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Rice bran arabinoxylan compound and quality of life of cancer patients (RBAC-QoL): Study protocol for a randomized pilot feasibility trial

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ABSTRACT

Introduction: Rice bran arabinoxylan compound (RBAC) is a nutraceutical for enhancing a depleted immune system during and after cancer treatment. This pilot feasibility trial aims to evaluate the effects of RBAC on cancer patients' quality of life during active treatment, compared to placebo, using a validated questionnaire. Other outcome measures include changes in inflammatory and nutritional status, cytokine profile, and gut microbiota.

Methods/Design: The study will recruit 50 participants from a regional cancer center in Australia. Patients aged 18–70, diagnosed with solid organ cancers stage II and above, and currently undergoing active systemic therapies, are eligible. Random allocation of participants into two groups is stratified based on metastatic status and treatment type. The dosage is either 3 g/day of RBAC or placebo in identical packaging. The participants, study coordinator, and treating oncologists are blinded to the interventions. Data collections are at baseline and at four follow-up sessions, which are six weeks apart (24 weeks). Statistical analysis will involve a protected p-value with multiple dependent values and analyzed by ANOVA with repeated measures on the occasion of testing and with both a full Bonferroni or Sidak corrections applied to protect against Type I errors. Any observed significance warrants further analysis with pairwise comparisons. Analysis of covariance will also be performed to assess any influence of the demographic data, cancer diagnosis, as well as changes in physical activity, dietary habits, and complementary medicine usage. Comparisons of gut microbiota will be based on the analysis of the fecal microbiome using 16S ribosomal ribonucleic acid amplicon sequencing. The proposed research timeline is from October 2018 to May 2022.

Trial registration: ANZCTR. Reg No: ACTRN12619000562178p.

1. Introduction

The health-related quality of life (QoL) of cancer patients includes the patients' subjective perceptions of symptoms, physical, emotional, social, and cognitive functions, as well as side effects of treatment [1]. Achieving benefits in terms of QoL has become increasingly important in cancer treatment, with the traditional endpoint of survival deemed insufficient as the only treatment outcome [1].

Immune dysfunction leading to inflammation is the underlying mechanism that affects the patient physically and emotionally, which also indirectly impacts social functioning [2]. Inflammation is a hallmark of cancer as it is associated with the microenvironment of almost all tumor sites [3–5]. Persistent, localized inflammation can lead

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to the leaking of pro-inflammatory cytokines into circulation and initiates a systemic inflammatory cascade [6,7]. There is a consistent relationship between increasing systemic inflammation and worsening of all QoL parameters, such as global health, role, physical and social functioning, and fatigue, pain, appetite symptoms [3,8]. Increased inflammation in the central nervous system also triggers behavioral comorbidities, including depression, anxiety, fatigue, cognitive disturbances, and neuropathic pain, which affect QoL [9].

Rice bran arabinoxylan compound (RBAC) can potentially improve the QoL of cancer patients by modulating the immune and inflammatory responses. The partially absorbed RBAC directly exerts immunomodulating effects, which include upregulating natural killer (NK) cell activity, augmenting phagocytic cellular functions, modulating cytokines production, and promoting T and B lymphocyte proliferation, in addition to acting as a natural adjuvant for dendritic cells (DCs) [10–13]. The remaining components that are resistant to digestion serve as prebiotics to the gut microbiota. The gut microbiota can indirectly induce anti-inflammatory and immunomodulating effects in the host [14], and affect behavioral changes via the gut-brain axis [15]. The combined effects upregulate the immune cells into the anti-tumor phenotypes and balance the secretion of pro- and anti-inflammatory cytokines, leading to the reduction in systematic inflammation. QoL enhancements such as subjective improvements in sleep, appetite, digestion, physical activity, and decrease in anxiety and pain as well as reduced adverse effects during cancer therapy, have been reported in several RBAC case studies [16–23]. Supplementation with RBAC (250 mg/d) for three months also significantly enhanced the QoL scores (measured with SF-12v2 questionnaire) of healthy old adults (n = 60) in a randomized controlled trial (RCT) [24].

Clinical research on the effect of RBAC on cancer patients' QoL is still in its early stage. Only a small number of clinical trials [25–28] are available in the literature (see Table 1). These trials suffer from several limitations, including inadequate study design with unclear risks of bias as well as the use of non-validated QoL measurements. Furthermore, placebo treatment is well known to positively affect QoL, especially in improved control of symptoms such as pain, appetite, and fatigue but rarely with actual tumor response [29,30]. None of the existing trials attempted to rule out the impact of placebo in the observed QoL improvement. As such, there is a lack of well-designed RCTs that investigate the effect of RBAC on the QoL of cancer patients. Specifically, there is no clinical trial that attempts to assess the effect of RBAC on cancer patients' QoL compared to placebo using a validated QoL questionnaire alongside measures of cytokines and gut microbiome responses.

2. Methods/Design

2.1. Objectives

The RBAC-QoL study (Protocol No. H19244, version 2.2.1, release February 24, 2020) is a 24-week randomized placebo-controlled pilot feasibility trial with the study coordinator, patients, and the oncologists blinded to the intervention. The primary objective is to determine the potential effect of RBAC compared to placebo on the QoL of cancer patients undergoing active treatment, based on the European Organisation for the Research and Treatment of Cancer (EORTC) core 30-item QoL questionnaire (QLQ-C30 version 3.0). The effect size estimate on the QLQ-C30 scores will inform the planning of a larger trial for further hypothesis testing.

A secondary objective is to determine changes in the nutritional and inflammatory status of the body as additional outcome measures associated with the changes in the patients' QoL. As exploratory measures, this study also aims to assess the immunomodulating effects of RBAC based on changes in cytokines profile, as well as changes in the diversity and composition of gut microbiota as potential underlining mechanisms of RBAC supplementation.

2.2. Study setting and recruitment

The study site is a regional cancer center in the Central Western of New South Wales, Australia. Recruitment will target patients starting active treatment in the center, including those with newly diagnosed or recurrent cancer. Eligible patients will be referred to the trial by their treating oncologists. A study coordinator, trained in Good Clinical Practice, will discuss the trial with potential participants based on the information provided on the Patient Information Sheet and Consent Form (Supplementary S1). Patients will be given at least 24 h for consideration of the project and undertake informed discussions with their primary-care doctors and with family members. The study coordinator will follow up with potential participants to provide clarification and subsequently obtain written consent from willing participants in the presence of the principal investigator on site.

Table 1
Summary of clinical trials evaluating the effects of RBAC on the QoL of cancer patients.

Study	Patients	Design	Interventions	Outcomes	Limitations
Takahara & Sano [26]	Progressive and metastasized cancer patients. N = 205 (RBAC: 96, Control: 109)	Randomized control trial. Duration: 18 months.	3 g/day RBAC with CAT versus CAT only.	RBAC group achieved a higher survival rate and better appetite than the control group.	Non-validated QoL questionnaire for appetite, pain, malaise, and nausea only; Unclear effect of CAT as active control; High risk of bias.
Masood et al. [25]	Breast cancer patients. N = 50 (RBAC: 25, Control: 25)	Randomized control trial. Duration: 6 months.	3 g/day RBAC 1 week before & 1 week after each chemotherapy cycle versus chemotherapy only. 6 cycles of chemotherapy.	RBAC group experienced a significant reduction in tiredness, increased appetite; no anti-emetic needs; and less hair fall compared to the control group.	Non-validated QoL questionnaire; No placebo-control; Lack of detailed statistical analysis.
Hajto et al. [27]	Advanced (II-IV) stages cancer patients of various malignancies. N = 35.	Non-randomized trial. Duration: 6 months.	12–45 mg/kg of RBAC plus 0.5–1.0 ng/kg mistletoe lectin twice a week. Conventional oncologic therapy.	Improvement of physical activity and decrease of side effects during conventional oncotherapy.	Non-randomized study; RBAC was not applied as a monotherapy.
Petrovics et al. [28]	Cancer patients (with different malignancies) with chronic fatigue syndrome. N = 50 (RBAC: 25, Control: 25)	Randomized control trial. Duration: 6 months.	3 g/day of RBAC and Oncothermia for 24 weeks with chemo- or radiotherapy as routine care versus routine care only.	RBAC group showed changes in body pH levels to be less acidic. The average fatigue scale was significantly reduced in the RBAC group compared to no change in the control group.	RBAC was not applied as a monotherapy; the QLQ-C30 questionnaire was used but results not reported.

Abbreviations: RBAC, rice bran arabinoxylan compound; CAT, complementary and alternative therapies; QoL, quality of life; QLQ-C30, quality of life questionnaire – core 30 questions.

2.3. Sample size

As there is no previous study of RBAC supplement on the QoL of cancer patients based on the QLQ-C30 questionnaire, there is no effect size data for performing *a priori* analysis for the required sample size. We have selected the sample size of the present study based on the following considerations:

1. The guidelines for sample size calculations for QLQ-C30 scores by Cocks et al. [31] indicate that a standardized effect size of 0.35 for the Global QoL score is considered a small effect that is likely to be clinically relevant. Analysis with F-tests (ANOVA with two groups and five repeated measures) using *a priori* parameters with an alpha of 0.05, power 0.8, and an effect size of 0.35 resulted in a total sample size of 42.
2. For a standardized effect size of 0.25, Cocks and Torgeson [32] also recommended a sample size of 42 for the main trial of continuous outcome measures with a power of 0.8 based on one-sided confidence interval calculation.
3. Whitehead et al. [33] recommended the sample size per intervention arm to be 25 in a pilot trial for any main trial designed with 90% power, two-sided 5% significance, and small standardized effect size (0.2).

Hence, a total sample size between 42 and 50 is deemed reasonable. This study will have a sample size of 50, with 25 in each group to cater for any potential dropout. This number also represents a practical choice since the study site is a small center with a limited number of patients. Recruitment will be on-going until the desired sample size is reached.

2.4. Eligibility criteria

Inclusion criteria: Adult patients aged 18–70 years old at the time of providing informed consent; Diagnosed with any solid organ cancer (including colon, breast, melanoma, lung, pancreatic, bladder, and prostate) of stage II and above; Currently undergoing active treatment for cancer; Received an explanation of the purpose and methods of the study; Provided written consent prior to the start of the trial; Adequately maintained major organ function (bone marrow, liver, and kidneys) with laboratory parameters as shown in Table 2.

Exclusion criteria: Existing mental health conditions that may impede the ability to provide consent; Inability to complete QoL questionnaire with minimal assistance; Pregnant, lactating, or plan to get pregnant during the period of the study; Active or prior documented autoimmune or inflammatory disorders within the last five years, except for vitiligo or alopecia, stable hypothyroidism on hormone replacement, and any chronic skin condition that does not require systemic therapy. Patients with chronic but stable conditions, including diabetes, hypertension, and chronic obstructive pulmonary disease, will not be excluded.

Table 2
Screening parameters for eligible patients.

#	Parameter	Required level
A. Bone Marrow Function		
i.	Absolute neutrophil count (ANC)	$>1.5 \times 10^9$/L
ii.	Platelet count	$\geq 100 \times 10^9$/L
iii.	Haemoglobin	≥10.0 g/dl
B. Hepatic Function		
i.	Aspartate transaminase (AST)	≤3x ULN
ii.	Alanine transaminase (ALT)	≤3x ULN
iii.	Bilirubin	≤1.5x ULN (<2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)
C. Renal Function		
i.	Estimated glomerular filtration rate (eGFR)	≥45 ml/min using the Cockcroft-Gault

Abbreviations: dl – decilitre; g – gram; L – Litre; ml – milliliter; min – minute; ULN – Upper Limit of Normal.

2.5. Interventions

The interventions are either RBAC or placebo powder for 24 weeks. As shown in Table 3, each RBAC sachet contains 1 g of the active ingredient with 1 g of excipients (Total = 2 g). The placebo powder contains 1.26 g of inert corn starch and 0.74 g of other excipients (Total = 2 g). The placebo has a slight difference in excipient contents to achieve acceptable melt in the mouth, as well as a negligible amount of caramel, which is for binding and color matching. The placebo is similar in color, odor, and taste compared to the active compound. The plastic sachets that contain both RBAC and placebo powder are also identical in appearance, making them indistinguishable by the participants.

The participants will take two sachets in the morning and one sachet in the evening as a dietary supplement during or after meals for a total daily dosage of 3 g of RBAC. The participants are to thoroughly mix the contents into half a glass (approximately 125 ml) of water and drink it right away. Should the participants need to fast before their treatment, they should also stop taking the supplement until they resume eating.

To ensure adherence, the study coordinator will repeatedly provide instructions for taking supplement sachets, including timing, storage, and what to do in the event of a missed dose during initial dispensing and every subsequent visit. The participants are to return unused sachets at each follow-up visit to be counted and recorded for compliance assessment.

Participants will continue their active cancer treatment and medications as instructed by their treating oncologists. However, all concomitant medications used during the study will be recorded and updated at baseline and during each visit.

2.6. Assignment of interventions

To ensure both groups have the same size, the manufacturer will supply a total of 50 intervention packages equally divided between RBAC and placebo (25:25). The packages will be labeled sequentially from 1 to 50 by intermixing RBAC and placebo. Each sachet within will also be marked according to the number assigned to the containing package. A master list that records the actual contents will be kept in a secure folder with access limited to the research team only after the experiment is complete.

As stages of cancer diagnosis at baseline and the types of treatment undergone are confounding variables that can affect QoL, participants are allocated into the two groups using stratified randomiza-

Table 3
The ingredients of an active or placebo intervention sachet (net weight in milligram, mg).

Ingredient	Active	Placebo
Microcrystalline Cellulose	500	500
Modified Starch	260	1260
Dextrin	200	200
Tricalcium Phosphate	40	40
Rice bran arabinoxylan compound	1000	–
Caramel	–	Δ
Total	2000	2000

Δ – An infinitesimal amount of caramel is added for coloring and as a binder.

tion, based on metastatic status (yes or no) and treatment type (chemotherapy or immunotherapy). Upon recruitment, the participant will be assigned a unique identifier (Range: 1–50), generated with a computer program, to receive the supplement package of the corresponding number. The study coordinator who recruits the participants has no means to influence the allocation and no knowledge of the potential allocation outcome. The participant, the treating oncologist, and the study coordinator (data collector) interacting with the participants during each visit for assessment will be blinded to study intervention.

To conceal allocation but allow for emergency code-breaking, the information of the actual intervention contents is kept in opaque envelopes that are numbered and sealed in advance. A code break is done through opening the corresponding sealed envelope and should occur only in exceptional and highly unlikely circumstances. For instance, when knowledge of the actual content is essential in the opinion of the treating oncologist for management of an adverse event, potentially due to RBAC. All code breaks (with reason) will be recorded.

2.7. Outcome measures

The QLQ-C30 has both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea & vomiting, pain), a global health status/QoL scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). Scoring of QoL follows the EORTC/QLQ-C30 manual [34], with each item/scale mapped to a linear transformation of 0–100. The mean score of each item/scale on the QLQ-C30 will be calculated for each group at each study time point for the mean difference between-group comparison. This pilot study aims to determine which of these scales/items are the most appropriate primary outcome measures that best reflect any potential effect of RBAC compared to placebo on the QoL of cancer patients.

Secondary outcome measures are the assessment of the nutritional and inflammatory status of the patients, which include body composition (body weight, muscle mass, body fat percentage), body mass index, the neutrophil to lymphocyte ratio (NLR), and the inflammatory-nutritional index (INI = the ratio of C-Reactive Protein [CRP] and albumin).

Exploratory outcome measures are cytokines profile, as shown in Table 4, which will be evaluated separately to assess the potential immunomodulating effects of RBAC. Additionally, stool samples will be collected throughout the trial for the analysis of changes in the gut microbiota of the participants who provide additional consent. The study will assess comparisons of the microbiota diversity (alpha diversity) and composition of different gut bacteria groups (beta diversity) between the two different groups of patients by studying the fecal microbiome based on 16S ribosomal ribonucleic acid (rRNA) gene sequencing.

Table 4
Human cytokine/chemokine array 42-plex.

#	Cytokine/Chemokine	Name
1	EGF	Epidermal growth factor
2	Eotaxin-1	Eosinophil chemotactic protein (CCL11)
3	FGF-2	Basic fibroblast growth factor
4	Flt-3L	Fms-related tyrosine kinase 3 ligand
5	Fractalkine	Chemokine (C-X3-C motif) ligand
6	G-CSF	Granulocyte colony-stimulating factor
7	GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
8	GROα	Chemokine (C-X-C motif) ligand 1
9	IFNα2	Interferon alpha-2
10	IFNγ	Interferon-gamma
11	IL-10	Interleukin 10 (cytokine synthesis inhibitory factor)
12	IL-12P40	Interleukin-12 subunit p40
13	IL-12P70	Interleukin-12 subunit p70
14	IL-13	Interleukin-13
15	IL-15	Interleukin-15
16	IL-17A	Interleukin-17A
17	IL-18	Interleukin 18
18	IL-1α	Interleukin 1 alpha
19	IL-1β	Interleukin 1 beta
20	IL-1RA	Interleukin 1 receptor antagonist
21	IL-2	Interleukin 2
22	IL-3	Interleukin 3
23	IL-4	Interleukin 4
24	IL-5	Interleukin 5
25	IL-6	Interleukin 6
26	IL-7	Interleukin 7
27	IL-8	Interleukin 8
28	IL-9	Interleukin 9
29	IP-10	Interferon gamma-induced protein 10 (CXCL10)
30	MCP-1	Monocyte Chemoattractant Protein-1
31	MCP-3	Monocyte chemotactic protein 3
32	MDC	Macrophage-derived chemokine
33	MIP-1α	Macrophage Inflammatory Proteins 1α (CCL3)
34	MIP-1β	Macrophage Inflammatory Proteins 1β (CCL4)
35	PDGF-AA	Platelet-Derived Growth Factor-AA
36	PDGF-BB	Platelet-Derived Growth Factor-BB
37	RANTES	Regulated on activation, normal T cell expressed and secreted (CCL5)
38	sCD40L	Soluble CD40 ligand
39	TGF-α	Transforming growth factor-alpha
40	TNF-α	Tumour necrosis factor-alpha
41	TNF-β	Tumour necrosis factor-beta
42	VEGF-A	Vascular endothelial growth factor-A

2.8. Data collection, management, and analysis

Fig. 1 shows the timeline of participation. Participants will complete the QLQ-C30 questionnaire at baseline and on four visits, each at six weeks apart. The body composition of the participants will be measured using a body composition monitor (Tanita Inner Scan BC-587) based on the Bioelectric Impedance Analysis technology.

Diet, exercise, and concurrent use of complementary therapies are known confounding variables that may affect cancer patients' QoL outcomes. To ensure the changes of QoL are the effect associated with the intervention and not due to changes in lifestyle behaviors, data on the participants' diet, physical activities, and use of complementary therapies during the trial will also be collected using an online food frequency questionnaire (The Australian Eating Survey® FFQ), the International Physical Activity Questionnaire, and a Use of Complementary and Alternative Medicine Questionnaire specifically developed for this study (See supplementary S2), respectively. However, in order not to overburden the participants, completion of these additional questionnaires is optional. Participants can decide whether to complete these questionnaires at the time of providing consent.

Blood samples will be collected by a local pathological laboratory within four days before or three days after every visit. All blood tests required, except the cytokine profile, will be tested locally with the results transmitted to the cancer center electronically for routine clinical use. The study coordinator will record all required blood test results in a data collection form. Additional blood samples will be centrifuged into serum and stored at −80 °C. The serum samples will be sent to a reputable commercial company for the profiling of cytokines in batches.

Stool sample collection, storage, and analysis will follow a standardized protocol to ensure reliable gut microbiome analysis [35]. Since fecal testing is not part of the standard of care in cancer treatment, the collection of stool samples is also an optional study component. The participants can choose not to provide their stool samples at the time of consent. A consented participant will be instructed to take a swab of his/her stool sample using a fit-for-purpose specimen collection kit (Microba Research Participant Sampling Kit) between one to

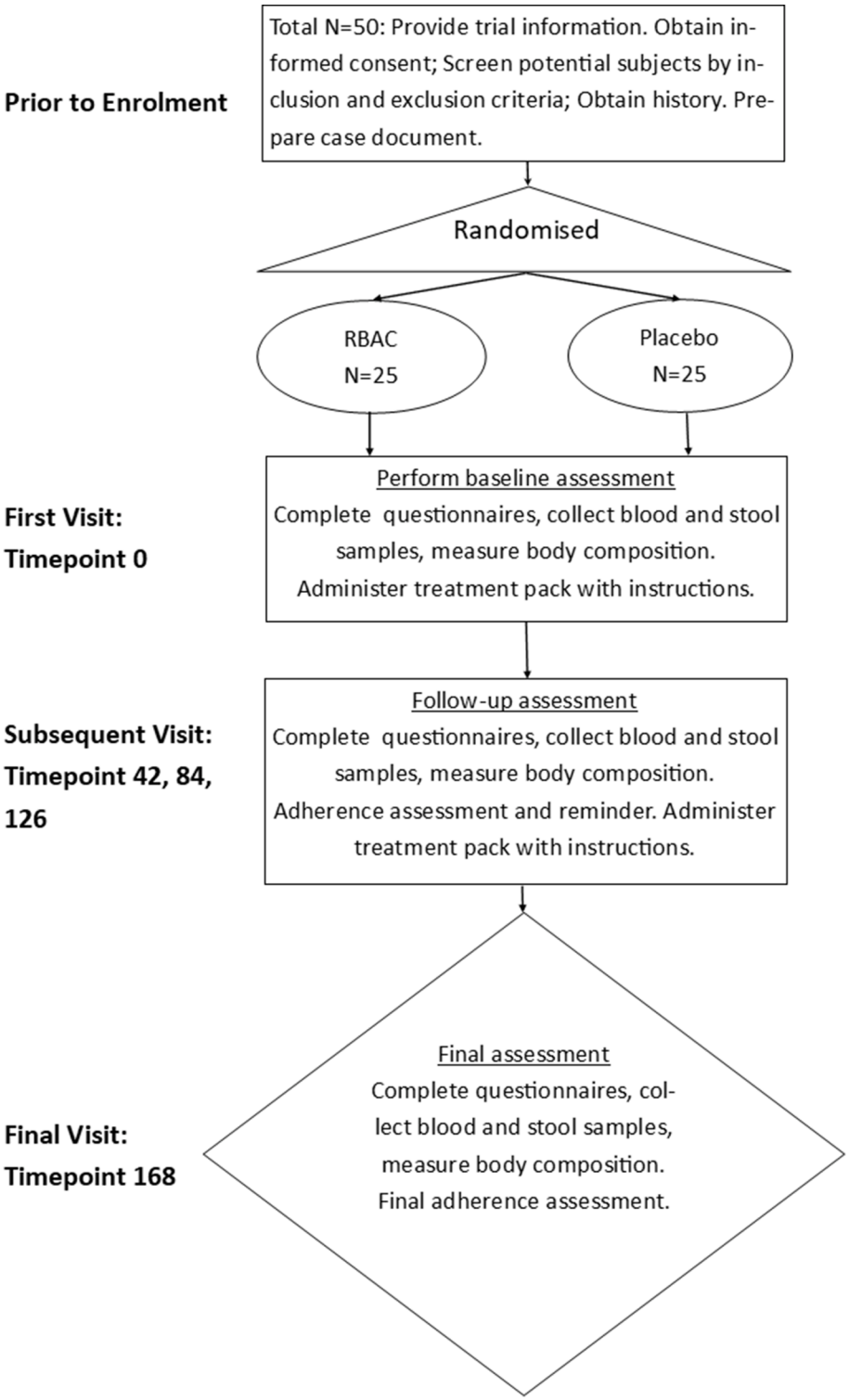

Fig. 1. RBAC-QoL clinical trial participation timeline.

three days before the next visit to the pathological laboratory. The participant is to submit the collected sample to the pathological laboratory. The collected sample is stored at −80 °C until dispatching to a microbiology laboratory for extraction of deoxyribonucleic acids (DNA) using the QIAamp® PowerFecal® Pro DNA Kit. Sequencing of the V4 region of the 16S rRNA amplified from extracted DNA will be conducted using the Illumina MiSeq platform.

The timing of the study visit will be synchronized with the participants' treatment cycles to promote retention and complete follow-up. A scheduled visit that is within one week before or after (±7 days) the six-week interval is permitted. The trial will follow the participants for the entire study period. However, participants can withdraw consent from the study for any reason at any time. Furthermore, the principal investigator may remove participants from the trial either for safety reasons or if they are unwilling or unable to comply with required study procedures. Any reason for dropout will be recorded.

The confidentiality of participants will be maintained throughout the study. Data will be captured directly at the cancer center with all

case forms (See supplementary S3 – Case Report Forms) and study documents kept in locked cabinets. No individual participant can be identified in any study reports and publications. All completed forms will be electronically scanned and uploaded to secure cloud storage (CloudStor). Other electronic study data will be stored at the research data storage of the sponsor. Only the research team can access, manage, and analyze the data. All data storage and management follows the Research Data Management Guidelines of the sponsor and will be retained for 15 years after the completion and publication of results. De-identified study data may be shared with the funders or other institutions for research use with explicit agreements. All sharable data will not contain any personal information.

Statistical analysis of the collected results will be conducted using R version 3.4.0 or later. The RBAC group will be compared against the placebo group for analysis. A protected p-value with multiple dependent values will be analyzed by ANOVA with repeated measures on the occasion of testing with a full Bonferroni, or Sidak, adjusted p-value depending on the correlation among the dependent variables. Pairwise comparisons will be performed where significance is observed. Analysis of covariance will also be performed to assess any influence of the demographic data (age, gender, ethnicity) and cancer diagnosis (primary cancer type, disease stage, recurrence, etc.), changes in physical activity, changes in dietary habits, as well as changes in complementary medicine usage level on the outcome variables with observed between and/or within-group significance. Additional analysis in subgroups or based on protocol non-adherence will be performed if applicable. A detailed statistical analysis plan will be prepared before the start of data analysis.

Data analysis of the 16S rRNA sequences will be analyzed with QIIME2 (Quantitative Insights into Microbial Ecology 2 software) pipeline [36]. Alpha diversity will be calculated using the richness of ASVs (Amplicon Sequence Variants), Chao1 index, Shannon index, and Faith's phylogenetic diversity [37,38] and displayed with R software. Beta diversity will be measured using both weighted and unweighted UniFrac distance metrics [39]. Patterns in diversity as a response to the application of RBAC will be visualized with PCoA (Principal Coordinate Analysis) [40] with the statistical significance of groupings validated with an ANOSIM (Analysis Of SIMilarity) test [41] in the context of other potentially interacting variables in the dataset. Differentially abundant microbial taxa that distinguish between treatments will be identified using ANCOM (Analysis of Composition of Microbiomes) [42] and further visualized with the WGCNA (Weighted Correlation Network Analysis) package, ggplot2 packages and stat package in R software with $p < 0.05$ taken as statistical significance.

A final study report providing full details of the study methods and results will be compiled as a doctoral thesis by the lead author for examination. Summary of the study results will be submitted for publication in an international peer-reviewed journal with the attribution of authorship based on substantial contributions. The study participants will also receive a copy of the summary of results. This study protocol conforms with the Standard Protocol Items Recommendations for International Trials (See Supplementary S4 – SPIRIT 2013 Checklist).

2.9. Safety monitoring

A pilot feasibility trial with a small sample size does not warrant the formation of an independent data safety monitoring board and external auditing. Hence, the Trial Executive Committee (TEC) consisting of four research team members (SCP, PM, RZ, and SLO) who oversee all aspects of the trial management, will conduct safety data monitoring. All adverse events occurring during the study will be tracked using the Common Terminology Criteria for Adverse Events version 5.0 grading. Safety data will be reviewed by the TEC every four weeks in accordance with the National Health and Medical Research Council's Guidance on 'Safety monitoring and reporting in clinical trials involving therapeutic goods' [43]. A participant will only discontinue the intervention under the advice of the treating oncologist, should any intervention-related adverse event of Grade 3 (severe or medically significant but not immediately life-threatening) or above occur. The participant will be retained in the study, whenever possible, for follow-up data collection to minimize missing data even after discontinuing the assigned intervention. Should a participant suffer from complications as a result of the study, medical treatment will be rendered free of charge under Medicare in any Australian public hospital as a public patient. The TEC will have the ability to terminate the study for safety reasons.

2.10. Research ethics and approval

This study conforms to the Australian National Statement on Ethical Conduct in Human Research [44]. The ethical aspects of this research project have been approved by the Human Research Ethics Committee (HREC) of Concord Repatriation General Hospital, Sydney Local Health District (Application No. 2019/ETH00489), and the sponsoring university's HREC (Protocol No. H19244). We also received a site-specific authorization from the Greater Western NSW Local Health District Research Ethics and Governance Office (Application No. 2019/STE10547). As this clinical trial involves the use of an 'unapproved' therapeutic good (namely, RBAC) and its placebo, a notification is submitted to the Therapeutic Goods Administration of Australia before commencement. This study is registered on the Australian New Zealand Clinical Trials Registry (Registration No. ACTRN12619000562178p). All the governing bodies will be notified in case of any material changes to the study protocol.

3. Discussion

The RBAC used in this study is a water-soluble, low molecular weight (30–100 kDa), modified arabinoxylan with xylose in its main chain and an arabinose polymer in its side chain [45]. This compound is marketed in Australia under the brand name Ribraxx, whereas it is better known internationally as Biobran/MGN-3, Lentin Plus (Asia), or BRM4 (United States). It is a safe and non-toxic substance, as demonstrated in a series of animal studies [46]. Furthermore, a systematic review of RBAC for cancer patients found no adverse event due to RBAC reported in the included clinical trials ($n = 11$) or clinical case reports ($n = 14$) [16]. Hence, the safety of RBAC with a dosage of 3 g/day is assured.

QLQ-C30 is considered a reliable and valid self-reported questionnaire and is, therefore, one of the most widely used QoL questionnaires in cancer research [47]. A systematic review that compares QLQ-C30 to another widely used cancer-specific QoL questionnaire, namely Functional Assessment of Cancer Therapy-General (FACT-G), found substantial evidence for the reliability and validity of both the QLQ-C30 and FACT-G in a range of cancer settings as well as availability in many language translations [48]. QLQ-C30 is recommended over FACT-G when social activities, financial impact, and symptom scales are outcome measures of interest in a clinical trial [48]. However, the global QoL scale of QLQ-C30 is less responsive than the FACT-G total score and thus requires more trial participants to detect changes in overall QoL [49]. With the symptom scales being one of the primary outcomes of interest in this research, QLQ-C30 is the QoL instrument of choice.

Malnutrition in cancer is common, and it is a cause of diminished physical and mental functions, thus severely lowering the QoL [50,51]. Being underweight (body mass index, BMI, $\{kg/[height\ in\ m]^2\} < 18.5$) is associated with reduced QoL, as suggested in studies of various cancer survivors, including breast [52], ovarian [53], lung

[54], and colorectal [55] cancers, as well as patients with metastatic cancer [56]. Additionally, poor nutritional status leading to weight loss during or after cancer treatment is a strong predictor of poorer QoL [50]. Assessment of body composition is recommended for the evaluation of nutritional status and detection of malnutrition in clinical practice [57].

For patients undergoing active treatment such as chemotherapy, the presence of poor nutritional status, anorexia, and elevated systemic inflammation also affects QoL [58]. While levels of prealbumin and albumin are plasma proteins commonly used to detect impairment in nutritional status, systemic inflammation can also deprive the productions of prealbumin and albumin [59]. To account for the effect of systemic inflammation, the ratio of CRP and albumin, referred to as INI, is a suitable biochemical index for nutritional assessment [60]. This study also adopts NLR as a systemic inflammatory indicator associated with the nutritional status of cancer patients. Studies have shown that both INI and NLR ratios are useful and reliable inflammatory and prognostic indicators in cancer patients [60–63].

Pro-inflammatory cytokines can also affect the QoL of cancer patients [64–66]. Results from preclinical studies suggest that RBAC can modulate the production of many different cytokines, including IL-1β, IL-6, IL-10, IL-17, TNF-α, and IL-12p40 [10,67]. There are only a limited number of human studies that validate the cytokine modulating capability of RBAC. An open-label RCT with 20 healthy participants showed that levels of IFN-γ, TNF-α, IL-1α, IL-1β, IL-6, IL-10, and epidermal growth factor peaked at 30 days after supplementing with RBAC [68]. Only one RBAC clinical trial examined the cytokine profiles of cancer patients. Thirty multiple myeloma patients were observed to have increased levels of TNF-α, IFN-γ, IL-5, IL-9, IL-12, and IL-17 after taking RBAC for three months, indicating increased activity in DCs [69]. Hence, modulation of cytokine production can be a potential mechanism that leads to the effects of RBAC on QoL of cancer patients.

The present study will explore the feasibility of assessing the immunomodulating effects of RBAC based on the quantity and activities of the various cytokines important in cancer, leveraging on the addressable laser bead immunoassay (ALBIA) technology. ALBIA is more efficient and cost-effective than the traditional enzyme-linked immunosorbent assay (ELISA) for testing multiple targets using small sample volumes while offering similar measurement accuracy to ELISA [70]. The 42 parameters, as shown in Table 4, can be tested in duplicate with only two 0.6 ml microcentrifuge tubes of serum. The results of such broad-spectrum cytokine profile analysis will validate the findings on the preclinical studies and enhance the understanding of RBAC's immunomodulating properties in cancer patients.

Arabinoxylan is known to affect human immunity as a prebiotic for gut microbiota [14]. As a form of glycans, arabinoxylan is resistant to digestion by human enzymes. Ingested arabinoxylans are fermented by microbial enzymes in the gut to fuel the microbial growth. The residual short-chain fatty acids not only serve as energy sources to tissue cells but also have a multitude of health benefits such as reducing inflammation, promoting intestinal epithelial barrier integrity, and suppressing tumor growth [14]. Components of rice bran, particularly soluble feruloylated arabinoxylan oligosaccharides (F-AXOS), have also been shown to modulate the gut microbiome, especially in the abundance of *Bacteroides*, *Prevotella*, and *Dorea* populations [71].

While the pharmacokinetics of RBAC remains unclear, Endo and Kanbayashi [72] demonstrated in a preclinical study that constituents of RBAC could enter the bloodstream after oral administration, albeit the absorption was incomplete. Most preclinical studies on RBAC have been focusing on the direct pathway where the presence of RBAC in serum exerts effects on both the innate and adaptive immune systems [13,16]. Inferring from the research of other cereal arabinoxylans and rice bran F-AXOS, the undigested RBAC may potentially serve as prebiotics to the gut microbiota to further modulate the immune system. The possibility of this indirect pathway remains unexplored. To date, no study has attempted to perform an analysis using 16S rRNA sequencing to understand the potential impact of RBAC on the alpha and beta diversities of gut microbiome. The absence of evidence in this area represents a gap in the current research which the current study attempts to address.

4. Conclusion

RBAC is one of the most well-researched low-molecular-weight arabinoxylan compounds demonstrating strong immunomodulating properties [73]. This study is a 24-week randomized, double-blind placebo-controlled pilot feasibility trial on RBAC and the QoL of cancer patients. The results of this study will inform the planning of a larger clinical trial. Such translational research will have a positive impact in the field of immunotherapy, validating the potential application of RBAC as a biological response modifier. The findings from this study and further research can improve the understanding of the effect of RBAC during cancer treatment, supply data to validate the immunotherapeutic benefits of RBAC, and potentially contribute to better cancer care in the future.

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Daiwa Pharmaceutical Co., Ltd. (Daiwa) provided financial funding to commence the RBAC-QoL project with the affiliating university of the corresponding author as the trial sponsor. Daiwa agreed to the preliminary study proposal before funding commitment. BioMedica Nutraceuticals Pty Ltd (BioMedica) provided additional funding to conduct the gut microbiome study of this research. The RBAC and placebo powder will be manufactured and supplied by Daiwa. The funders have no role in study implementation, analyses, data interpretation, or decision to submit results.

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Authors' contributions

SLO wrote the study protocol. SLO, SCP, PM, and RZ designed the study jointly. TJ contributed to the study design of the gut microbiome component. ES, GH, TG, and DM reviewed the manuscript and contributed substantially to its final version.

Declaration of competing interest

GH is a co-founder and the Clinical Director of BioMedica, the sole distributor of Daiwa's RBAC product in Australia. GH contributed to the initial design of the study protocol but will not involve in the implementation, analyses, data interpretation, or decision to submit results of the study.

All other authors declare no financial and any other competing interests relevant to this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2020.100580.

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