.

Primary outcome analysis

The global QoL scale (QL2) was analysed with RM ANOVA and showed statistical differences between groups ($F[1,15] = 5.67$, $p = 0.031$, $eta^2[g] = 0.147$). However, the effects of time and the interaction between time and group were not statistically significant (See Table S2.1 in Supplementary S2). Pairwise comparisons of mean QL2 between groups for each time point are shown in Table 2. Clinically and statistically significant differences were observed at week 6 and week 24 with large effect sizes. At week 6, the RBAC group scored 75.8 ± 14.41 in mean QL2 compared to 57.6 ± 17.93 in the placebo group ($p = 0.017$, Cohen's $d = 1.118$). The mean QL2 difference between RBAC and placebo at week 24 was 79.2 ± 19.74 and 57.41 ± 24.81, respectively ($p = 0.041$, Cohen's $d = 0.971$).

Figure 2 shows the difference in mean QL2 scores between groups over time. The plot shows a dip in the global QoL of the placebo group at week 6, which recovered over the subsequent two visits before dropping

Visit	Variable (unit)	RBAC	Placebo	*p*-value	Cohen's d
0 (Baseline)	QL2 (1–100)	70.8 ± 21.6	60.0 ± 19.0	0.156	0.533
1 (Week 6)	QL2 (1–100)	75.8 ± 14.4	57.6 ± 17.9	**0.017***	**1.118**
2 (Week 12)	QL2 (1–100)	73.1 ± 14.9	66.7 ± 13.4	0.315	0.457
3 (Week 18)	QL2 (1–100)	70.4 ± 12.6	63.89 ± 19.5	0.486	0.394
4 (Week 24)	QL2 (1–100)	79.2 ± 19.7	57.41 ± 24.8	**0.041***	**0.971**

Table 2. Pairwise comparisons of mean global quality of life score (QL2) between groups over time. Significant values are in bold. ^Statistically significant difference between two means based on the two-sided Student's t-test with $p \leq 0.05$ (with multiplicity adjusted with false discovery rate). RBAC = rice bran arabinoxylan compound.

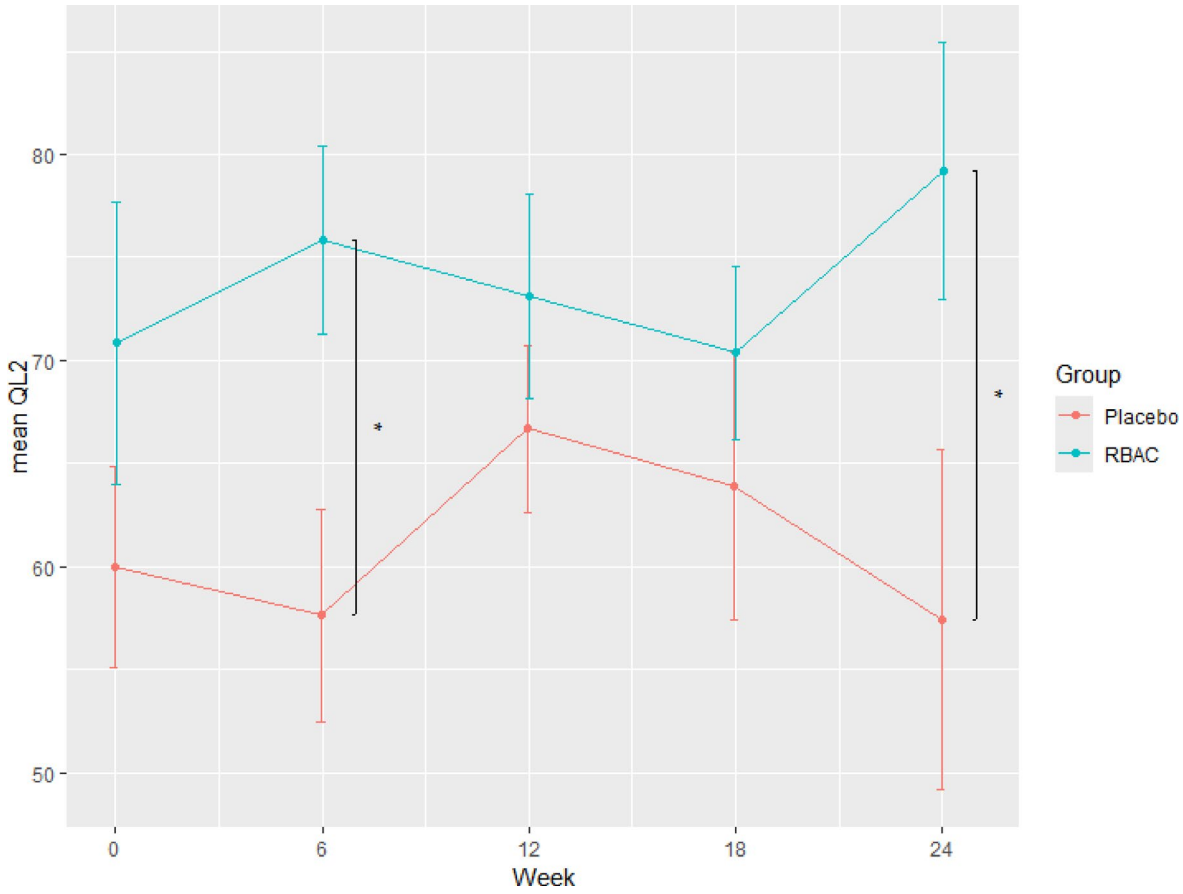

Fig. 2. Plots showing the mean (± standard error) for global quality of life scores (QL2) for RBAC and placebo groups over time. *Significant difference $p \leq 0.05$. RBAC = rice bran arabinoxylan compound.

again at the last visit (week 24). Conversely, the RBAC group showed an upward trend at week 6 and minor drops at weeks 12 and 18 before improvement at week 24. However, these differences over time were not statistically significant in pairwise comparison.

Datasets of the remaining 14 scales/items for QLQ-C30 did not fulfil the normality criterion of RM ANOVA and were analysed based on nonparametric tests with ANOVA-type statistics. The results are shown in Table 3.

Among the five functional scales of QLQ-C30, statistical differences between groups were detected in role (RF2, $p < 0.001$) and social functioning (SF, $p = 0.037$). Meanwhile, the difference in cognitive functioning was marginally significant (CF, $p = 0.054$). There was also a marginally significant difference between groups concerning financial difficulties (FI, $p = 0.058$).

The relative treatment effects (RTE) of both groups were compared at each visit for these functional scales, as visualised in Fig. 3. The RBAC group demonstrated superior results compared to the placebo group on these functional scales, indicating a higher or healthier level of functioning in these domains. Most notably, participants taking RBAC reported significantly better role functioning ($p < 0.05$) than their placebo counterparts at every visit after baseline, most prominently at weeks 12 and 18 ($p < 0.01$). The RBAC group also reported significantly

Scale/item	mATS	Df1	Df2	*p*-value
Physical functioning (PF2)	2.36	1	18.35	0.141
Role functioning (RF2)	22.21	1	19.85	**<0.001***
Emotional functioning (EF)	0.09	1	18.82	0.767
Cognitive functioning (CF)	4.17	1	19.49	0.054 $^{+}$
Social functioning (SF)	4.99	1	19.41	**0.037***
Fatigue (FA)	4.59	1	19.17	**0.045***
Nausea and vomiting (NV)	< 0.01	1	18.16	0.967
Pain (PA)	4.43	1	19.42	**0.048***
Dyspnoea (DY)	4.53	1	18.49	**0.047***
Insomnia (SL)	0.45	1	19.96	0.508
Appetite loss (AP)	4.64	1	20.00	**0.044***
Constipation (CO)	0.06	1	19.35	0.804
Diarrhoea (DI)	0.80	1	13.91	0.387
Financial difficulties (FI)	4.25	1	13.71	0.058 $^{+}$

Table 3. The modified ANOVA-type statistic based on the group effect for 14 QLQ-C30 scales/items. Significant values are in bold. *The statistically significant difference between groups (RBAC vs. Placebo) was based on the modified ANOVA-type statistic for the whole-plot factors (mATS) with $p \leq 0.05$. $^{+}$ Marginal significance $p \approx 0.05$. Df = Degree of freedom; RBAC = rice bran arabinoxylan compound.

higher social functioning than the placebo group at weeks 6 and 12. Pairwise comparisons in cognitive functioning found no significant differences between the groups over time. Worsening outcomes in functioning may have contributed to greater concerns over financial difficulties in the placebo group, as shown in Fig. 3.

In terms of symptom scores, significant between-group differences ($p < 0.05$) were detected for fatigue, pain, dyspnoea, and appetite loss. As shown in Fig. 3, the placebo group exhibited higher RTE values than the RBAC group in each of these symptom measures, indicating a greater level of symptomatology or problems in these areas. Pairwise comparisons found significant differences between the groups at weeks 18 and 24 for dyspnoea ($p < 0.05$) and at week 12 for appetite loss ($p < 0.01$).

Secondary outcome analysis

RM ANOVA was conducted on body weight, BMI, plus nutritional status indices of NLR and INI (See Table S2.2, S2.3 in Supplementary S2). No statistically significant differences were detected between the groups at baseline and across all time points for these parameters. Therefore, this study was not able to explain the effect of RBAC on QoL beyond that of placebo based on the outcome measures.

Cytokine profile analysis

Cytokine profile analysis was an optional exploratory outcome measure for study sites due to additional logistics requirements for collecting, centrifuging, transporting and storing serum samples. Consequently, the cytokine profile analysis was performed with samples from only 19 participants (RBAC = 9, placebo = 10). Fourteen participants (7 in each group) fully completed the trial. Notwithstanding. among the 15 cytokines/chemokines analysed with RM ANOVA, three parameters yielded significant differences across time: IFN-γ ($F[4, 44] = 2.887$, $p = 0.033$, $eta^2[g] = 0.017$), IL-1RA ($F[4, 44] = 2.716$, $p = 0.042$, $eta^2[g] = 0.030$), and IL-12p40 ($F[4, 44] = 2.716$, $p = 0.038$, $eta^2[g] = 0.027$). However, the effect sizes ($eta^2[g]$) of the differences are considered small (Details are shown in Table S2.4 in the Supplementary S2).

Table 4 shows the pairwise comparisons of the means of IFN-γ, IL-1RA, and IL-12p40 for the two groups across different time points. Due to the small effect sizes, no significant differences were detected for all measures at individual time points. Nonetheless, for IFN-γ, at week 18, the difference between RBAC and placebo groups was marginally significant (1.91 ± 0.20 vs. 1.69 ± 0.23, $p = 0.065$). Overall, the RBAC group demonstrated slightly higher cytokine activities than the placebo group (Fig. 4).

Safety outcome analysis

The study did not detect any safety issues in any of the participants based on routine clinical assessments, including complete blood count, liver function, electrolytes, urea, creatinine and prealbumin. Based on RM ANOVA analysis, three markers, namely white blood cell count (WBC), total protein (TP) and aspartate transferase (AST), showed significant differences (See Table S2.5, S2.6, S2.7 and S2.8 in Supplementary S2). The WBC ($F[4, 60] = 2.540$, $p = 0.049$, $eta^2[g] = 0.071$) and AST ($F[4, 60] = 2.855$, $p = 0.031$, $eta^2[g] = 0.040$) were significantly different across time, whereas TP showed a significant interaction effect between group and time ($F[4, 56] = 3.057$, $p = 0.024$, $eta^2[g] = 0.051$).

Table 5 shows the pairwise comparisons of the means of WBC, TP, and AST for the two groups across different time points. A significant difference in TP was observed at week 18, with the RBAC group showing 74.88 ± 6.81 g/L compared to 67.78 ± 5.36 g/L) in the placebo group ($p = 0.030$, Cohen's $d = 1.158$). Trends in the WBC, TP, and AST for the two groups over time are visualised in Fig. 5. Although time effects were detected as

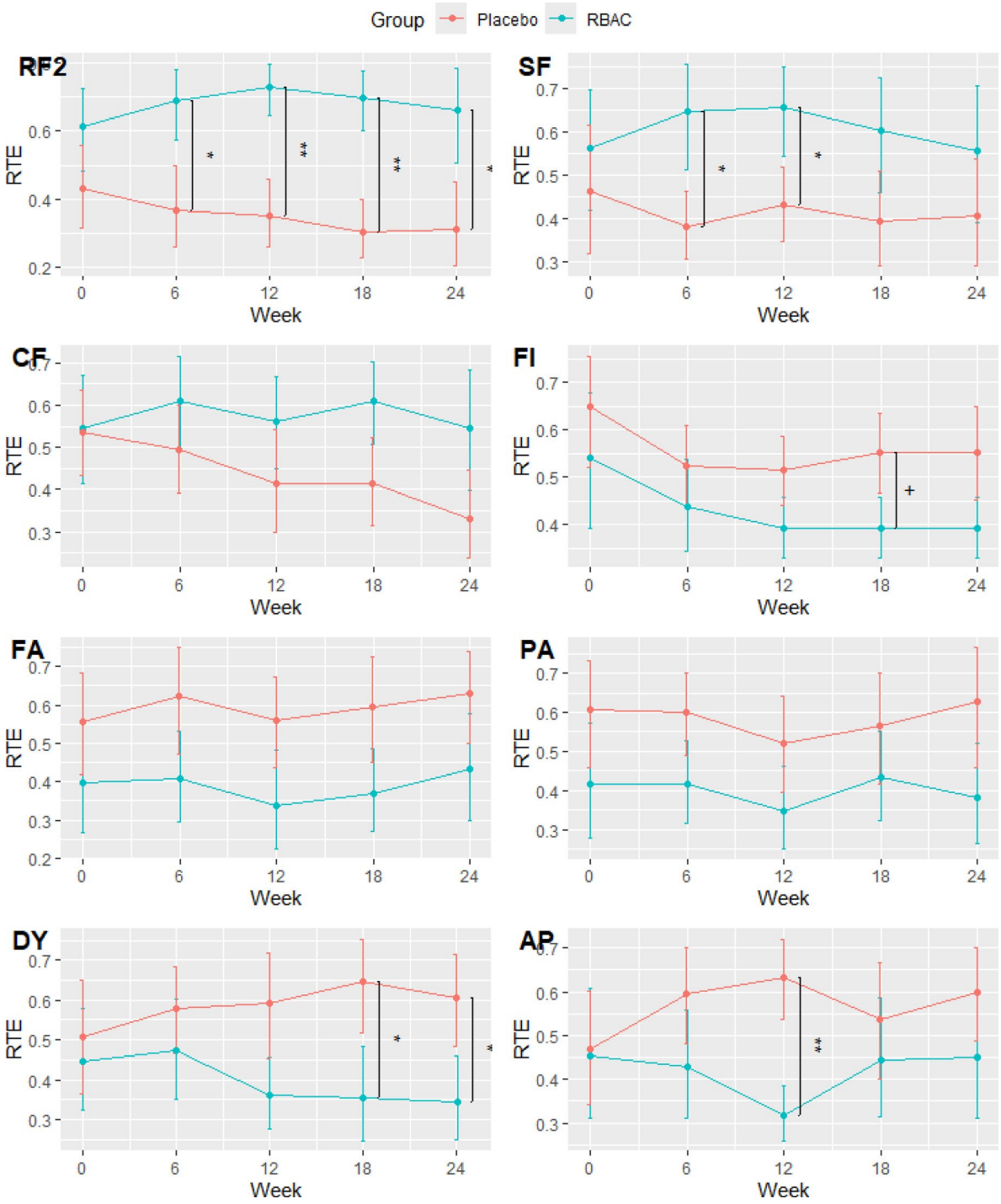

Fig. 3. Plots showing the relative treatment effects (RTE with 95% confidence interval) between RBAC and placebo groups in terms of role functioning (RF2), social functioning (SF), cognitive functioning (CF), financial difficulties (FI), fatigue (FA), pain (PA), dyspnoea (DY) and appetite loss (AP) over time. Significant difference$^{*}p \leq 0.05$,$^{**}p \leq 0.01$ and marginally $^{+}p \approx 0.05$. RBAC = rice bran arabinoxylan compound.

statistically significant with RM ANOVA, pairwise comparisons of different time points by groups did not yield any significant difference.

Adverse events

Comparisons between the two groups regarding the adverse events reported during the trial period are shown in Table 6. The mean adverse events reported per participant in the RBAC group was lower at 2.33 ± 3.22 compared to 4.59 ± 2.87 in the placebo group, although the difference did not reach statistical significance ($p = 0.066$).

Visit	Variable (unit)	RBAC	Placebo	*p*-value	Cohen's d
0 (Baseline)	IFN-γ (pg/ml)	1.86 ± 0.21	1.70 ± 0.26	0.164	0.673
1 (Week 6)	IFN-γ (pg/ml)	1.84 ± 0.22	1.76 ± 0.19	0.468	0.400
2 (Week 12)	IFN-γ (pg/ml)	1.91 ± 0.20	1.69 ± 0.23	**0.065**	1.019
3 (Week 18)	IFN-γ (pg/ml)	1.86 ± 0.30	1.66 ± 0.21	0.147	0.786
4 (Week 24)	IFN-γ (pg/ml)	1.92 ± 0.28	1.74 ± 0.20	0.186	0.714
0 (Baseline)	IL-1RA (pg/ml)	1.70 ± 0.06	1.69 ± 0.08	0.703	0.179
1 (Week 6)	IL-1RA (pg/ml)	1.73 ± 0.05	1.68 ± 0.07	0.195	0.762
2 (Week 12)	IL-1RA (pg/ml)	1.72 ± 0.06	1.67 ± 0.08	0.166	0.752
3 (Week 18)	IL-1RA (pg/ml)	1.71 ± 0.07	1.67 ± 0.08	0.360	0.493
4 (Week 24)	IL-1RA (pg/ml)	1.74 ± 0.05	1.70 ± 0.05	0.157	0.780
0 (Baseline)	IL-12p40 (pg/ml)	1.34 ± 0.06	1.34 ± 0.07	0.887	0.067
1 (Week 6)	IL-12p40 (pg/ml)	1.35 ± 0.06	1.31 ± 0.07	0.297	0.592
2 (Week 12)	IL-12p40 (pg/ml)	1.37 ± 0.06	1.31 ± 0.09	0.168	0.750
3 (Week 18)	IL-12p40 (pg/ml)	1.37 ± 0.06	1.33 ± 0.08	0.308	0.556
4 (Week 24)	IL-12p40 (pg/ml)	1.37 ± 0.05	1.34 ± 0.08	0.523	0.345

Table 4. Pairwise comparisons of interferon-gamma (IFN-γ), interleukin-1RA (IL-1RA), and interleukin-12p40 (IL-12p40) between groups over time. Significant values are in bold. *The statistically significant difference between the two means is based on the two-sided Student's t-test with $p \leq 0.05$ (multiplicity adjusted with false discovery rate). RBAC = rice bran arabinoxylan compound.

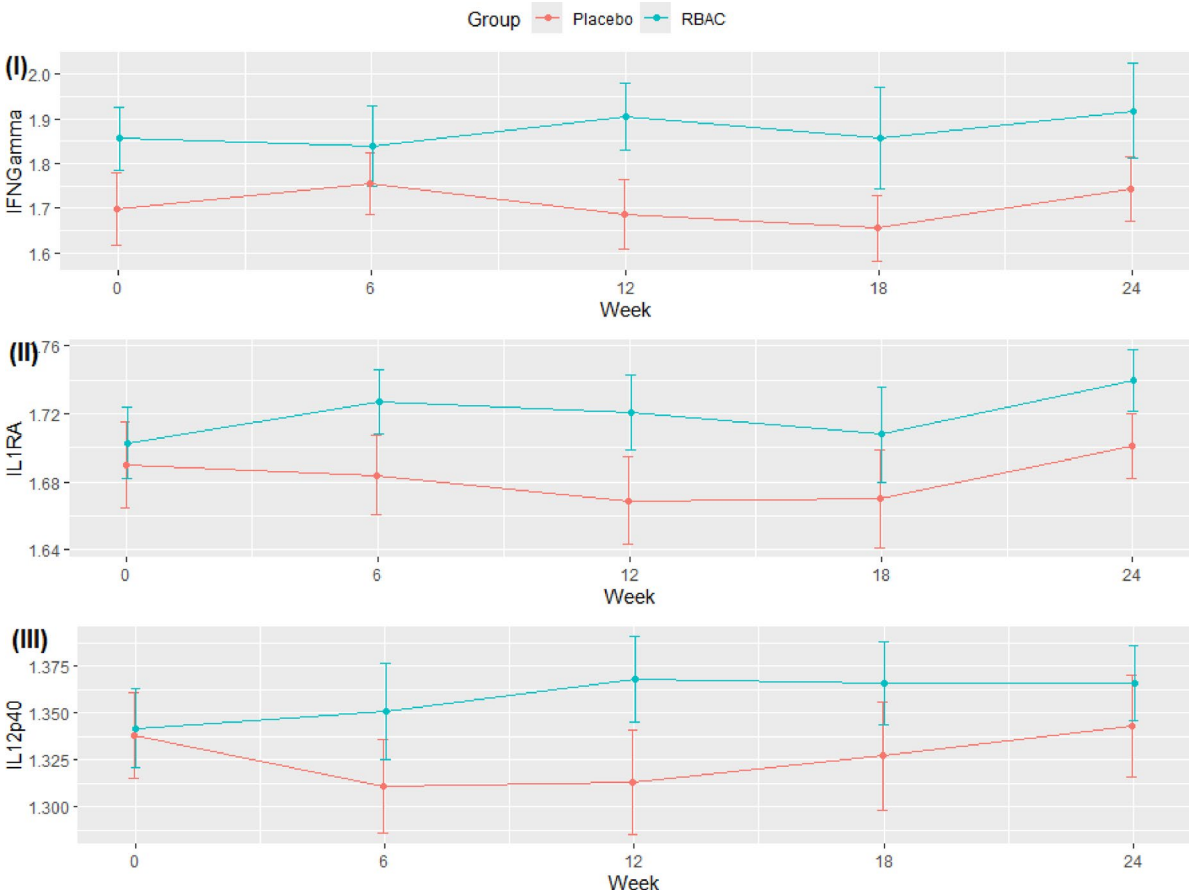

Fig. 4. Plots of (I) mean interferon-gamma (IFN-γ), (II) interleukin-1RA (IL-1RA), and (III) interleukin-12p40 (IL-12p40) for RBAC and placebo groups over time.*Significant difference $p \leq 0.05$. RBAC = rice bran arabinoxylan compound.

Visit	Variable (unit)	RBAC	Placebo	*p*-value	Cohen's d
0 (Baseline)	WBC ($\times 10^9$/L)	5.86 ± 2.25	6.01 ± 1.91	0.844	− 0.074
1 (Week 6)	WBC ($\times 10^9$/L)	5.36 ± 1.74	5.88 ± 2.11	0.545	− 0.266
2 (Week 12)	WBC ($\times 10^9$/L)	6.41 ± 1.85	5.48 ± 2.76	0.392	0.398
3 (Week 18)	WBC ($\times 10^9$/L)	6.93 ± 1.88	5.70 ± 1.15	0.109	0.788
4 (Week 24)	WBC ($\times 10^9$/L)	6.88 ± 2.43	6.41 ± 2.35	0.686	0.196
0 (Baseline)	TP (g/L)	71.80 ± 4.59	70.42 ± 6.45	0.576	0.247
1 (Week 6)	TP (g/L)	70.88 ± 4.45	70.33 ± 5.29	0.824	0.111
2 (Week 12)	TP (g/L)	74.13 ± 6.03	69.22 ± 4.71	0.080	0.906
3 (Week 18)	TP (g/L)	74.88 ± 6.81	67.78 ± 5.36	**0.030***	**1.158**
4 (Week 24)	TP (g/L)	71.56 ± 6.33	68.88 ± 4.61	0.340	0.484
0 (Baseline)	Cr (μmol/L)	24.67 ± 9.36	24.00 ± 3.87	0.793	0.093
1 (Week 6)	Cr (μmol/L)	28.80 ± 7.73	30.50 ± 7.45	0.606	− 0.224
2 (Week 12)	Cr (μmol/L)	26.78 ± 6.91	28.00 ± 4.77	0.636	− 0.206
3 (Week 18)	Cr (μmol/L)	27.90 ± 8.25	29.33 ± 6.06	0.675	− 0.198
4 (Week 24)	Cr (μmol/L)	31.50 ± 5.96	31.00 ± 9.37	0.946	0.034

Table 5. Pairwise comparisons of white blood cell count (WBC), total protein (TP), and transferase (AST) between groups over time. Significant values are in bold. *The statistically significant difference between the two means is based on the two-sided Student's *t* test with $p \leq 0.05$ (multiplicity adjusted with false discovery rate). RBAC = rice bran arabinoxylan compound.

Adverse events based on the CTCAE classification were mostly mild (RBCA = 75.0%, placebo = 79.5%) and moderate (RBCA = 21.4%, placebo = 11.5%), with the grading distribution not significantly different between groups. Notwithstanding, there was one incident of life-threatening bowel obstruction in the placebo group where the patient was hospitalised. The event was resolved and deemed unlikely to be related to the study intervention. In the RBAC group, one death resulted from complications from a fast-growing malignancy unrelated to the study intervention two weeks after starting the trial. There was also a death incident in the placebo group; the participant missed visit 3 and subsequently withdrew from the trial due to a deteriorating condition and passed away one week later.

Overall, there was a significant difference in the distribution of the most commonly reported adverse events between groups ($p = 0.006$). Fatigue was the most common adverse event reported in both groups (RBAC = 14.3%, placebo = 12.8%), followed by diarrhoea and nausea. Oral thrush and rash were reported in the placebo group, but not in the RBAC group. Other commonly reported adverse events include constipation, cough, peripheral neuropathy, pain, and shortness of breath. These adverse events were typical side-effects of oncological treatment and thus considered not related (RBAC = 53.6%, placebo = 70.5%) or unlikely to be related (RBAC = 42.9%, placebo = 26.9%) to the study interventions. Nonetheless, the oncologists rated three adverse events (diarrhoea, abdominal pain, and dysgeusia) as possibly study-related at the time of reporting, with one in the RBAC group and two in the placebo group. As these adverse events were mild and mostly resolved during the trial, they were subsequently deemed not likely to be caused by the study interventions. Overall, RBAC was considered safe to consume.

Correlations of significant outcomes

Table 7 shows the pairwise correlation coefficients of the QL2, IFN-γ, IL-1RA, IL-12p40, WBC, AST, and TP as significant outcomes of this trial. A linear association between the global QoL of the participants (QL2) with IL-1RA ($r = 0.245$), IL-12p40 ($r = 0.246$) and TP ($r = 0.310$) was detected, demonstrating a positive link between QoL and the immune response (IFN-γ, IL-1RA, IL-12p40) and nutritional status (TP). IL-1RA and IL-12p40 exhibited a very high correlation ($r = 0.907$), indicating the interrelatedness of these two cytokines. Although the correlation between IFN-γ and QL2 was not significant ($r = 0.168$), the level of antitumour IFN-γ did exhibit strong correlations with both IL-1RA ($r = 0.738$) and IL-12p40 ($r = 0.804$). Moreover, the WBC level was also shown to correlate positively with TP ($r = 0.407$) and with the cytokines of IFN-γ ($r = 0.211$), IL-1RA ($r = 0.205$) and IL-12p40 ($r = 0.200$). These results suggest that cellular immunity plays a vital role in the observed improved QoL of the RBAC group over the placebo group. In contrast, the liver function marker AST correlates negatively with IFN-γ ($r = 0.240$), IL-12p40 ($r = 0.270$) and TP ($r = 0.258$).

Analysis of lifestyle factors

RM ANOVA was applied to analyse the Australian Recommended Food Score (ARFS) derived from AES for diet assessment[19], metabolic equivalent of task (MET) score for physical activity and CAMQ score for usage and belief in complementary therapies. Analyses of ARFS and CAMQ scores were unremarkable. Only the MET score showed a significant difference for time effect ($F[4, 56] = 4.193$, $p = 0.005$, $eta^2[g] = 0.134$). However, pairwise comparisons between time points by group did not reveal any significant difference for both groups after adjustment for multiple comparisons. Hence, physical activity level was unlikely to be a confounding variable that could influence the between-group differences in the current research.

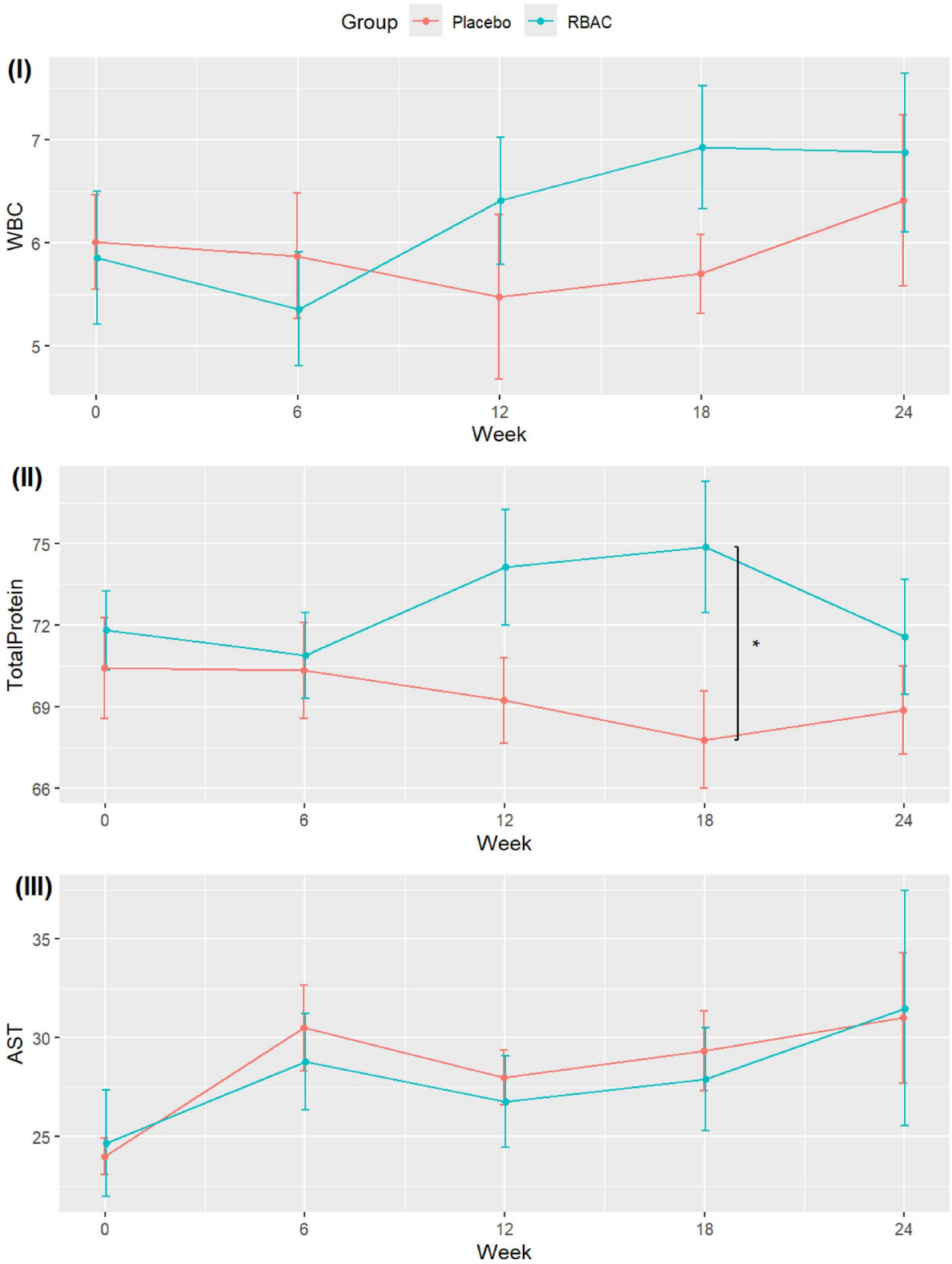

Fig. 5. Plots of (I) mean white blood cell count (WBC), (II) total protein, and (III) aspartate transferase (AST) for RBAC and placebo groups over time.*Significant difference $p \leq 0.05$. RBAC = rice bran arabinoxylan compound.

	RBAC	Placebo	*p* value
Number of participants (*N*)	**12**	**17**	
Number of AEs reported	28 (100%)	78 (100%)	
Mean AE per patient	2.33 ± 3.22	4.59 ± 2.87	$p = 0.066$
CTCAE grade			
1—Mild	21 (75.0%)	62 (79.5%)	$p = 0.365$
2—Moderate	6 (21.4%)	9 (11.5%)	
3—Severe	0 (0%)	0 (0%)	
4—Life-threatening	0 (0%)	1 (1.3%)	
5—Death	1 (3.6%)	1 (1.3%)	
Trial			
1—Not related	15 (53.6%)	55 (70.5%)	$p = 0.191$
Relationship			
2—Unlikely	12 (42.9%)	21 (26.9%)	
3—Possible	1 (3.6%)	2 (2.6%)	
4—Probable	0 (0%)	0 (0%)	
5—Definite	0 (0%)	0 (0%)	
Most common			
Fatigue	4 (14.3%)	10 (12.8%)	$\mathbf{p = 0.006}$**
Events			
Diarrhoea	2 (7.1%)	4 (5.1%)	
Nausea	2 (7.7%)	4 (5.1%)	
Oral thrush	0 (0%)	6 (7.7%)	
Rash	0 (0%)	6 (7.7%)	
Constipation	1 (3.6%)	4 (5.1%)	
Cough	2 (7.1%)	3 (3.9%)	
Peripheral neuropathy	1 (3.6%)	3 (3.9%)	
Pain	1 (3.6%)	2 (2.6%)	
Shortness of breath	1 (3.6%)	2 (2.6%)	
Other isolated events	14 (50.0%)	34 (43.6%)	

Table 6. Comparisons of the adverse events reported between RBAC and placebo groups. Significant values are in bold. Continuous variable is presented in mean ± standard deviation, and the hypothesis testing of two means is based on the two-sided Student's t-test. Significant testing of categorical variables is computed with Fisher's exact test. AEs = Adverse events; CTCAE = Common Terminology Criteria for Adverse Events; RBAC = rice bran arabinoxylan compound.

Pearson's *r*	QL2	IFN-γ	IL-1RA	IL-12p40	WBC	AST	TP
QL2	1						
IFN-γ	0.168	1					
IL-1RA	**0.245***	**0.738*****	1				
IL-12p40	**0.246***	**0.804******	**0.907******	1			
WBC	0.087	**0.211***	**0.205***	**0.200***	1		
AST	-0.054	**-0.240***	-0.111	**-0.270***	0.029	1	
TP	**0.310****	0.051	-0.008	0.102	**0.407*****	**-0.258***	1

Table 7. Pairwise comparisons of the correlation among global quality of life score (QL2), interferon-gamma (IFN-γ), interleukin-1RA (IL-1RA), interleukin-12p40 (IL-12p40), white blood cell count (WBC), creatinine (Cr) and total protein (TP). Significant values are in bold. Pearson correlation coefficient (*r*):*weak,**moderate,***strong,****very strong. Supplementary materials. S1. Details of Study Methodology. S2. Summary of RM-ANOVA Results (F-statistics).

Discussion

This pilot study determined that RBAC improved patients' overall QoL during active cancer treatment, with a statistically significant difference compared to placebo. Notably, the mean global QoL scales of participants taking RBAC were significantly higher than those taking placebo at weeks 6 and 24, with effect size estimates (Cohen's *d*) of 1.118 and 0.971, respectively. Based on the evidence-based guidelines by Cocks, King[23] for the

interpretation of QLQ-C30, the effect size of cross-sectional differences in the global QoL for clinical relevance can be interpreted as small (0.2–0.4), medium (0.4–0.6), or large (>0.6). Hence, the QoL differences observed in this study were considered large and thus clinically significant. Such favourable results in QoL maintenance with RBAC are consistent with the findings of Tan and Flores[24], who reported a statistically significant difference in the mean global QoL scales ($p=0.019$), favouring RBAC over placebo two months after radiation treatment in participants with head and neck cancers.

The final results of global QoL scores are also consistent with those observed during the interim analysis[15], albeit with a marginally lower effect size estimate (0.147 vs. 0.267). Since the effect size statistic measures the variance of the sample rather than the population, it will tend to overestimate the effect size with a small sample and the bias is reduced with a larger cohort[25]. Notably, a matched comparison of 33 interim-final analyses in oncology clinical trials reported that the effect sizes of final analyses were lower by a median of 31% compared to the effect sizes from interim analyses[26]. Hence, a reduction in the effect size estimate in the present study is within expectation.

In addition to improving global QoL, participants in the RBAC group reported significantly lower symptom severity for fatigue, pain, dyspnoea, and appetite loss compared to the placebo group, as measured by the EORTC QLQ-C30. RTE estimates indicated significantly greater reductions in these symptoms in the RBAC group compared to the placebo group at multiple time points, most notably for appetite loss at week 12 ($p<0.01$) and dyspnoea at week 18 ($p<0.05$). This finding is supported by a marginally lower mean number of adverse events per participant in the RBAC group compared to the placebo group (2.33 ± 3.22 vs. 4.59 ± 2.87). These findings suggest that the relatively reduced symptom burden during cancer treatment may have contributed to improved role, social, and possibly cognitive functioning in the RBAC group as well as lowering the perceived cancer-related financial stress.

Consistent with these results, Masood, Sheikh[27] reported that breast cancer patients taking RBAC during six cycles of chemotherapy experienced fewer incidences of anorexia/tiredness, nausea/vomiting, alopecia, and weight loss compared to the control group who did not take RBAC. Similarly, Petrovics, Szigeti[28] demonstrated that in cancer patients with chronic fatigue syndrome, RBAC plus oncothermia, a specialised type of hyperthermia targeting tumours, significantly alleviated fatigue symptoms ($p<0.001$) compared to the control group, during active treatment.

The higher occurrence of adverse events and side effects from the cancer treatment led to a higher dropout in the placebo group in this study. Specifically, seven out of the 16 who received the placebo (43.75%) discontinued the trial, compared to only one out of 11 participants in the RBAC group (9.09%). The higher dropout rate in the placebo group could be partially due to the higher number of participants receiving chemotherapy treatment in the placebo ($n=12$) versus RBAC ($n=7$), as chemotherapy is known to be less tolerable than immunotherapy in advanced solid-organ malignancies[29]. Five of the seven participants in the placebo group who dropped out were undergoing chemotherapy (one with stage IV cancer and four with stage III cancer).

This disparity in attrition rates, despite the blinded design, raises potential concerns about the study's internal validity; however, it does not necessarily bias the results[30]. In clinical research, lower health-related QoL values are known to be related to dropout and death. Most prominently, the global QoL scale, role functioning, physical functioning, and fatigue symptom score in the QLQ-C30 were key early dropout indicators, according to Gebert, Schindel[31]. Hence, unequal dropout rates should be expected if one group has a significantly better QoL in a controlled trial.

Another randomised controlled trial of RBAC also observed a considerable disparity in dropout rates, albeit in a different cancer patient group. Takahara and Sano[32] evaluated the adjunctive effects of RBAC on standard complementary and supportive care in people with progressive and metastasised cancer over 18 months. Of the 109 assigned to the control group, 53 (49%) patients dropped out due to increased intensity of cancer-related symptoms and did not survive at the end of the trial. In contrast, no dropout was observed in the RBAC group ($n=96$). The QoL scores improved in both groups among those who remained in the trial, but the RBAC group had a better increase in appetite. Thus, future trials of RBAC supplements should consider incorporating dropout rates due to adverse events as a formal outcome measure as it could be an indirect indicator for QoL.

Nutritional status strongly predicts QoL in cancer patients[33]. However, no significant between-group differences in body composition parameters and nutritional status indices (INI and NLR) were detected in this study. The discordance could be due to the small sample size, the heterogeneity in cancer types, and the aptness of the chosen outcome measures. Notwithstanding, the present research revealed significant differences in TP between RBAC and the placebo group with a medium effect size. Specifically, the RBAC group showed a significantly higher TP level at week 18 compared to the placebo group, even though TP levels of both groups remained within the normal range. Furthermore, TP and global QoL scores showed a positive correlation. Chemotherapy is known to lower serum TP due to its toxicity[34]. An improved TP level in the present study suggests that RBAC could better preserve the hepatic and renal function during treatment contributing to better QoL. Serum TP level, along with its components of albumin and globulin and their ratio (A/G ratio), has been suggested as markers for protein-energy malnutrition by Rahman and Begum[35]. However, this study found no significant between-group differences in albumin level and A/G ratio over time. Thus, the impact of RBAC on the nutritional status of cancer patients during treatment remains unclear and needs further investigation.

In the previous interim analysis of the same trial[15], there was also a significant difference in WBC between group and time. Additionally, the TP level was strongly correlated with WBC. This final analysis, however, yields a much weaker correlation between TP and WBC, and thus does not support the proposition that RBAC could potentially improve QoL through preserving WBC level and nutritional status. Hence, further research is required to explore the underlying mechanisms that influence the QoL enhancement effect of RBAC in cancer patients. For example, the inflammation-induced tryptophan-kynurenine pathway linked to fatigue, depression,

and decreased QoL in patients with solid tumours can be a potential candidate for investigation in future studies[36].

This study also found evidence of cytokine modulation by RBAC with significant differences in IFN-γ, IL-1RA, and IL-12p40 over time between RBAC and placebo groups. The RBAC group appeared to have elevated levels of these cytokines compared to the placebo group. Moreover, these cytokines showed positive correlations with global QoL and WBC. IFN-γ is a pleiotropic cytokine produced mainly by NK cells and NK T cells, which exhibits antitumour, antiviral, and immunomodulatory functions[37]. An animal study by Badr El-din, Noaman[38] showed that tumour-bearing mice treated with RBAC had significantly higher IFN-γ levels (154.54%) that contributed to significantly lower tumour volume (63.27%) and tumour weight (45.2%) as compared to controls ($p < 0.01$). It is well known that RBAC can elevate NK cell activity[39,40]. The activation of NK cell function depends on type-1 macrophages and type-1 dendritic cells producing IL-12[41]. IL-12p40 is a subunit of the IL-12 cytokine produced by dendritic cells to activate the Th1 response and stimulate NK cells to secrete IFN-γ[42]. Hence, the observed elevation in IFN-γ and IL-12p40 in the RBAC group is consistent with increased NK cell activation. Similarly, Cholujova, Jakubikova[43] has also reported that the plasma concentrations of the Th1 cytokines (IL-12, IL-17, TNF-α, and INF-γ) in multiple myeloma patients were significantly elevated ($p < 0.05$) by RBAC ($n = 32$) compared with placebo ($n = 16$) after 3 months in a randomised controlled trial.

It should be noted that IFN-γ levels are expected to be higher in immunotherapy recipients than in those receiving chemotherapy, as immune checkpoint therapy is known to upregulate IFN-γ[44]. The observed high dropout rate among chemotherapy recipients (in both groups) may have influenced its absolute values (in the within-group analysis) in this study. Nevertheless, the effect of RBAC in activating NK cells to increase IFN-γ secretion could potentially enhance the efficacy of immunotherapy and thus has high clinical relevance, given the increasing use of immunotherapy in cancer treatment.

The elevation of IL-1RA in the RBAC group needs further examination. IL-1RA is generally an anti-inflammatory cytokine that binds to IL-1 receptors, thereby preventing the signalling pathway of pro-inflammatory IL-1α and IL-1β. IL-1RA is closely associated with M2 macrophages, along with IL-10, insulin-like growth factor-I, and transforming growth factor-β, in promoting tissue repair, remodelling, and immune suppression[45]. Thus, elevated IL-1RA levels could reduce NK cell activity. However, research has also found that excessive IL-1 is involved in suppressing the immune response in the tumour microenvironment, leading to tumour resistance to immunotherapy[46]. Increasing IL-1RA to counteract the pro-inflammatory effects of IL-1 indirectly stimulates IL-2 production, which enhances NK cell activity against tumour cells[47]. As such, IL-1RA therapy has been used as an anticancer adjuvant to augment the therapeutic efficacy of immunotherapy[48]. Hence, the elevated levels of IFN-γ, IL-1RA, and IL-12p40 in the RBAC group could result from the immunomodulatory effects of RBAC, particularly through inducing dendritic cell maturation, upregulating NK cell activity, promoting tumour cell apoptosis as previously described in the literature[11,50].

It should be noted that the effect size estimates of IFN-γ, IL-1RA, and IL-12p40 were small, and no significant differences were detected in post-hoc analysis with pairwise comparisons. The cytokine profile analysis was an optional trial component performed on a subset of participants (19 out of 29). Due to the small sample size and limited effect sizes, this pilot trial has insufficient power to detect the between-group differences in cytokine profiles at each time point. Therefore, the impact of RBAC intervention on cytokine profiles during active cancer treatment observed in this study is suggestive, and the potential link to patient QoL remains speculative based on the observed trends. These results should be validated in future research.

This pilot study aimed to inform the design of a large-scale clinical trial. Based on the effect size (eta2[g]) of 0.147 for the global QoL scale, a sufficiently powered study needs a sample size of 88 to achieve the estimated power of 95% based on the a priori power analysis of RM ANOVA (2 groups and 5 measurements, $\alpha = 0.5$, $1\text{-}\beta = 0.95$) for within-between interactions. However, anticipating an unequal dropout rate between groups, the future trial should target to recruit up to 115 participants, randomly allocating 66 (~ 40% extra) in the placebo group and 49 (~ 10% extra) in the RBAC group based on an allocation ratio of approximately 1.35 (placebo) to 1 (RBAC).

This study has several limitations. The most notable is the small sample size, which necessitates validation of the results with a larger study. The short trial duration (6 months) also offers no opportunity to observe the participants' QoL posttreatment. Thus, it is unclear how long the QoL-improving effects of RBAC could last. Additionally, the lack of posttreatment follow-up also renders no outcome data for validating whether RBAC treatment could improve the survival odds of cancer patients. Nonetheless, the positive findings provide valuable insights into the therapeutic potential of RBAC in cancer treatment and lay the foundation for further translational research of RBAC.

Conclusions

The RBAC-QoL study showed favourable results, indicating that RBAC improves the QoL for cancer patients undergoing active treatment. Compared to the placebo group, participants in the RBAC group reported better global QoL scores and significantly lower rates of fatigue, pain, dyspnoea, and appetite loss. RBAC was safe to consume with no known adverse effects. The observed reduction in symptoms experienced during cancer treatment also led to better role and social functioning. Additionally, significant increases in serum TP, IFN-γ, IL-1RA, and IL-12p40 were observed in the RBAC group over time, and the TP, IL-1RA, and IL-12p40 showed positive correlations with the global QoL scales. These findings suggest potential interactions between nutritional status, immune modulation, and QoL. However, with a small sample size, the findings should be interpreted cautiously and cannot be relied on as evidence of treatment efficacies. Regardless, this analysis provides valuable information and justification for a larger clinical trial to confirm RBAC's beneficial effects on cancer patients' QoL.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to commercial funding agreement but are available from the corresponding author for non-commercial research use on reasonable request.

Received: 16 January 2025; Accepted: 20 February 2026
Published online: 02 March 2026

References

1. Ferlay, J. et al. *Global Cancer Observatory: Cancer Today* (International Agency for Research on Cancer, Lyon, France, 2024). https://gco.iarc.who.int/today
2. Bray, F. et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J. Clin.* **74**(3), 229–263 (2024).
3. Tamburini, M., Casali, P. G. and Miccinesi, G. Outcome assessment in cancer management. *Surg. Clin. N. Am.* **80**(2), 471–486 (2000).
4. Palumbo, M. O. et al. Systemic cancer therapy: achievements and challenges that lie ahead. *Front. Pharmacol.* **4**, 57 (2013).
5. Katta, B., Vijayakumar, C., Dutta, S., Dubashi, B. and Nelamangala Ramakrishnaiah, V. P. The incidence and severity of patient-reported side effects of chemotherapy in routine clinical care: A prospective observational study. *Cureus* **15**(4), e38301 (2023).
6. Firkins, J., Hansen, L., Driessnack, M. and Dieckmann, N. Quality of life in chronic cancer survivors: A meta-analysis. *J. Cancer Surviv.* **14**(4), 504–517 (2020).
7. Jitender, S., Mahajan, R., Rathore, V. and Choudhary, R. Quality of life of cancer patients. *J. Exp. Ther. Oncol.* **12**(3), 217–221 (2018).
8. Nguyen, L. B. et al. Impact of interventions on the quality of life of cancer patients: A systematic review and meta-analysis of longitudinal research. *Health Qual. Life Outcomes* **21**(1), 112 (2023).
9. Nolazco, J. I. and Chang, S. L. The role of health-related quality of life in improving cancer outcomes. *J. Clin. Translational Res.* **9**(2), 110–114 (2023).
10. Olver, I. et al. Supportive care in cancer—a MASCC perspective. *Support. Care Cancer* **28**(8), 3467–3475 (2020).
11. Ooi, S. L., Micalos, P. S., Kim, J. and Pak, S. C. Rice bran arabinoxylan compound as a natural product for cancer treatment—an evidence-based assessment of the effects and mechanisms. *Pharm. Biol.* **62**(1), 367–393 (2024).
12. Ooi, S. L., McMullen, D., Golombick, T. and Pak, S. C. Evidence-based review of BioBran/MGN-3 arabinoxylan compound as a complementary therapy for conventional cancer treatment. *Integr. Cancer Ther.* **17**(2), 165–178 (2018).
13. Ooi, S. L., Pak, S. C. and Micalos, P. S. Health-related quality of life. In *Modified rice bran arabinoxylan: Therapeutic applications in cancer and other diseases*, (eds Pak, S. C., Ooi, S. L., Micalos, P. S. and Ghoneum, M. H.) 87–99. (Springer, Singapore, 2023).
14. Ooi, S. L. et al. Rice bran arabinoxylan compound and quality of life of cancer patients (RBAC-QoL): Study protocol for a randomized pilot feasibility trial. *Contemp. Clin. Trials Commun.* **19**, 100580 (2020).
15. Ooi, S. L., Micalos, P. S., Zielinski, R. and Pak, S. C. Rice bran arabinoxylan compound and quality of life (RBAC-QoL) of cancer patients: An interim analysis of the RBAC-QoL Study. *Cureus* **16**(1), e53188 (2024).
16. *The National Clinical Trials Governance Framework and User Guide for Health Service Organisations Conducting Clinical Trials* (Australia Government Department of Health, The National Clinical Trials Governance Framework and User Guide for Health Service Organisations Conducting Clinical Trials, 2022).
17. Schulz, K. F., Altman, D. G. & Moher, D. The CG CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMC Med.* **8**(1), 18 (2010).
18. Fayers, P. M. et al. *EORTC QLQ-C30 Scoring Manual* (European Organisation for Research and Treatment of Cancer, 2001).
19. Collins, C. E. et al. The comparative validity and reproducibility of a diet quality index for adults: The Australian Recommended Food Score. *Nutrients* **7**(2), 785–798 (2015).
20. Lee, P. H., Macfarlane, D. J., Lam, T. H. and Stewart, S. M. Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic review. *Int. J. Behav. Nutr. Phys. Activity* **8**(1), 115 (2011).
21. Noguchi, K., Gel, Y. R., Brunner, E. & Konietschke, F. nparLD: An R software package for the nonparametric analysis of longitudinal data in factorial experiments. *J. Stat. Softw.* **50**(12), 1–23 (2012).
22. Falci, S. G. and Marques, L. S. CONSORT: When and how to use it. *Dent. Press. J. Orthod.* **20**(3), 13–15 (2015).
23. Cocks, K. et al. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J. Clin. Oncol.* **29**(1), 89–96 (2011).
24. Tan, D. F. S. & Flores, J. A. S. The immunomodulating effects of arabinoxylan rice bran (Lentin) on hematologic profile, nutritional status and quality of life among head and neck carcinoma patients undergoing radiation therapy: A double blind randomized control trial. *Radiol. J.* **12**, 11 (2020).
25. Olejnik, S. and Algina, J. Generalized eta and omega squared statistics: measures of effect size for some common research designs. *Psychol. Methods* **8**(4), 434–447 (2003).
26. Wayant, C. and Vassar, M. A comparison of matched interim analysis publications and final analysis publications in oncology clinical trials. *Ann. Oncol.* **29**(12), 2384–2390 (2018).
27. Masood, A. I., Sheikh, R., Anwer, R. A. and BIOBRAN MGN-3; effect of reducing side effects of chemotherapy in breast cancer patients. *Prof. Med. J. [Internet]* **20**(1), 13 (2013).
28. Petrovics, G. et al. Controlled pilot study for cancer patients suffering from chronic fatigue syndrome due to chemotherapy treated with BioBran (MGN-3 Arabinoxylane) and targeted radiofrequency heat therapy. *Eur. J. Integr. Med.* **8**, 29–35 (2016).
29. Magee, D. E. et al. Adverse event profile for immunotherapy agents compared with chemotherapy in solid organ tumors: A systematic review and meta-analysis of randomized clinical trials. *Ann. Oncol.* **31**(1), 50–60 (2020).
30. Bell, M. L., Kenward, M. G., Fairclough, D. L. and Horton, N. J. Differential dropout and bias in randomised controlled trials: when it matters and when it may not. *BMJ* **346**, e8668 (2013).
31. Gebert, P., Schindel, D., Frick, J., Schenk, L. and Grittner, U. Characteristics and patient-reported outcomes associated with dropout in severely affected oncological patients: An exploratory study. *BMC Med. Res. Methodol.* **21**(1), 77 (2021).
32. Takahara, K. and Sano, K. The life prolongation and QOL improvement effect of rice bran arabinoxylan derivative (MGN-3, Biobran) for progressive cancer. *Clin. Pharmacol. Therapy* **14**(3), 267–271 (2004).
33. Lis, C. G., Gupta, D., Lammersfeld, C. A., Markman, M. and Vashi, P. G. Role of nutritional status in predicting quality of life outcomes in cancer—a systematic review of the epidemiological literature. *Nutr. J.* **11**(1), 27 (2012).
34. Abbasi, B., Hayat, A., Lyons, M., Gupta, A. and Gupta, S. Serum protein and electrolyte imbalances are associated with chemotherapy induced neutropenia. *Heliyon* **8**(7) (2022).
35. Rahman, M. Z. and Begum, B. A. Serum total protein, albumin and A/G ratio in different grades of protein energy malnutrition. *Mymensingh Med. J.* **14**(1), 38–40 (2005).
36. Lanser, L. et al. Inflammation-induced tryptophan breakdown is related with anemia, fatigue, and depression in cancer. *Front. Immunol.* **11**, 249 (2020).

37. Jorgovanovic, D., Song, M., Wang, L. and Zhang, Y. Roles of IFN-γ in tumor progression and regression: A review. *Biomark. Res.* **8**(1), 49 (2020).
38. Badr El-din, N. K., Noaman, E. and Ghoneum, M. In vivo tumor inhibitory effects of nutritional rice bran supplement MGN-3/Biobran on Ehrlich carcinoma-bearing mice. *Nutr. Cancer* **60**(2), 235–244 (2008).
39. Ghoneum, M. Enhancement of human natural killer cell activity by modified arabinoxylane from rice bran (MGN-3). *Int. J. ImmunotherAcademic* **14**(2), 89–99 (1998).
40. Ghoneum, M. and Abedi, S. Enhancement of natural killer cell activity of aged mice by modified arabinoxylan rice bran (MGN-3/Biobran). *J. Pharm. Pharmacol.* **56**(12), 1581–1588 (2004).
41. Hajto, T. The therapeutic application of rbac in cancer. In: (eds Pak, S. C., Ooi, S. L., Micalos, P. S. and Ghoneum, M. H.) Modified Rice Bran Arabinoxylan: Therapeutic Applications in Cancer and Other Diseases. Singapore: Springer Nature Singapore; 67–79. (2023).
42. Shemesh, A., Pickering, H., Roybal, K. T. and Lanier, L. L. Differential IL-12 signaling induces human natural killer cell activating receptor-mediated ligand-specific expansion. *J. Exp. Med.* **219**(8), e20212434 (2022).
43. Cholujova, D. et al. MGN-3 arabinoxylan rice bran modulates innate immunity in multiple myeloma patients. *Cancer Immunol. Immunother* **62**(3), 437–445 (2013).
44. Ni, L. and Lu, J. Interferon gamma in cancer immunotherapy. *Cancer Med.* **7**(9), 4509–4516 (2018).
45. Viola, A., Munari, F., Sánchez-Rodríguez, R., Scolaro, T. and Castegna, A. The metabolic signature of macrophage responses. *Frontier Immunol.* **10**, 1462 (2019).
46. Singh, M. Chapter 3 - Interleukin-1-mediated immune suppression and resistance to immunotherapy in cancer. In *Multifaceted Role of IL-1 in Cancer and Inflammation* (ed Singh, M.) 87–98 (Academic, 2023).
47. Conti, P. et al. Human recombinant interleukin-1 receptor antagonist (hrIL-1ra) enhances the stimulatory effect of interleukin-2 on natural killer cell activity against molt-4 target cells. *Int. J. Immunopharmacol.* **14**(6), 987–993 (1992).
48. Fang, Z., Jiang, J. and Zheng, X. Interleukin-1 receptor antagonist: An alternative therapy for cancer treatment. *Life Sci.* **335**, 122276 (2023).
49. Stanilov, N., Miteva, L., Jovchev, J., Cirovski, G. and Stanilova, S. The prognostic value of preoperative serum levels of IL-12p40 and IL-23 for survival of patients with colorectal cancer. *APMIS* **122**(12), 1223–1229 (2014).
50. Ooi, S. L. et al. The health-promoting properties and clinical applications of rice bran arabinoxylan modified with shiitake mushroom enzyme—a narrative review. *Molecules* **26**(9), 2539 (2021).

Acknowledgements

The authors acknowledge the assistance of Emily Schupfer, Tegan Grosfeld, and Ki Kwon in trial coordination and data collection for this study.

SLO acknowledges support through the Australian Government Research Training Program scholarship for his PhD study. This study contributed toward the Ph.D. degree for SLO.

Author contributions

SLO: Conceptualisation, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Visualisation.**PSM:**Conceptualisation, Methodology, Validation, Writing - Review and Editing.**RZ**: Conceptualisation, Methodology, Investigation, Validation, Resources, Writing - Review and Editing.**SCP**: Conceptualisation, Methodology, Validation, Resources, Writing - Review and Editing, Supervision, Project administration.**JL**: Resources, Writing - Review and Editing.**SK**: Investigation, Resources, Writing - Review and Editing.**SG**,**TG**: Writing - Review and Editing.

Funding

This clinical trial is funded by Daiwa Pharmaceutical Co., Ltd. (Japan) and BioMedica Nutraceuticals Pty Ltd. (Australia). The funding bodies were not involved in study design, data collection, management, analysis, interpretation, or the decision to submit for publication.

Declarations

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee (HREC) of Concord Repatriation General Hospital, Sydney Local Health District (Application No. 2019/ ETH00489) and Charles Sturt University HREC (Protocol No. H19244). All participants in the study provided written informed consent before starting the trial.

Consent for publication

The manuscript has been read and approved by all named authors, and there are no other persons who satisfied the criteria for authorship but are not listed. All authors had agreed to the publication. The manuscript contains no participant's personal data in any form.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-026-41554-8.

Correspondence and requests for materials should be addressed to S.C.P.

Reprints and permissions information is available at www.nature.com/reprints.