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ARTICLE

The Novel Effects of a Hydrolyzed Polysaccharide Dietary Supplement on Immune, Hepatic, and Renal Function in Adults with HIV in a Randomized, Double-Blind Placebo-Control Trial

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ABSTRACT
The primary objective of the study was to evaluate the effects of a hydrolyzed polysaccharide, rice bran arabinoxylan compound (RBAC), on immune, hepatic, and renal function in HIV + individuals. A six-month randomized double-blind placebo-controlled trial was utilized to conduct the intervention. Forty-seven HIV + participants on stable antiretroviral therapy were enrolled and randomly assigned to one of the two study conditions ($n = 22$ RBAC and $n = 25$ placebo) and consumed 3 gram/day of either compound for six months. Participants were assessed at baseline and 3 and 6 months follow-up for CD4+ and CD8+, liver enzymes, and kidney function. No side effects were reported, and liver and kidney markers nearly remained completely within normal limits. The percentage change in CD4+ was similar for the placebo (+2.2%) and RBAC (+3.1%) groups at 6 months follow-up. The percentage change in CD8+ count significantly decreased from baseline to 6 months in the RBAC group (−5.2%), whereas it increased in the placebo group (+57.8%; $p = 0.04$). The CD4+/CD8+ ratio improved clinically in the RBAC group from 0.95 (SD =0.62) at baseline to 1.07 (SD =0.11) at 6 months, whereas it declined in the placebo group from 0.96 (SD =0.80) at baseline to 0.72 (SD =0.59) at 6 months. Our results showed a statistically significant decrease in CD8+ count and a clinically significant increase in CD4+/CD8+ ratio for the RBAC group compared to the placebo group. Thus, the results of this study suggest that the immunomodulatory and antisenescent activities of RBAC are promising for the HIV population.

KEYWORDS
arabinoxylan; CD4-CD8 ratio; CD8; dietary supplements; HIV infections; immune system phenomena; polysaccharides

Introduction

Over 1 million people are living with HIV in the United States. This once-lethal disease, and leading cause of death among Americans aged 25–44 in the 1990s, is now a

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manageable chronic condition thanks to advances in pharmacology. HIV still remains in the top 10 leading causes of death for this age group (Centers for Disease Control and Prevention 2008; 2016), but patients now live longer and face new challenges that were rare in the pre-antiretroviral-therapy era. Cardiometabolic, renal, and quality-of-life issues currently represent major treatment challenges for HIV + patients, as the threat of opportunistic infections has been transformed by modern medicine.

Antiretroviral therapy in HIV + patients has been associated with inflammation, presumably related to overstimulation of CD8+ cells (Krantz et al. 2011; Ku et al. 2016). Such CD8+ overstimulation, when coupled with a concomitant fall in CD4+ cells, can indicate a form of virologic treatment failure referred to as "blind T-cell homeostasis" (Adleman and Wofsy 1993; Appay and Sauce 2008; Hazenberg et al. 2003; Krantz et al. 2011).

Recently, the CD4+/CD8+ ratio has shown clinical utility in the assessment of immune activation and chronic inflammation (Buggert et al. 2014; De Biasi et al. 2016). An inverted ratio (<1.0) is indicative of immunosenescence and is independently associated with markers of age-associated disease such as atherosclerosis and renal impairment (Serrano-Villar et al. 2014). If the ratio is persistently below 1.0, the risk of comorbidities is even greater (Hema et al. 2016; Zheng et al. 2014). Given that nearly 80% of the HIV population on antiretroviral therapy are below this clinical threshold of 1.0 (Caby et al. 2016; Mussini et al. 2015; Tinago et al. 2014), and modifying the antiretroviral therapy regimen to increase this ratio has proven to be challenging, the investigation of therapies that target the CD4+/CD8+ ratio is warranted.

Therapeutic dietary supplementation is an important potential adjunct to antiretroviral therapy in the treatment of HIV disease that merits further study. A wide range of physiologic targets are described in the literature, outlining clear biologic plausibility of nutritional therapies in HIV + patients. For example, antioxidants enhance mitochondrial energy production, decrease the release of lactic acid into the bloodstream, and enhance T and B lymphocyte proliferation (Kalebic et al. 1991), which would counteract elevated reactive oxygen species, commonly known as oxidative stress (Ivanov et al. 2016). In addition, several *in vitro* and *ex vivo* studies have shown a hydrolyzed polysaccharide, rice bran arabinoxylan compound (RBAC), to possess a biologic response modifier effect on immune system function, particularly in natural killer (NK) cell activity. One *in vitro* study showed RBAC blocked HIV-1 replication by inhibiting p24 antigen production in a dose-dependent manner (Ghoneum 1998a). Another study found significant increases in NK cell cytotoxicity compared to baseline when a similar RBAC-based agent was administered orally to human subjects (Ghoneum 1998b). RBAC has also been shown to enhance macrophage phagocytic activity and nitric oxide release and scavenge free radicals in a dose-dependent manner. Thus, it may also function in an antioxidant capacity (Ghoneum and Matsuura 2004; Tazawa et al. 2000). In our lab, we previously showed that RBAC demonstrated true immunomodulation by enhanced NK cell cytotoxicity, significant changes in 9 out of 12 cytokines and growth factors, and safety and tolerability of the product in a sample of healthy adults (Ali et al. 2012). We have also shown several clinically and statistically significant improvements, e.g., alkaline phosphatase, platelets, neutrophils, neutrophil-lymphocyte ratio, and γ-glutamyl transferase, in response to 90 days of RBAC compared to placebo in adults with nonalcoholic fatty liver disease (Lewis et al. 2018). To the best of our knowledge, no study has investigated the effect of a polysaccharide such as RBAC on CD4+ and CD8+ in patients with HIV. The purpose of this study is to determine the effects of 6 months of RBAC treatment on immune function and secondarily on liver enzymes and kidney function in HIV + patients.

Methods

Participants

The study was conducted with the approval of the University of Miami Institutional Review Board for human subject research (registry name: www.clinicaltrials.gov; registry number: NCT02214173; available at: https://www.clinicaltrials.gov/ct2/show/NCT02214173). Potential participants were initially identified from physician referrals, the Medical Wellness Center, and the Departments of Psychiatry and Behavioral Sciences and Medicine at the University of Miami Miller School of Medicine, where the data were collected. Recruitment began in January 2015 and ended in October 2015 after target enrollment was achieved. Inclusion criteria were (a) age 18 or older; (b) confirmed HIV diagnosis, as per the referring infectious disease physician; (c) CD4+ T cell count nadir 50–250 µL; (d) on a stable antiretroviral therapy regimen before (≥ 6 months) and during the intervention; (e) planning to maintain current medication during the course of the intervention; (f) not on any lipid-lowering pharmaceuticals or dietary supplements for a minimum of 3 months before the enrollment; (g) previous dietary supplement usage of similar polysaccharide formulas permitted, but agreed to discontinue 2 weeks before and for the duration of the trial; (h) willing to follow recommendations for assessment and intervention of the study protocol; and (i) able to provide informed consent. Exclusion criteria were (a) currently enrolled in another research trial for similar investigative nutritional therapies; (b) known allergy to rice, rice bran, mushrooms, or related food products; (c) any gastrointestinal disorders that could lead to uncertain absorption of the study supplement; (d) other medical complications that might preclude study participation (e.g., recent heart attack or stroke or chronic kidney disease); (e) current immunomodulatory medication use (e.g., interferon); (f) active chemotherapy; (g) multiple drug resistance to antiretroviral therapy; (h) current smoker; (i) severe anemia or other medical condition that would preclude a safe blood draw; (j) bleeding disorder; or (k) active pregnancy or attempting conception.

Seventy-three individuals were screened for inclusion and exclusion criteria, and 26 potential participants failed to meet criteria. Forty-seven individuals met the criteria and were enrolled in the study after signing the informed consent and HIPAA privacy forms prior to study entry. The participants were assigned to 1 of 2 conditions by study staff (RBAC or placebo) using a simple random permutations table. All participants and investigators were blinded to the treatment condition and remained blinded until after data analysis. Placebo and supplements were provided by Daiwa Health Development (Gardena, CA, USA) labeled as Protocol A and Protocol B. Only a staff member at Daiwa Health Development knew the assignment of treatment to Protocol A or B. After randomization, participants were scheduled for assessments at baseline and 3 and

6 months follow-up, and blood was drawn at each time point to assess the biomarkers. Participants were compensated $40 for completing the assessment at each time point.

Intervention

Individuals enrolled in the study were randomly assigned to either (a) RBAC ($n = 22$) or (b) placebo ($n = 25$). Regardless of study arm assignment, participants were instructed to take 2 capsules 3 times per day (3 g/day total) for the 6-month intervention period. Participants were advised to not modify dietary or physical activity habits or prescription medication use. Participants were also instructed not to consume any known immune-active pharmaceutical agents or any dietary supplements containing mushroom products for 2 weeks prior to having the baseline assessment and until the conclusion of the 6-month intervention period. Because of the production process for RBAC, taking this product should be very similar to consuming rice bran and should be tolerated as such. We are not aware of any documented side effects of RBAC, and our first two studies with this product showed no adverse events (Ali et al. 2012; Lewis et al. 2018). According to the company's literature, RBAC is a water-soluble extract of rice bran that has been hydrolyzed by an enzyme complex extracted from shiitake mushroom. In addition, RBAC contains microcrystalline cellulose, hypromellose, sucrose fatty acid ester, gellan gum, and potassium acetate. Each capsule contained 500 mg of RBAC. The placebo capsules were indistinguishable from RBAC but contained cellulose.

Outcomes and assessments

Each participant completed a basic demographics and medical history questionnaire at baseline. Participants were also asked to list their current medications and note any changes in type or amount during the course of the study. All outcome variables were assessed at baseline and at the end of 3 and 6 months (±1 week). Criteria used to select the assessment instruments included (a) appropriateness for the population; (b) ease of administration and scoring; (c) experience administering these measures; and (d) employment of measures involving a multimethod (i.e., self-report and biological values) approach to enhance the validity of the overall assessment.

Immune function

CD4+ and CD8+ T cell counts were obtained at each assessment.

HIV Status

Viral load was recorded at baseline. Any changes in HIV status according to CDC criteria were noted and included in the analyses (Centers for Disease Control and Prevention 1992).

Liver enzymes and kidney function

Liver enzymes (alanine transaminase [ALT] and aspartate transaminase [AST]) and kidney function (bilirubin, total protein, and creatinine) were assessed at each time point.

Descriptive and control variables

Demographics such as age, race/ethnicity, socioeconomic status, education, employment status, and current living situation were assessed at baseline. The basic health assessment questionnaire included past medical history with an emphasis on opportunistic infections, family history, and review of systems. Information regarding any history of infection, respiratory disease, diabetes, cardiovascular disease, oral disease, cancer, and drug, alcohol, and tobacco use was obtained. At the follow-up visits, participants were asked about the occurrence of opportunistic infections and hospitalizations during that time. Antiretroviral therapy-related effects were assessed at each visit, and current non–HIV related medications were documented. Past history of antiretroviral therapy use was recorded and confirmed with medical records.

Adverse events

Participants were monitored until the end of the study. Potential side effects were explained to each participant during informed consent.

Compliance

Compliance was measured using a modified version of the eight-item Morisky Medication Adherence Scale (MMAS-8). MMAS-8 is a generic, validated, self-reported measure of medication-taking behavior that does not target a specific age, disease, or treatment group.

Statistical analyses

Frequency and descriptive statistics were calculated on all variables. Independent samples t tests and chi-squares were used to evaluate differences in sociodemographic and clinical history characteristics between groups at baseline. The percentage change was calculated for the difference between (a) baseline and 3 months follow-up, (b) baseline and 6 months follow-up, and (c) 3 and 6 months follow-up for CD4+, CD8+, CD4+/CD8+ ratio, liver enzymes (ALT and AST), and kidney function (bilirubin, total protein, and creatinine). Then the percentage change variables were used in one-way analysis of variance to compare differences between the placebo and RBAC groups. IBM SPSS Statistics 24 for Windows (IBM, Inc., Chicago, IL, USA) was used for statistical analyses, and $\alpha < .05$ was considered statistically significant. Using a test of independence with a 40% difference in the values of CD8+ cells between the two groups at 6 months follow-up with $\alpha = .05$ significance and 80% power, the total sample size calculated using ZumaStat statistical software (Applied Scientific Analysis, Inc., Miami, FL, USA) was 42.

Table 1. Sociodemographic characteristics of the sample.

Variable	Category	RBAC ($n=22$)	Placebo ($n=25$)	Statistic
Age	—	M = 50.3, SD = 10.5, R = 18, 64	M = 48.1, SD = 9.8, R = 24, 66	$t=0.8$ (45), $p=.45$
Gender	Male	9 (41%)	13 (52%)	$\chi^2=0.6$ (1), $p=.45$
	Female	13 (59%)	12 (48%)	
Race/ethnicity	White, non-Hispanic	—	2 (8%)	$\chi^2=0.6$ (1), $p=.45$
	Black, non-Hispanic	16 (73%)	16 (64%)	
	Hispanic	6 (27%)	6 (24%)	
	Other	—	1 (4%)	
Education	Up to high school	7 (32%)	5 (21%)	$\chi^2=4.4$ (3), $p=.22$
	High school graduate	7 (32%)	6 (25%)	
	Post–high school/ some college	8 (36%)	9 (38%)	
	College graduate	—	4 (17%)	
Marital status	Never married	12 (55%)	18 (72%)	$\chi^2=4.0$ (2), $p=.14$
	Married	1 (5%)	3 (12%)	
	Widowed/divorced	9 (41%)	4 (16%)	

M = mean; SD = standard deviation; R = range.

Results

Sociodemographics, comorbid disorders, and medication use at baseline

See Table 1 for the descriptive information of the sample for age, gender, race/ethnicity, education, and marital status. No significant differences were detected between the RBAC and placebo groups. The most prevalent comorbid conditions were depression ($n=4$ [18%] RBAC and $n=12$ [48%] placebo), hypertension ($n=4$ [18%] RBAC and $n=11$ [44%] placebo), anxiety ($n=5$ [23%] RBAC and $n=6$ [24%] placebo), and dyslipidemia ($n=4$ [18%] RBAC and $n=7$ [28%] placebo). The difference between groups for depression was statistically significant (χ^2=4.6[1], $p=.03$), whereas the differences for all other disorders were insignificant. The difference between groups for HIV viral load was non-significant ($t=0.9$[38], $p=.38$). Participants were on the following HIV medication regimens (by drug categories): (a) two nucleoside reverse transcriptase inhibitors (NRTI) and one nonnucleoside reverse transcriptase inhibitor (NNRTI; $n=17$); (b) two NRTIs and boosted PI ($n=16$); (c) two NRTIs and one integrase inhibitor ($n=10$); (d) two NRTIs, boosted PI, and one integrase inhibitor ($n=3$); and (e) boosted PI ($n=1$). The frequency of these regimens was not significantly different between the two groups (χ^2[4] = 1.5, $p=.83$). Other commonly taken medications were Crestor ($n=4$), metformin ($n=4$), lisinopril ($n=4$), acyclovir ($n=3$), and Bactrim ($n=3$), and these frequencies were not significantly different between the two groups.

Attrition, compliance, liver enzymes, and kidney function

Ten participants dropped out of the study at 3 months ($n=4$ RBAC and $n=6$ placebo), and three more dropped out at 6 months ($n=1$ RBAC and $n=2$ placebo). Thus, 34 individuals ($n=17$ RBAC and $n=17$ placebo) completed the study. The 13 dropouts changed contact information between assessments and could no longer be reached by study personnel. According to the MMAS-8 total scores, 51.4% of the sample had medium to high compliance at 3 months, and 64.7% of the sample had medium to high compliance at 6 months. During the entire study period, no side effect was reported by

Table 2. Liver enzymes and kidney function at baseline and 3 and 6 months.

Measure	Time	RBAC	Placebo	Statistic
ALT (IU/L)	Baseline	25.9 ± 16.1 (7, 78)	28.8 ± 31.3 (6, 165)	F(1, 33) = 2.3, p = .14
	3 Months	27.8 ± 20.9 (9, 101)	29.9 ± 34.4 (11, 166)	
	6 Months	25.3 ± 12 (11, 54)	22 ± 9.5 (11, 43)	
AST (IU/L)	Baseline	26.9 ± 10.9 (11, 47)	33.3 ± 36.5 (13, 201)	F(1, 33) = 0.8, p = .39
	3 Months	26.3 ± 10.4 (12, 48)	29.9 ± 24.2 (14, 125)	
	6 Months	25.2 ± 8.1 (15, 43)	26.3 ± 11.3 (15, 51)	
Bilirubin (mg/dL)	Baseline	0.37 ± 0.23 (0.2, 1.0)	0.44 ± 0.39 (0.2, 2.1)	F(1, 33) = 0.3, p = .58
	3 Months	0.40 ± 0.22 (0.2, 0.9)	0.44 ± 0.27 (0.2, 1.3)	
	6 Months	0.38 ± 0.23 (0.2, 1.0)	0.46 ± 0.42 (0.2, 2.0)	
Total protein (g/dL)	Baseline	7.4 ± 0.8 (5.6, 8.7)	9.6 ± 7.5 (5, 9.6)	F(1, 32) = 0.2, p = .66
	3 Months	7.6 ± 0.7 (6.3, 9.2)	7.5 ± 0.7 (6.1, 9.1)	
	6 Months	7.4 ± 0.6 (6.6, 8.6)	7.5 ± 0.7 (6.6, 9.3)	
Creatinine (mg/dL)	Baseline	0.92 ± 0.22 (0.6, 1.3)	1.2 ± 0.88 (0.3, 1.2)	F(1, 33) = 0.03, p = .87
	3 Months	0.85 ± 0.19 (0.6, 1.2)	0.89 ± 0.23 (0.5, 1.3)	
	6 Months	0.91 ± 0.22 (0.5, 1.2)	0.91 ± 0.23 (0.6, 1.4)	

Values are expressed as mean ± standard deviation (minimum, maximum). All statistics are for the change from baseline to 6 months, as all other statistics (from baseline to 3 months and 3 months to 6 months) were also non-significant. ALT = alanine transaminase; AST = aspartate transaminase.

any participant. Table 2 shows the descriptive statistics for ALT, AST, bilirubin, total protein, and creatinine for both groups. No significant differences were observed for these measures between the groups from baseline to 6 months. For both groups at each time point, nearly all of these lab values remained within normal limits.

Percentage change for immune markers from baseline to 6 months follow-up

Table 3 shows the descriptive statistics for CD4+, CD8+, and CD4+/CD8+ ratio for both groups. The percentage change between values from baseline to 6 months follow-up was calculated for all variables. The percentage change was not different between the groups for CD4 + (F[1, 32] = 0.1, p = .95), as the placebo group increased by 2.2% (SD =59.7) and the RBAC group increased by 3.1% (SD =21.0). We noted a statistically significant difference in the percentage change in CD8+ between the groups (F[1, 32] = 4.8, p = .04), as the placebo group increased by 57.8% (SD =114.3), whereas the RBAC group decreased by 5.2% (SD =11.8). Although the change was statistically marginal (F[1, 31] = 3.2, p = .085), the RBAC group showed a clinically significant increase in the CD4+/CD8+ ratio to 1.07 (SD =0.11) at 6 months from 0.95 (SD =0.62) at baseline (8.6%), whereas the placebo group decreased from 0.96 (SD =0.80) at baseline to 0.72 (SD =0.59) at 6 months (−12.2%).

Discussion

Studies indicate that HIV + patients taking antiretroviral therapy are at risk of virologic failure associated with elevated CD8+ levels (Ku et al. 2016; Zheng et al. 2014). In addition, persons with HIV represent a model of accelerated aging due to immunosenescence. Adjunctive therapies such as RBAC may attenuate this phenomenon. RBAC, with a long-published track record of efficacy, could support innate biochemical and physiological optimization and restoration by ensuring needed cellular raw materials (Ali et al. 2012; Ghoneum 1998b; Lewis et al. 2018; Tazawa et al. 2000). Moreover, RBAC causes no side effects or adverse changes to hepatic or renal function, according

Table 3. Immune function at baseline and 3 and 6 months.

Measure	Time	RBAC	Placebo	Statistic
CD4 + (cells/uL)	Baseline	705.9 ± 372.3 (107, 1559)	621.4 ± 366.7 (72, 1341)	F(1, 32) = 0.1, p = .95
	3 Months	800.3 ± 708.7 (110, 3136)	548.5 ± 381.2 (9, 1335)	
	6 Months	704.2 ± 358.7 (187, 1329)	605.5 ± 435.7 (1, 1330)	
CD8 + (cells/uL)	Baseline	851.4 ± 368.6 (323, 1603)	866.4 ± 581.1 (253, 2203)	F(1, 32) = 4.8, p = .04
	3 Months	858.8 ± 486.8 (292, 1922)	912.8 ± 457.5 (354, 2303)	
	6 Months	806.7 ± 379.3 (339, 1780)	1012.9 ± 401.8 (446, 1728)	
CD4+/CD8+ Ratio	Baseline	0.95 ± 0.62 (0.07, 2.65)	0.96 ± 0.80 (0.07, 3.3)	F(1, 31) = 3.2, p = .085
	3 Months	0.87 ± 0.62 (0.09, 2.5)	0.72 ± 0.54 (0.01, 1.96)	
	6 Months	1.07 ± 0.7 (0.11, 2.55)	0.72 ± 0.59 (0, 2.1)	

Values are expressed as mean ± standard deviation (minimum, maximum). All statistics are for the change from baseline to 6 months.

to the current study and our previous research (Ali et al. 2012; Lewis et al. 2018). In addition, RBAC has historically demonstrated efficacy on a variety of immune cells (e.g., NK and dendritic), cytokines (e.g., interleukin-6, tumor necrosis factor-α, and interferon-γ), and growth factors (e.g., vascular endothelial growth factor) (Ali et al. 2012; Cholujova et al. 2013; Ghoneum 1998b; Ghoneum and Agrawal 2014), among others. Given our previous work in healthy adults showing that RBAC dramatically increases NK cell cytotoxicity and improves the overall inflammatory profile according to a number of cytokines and growth factors (Ali et al. 2012), we chose to evaluate its effect on immune markers relevant to the HIV population.

Most notably, we showed a statistically significant percentage change decrease in CD8+ cells from baseline to 6 months in the RBAC group compared to the placebo group. This finding is important considering several recent studies that describe high CD8+ counts in conjunction with antiretroviral therapy are associated with progression to virologic treatment failure (Krantz et al. 2011; Ku et al. 2016). In addition, an overstimulated CD8 immune response, marked by the initiation of CD8 subsets, a higher total CD8+ count, and a lower level of CD4+, may accelerate immune dysfunction and hasten pathogenesis (Appay and Sauce 2008; Hazenberg et al. 2003; Krantz et al. 2011). Nonetheless, the data have been inconsistent regarding whether the CD8 immune response is truly pathological, but in the meantime it appears that a lowered CD8+ total cell count may be beneficial for avoiding virologic treatment failure (Krantz et al. 2011). Therefore, our results suggest that RBAC might be a useful tool in lowering CD8+ cell count to help prevent virologic treatment failure, particularly given that it occurs in 20%–40% of cases within 2 years of initiation of antiretroviral therapy (Krantz et al. 2011).

Of additional particular importance is the clinically significant improvement at 6 months in the CD4+/CD8+ ratio in the RBAC group, increasing to over 1.0, whereas the placebo group declined to 0.72. Although the difference between groups was statistically marginal, the clinical importance of the CD4+/CD8+ ratio in the HIV population is now accepted as a proxy for systemic immune activation and chronic inflammation (Buggert et al. 2014; De Biasi et al. 2016). If the ratio is regularly below 1.0, then risk of comorbid disease is higher (Hema et al. 2016; Zheng et al. 2014). Nearly 80% of HIV + patients on antiretroviral therapy have a ratio consistently less than 1.0, and efforts to reverse the ratio to above 1.0 have proven to be difficult (Caby et al. 2016; Mussini et al. 2015; Tinago et al. 2014). In fact, a very recent study showed that only about one-third of individuals studied met what was termed "CD4/CD8 ratio restoration" to prevent virologic failure (Caby and Writing Committee of the C. D. C. D. Ratio Working Group of the French Hospital Database on HIV 2017). In light of the typical inability of antiretroviral therapy to increase the CD4+/CD8+ ratio for most HIV + patients, our results indicating RBAC's ability to improve this value above a clinical threshold (>1.0) has broad implications for reducing the risk of other chronic complications associated with HIV. To our knowledge, this is the first study showing a dietary supplement can restore the CD4+/CD8+ ratio to above the clinically important threshold of >1.0 over a 6-month period, demonstrating the potent immunomodulatory and antisenescent abilities of RBAC.

Even though we did not find a statistically significant percentage increase in CD4+ count, our data indicate that RBAC may help to stabilize CD4+ in persons with HIV. CD4+ cells are targeted by the virus, are affected by nonviral characteristics such as age, and therefore tend to be highly variable (Merci et al. 2017; Nanzigu et al. 2013). In addition, a decrease in CD4+ cells has been previously related to elevated CD8+ count, that is, "blind T-cell homeostasis" (Adleman and Wofsy 1993). Thus, even if RBAC only helped to maintain the CD4+ level, that might be important in regulating CD8+ count, helping to prevent virologic treatment failure, and assisting in the prevention of disease progression.

Limitations

HIV + patients on antiretroviral therapy constitute a challenging population for dietary supplement intervention due to the high likelihood of multiple comorbidities that may unknowingly impact clinical outcomes. These patients live with continual medical surveillance, appointments with various clinicians, and a high daily pill burden, leaving limited time and interest in participating in research for what would be considered secondary to their basic needs. Thus, confounding from so many different comorbid complications cannot be entirely ruled out in a study such as this. Clearly, this type of intervention is significantly different from what is typically provided to HIV + patients. Recruiting interested, willing, and reliable candidates for this study proved challenging. In addition, the small sample size and minor rate of attrition likely had a negative impact on the power of the study, which may have further limited the findings. The next step in the evaluation of RBAC would be to replicate the current study for a longer period in a larger sample size and expand the outcomes to include the effect of RBAC on the incidence of opportunistic infections and viral load.

Conclusions

A dietary supplement that could attenuate the inflammation and immune dysregulation in HIV + patients on antiretroviral therapy would be beneficial, but studies are limited. HIV is now considered a chronic disease; hence, efficacious dietary supplements may provide HIV + patients alternatives to counteract CD8+ overstimulation and sequelae of chronic inflammation. Judging from the positive statistically significant percentage change decrease in CD8+ count and the clinically significant improvement in CD4+/CD8+ ratio, RBAC may offer a tool to counteract the negative effects of inflammation and other complications of HIV. Our finding that RBAC improves the CD4+/CD8+ ratio above a clinically defined important threshold (> 1.0) is particularly promising in light of the absence of therapies that lead to CD4/CD8 ratio restoration. Combined with our prior documented effects of RBAC and those of others showing clear immunomodulatory activity, the results of the present study extend the function of RBAC to antisenescence (i.e., halt pathological aging) to slow the pace of accelerated aging in the HIV population. Furthermore, given that RBAC is an all-natural product causing no side effects and has no known negative interactions with pharmaceuticals, HIV + patients may delay disease progression by taking this hydrolyzed polysaccharide.

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Declaration of interest

John E. Lewis has been paid by Daiwa Pharmaceutical to speak at international conferences and write articles on health and wellness for their website. Steven E. Atlas, Muhammad H. Abbas, Ammar Rasul, Ashar Farooqi, Laura A. Lantigua, Lucas C. Lages, Frederick Michaud, Sharon Goldberg, Oscar L. Higuera, Andrea Fiallo, Eduard Tiozzo, Judi M. Woolger, Stephanie Ciraula, Armando Mendez, Allan Rodriguez, and Janet Konefal have no conflicts of interest.

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Data availability statement

The data that support the findings of this study are available from the corresponding author (JEL) upon reasonable request.

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