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ORIGINAL RESEARCH

Effects of a Natural Carotenoid Complex (CaroRite) on Psychological Well-Being and Oxidative Stress: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Stress significantly influences mental and physical well-being with crucial markers implying the correlation. Carotenoids have been associated with immunomodulatory and protective functions against oxidative stress. Their ability to interact with nuclear factors helps enhance the expression of antioxidative enzymes, leading to the attenuation of these markers. They also curb inflammatory effects of neurodegeneration through microglial activation.

Purpose: The study explored the effects of CaroRite (Research Code – CAR), a mixed carotene compound on the levels of oxidative stress markers, mental and physical well-being and quality of life.

Patients and Methods: In this randomized trial, 77 males and females, aged 18 to 60 years, were allocated to the investigational product (IP) or the placebo arm. The participants received one capsule of IP (28 mg)/placebo daily for 90 days. The impact on psychological well-being was measured through the Psychological General Well-Being Index, whereas the effects on oxidative stress and immunity were measured through the 8-Isoprostane and Immunoglobulin-A (IgA). Data have been analysed using ANCOVA and paired/unpaired *t* test.

Results: Both the groups, namely the IP and the placebo, were statistically similar in the age, body mass index (BMI) and PGWBI score at baseline ($p>0.05$). At Day 90, a significant increase in total PGWBI scores of 3.09 and 2.73 from baseline ($p < 0.05$) was observed in the CAR and placebo group subsequently, although the change between the groups was not significant. Post-hoc age stratified analysis revealed a statistically significant increase in the scores among older CAR recipients ($p = 0.045$) as compared to placebo with a moderate effect size (Cohen's $D = 0.7886$). In the younger population, a higher non-significant reduction was observed in serum 8-isoprostane in the CAR group compared to the placebo group ($p > 0.05$) with the small to moderate intervention effect size (Cohen's $d = 0.3444$). A non-significant increase was observed in sIgA levels in the CAR group as compared to placebo ($p > 0.05$) suggesting potential immunomodulatory benefits. CAR was well tolerated, with no adverse effects reported.

Conclusion: The results indicate that CAR could be helpful in enhancing psychological health in older individuals. The decline in the levels of oxidative stress in the younger population suggests that CAR may render antioxidative effects, consequently managing psychological well-being.

Keywords: carotenoids, oxidative stress, psychological wellbeing, immunoglobulin A, 8-isoprostane, Bio-gen

Introduction

Well-being encompasses a balanced state of emotional satisfaction and general contentment, typically associated with minimal psychological stress, good physical and mental health with an optimistic view of life.[1] Mental well-being is thus

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recognized as a core component of health, as defined by the American Psychological Association and the World Health Organization.[1]

In recent times, mental health has become a global issue with a high prevalence of related disorders such as anxiety and depression.[2] A study by Daly et al reported a marked increase in psychological distress, with the proportion of affected individuals rising from 25.16% in 2009 to 31.19% in 2021.[3] Genetic predisposition, neurochemical imbalances, nutrition and physical health conditions are significant biological contributors.[4] Pharmacological interventions such as antidepressants and anxiolytics outweigh in risk as compared to the benefits. Evidence also suggests that the mental well-being index significantly correlates with lifestyle factors, such as physical activity levels as well as consumption of fruits and vegetables.[5] Other factors include issues such as metabolic syndrome and obesity which have been correlated with worse mental health outcomes, specifically with increased depression and anxiety symptoms.[6] A National Health and Nutrition Examination Survey, comprising more than sixteen thousand adults, established an inverse relationship between depressive symptoms and the consumption of fibers from vegetables and fruits.[7] Several phytochemicals present in fruits and vegetables are found to have anti-oxidant and immune-protective effects.[8] Carotenoids, a class of naturally occurring pigments, are recognized as important dietary components which helps improving mental well-being.[6,9] Several observational studies have associated carotenoid levels to late-stage mental health issues.[10,11] Concurrently, a review of six human studies indicated that carotenoids may confer specific cognitive and motor benefits, particularly in younger individuals.[12] Studies have increasingly demonstrated that carotenoids help enhance psychological function by alleviating oxidative stress. This effect is credited to the singlet oxygen quenching and peroxyl radical scavenging activity of the apocarotenoid, a byproduct of carotenoid metabolism,[13] which in turn protects cells from oxidative damage, helps maintain cellular homeostasis and modulates intercellular communication.[14]

Further, evidence indicates an intricate interplay between psychological processes and the body's immune defense system.[15] A study conducted by Phillips et al associated significantly high mental stress with reduced salivary IgA levels, an immunoglobulin-based marker of innate immunity.[16] Carotenoid supplementation has been found to significantly increase the IgA levels in the gastrointestinal tract.[17] These findings support the role of carotenoids as potential nutraceutical agents for improving quality of life through their diverse biological actions.[18]

Albeit the mechanistic basis supporting the role of carotenoids in mental health is compelling, clinical evidence from human studies remains limited and inconclusive. Most trials test carotenoids in healthy volunteers, older adults with cognitive complaints, or metabolic/age-related conditions, rather than in well-defined clinical mood or anxiety disorders.[19] This limits generalizability to individuals experiencing extreme levels of psychological stress on a daily basis. This suggests a lack of evidence for the effects of Carotenoids, in people experiencing psychological stress on a daily basis. Additionally, majority of available data is derived from retrospective, observational studies, reporting associations between elevated plasma carotenoid levels and lower incidence of depression, anxiety, and stress-related symptoms.[20] Therefore, the current prospective study aimed to evaluate the effects of 90-day supplementation with a Natural Carotenoid Complex, CAR, on psychological well-being and oxidative stress in adults experiencing moderate psychological distress. As the studies involving mental wellbeing measures have often demonstrated significant placebo effects,[21] placebo was used as a comparator for the study, to assess the effect size of the CAR supplementation. Further, the study also aimed to observe the effect of CAR on immune response and quality of life in these adults.

Materials and Methods

Ethical Consideration

The study was conducted in compliance with the Declaration of Helsinki and National Ethical Guidelines for Biomedical and Health Research involving Human Participants. The study was registered with the NIH ClinicalTrials.gov (Identifier: NCT05931315) and Clinical Trials Registry India (Registration Number: CTRI/2023/07/055534). Written informed consent, having details about study design, IP and risks involved, was obtained from all participants prior to initiation of study procedures. The study report conformed to the Consolidated Standard Reporting of Trials (CONSORT) guidelines[22] (Supplementary Material –1. CONSORT Checklist). The Saikrupa Hospital Institutional Ethics Committee (Registration ID: ECR/1350/Inst/MH/2020) approved the study for Sangvi and Saikrupa Hospitals whereas

Harmony Ethical Research Committee (Registration ID: ECR/1411/Inst/MH/2020) approved the study for Dr Praphulla Awate's Clinic and The Kewalramani Clinic.

Study Participants

This trial was conducted across three sites in India between August 2023 and March 2024. A total of 77 participants meeting the pre-defined inclusion criteria were enrolled; male and female aged 18 to 60 years and reported physical and mental exhaustion for the last 4 weeks with moderate psychological distress as evident by PGWBI score between 61 and 72. Out of the 77 participants enrolled, 37 participants were allocated to CAR and 40 to the placebo arm. A total of 15 participants were lost to follow-up or withdrew from the study, 4 belonging to the test arm and 11 to the placebo. Sixty-two participants (33 in CAR and 29 in placebo) were considered for efficacy outcome analysis.

Inclusion Criteria

Individuals meeting all of the following criteria were recruited for the study:

1. Male and female individuals aged between 18 and 60 years (both values included) with low to moderate physical activity level as per International Physical Activity Questionnaire – Short Form (IPAQ-SF).
2. BMI $\geq$ 25 and $\leq$ 29.9 kg/m^2.
3. Individuals with at least two of the following five metabolic risk factors:
   - Waist circumference > 101.6 cm for men and > 88.9 cm for women
   - Triglycerides > 150 mg/dL
   - Systolic blood pressure > 130 mm Hg and/or diastolic blood pressure > 80 mm Hg
   - Fasting blood glucose $\geq$ 100 mg/dL
   - Low HDL cholesterol level (<40 mg/dL in men and <50 mg/dL in women)
4. Individuals with PGWBI scores $\geq$61 and $\leq$72 indicating moderate distress.
5. Individuals with history of physical and/or mental exhaustion since last 4 weeks.
6. Willingness to complete all study procedures and study-related questionnaires and comply with study requirements.
7. Willingness to abstain from other supplements or medication.
8. Ready to give voluntary, written, informed consent to participate in the study.
9. History of stable weight over the last 6 months.
10. Not currently pregnant, planning to become pregnant, or currently breastfeeding.
11. Willingness to maintain current dietary and exercise habits, aside from any changes to be made per the study exercise protocol.

Exclusion Criteria

Simultaneously, any individuals having any of the following criteria were excluded from the study:

1. Heavy alcohol drinkers or smokers.
2. Presence of unstable, acutely symptomatic, or life-limiting illness.
3. Individuals with uncontrolled hypertension with systolic blood pressure $\geq$140 mm Hg and diastolic blood pressure $\geq$90 mm Hg.
4. Individuals with FBG $\geq$ 126 mg/dL.
5. Neurological conditions causing functional or cognitive impairments.
6. Unwillingness or inability to be randomized to one of the two intervention groups.
7. Thyroid Stimulating Hormone (TSH) levels < 0.4 μIU/L and > 4.50 μIU/L.
8. History or presence of clinically significant renal, hepatic, endocrine, biliary, gastrointestinal pancreatic or neurologic disorders.
9. Use of any psychotropic medication within four weeks of screening and throughout the study.

10. Use of antibiotics or signs of active systemic infection at the time of screening.
11. Use of any supplements within two weeks of screening and throughout the study.
12. Individuals that are currently being prescribed medication or using any over-the-counter product that in the opinion of the study physician will have an effect on food digestion or nutrient absorption during the study.

Study Design

This randomized, double-blind, placebo-controlled, parallel-group, multicentric study enrolled individuals aged 18 to 60 years. Volunteers qualified for participation in the study based on the pre-defined inclusion – exclusion criteria. The participants were randomly allocated to one of the study arms (CAR or placebo) in a 1:1 ratio. A computer-generated randomization list, with a block size of six using StatsDirect Statistical Software version 3.1.17, was generated by statistician. Study-visit schedule (Figure 1) provides further details of the study design.

Intervention

Natural Carotenoid Complex – CAR – has been developed and manufactured by Bio-gen Extracts Private Limited, Bangalore, Karnataka, India. Each 200 mg capsule of CAR contained 28 mg of total carotenoids containing a proprietary blend of lutein, zeaxanthin, meso-zeaxanthin, alpha carotene, beta carotene and lycopene with sunflower oil as excipient. The placebo capsules consisted of 200 mg of sunflower oil. The participants were randomized using the Interactive Web Response System (IWRS; Microsoft Azure) with a 1:1 allocation rate for test supplement and placebo. The randomization chart was secured, saved, and maintained in the electronic trial master file with restricted access to only designated personnel. The participants, the research team, and the investigator, were blinded to the sequence allocation. To preserve blinding, the CAR and the placebo capsules were matched for size, shape, colour, and texture and stored in identical packaging. The participants were asked to take the assigned investigational products at a dose of one capsule once a day (200 mg) for 90 days.

Study Outcomes

Primary Outcomes

Psychological Well Being

The primary outcome of the study was to assess the effects of CAR on psychological well-being, evaluated through the Psychological General Well-Being Index (PGWBI) scores. PGWBI is an inventory designed by Dupuy[23] that measures the level of subjective psychological well-being along six domains, namely anxiety, depression, positive well-being, self-control, and general health. The PGWBI was assessed at baseline, Day 30 and Day 90 after randomization of the participants.

Secondary Outcomes

Oxidative Stress

8-Isoprostane (8-iso-PGF2α), a type of F2-Isoprostane, serves as a gold standard for assessing oxidative stress.[24] This prostaglandin-like compound is formed when free radicals react with the cell membrane lipids leading to the release of more free radicals. It can be used as a direct indicator of oxidative damage within the body.[25] Blood sample was collected after overnight fasting using serum separating tube. Samples were shipped using a cold chain. Quantitative determination of the serum 8-isoprostane (ELISA kit Cat# MBS1603188, MyBioSource, San Diego, CA, USA) was executed with commercial ELISA immunoassays in accordance with the manufacturer's instructions.

Immune Response

Salivary IgA is one of the most important antibodies responsible for mucosal response and offers the first line of immune defense. Research suggests that during chronic stress, the levels of IgA decrease leading to a suppression in the immune response.[26] Participants were instructed to collect the saliva sample after overnight fasting, before brushing teeth. The samples were shipped in dry ice to the central laboratory, and the sIgA was assessed using ELISA Kit (Cat# E-TSELH0019, Elabscience Biotechnology Co., Ltd., Houston, TX, USA).

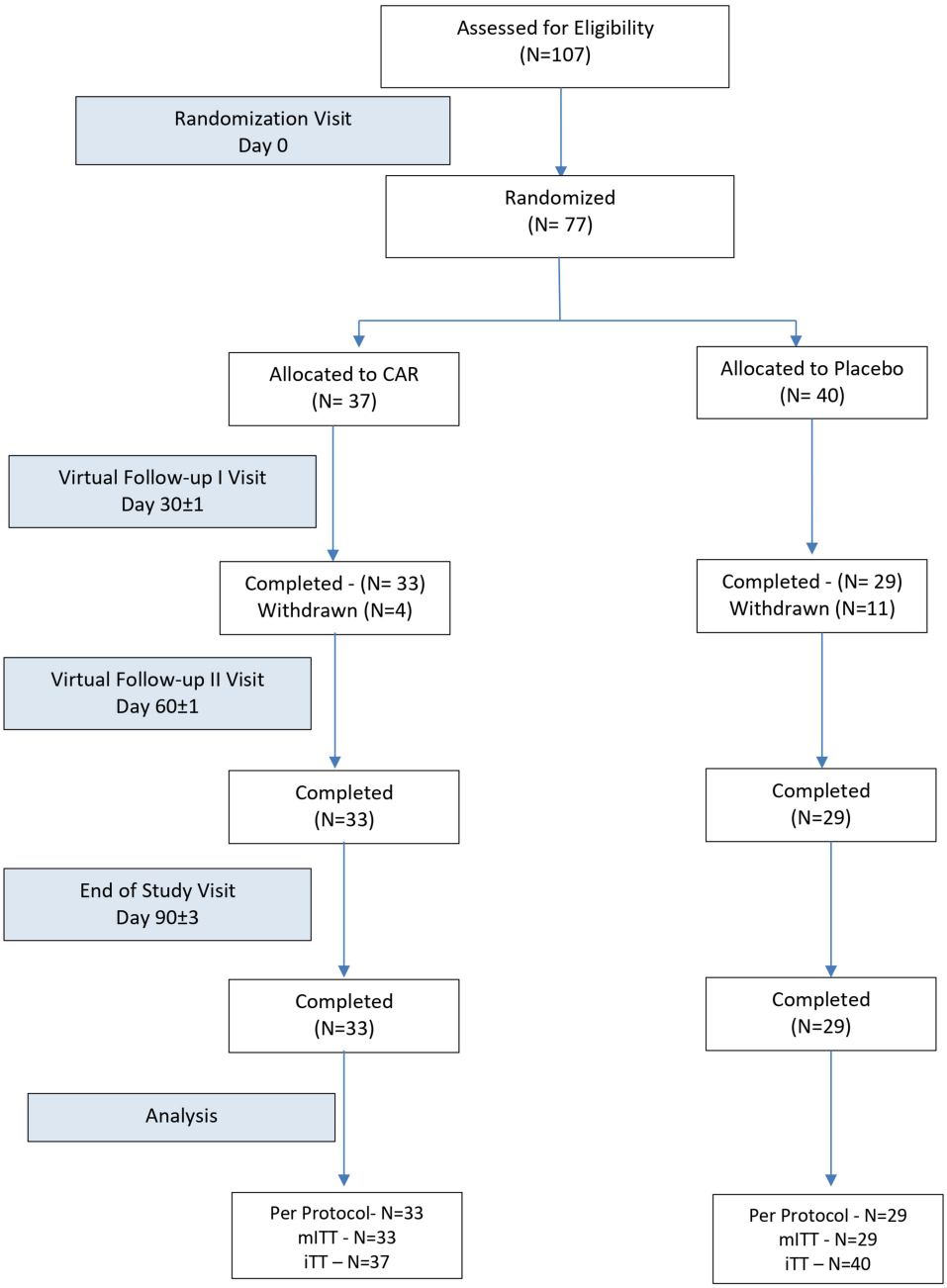

Figure 1 Study Flow Chart.

Quality of Life

The SF-36 health survey was included as an efficacy outcome to assess the impact of CAR on participants' overall quality of life. This validated tool self-reports multiple dimensions of physical and mental well-being, enabling a comprehensive assessment of treatment-related changes in health status.[27]

Sleep Quality

In the present study, the effect of IP on sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a validated tool designed to assess sleep quality and patterns in adults.[28]

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Safety Outcome

Vitals such as blood pressure and pulse rate as well as adverse events (AEs)/serious adverse events (SAEs) were recorded throughout the study at all the timepoints.

Statistical Analysis

The hypothesis was considered to be rejected, in case CAR showed statistically significant improvement in the psychological well-being at the End of Study (EoS), when compared to the placebo. Continuous variables were subjected to normality testing using the Shapiro–Wilk test. All normal data were analyzed using parametric tests, and non-normal data was analyzed using non-parametric tests for hypothesis testing. For continuous data, ANOVA and chi-square/fisher's exact test for categorical variables were used to compare the baseline demographic data between groups. Changes in the PGWBI score from baseline to the end of study compared between the groups were analyzed using analysis of covariance (ANCOVA). Within group comparisons from baseline to the EoS were done using paired t-tests. All statistical analyses for efficacy outcomes were performed on the modified intention to treat population (mITT), which comprised all randomized participants who received at least one dose of the interventional product and completed one post-baseline assessment. Safety data was analyzed for the intention to treat the population (ITT) with all randomized participants. As evidence suggests that emotional well-being tends to progressively differ from early adulthood through later life, a post hoc subgroup analysis homeostasis was conducted, comparing participants aged ≥35 years with those <35 years. The cutoff at 35 years was selected for exploratory testing based on anticipated physiological and psychosocial transitions in mid-adulthood that may influence antioxidant status and subjective well-being[29] (Supplementary Material - 2. Statistical Analysis Plan). Based on the post-hoc analysis, it can be hypothesized that CAR has an age specific effect on stress (Supplementary Material - 3. Statistical Analysis Plan for Exploratory Analysis).

Determination of Sample Size

The sample size for the present study, assuming a small to moderate effect (Cohen's D = 0.4) with an alpha error 0.05, and 80% power, was estimated to be a minimum of 32 participants per arm. Considering dropouts and withdrawal, each arm was further optimized to have a maximum of 35 participants.

Quality Assurance

The study was monitored and audited by the Contract Research Organization, Vedic Lifesciences (Mumbai, Maharashtra, India) to ensure compliance with the study protocol and with the ICH-GCP E6 (R2) guidelines.

Results

Baseline & Demographics

Both the intervention groups were comparable with respect to the baseline demographic characteristics (Table 1). Of the 107 screened participants, 77 were randomized and 33 and 29 participants completed the study in the CAR and placebo arms, respectively. Most participants were dropped out due their unwillingness to continue the study and their non-compliance to the study protocol.

Psychological Well-Being

The mean PGWBI scores at baseline were comparable with no statistically significant intergroup difference ($p = 0.7236$). A mild 1.3% increase, though not statistically significant in total PGWBI scores, was observed in the CAR group compared to the 0.4% in the placebo group, apparent at day 30. The scores remained almost the same at Day 60. A statistically significant ($p < 0.05$) increase of 3.09 (±5.24) and 2.73 (±6.63) units from baseline were noted at Day 90 in the CAR and placebo arms, respectively (Table 2). The change, when compared between the groups, was not significant. This placebo effect on PGWBI could be an outcome of the psychological expectancy, increased self-awareness, and contextual factors of clinical participation.[30]

As age negatively correlates with the PGWBI score,[31] a subgroup analysis for each domain of PGWBI was performed in individuals below 35 years and those more than equal to 35 years of age. The baseline score for each domain was

Table 1 Demographic and Baseline Characters

Parameter	Statistics	CAR (N = 37)	Placebo (N = 40)	P-Value vs Placebo
Age (years)	Mean (SD)	36.80 (10.86)	36.18 (10.05)	0.809a
	Min, Max	20.00, 59.00	19.00, 56.00	
Gender	Male	30 (85.71%)	23 (69.70%)	0.111b
	Female	5 (14.29%)	10 (30.30%)	
BMI (kg/m2)	Mean (SD)	26.71 (1.11)	26.68 (1.33)	0.929a
	Min, Max	25.20, 29.10	25.30, 29.90	
Waist Circumference (cm)	Mean (SD)	103.09 (6.26)	101.08 (5.51)	0.167a
	Min, Max	89.20, 120.55	89.50, 112.20	
Fasting blood glucose (mg/dl)	Mean (SD)	89.65 (13.24)	89.25 (12.87)	0.894a
	95% C.I.	(85.24, 94.06)	(85.13, 93.37)	
Triglycerides (mg/dl)	Mean (SD)	167.49 (101.50)	153.15 (70.69)	0.478a
	95% C.I.	(133.64, 201.33)	(130.54, 175.76)	
High Density Lipoprotein (mg/dl)	Mean (SD)	42.49 (15.68)	40.40 (10.38)	0.497a
	95% C.I.	(37.26, 47.72)	(37.08, 43.72)	
Thyroid Stimulating Hormone (IU/L)	Mean (SD)	1.99 (0.68)	2.86 (5.15)	0.294a
	95% C.I.	(1.76, 2.21)	(1.21, 4.51)	

Notes: a, Student's t-test; b, chi-square.

Table 2 Change in PGWBI Total Score

Visit	CAR (N = 33)	Placebo (N = 29)	p-Value[b] vs Placebo
	Mean (SD)		
Day 0	65.23 (2.54)	65.42 (1.94)	0.724
Day 30	66.09 (2.28)	65.73 (2.18)	0.511
Change from baseline	0.86 (2.78)	0.30 (2.17)	0.395
Day 60	66.00 (2.13)	65.45 (2.32)	0.316
Change from baseline	0.77 (2.81)	0.03 (2.59)	0.2570
Day 90	68.31 (4.35)	68.15 (6.39)	0.903
Change from baseline	3.09 (5.24)	2.73 (6.63)	0.911
p-value[a] Day 90 vs Baseline	0.001	0.024	

Notes: a were calculated using paired t-test; b were calculated using ANCOVA with treatment as factor and baseline as covariate vs. Placebo.
Abbreviations: N, number of participants; SD, standard deviation; vs., versus.

assessed between both the arms and no statistically significant differences were found between the two arms ($p > 0.05$). The results revealed that for specific domains such as "Anxiety", "Depressed Mood", "Positive Well-being" and "Vitality", scores in the age group ≥35 years, increased significantly ($p < 0.05$), from Day 0 to Day 90, indicating improvement in psychological well-being (Figure 2A). Simultaneously, the placebo arm showed non-significant changes

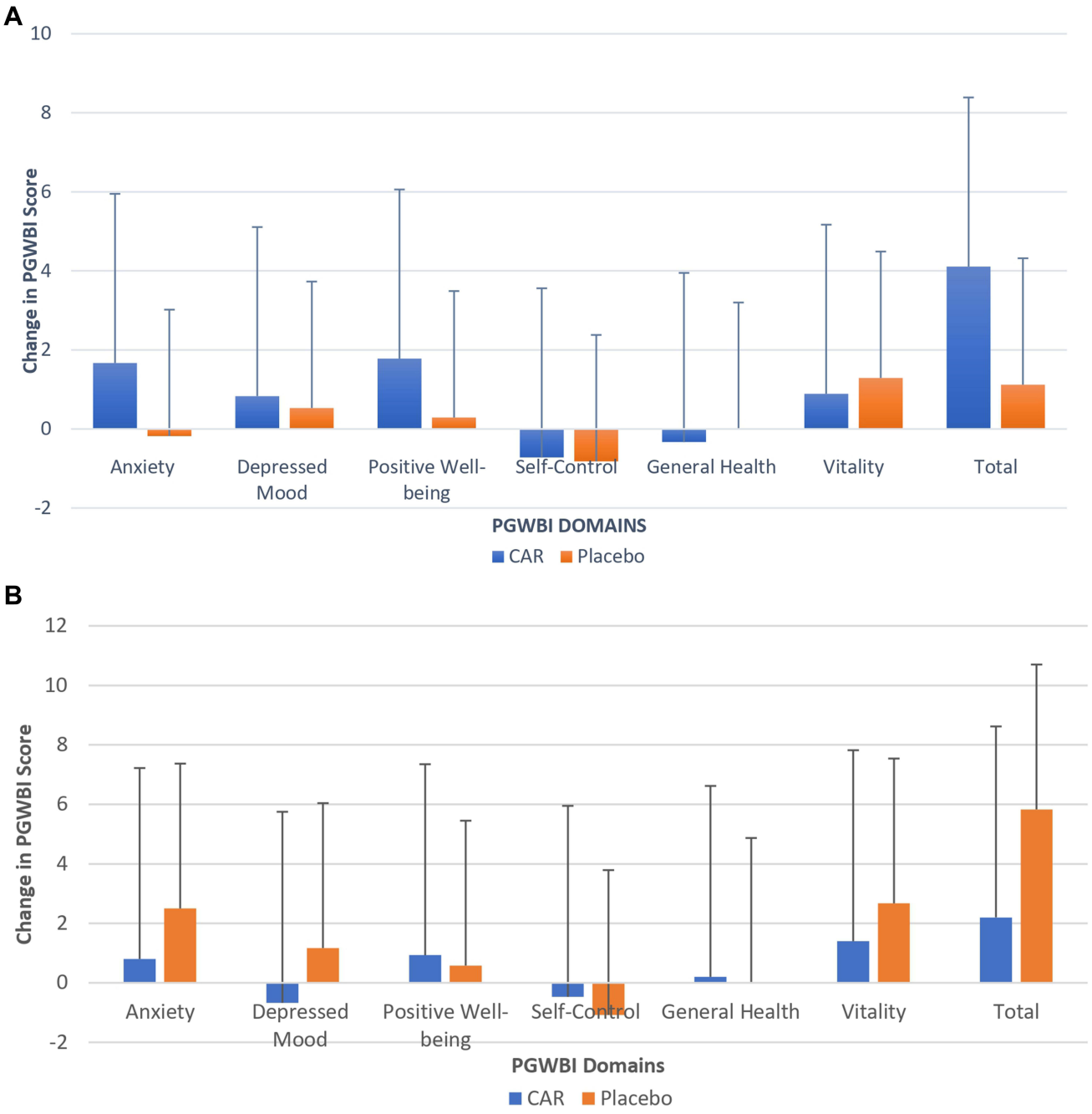

Figure 2 (**A**) Change in PGWBI Score in Older Population. (**B**) Change in PGWBI Score in Younger Population.

in all these domains, except for positive well-being. The CAR group, on the other hand, showed an increase in the positive well-being scores by approximately 6 times. The changes compared between the groups remained non-significant. The domains "Self-control" and "General health" are broadly influenced construct and are often affected by mood, motivation, sleep, stress, and other factors.[32] The scores in these indiscernible domains showed no significant changes. Finally, the total PGWBI score of this group demonstrated a statistically significant increase of 4.11 (±4.28) points from baseline in the CAR arm as compared to 1.12 (±3.20) points in the placebo ($p = 0.045$) (Table 3).

Table 3 Change in PGWBI Score – Domain Wise Subgroup Analysis

PGWBI Domain	Visit	≥35 Years of Age			<35 Years of Age		
		Mean (SD)		p-Value[a] *vs Placebo*	Mean (SD)		p-Value[a] *vs Placebo*
		CBS (N = 18)	Placebo (N = 17)		CBS (N = 15)	Placebo (N = 12)	
Anxiety	Day 0	13.83 (2.07)	15.12 (2.55)	0.109	14.40 (1.80)	14.33 (1.23)	0.914
	Day 90	15.50 (2.28)	14.94 (2.36)	0.481	15.20 (2.57)	16.83 (4.22)	0.226
	p-Value[b] vs Baseline	0.008	0.850	-	0.257	0.103	-
	Change (Day 90)	1.67 (2.35)	-0.18 (3.78)	0.421	0.80 (2.62)	2.50 (4.87)	0.236
Depressed Mood	Day 0	8.83 (1.42)	8.53 (1.55)	0.549	8.67 (1.84)	8.25 (1.66)	0.547
	Day 90	9.67 (1.33)	9.06 (1.95)	0.287	8.00 (1.60)	9.42 (3.03)	0.163
	p-Value[b] vs Baseline	0.047	0.285	-	0.164	0.132	-
	Change (Day 90)	0.83 (1.65)	0.53 (1.97)	0.368	-0.67 (1.76)	1.17 (2.48)	0.046
Positive Well-being	Day 0	9.56 (2.66)	9.94 (2.84)	0.681	10.07 (1.98)	10.92 (1.98)	0.278
	Day 90	11.33 (4.14)	10.24 (4.16)	0.440	11.00 (2.78)	11.50 (2.07)	0.609
	p-Value[b] vs Baseline	0.012	0.569	-	0.430	0.267	-
	Change (Day 90)	1.78 (2.69)	0.29 (2.08)	0.056	0.93 (1.62)	0.58 (1.73)	0.666
Self-Control	Day 0	10.11 (1.60)	9.18 (1.94)	0.130	9.53 (2.10)	10.33 (1.30)	0.26
	Day 90	9.39 (2.15)	8.35 (2.03)	0.152	9.07 (1.62)	9.25 (2.26)	0.808
	p-Value[b] vs Baseline	0.079	0.241	-	0.363	0.071	-
	Change (Day 90)	-0.72 (1.64)	-0.82 (2.79)	0.338	-0.47 (1.92)	-1.08 (1.88)	0.742
General Health	Day 0	10.50 (0.92)	10.35 (1.17)	0.682	10.87 (1.41)	10.67 (1.56)	0.729
	Day 90	10.17(1.20)	10.35 (1.46)	0.682	11.07 (1.67)	10.67 (2.31)	0.606
	p-Value[b] vs Baseline	0.269	1.000	-	0.638	1.000	-
	Change (Day 90)	-0.33 (1.24)	0.00(1.66)	0.596	0.20 (1.61)	0.00 (2.63)	0.669
Vitality	Day 0	11.61 (2.43)	12.00 (2.76)	0.661	12.47 (2.50)	11.33 (2.61)	0.262
	Day 90	12.50 (2.15)	13.29 (2.82)	0.354	13.87 (3.27)	14.00 (2.89)	0.913
	p-Value[b] vs Baseline	0.0490	0.062	-	0.108	0.029	-
	Change (Day 90)	0.89 (1.78)	1.29 (2.66)	0.413	1.40 (3.16)	2.67 (3.68)	0.660
Total	Day 0	64.44 (2.23)	65.12 (1.76)	0.331	66.00 (2.67)	65.83 (2.37)	0.867
	Day 90	68.56 (4.16)	66.24 (3.38)	0.081	68.20 (4.83)	71.67 (8.91)	0.243
	p-Value[b] vsBaseline	0.001	0.206	-	0.169	0.063	-
	Change (Day 90)	4.11 (4.28)	1.12 (3.20)	0.0451	2.20 (6.42)	5.83 (9.78)	0.2143

Notes: a was calculated using Student's test; b was calculated using paired t-test.
Abbreviations: CBS, Carotene Base Supplement; SD, Standard deviation; N, Number of participants.

In the younger sub-group, both interventions had small, non-significant increases with the exception of "Vitality" domain. The "Vitality" score increased significantly in the placebo arm. Figure 2B summarises the domain specific scores and the changes in both the subgroups.

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Oxidative Stress

The serum 8-Isoprostane levels at baseline were recorded above the normal reference range indicating moderate oxidative stress in both the arms.[33] At day 90, the levels decreased significantly in both the arms. Post-hoc analysis of 8-isoprostane levels revealed that the older subgroup had almost similar reduction of 161.62 (±172.45) and 149.90 (±96.76) pg/mL in the CAR and placebo arm, respectively.

At the same time, the younger group demonstrated a mean reduction of 157.41 (±178.27) pg/mL and 104.50 (±114.84) pg/mL in the CAR and placebo arms, respectively. Compared to the placebo, CAR resulted in greater decrease with a difference estimate of 33.72 units (95% CI: –17.92, 85.37) which further supports the possibility of greater responsiveness to the product among younger individuals, potentially due to more dynamic redox homeostasis or differences in baseline oxidative load. Despite the change being non-significant ($p = 0.190$) as compared to the placebo, the effect size (Cohen's $d = 0.3444$) suggests a small to moderate intervention effect.

Table 4 presents the mean and the change in the serum 8-iosprostane level along with subgroup analysis.

A graphical representation of the change in the 8-isoprostane levels has been provided (Figure 3).

Immune Response

At baseline, mean salivary IgA levels were 0.33 (±0.77) and 0.66 (±1.81) ng/mL in the CAR and placebo arm, respectively ($p = 0.347$). By Day 90, the IgA levels increased by 2.76 (±9.37) and 0.83 (±5.12) ng/mL in the CAR and the placebo arm, respectively. While the CAR group demonstrated a comparatively greater improvement in immune parameters than the placebo group, this change was not statistically significant. This increase in sIgA level as compared to placebo indicates a link between immune boost and psychological well-being which warrants further exploration.

A visual representation of the change has been provided (Figure 4).

Quality of Life

The mean scores across all SF-36 domains were comparable between the two study arms at baseline ($p > 0.05$), except for the bodily pain domain, where the placebo group reported significantly higher scores ($p = 0.0199$). After 90 days of supplementation, participants in the CAR group exhibited modest within-group improvements in the physical health problem domains, as reflected by increases in mean scores from baseline. In line with the positive well-being domain of PGWBI, the CAR arm exhibited a mean increase of 0.46 (±1.56) units in the physical health problems domain as compared to 0.27 (±1.26) units in the placebo arm. These changes (Figure 5), although not statistically significant, serve as proof to the concept that CAR has the potential to enhance the quality of life in people with poor psychological well-being.

Table 4 Serum 8-Isoprostane Level (pg/ml) – Age Stratified Analysis

Visit	≥35 Years of Age			<35 Years of Age		
	Mean (SD)		p-Value[a] vs Placebo	Mean (SD)		p-Value[a] vs Placebo
	CAR (N = 18)	Placebo (N = 17)		CAR (N = 15)	Placebo (N = 12)	
Day 0	501.90 (131.56)	490.41 (93.51)	0.769	551.84 (178.12)	458.64 (110.08)	0.126
Day 90	340.27 (123.41)	340.51 (50.53)	0.994	394.43 (67.12)	354.14 (52.94)	0.102
p-Value[b] vs Baseline	0.0010	<.0001	-	0.0041	0.0092	-
Change Day 90	-161.62	-149.90	0.969	-157.41	-104.50	0.190

Notes: a was calculated using Student's t-test (T); b was calculated using paired t-test (t).
Abbreviations: C.I., Confidence Interval; SD, Standard deviation; N, Number of participants.

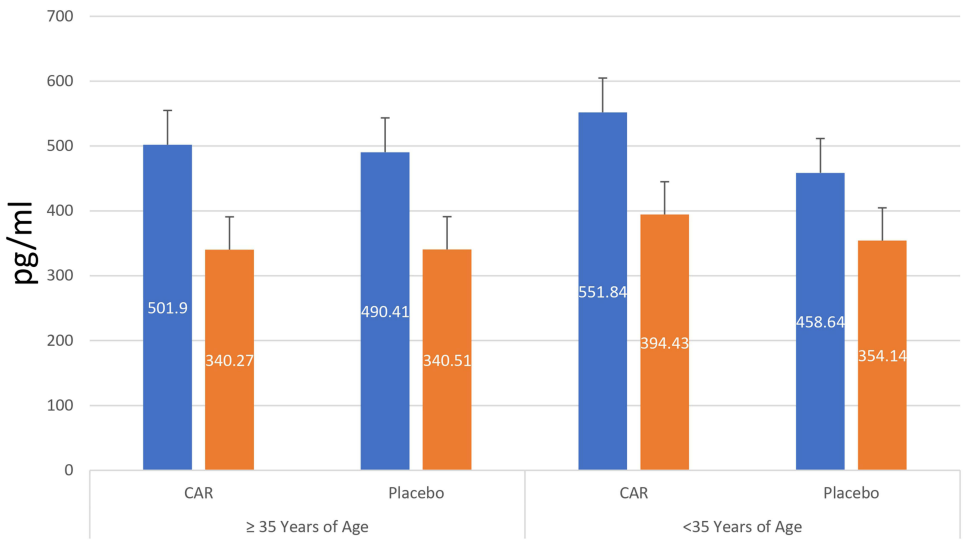

Figure 3 Change in 8-isoprostane levels – Subgroup Analysis.

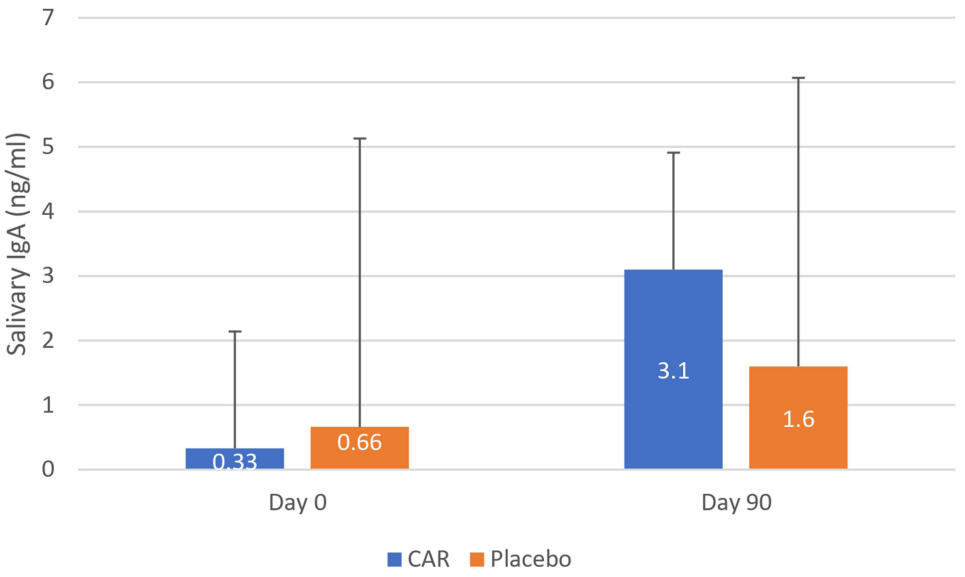

Figure 4 Visual Representation of Secretory IgA levels.

Sleep Quality

At baseline, the mean global PSQI scores of both the study groups (CaroRite™ and Placebo) were comparable with no statistically significant intergroup difference (p = 0.3957). No significant effect was observed on the sleep quality by the CAR supplementation, at the end of the study.

Vital Signs

Vital signs, including pulse rate and blood pressure, were assessed at baseline and at the end of the 90-day intervention period to evaluate the safety of the test supplement. At baseline, no significant differences were observed between the test arm and placebo arm for pulse rate, systolic blood pressure, or diastolic blood pressure (all $p > 0.05$). By day 90, no

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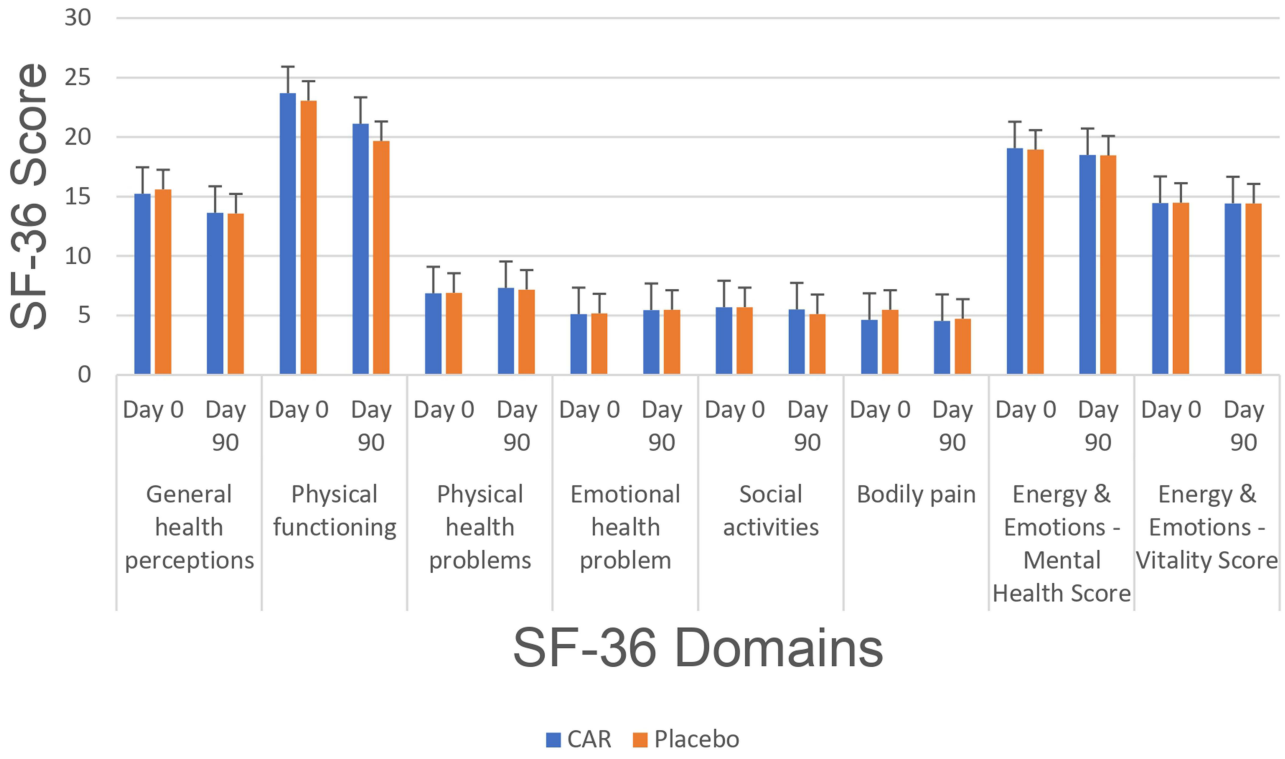

Figure 5 Change in SF-36 Domain Score at Day 0 and 90.

clinically meaningful or adverse shifts in vital signs were reported, and between-group comparisons did not indicate a significant differential effect of the test supplement on cardiovascular parameters (Table 5).

Adverse/Serious Adverse Event

A total of 10 adverse events were reported by 7 participants, during the study. All the adverse events reported during the study were mild in nature, and there was no serious adverse event. All the events resolved without any intervention and were deemed to be "unlikely" related to the study product. Supplementary Material - Table S1 provides a summary of adverse events.

Table 5 Summary of Vitals

Parameter	Visit	Mean (SD		p-Values vs Placebo
		CAR (N = 37)	Placebo (N = 40)	
Pulse rate (bpm)	Day 0	77.16 (5.94)	77.83 (4.73)	0.588
	Day 90	79.56 (6.46)	78.13 (4.38)	0.301
Systolic BP (mmHg)	Day 0	133.68 (2.25)	133.23 (3.13)	0.468
	Day 90	127.76 (8.20)	125.70 (10.06)	0.369
Diastolic BP (mmHg)	Day 0	82.51 (2.21)	82.90 (2.61)	0.486
	Day 90	81.44 (5.52)	80.10 (5.44)	0.333

Discussion

As a critical component of well-being, mental health influences every aspect of life and enables individuals to cope with stress, maintain resilience, and function effectively both personally and professionally.

Carotenoids are known to have a significant effect on mental well-being.[34] The present study with CAR supplementation reconfirms this effect. In current study, 90 days supplementation with CAR led to a significant increase in the PGWBI score from baseline. However, a similar effect was observed in the placebo arm as well. Placebo response has been recognised as a well-established phenomenon for psychological variables[35] and has been credited to within-person variability of psychological state and some innate biomarkers.[36] Interestingly, upon post-hoc analysis, older participants exhibited statistically significant improvements of psychological well-being score with CAR as compared to the placebo group, supporting efficacy of the product. In the absence of a well-defined benchmark for what counts as meaningful change for PGWBI scores, the current improvement of approximately 6%, along with a Cohen's D value of 0.79, suggests a moderate and noticeable effect.[37] The CAR supplementation led to an increase of more than 10% in the emotional domains namely "Anxiety", "Depressed mood" and "Positive wellbeing". This effect can be linked to the increase of the in-situ levels of carotenoids, as seen in the InCHIANTI study.[38] In the younger cohort, except vitality, all PGWBI domain score changed non-significantly for both the study arms. The placebo effect can be attributed to the higher baseline plasma carotenoid levels as well as the pronounced Hawthorne effect,[39] wherein participants show behavioural improvements in response to being under observation. The lower response in the CAR supplemented arm of younger cohort can be attributed to contra-hedonic inclination of young individuals.[40]

In contrast to PGWBI scores, the oxidative stress response showed an opposing trend. The younger participants exhibited a more pronounced reduction by 28.5% in oxidative stress markers following CAR supplementation compared to 22% in placebo. While the effect did not reach statistical significance, it nonetheless provides a meaningful direction for future investigations. A study with 4 week supplementation of high vegetable-fruit diet demonstrated similar reduction of approximately 20% in 8-isoprostane levels as compared to low vegetable-fruit diet.[41] The potentially greater response among younger adults may be attributed to more efficient oxidative balance and stronger upregulation of endogenous antioxidant defenses when challenged.[42] The current observation also aligns with the mechanistic insights that in young adults, improvements in redox balance can occur rapidly with nutritional supplementation due to more robust endogenous antioxidant defenses.[42] This enzyme is known to have a negative corelation with age,[43] which could serve as basis for better effect of CAR supplementation on 8-isoprostane levels in the younger cohort. At the same time, interpersonal variability in baseline 8-Isoprostane levels may be the prime contributor for the observed decline in the placebo group. However, based on the effect sizes, the observed age-related patterns serve as foundation to further explore effect of CAR supplementation.

sIgA, a marker of immunomodulation, increased by almost five from baseline, as compared to placebo. Although not significant in comparison to placebo, the observed trend suggests that the CAR supplementation can help in improving immune status. This effect is in line with previous literature, wherein carotenoids such as β-carotene and astaxanthin enhance both innate and adaptive immune response.[17,44] Preclinical studies suggest that carotenoids, such as astaxanthin can induce the host immune responses by inducing B cell differentiation and maturation leading to increase in sIgA production.[45] However, a well powered long term study is required to quantify these immunomodulating properties of carotenoids in humans.

Although quality of life assessment through SF-36 did not show any significant changes, improvement in psychological health was paralleled by trends of better quality of life. Improved physical and emotional health scores after 90 days supplementation of CAR indicate a favourable trend. These findings are consistent a study by Stringham et al, which reported improved emotional and physical well-being following 12-month carotenoid supplementation with lutein, zeaxanthin, and meso-zeaxanthin.[46]

The incidences of adverse events observed in this study were low, with no CAR related adverse events reported. Furthermore, no significant abnormalities were detected in blood vital signs indicating the CAR to be safe and well tolerated.

This study reveals a multidomain trend suggestive of psychological benefits associated with CAR supplementation. The noteworthy improvement in PGWBI scores reflects a positive shift in emotional resilience and perceived psychological health by CAR, which align with carotenoids' proposed role in modulating stress pathways. Concurrently, a reduction in oxidative stress marker supports existing literature wherein carotenoids contribute to mood dysregulation and HPA axis activation by reduction in oxidative stress. The indicative increase in sIgA levels by CAR serves as proof of concept for further long-term clinical study with a larger sample size.

Limitations and Future Directions

While the trends observed across multiple study variables including psychological well-being, oxidative stress and immune response, suggest that CAR has beneficial effects, these findings should be interpreted with caution. The modest sample size may have reduced the statistical power needed to detect differences between the two intervention arms. The lack of statistically significant findings should be interpreted cautiously, as it may result from insufficient power and a possible Type II error, rather than a true absence of effect. Based on the available data and reflecting on the results obtained presently, a study conducted over a longer duration could produce more well-founded evidence. As indicated by previous literature, carotenoids tend to have a linear time dose response, especially to elucidate its effect on oxidative stress and immunomodulation. Last but not least, a study conducted within aging population with more stable biomarker such as protein carbonyls, might help in elucidating the true effect as well as the mechanism of action of the product on the oxidative stress.

Conclusion

The results of this placebo-controlled clinical study suggest that a Natural Carotenoid Complex – CAR – may offer age-dependent benefits for individuals experiencing moderate psychological distress with psychological well-being improvement in older adults and greater reductions in oxidative stress markers in younger individuals. Additionally, a trend towards enhanced immunomodulation, evidenced by increased sIgA levels, further supports CAR's potential role in immunoregulation. Importantly, CAR was well tolerated, with a low incidence of adverse events and no significant safety concerns. The effects on psychological well-being should be further explored in a dose dependent fashion.

Data Sharing Statement

The data derived from the study and the analyses are available from the corresponding author upon reasonable request.

Informed Consent Statement

Informed consent was obtained from all the subjects involved in the study.

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Disclosure

The authors report no conflicts of interest in this work.

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