

1 **Translational Sports Medicine**
2 **Effect of ThymoQuin Black Cumin Seed Oil as a Natural Immune**
3 **Modulator of Upper-Respiratory Tract Complaints and**
4 **Psychological Mood State**

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9

10 **Abstract**

11 This was a placebo-controlled, double-blind study designed to evaluate the effect of a
12 commercially available dietary supplement on upper-respiratory tract complaints (URTCs) and
13 psychological mood state. Thirty-seven marathon and half-marathon runners consumed 500mg
14 of black cumin seed oil extract (commercial name ThymoQuin®3%) or placebo daily during the
15 4 week supplementation period (3 weeks before and 1 week following a marathon or half-
16 marathon competition). We collected subjective and objective measures before and after
17 supplementation. Subjects completed the profile of mood state (POMS) psychological
18 assessment and a questionnaire style health log measuring health status and URTCs (subjective
19 measures), as well as provided saliva samples and fecal samples for measurement of cortisol and
20 microbiome balance, respectively (objective measures). Subjects in the ThymoQuin
21 supplementation group (500mg black cumin seed oil extract) reported significantly fewer upper-
22 respiratory tract complaints (URTCs) and better overall well-being, as well as lower cortisol and
23 superior microbiome diversity compared to placebo. These results suggest that ThymoQuin black
24 cumin seed oil extract may improve immune system vigilance and overall well-being following
25 the stress of endurance training and competition.

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27

28 **Introduction**

29 The immune system is traditionally thought of as the body's primary defense against external
30 pathogens such as viruses. Increasingly, research is demonstrating an expanded role of the
31 immune system as both a "shield" against viruses and also as a "communication organ" via its
32 contribution to psychological mood state and overall well-being.

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34 Numerous studies have shown the close links between psychological factors such as stress, sleep
35 deprivation, and immune suppression leading to poor vaccine responses and increased upper-
36 respiratory tract infections (URTIs) and non-infection upper-respiratory tract complaints
37 (URTCs). For example, in athletes, heavy exercise or intense training may lead to increased

38 susceptibility to URTI (Nieman et al., 1990; Peters and Bateman, 1983; Spence et al., 2007).
39 Intense exercise is a physical stressor that results in measurable immune challenges with
40 reductions in key immune system components such as neutrophils, natural killer cells, T cells
41 and B cells (Mackinnon and Hooper, 1994; Nieman et al., 1995; Ostrowski et al., 1998). Athletes
42 are particularly susceptible in the one to two-week recovery period after competitive endurance
43 events, partially due to elevations in hormones such as cortisol that coordinate the stress response
44 (Peters and Bateman, 1983). The net effect of an ongoing immune challenge is a weakened
45 immune system, which often results in URTIs/URTCs as well as detrimental effects on
46 psychological mood state.

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48 Exercise stress is similar in certain ways to other stressors, such as psychological stress, which
49 can lead to a weakened immune system and increased susceptibility to URTI/URTC and other
50 disease states (Mackinnon, 1997). Although regular exercise is generally regarded as a buffer
51 against many detrimental effects of stress, psychological stress can also result from prolonged
52 training and competition – in both elite and recreational athletes – with noticeable deteriorations
53 in mood state during intense training periods, and before and after endurance events (Achten et
54 al., 2004; Hassmen and Blomstrand, 1991). Lifestyle factors, such as coping with daily stress,
55 may influence the immune response to exercise (Konig et al., 2000). Reductions in immune cell
56 populations, lowered antibody production and altered cytokine response have been observed due
57 to psychological stress (Cohen et al., 1999; Glaser et al., 1999).

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59 A variety of intervention techniques can be used to ameliorate psychological and physical stress,
60 such as administering selective dietary supplements containing immune modulating compounds
61 (Akerstrom and Pedersen, 2007; Nieman and Bishop, 2006; Peters et al., 1993). In ultra-
62 marathon runners, 600mg of vitamin C, taken 21 days before and 14 days after a 90 km race,
63 reduced URTI symptoms (Peters et al., 1993). Biological response modifiers such as beta-glucan,
64 enhance the innate immune response (Luhm et al., 2006; Niederman et al., 2002), helping to
65 prime immune system function during and following various forms of chronic stress.

66
67 Black cumin seed (*Nigella sativa*) oil is widely used in various traditional Eastern and Ayurvedic
68 systems of medicine as a therapeutic tool for many different ailments and conditions. *Nigella*
69 *sativa* seeds have been used medicinally in the Middle East and Southeast Asia for over 2,000
70 years. Black cumin seeds are mentioned in the Bible and the Koran where they are referred to as
71 “the blessing seed,” created by God in order to relieve difficult medical conditions. Black seeds
72 were also buried with Egyptian pharaohs to aid in the afterlife journey.

73
74 Extensive preclinical, animal, and clinical research has been conducted on *N. sativa*’s properties
75 and it is among the top ranked evidence-based herbal medicines. Most of the therapeutic
76 properties of this plant are attributed to its essential oil constituent, ThymoQuinone (TQ), and
77 modern black seed extracts can be standardized for TQ content (e.g. ThymoQuin, 3% TQ;
78 TriNutra, Israel). A number of laboratory and animal studies have demonstrated immune
79 modulation of black cumin seed via effects on hematopoietic stem cells, lymphocytes,
80 macrophages, T cells, dendritic cells (DCs), natural killer (NK) cells, and a variety of cytokines
81 (IFN, IL-2, TNF-alpha, IL-6, and others).

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83 Approximately 500 clinical trials have evaluated the efficacy of black seed preparations for a
84 variety of conditions. ThymoQuin (black cumin seed oil standardized to 3% ThymoQuinone) is
85 known to have broad-spectrum antimicrobial effects (including anti-viral, anti-bacterial, and anti-
86 fungal) as well as for benefits related to longevity and overall well-being.

87
88 Stress-related immune alterations can be consequential for health; they can enhance
89 susceptibility to infectious agents and influence the severity of infectious disease, diminish the
90 strength of immune responses to vaccines, reactivate latent viruses, and slow wound healing.

91
92 **Materials and Methods**
93 This study was done in accordance with the Helsinki Declaration, as revised in 1983, for clinical
94 research involving humans and was reviewed and approved by an external advisory board
95 (WCG-IRB, Puyallup, WA; Protocol #20202070).

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97 The objective of this study was to recruit 40 healthy volunteers to participate in a research study
98 investigating the effects of dietary supplementation for one-month with black cumin seed oil
99 extract (500mg ThymoQuin 3% ThymoQuinone and 1.8 Free Fatty Acid, TriNutra, Israel; N=20)
100 that may be immunomodulatory for improving immune system vigilance and psychological
101 stress versus Placebo (500mg Maltodextrin; N=20).

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103 *Subjects*
104 We recruited healthy, fit, recreational runners who were experienced in training and competing
105 for half-marathon to marathon-distance events. Our subject pool completing all phases of
106 baseline pre-supplementation measurements, training, competition, and final post-
107 supplementation measurements included 37 subjects (Table 1). One subject in the ThymoQuin
108 group and two subjects in the Placebo group were lost to follow up. There were no adverse
109 events reported for either group.

110
111 *Health log*
112 Subjects completed a physical health questionnaire at baseline (pre-supplementation) and 4-
113 weeks (post-supplementation). The health log was a daily health perception log containing
114 questions related to overall health status and specific upper-respiratory tract complaints
115 (URTCs). The URTC-related symptoms measured included nasal congestion, runny nose, sore
116 throat, sneezing, cough, fatigue, headache, general malaise and body aches. Reported symptoms
117 were totaled for each assessment period.

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119 *Mood Assessment*
120 Changes in psychological mood state were assessed using the research-validated Profile of Mood
121 States (POMS) questionnaire to measure 6 primary psychological factors (tension, depression,
122 anger, fatigue, vigor, and confusion) plus the combined global mood state as an indication of
123 subjective well-being. The POMS methodology has been used in ~3,000 studies, and its validity
124 is well established. The POMS profile uses 65 adjective-based intensity scales scored on a 0–4
125 hedonic scale (e.g. “not at all” to “extremely”). The 65 adjective responses are categorized into
126 the 6 mood factors (tension, depression, anger, fatigue, vigor, or confusion), tabulated, scored,
127 and analyzed. The output of the POMS questionnaire is an assessment of the positive and
128 negative moods of each subject at baseline and post-supplementation.

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Salivary Cortisol

Cortisol is the major glucocorticosteroid stress hormone produced in the adrenal cortex and is actively involved in regulating many aspects of metabolism related to sports performance, including blood pressure, anti-inflammatory function, gluconeogenesis, and immune function. Cortisol production has a circadian rhythm. Levels peak in the early morning and drop to the lowest concentration at night. Levels rise independently of circadian rhythm in response to stress. In the blood only 1 to 15% of cortisol is in its unbound or biologically active form, with the remaining cortisol bound to serum proteins. Unbound serum cortisol enters the saliva via intracellular mechanisms, and in saliva the majority of cortisol remains unbound to protein where it can be easily collected and assayed as an index of overall stress exposure and recovery. Each subject provided “first morning” saliva samples (upon awakening) for analysis of free cortisol at baseline (pre-supplementation) and 4-weeks (post-supplementation).

Microbiome Assessment

Volunteers were provided with a take-home kit to obtain fecal samples in the privacy of their home for analysis. The kit included detailed instructions and postage paid packaging for return directly to the lab. Each kit was numerically coded so that samples were blinded to the lab. Microbiome analysis of fecal samples was carried out using the complete BiomeTracker system (Wasatch Scientific, Murray, UT). Briefly, fecal samples were obtained by nylon swab and placed into preservative binding buffer to lock the composition of bacteria in place. DNA was then purified using DNA columns and ~20ng of DNA from each sample was added to the reaction mixtures. Samples were processed on an ABI 7500 Fast (Applied Biosystems) instrument in duplicate. A “microbiome composite score” was generated as an overall average of many different aspects of microbiome balance, including Bifidobacterium, Lactobacillus, Akkermansia, Thermophilus, Firmicutes/Bacteroidetes (F/B) ratio, and others.

Data Management and Analysis

All questionnaires were hand-delivered or mailed to a central location and transcribed to a central database. Subjects who did not complete the questionnaires or who submitted incomplete questionnaires were dropped from the study and not included in the study analysis (3 subjects; 1 from the Supplement group and 2 from the Placebo group). Data were identified by subject number and examined for accuracy and completeness. Tabulated data were analyzed with JMP 14.0 (JMP Statistical Discovery, Cary, NC) using standard parametric paired t tests, and significance was assessed with a 2-tailed alpha level set at 0.05. Data are presented as average values for each group (Placebo and ThymoQuin) before and after supplementation.

Table 1. Subject Demographics

Group	Average Age	Men	Women
ThymoQuin	35+6	10	9
Placebo	36+5	10	8

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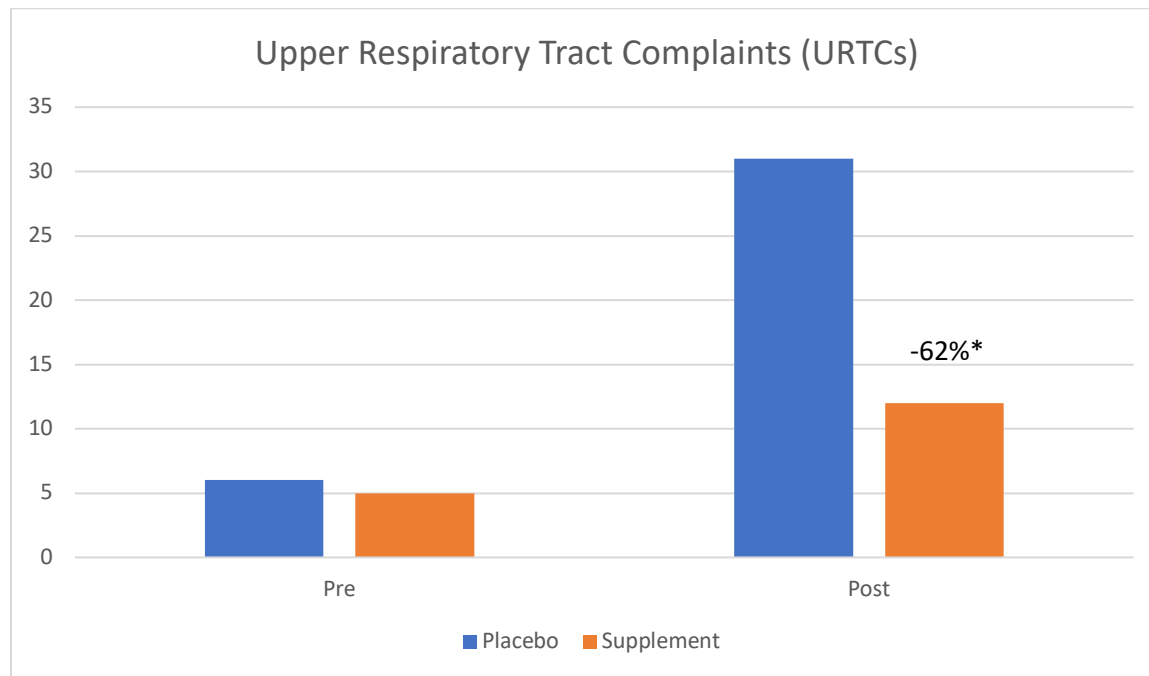
Results

Following 4 weeks of supplementation with ThymoQuin, (3 weeks before and 1 week following an intense endurance run), we observed the following differences between the Supplement and Placebo groups:

Subjective Measures

As expected, both groups reported dramatically more self-reported upper-respiratory tract complaints (URTCs) following the endurance run compared with before (**Figure 1**). However, URTCs, including the total number of symptoms reported such as cough, sore throat, sniffles, stuffiness, etc., were 62% lower in the ThymoQuin group compared to placebo (**Figure 1**).

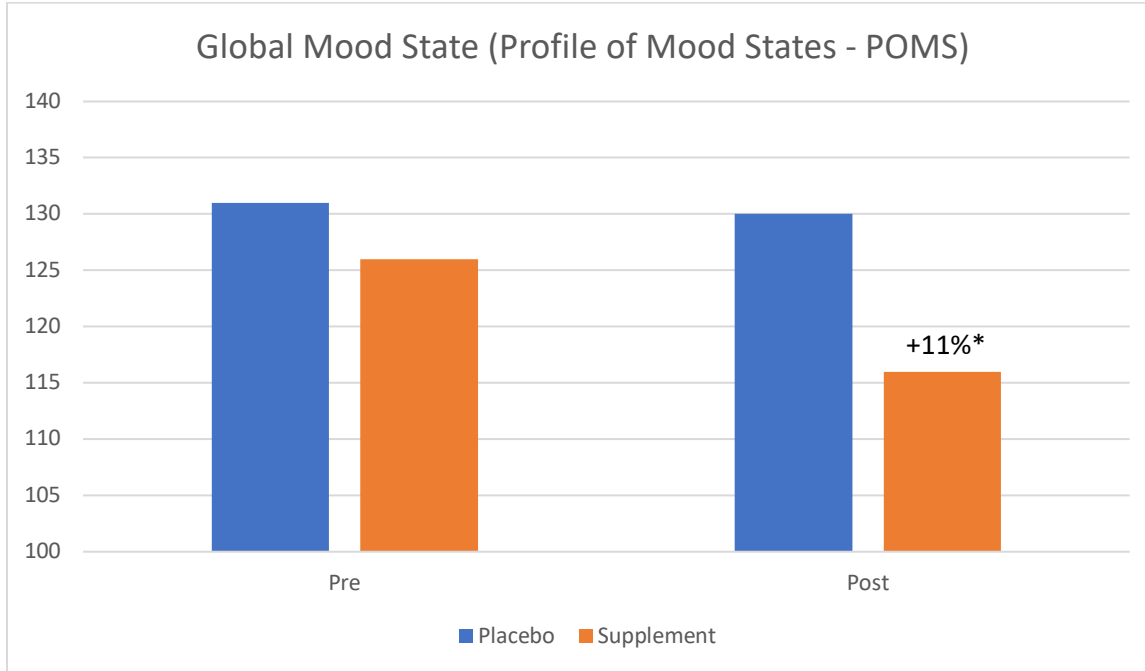
There was no significant change in Global Mood State (e.g. “overall well-being”), following the endurance run in the Placebo group (**Figure 2**), while the ThymoQuin group demonstrated a 11% improvement (a lower number indicates a less negative psychological mood state).



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Figure 1. Subjects in the ThymoQuin group had significantly fewer self-reported upper respiratory tract complaints (URTCs) compared to Placebo. (*significantly different from post-supplementation placebo value, $p < 0.05$).

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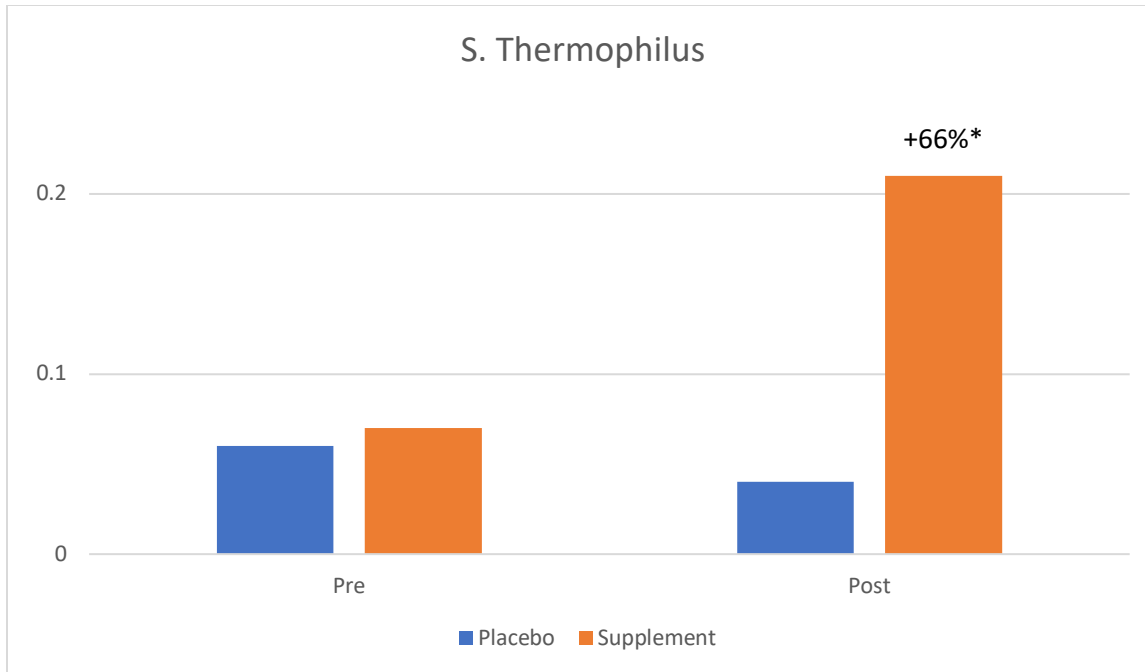
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Figure 2. Subjects in the ThymoQuin group had significantly better Global Mood State compared to Placebo (lower score indicates higher well-being index). (*significantly different from post-supplementation placebo value, $p < 0.05$).

Objective Measures

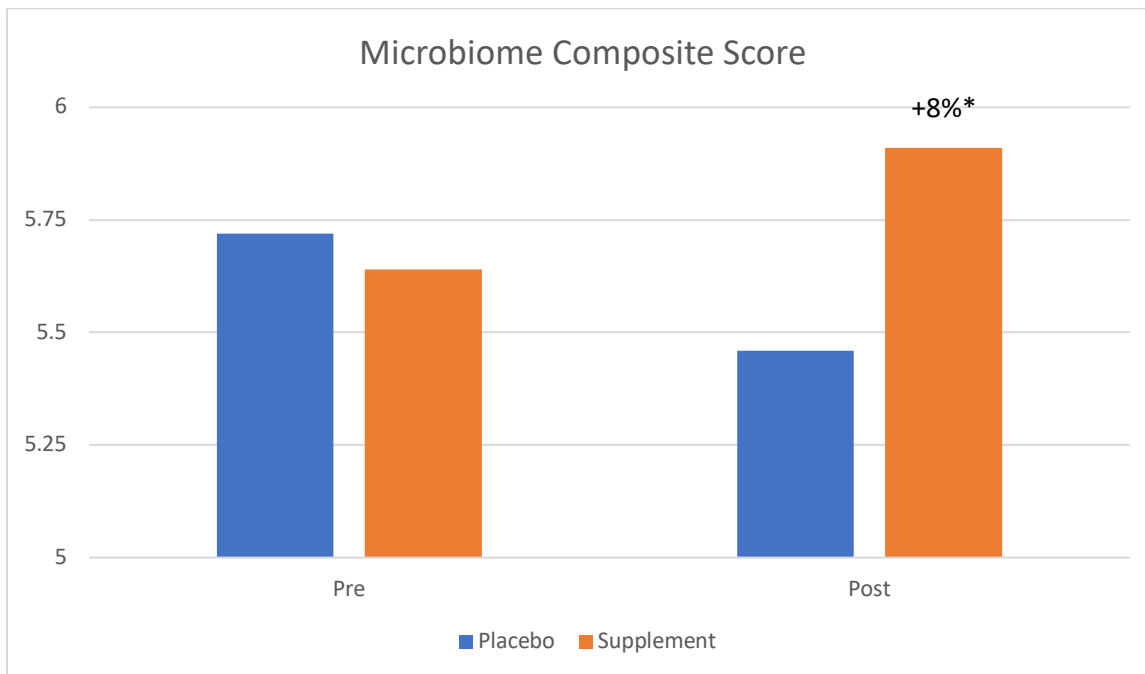
There was no significant difference in microbiome indices following the endurance run. However, following supplementation, *Streptococcus thermophilus* values were 66% higher in the ThymoQuin group, suggesting improved immune system regulation (**Figure 3**) and overall microbiome composite score was 8% higher, indicating improved microbiome diversity (**Figure 4**).

Cortisol, the primary stress hormone related to both mood and immune function, was slightly but not significantly elevated in the Placebo group following the endurance run, but was 44% lower in the ThymoQuin group post-supplementation compared to Placebo (**Figure 5**).



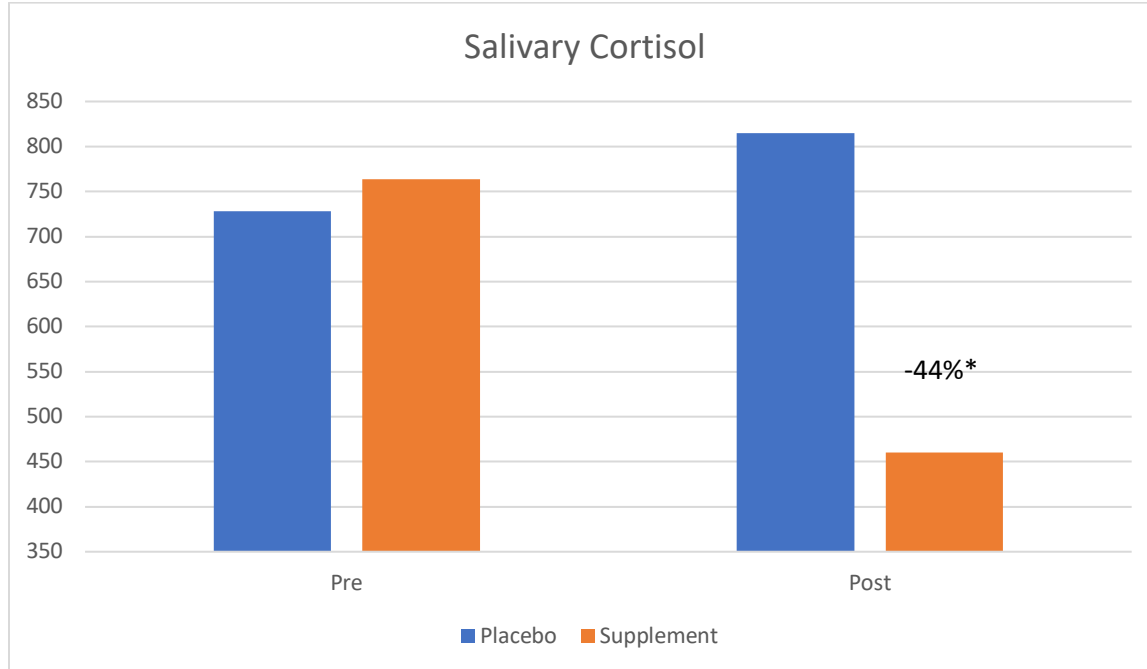
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 225 **Figure 3.** Subjects in the ThymoQuin group had significantly higher relative abundance of
 226 *Streptococcus thermophilus* bacteria compared to Placebo. (*significantly different from post-
 227 supplementation placebo value, $p < 0.05$).
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 232 **Figure 4.** Subjects in the ThymoQuin group had significantly higher Microbiome Composite
 233 Score compared to Placebo. (*significantly different from post-supplementation placebo value,
 234 $p < 0.05$).
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Figure 5. Subjects in the ThymoQuin group had significantly lower Salivary Cortisol (ng/ml) compared to Placebo. (*significantly different from post-supplementation placebo value, $p < 0.05$).

244 Discussion

245 These results demonstrate a significant and meaningful benefit of ThymoQuin supplementation
246 for the immune system as both a “shield” (protection from upper-respiratory complaints) and as a
247 “communication organ” (signaling well-being between body and mind and resulting in superior
248 psychological mood state). This linkage between body and mind across the Gut-Brain-Axis
249 involves many aspects of a coordinated and interconnected communication system linking the
250 gut microbiome (*S. thermophilus*) to the brain (psychological mood state) across the axis
251 (immune and stress response pathways). When the entire system is balanced, as evidenced here
252 in the ThymoQuin group, there is a noticeable benefit for physical health and mental wellness.

253

254 In order to “stress and suppress” the immune system of volunteers in our study, participants
255 trained for and completed a strenuous endurance running event (half-marathon to marathon
256 distance) to induce both physical and mental stress, as well as to create a “susceptibility window”
257 whereby a higher risk for upper-respiratory tract complaints (URTCs) is more likely to be
258 observed in the control/Placebo group. Our hypothesis was that the group supplementing with
259 ThymoQuin as a natural immune modulator would demonstrate fewer URTC symptoms and
260 lower indices of mental/physical stress.

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262 Rather than being an “immune-booster” to stimulate immune system activity, ThymoQuin may
263 be considered as a natural “immune-modulator” that can help to balance overall immune system
264 activity. Such natural substances represent an emerging approach to immunotherapy that either

265 elevates a suppressed immune system “up” to optimal – or calms an over-activated immune
266 system “down” to optimal – in a paradigm that we refer to as “priming” the immune system. A
267 properly primed immune system “pays attention” better to factors that it should fight (e.g.
268 viruses, bacteria, cancer cells, etc), while “ignoring” factors that should be considered non-
269 harmful (e.g. pollen, mucus membranes, joint cartilage, etc).

270
271 The majority of both the microbiome and the immune system reside in the gut – forming a
272 symbiotic relationship and ensuring that the human body is protected from harmful pathogens.
273 Over time, our immune system shapes the diversity of our microbiome, and our gut influences
274 the development and vigilance of our immune system. For example, the gut microbiome acts as a
275 gatekeeper, and a trainer, and increasingly as a communication organ. In addition, the gut
276 microbiome interacts with the brain in multi-directional ways that involve the immune system
277 using neural, inflammatory, and hormonal signaling pathways (Margolis et al., 2021). These
278 immune-mediated signals from gut to brain have been implicated in many aspects of mental
279 health and well-being, including depression, anxiety, and overall psychological mood states
280 (Margolis et al., 2021).

281
282 In this study, we report the effect of supplementing with ThymoQuin for 4 weeks on the physical
283 and psychological well-being of long-distance runners. The current study employed a series of
284 subjective self-assessment questionnaires that addressed overall health status and URTCs. In
285 addition to evaluation of subjects for physical health, a psychological assessment known as the
286 Profile of Mood States (POMS) was conducted to assess mood state. We also collected objective
287 markers of microbiome balance (*Streptococcus thermophilus*) and stress hormones (salivary
288 cortisol), both of which are associated with immune system vigilance and psychological stress
289 response, and which may represent a possible mechanism by which immune function and
290 psychological mood state are related.

291
292 During the course of the 4-week treatment period (3 weeks before and 1 week after an intense
293 endurance run), subjects in the ThymoQuin group reported fewer URTCs, better overall health
294 and a more positive mood state compared to Placebo. In addition, supplemented runners also
295 showed higher levels of *Streptococcus thermophilus* (*S. thermophilus*) and lower stress hormone
296 exposure (cortisol) – both of which being associated with immune vigilance and psychological
297 mood state.

298
299 Runners and other athletes, whose athletic activities cause significant physical stress, are more
300 susceptible to URTI (infections) and URTC (complaints). Previous research has reported that
301 athletes training for a marathon experience a deterioration in global mood state (Achten et al.,
302 2004; Hassmen and Blomstrand, 1991), and a number of studies have reported that nutritional
303 supplementation can modulate their health status (Nieman et al., 1990; Nieman and Bishop,
304 2006; Peters and Bateman, 1983; Peters et al., 1993; Spence et al., 2007).

305
306 Physical and psychological factors of subjects undergoing stressful situations are reported to
307 increase URTI and URTC (Cohen et al., 1999; Konig et al., 2000). In all cases, the subjects
308 supplemented with ThymoQuin experienced better physical health and a significantly improved
309 psychological status (Global Mood State), than those in the placebo group. ThymoQuin
310 participants reported both fewer URTC symptoms and a better overall health status. The URTC

311 symptoms reported by subjects are typical of cold and flu symptoms, and analogous to symptoms
312 reported in other studies (Cohen et al., 1999; Konig et al., 2000).

313
314 The POMS assessment for psychological health strongly supported and mirrored the physical
315 health assessment. Illness and stress impact the immune system in both physical and
316 psychological ways (Konig et al., 2000; Strasner et al., 2001). The POMS methodology has been
317 used in more than 2,900 studies (McNair et al., 1971); thus it has well-established validity. The
318 survey instrument employs 65 adjective based scales that are scored by subjects without
319 knowledge of how the scale scoring will be analyzed. The POMS survey instrument assesses the
320 overall global mood state of subjects – analogous to a measurement of overall well-being and
321 mental resilience.

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323 Previous work has shown benefits of beta-glucan for improving overall immune function,
324 including following intense endurance exercise (Hetland et al., 1998; Hong et al., 2004;
325 Kernodle et al., 1998; Vetvicka et al., 2002; 2008), and a range of other dietary supplements may
326 help reduce URTI symptoms in athletes (Cox et al., 2008; Kekkonen et al., 2007; Peters et al.,
327 1993), i.e., zinc treatment reduced duration and severity of cold symptoms (Prasad et al., 2000);
328 probiotics (*Lactobacillus fermentum*) reduced the severity and duration of URTI in athletes (Cox
329 et al., 2008); and vitamin C supplementation in ultramarathoners reduced the duration and
330 severity of URTI when taken 21 days before an ultramarathon (90 km) (Peters et al., 1993).

331

332 **Conclusion**

333 In this study, ThymoQuin significantly decreased upper-respiratory tract complaints and
334 improved psychological mood state following intense endurance training and competition.
335 Additionally, ThymoQuin subjects had lower cortisol and superior microbiome parameters,
336 suggesting that immune vigilance and mental well-being is linked through the microbiome and
337 stress response pathways. These results add to the growing scientific literature and natural
338 armamentarium for immune-modulation to both reduce URTI/URTC symptoms and improve
339 psychological mood state in “stressed” individuals (endurance athletes in this study).

340

341 **Conflicts of Interest and Funding Statement**

342 This study was funded by TriNutra, which manufactures and sells ThymoQuin black cumin seed
343 oil, and conducted by 3Waves Wellness, which was compensated to carry out the trial. ST is an
344 employee of Amare Global, which sells a multi-ingredient dietary supplement that includes black
345 cumin seed oil. ST and JT are owners of 3Waves Wellness, an independent research
346 organization.

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