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Synergistic benefits of phytoncide exposure and resistance exercise on muscle health, QoL, and immuno-myokine regulation in ovarian cancer survivors: A randomized controlled trial

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Abstract

Background

Although phytoncide exposure and resistance exercise are individually recognized for their beneficial effects on physiological parameters and immune-cell function in ovarian cancer survivors (OCS), this study aimed to investigate whether the integration of these two interventions could elicit synergistic improvements in myokine profiles, immunological responses, and muscle function, ultimately enhancing the quality of life (QoL) in OCS.

Methods

Participants aged 42 to 61 years were randomly selected from four hospital-based centers affiliated with a single medical institution. Those from one center were assigned to control group (CON, $n = 18$), while individuals from the other three centers were allocated to phytoncide group (PHYT, $n = 19$), exercise group (EXE, $n = 19$), and phytoncide plus exercise group (PHYT + EXE, $n = 20$), respectively. Each intervention was conducted for 60 min, 3 days per week, over a 12-week intervention.

Result

Relative to baseline, both muscle strength and endurance declined in the CON and PHYT after the intervention, whereas the EXE and PHYT + EXE showed improvements in these outcomes, demonstrating a significant interaction effect ($P = 0.001$). For the QoL domains, mobility ($P = 0.008$), self-care ($P = 0.023$), pain/discomfort ($P = 0.001$), and anxiety/depression ($P = 0.046$) scores increased in the CON, indicating worsening conditions, while these scores decreased across the other three groups, reflecting improving conditions. Interleukin (IL)-6 increased in CON, whereas they decreased in PHYT, EXE, and PHYT + EXE. In contrast, IL-10 exhibited an opposite trend to IL-6 ($P = 0.001$). Neutrophils ($P = 0.002$), lymphocytes ($P = 0.001$), monocytes ($P = 0.005$), and eosinophils ($P = 0.016$) decreased in CON, whereas those increased in PHYT, EXE, and PHYT + EXE, indicating significant interaction effects. Notably, PHYT + EXE demonstrated the greatest improvements in NK cells, $CD3^+$, $CD4^+$, and $CD8^+$T cells and $CD19^+$ B cells.

Conclusions

These findings indicate that the combination of phytoncide inhalation and resistance exercise improves muscle health and quality of life, and this effect appears to be mediated by enhancements in myokines and immune cell function in OCS. These multimodal approaches may serve as effective adjunct strategies for post-treatment rehabilitation.

Trial registration

This study was registered with the Clinical Research Information Service of the Korea Centers for Disease Control and Prevention under Clinical Trials KCT0008283 on 10/03/2023.

Introduction

Cancer is one of the leading causes of premature mortality worldwide, and even after treatment, it contributes to declines in muscle function and reductions in quality of life (QoL). Ovarian cancer, characterized by abnormal cellular proliferation within the ovaries, is the most lethal gynecologic malignancy, accounting for approximately 4.4% of all cancer-related deaths [1]. The five-year survival rate of ovarian cancer patients varies significantly depending on tumor stage, declining from 89% at stage I to 20% at stage IV [2,3]. Similar to other malignancies, ovarian cancer is frequently accompanied by sarcopenia, fatigue, and a decline in physical performance [4].

The extent of physical dysfunction and muscle loss has been estimated to account for 25–50% of their overall physical deterioration [5]. This deconditioning leads to a reduction in immunocytes responsible for identifying and eliminating malignant cells. Furthermore, even after achieving complete remission, many cancer survivors continue to experience psychological distress, particularly related to the fear of cancer recurrence [6]. Thoughts of potential cancer recurrence often manifest as fear, depression, anxiety, and distress, with ovarian cancer survivors (OCS) identifying fear as their most significant concern. These challenges extend beyond distress, affecting not only survivors' will to live but also their QoL [7,8].

To reduce cancer survivors' psychological fear of cancer recurrence, it is essential to help them feel physically healthy even after medical remission and to ensure they gain confidence that they have recovered to a level of health comparable to that before the onset of cancer [8]. Although numerous studies have reported various approaches to reducing the risk of cancer recurrence, recent research has drawn attention to methods that can decrease stress hormones through physical factors, promote psychological stability, and enhance the immunocytes function. Heo et al. reported that the diffusion of phytoncide essential oil improved neuroendocrine function and induced positive changes in natural killer (NK) cells' family and receptors, thereby helping to relieve stress in cancer survivors [6]. In fact, previous research has demonstrated that phytoncide, through forest bathing, enhances NK cell activity and increases intracellular anticancer protein levels in lymphocytes [9].

Engaging in regular exercise is also widely recognized as one of the most effective and accessible methods to improve stress levels and immunocytes' function [10,11]. Moreover, several studies have indicated that even after a cancer diagnosis, individuals who engage in regular exercise have a significantly higher survival rate. These findings suggest that physically active patients are nearly twice as likely to survive [12]. Resistance training offers substantial short- and long-term benefits for patients, as it can help mitigate many of the side effects associated with cancer treatment [13]. A study

consistent with this context reported that providing OCS with a 12-week resistance exercise program, performed four days per week, led to substantial improvements in muscle strength and endurance, accompanied by favorable changes in $CD4^+$ and $CD8^+$ T cells. The authors further suggested that enhanced sensitivity of both T cells may promote the secretion of myokines and cytokines in response to cytotoxic stimuli [14].

Cancer survivors often face long-term complications due to the disease and its treatments, including autonomic nervous dysfunction, hormonal imbalances, weakened immunocytes, and diminished QoL [6,7]. Lifestyle interventions, such as phytoncide inhalation and resistance exercise, have been proposed to mitigate the psychophysical adverse effects of cancer survivors. However, these two interventions are expected to create a synergistic effect, yet no studies have been conducted to explore their combined impact. Therefore, this study aimed to examine how the combined effects of phytoncide exposure and resistance exercise influence muscle function and QoL in OCS, and to further evaluate whether these outcomes are mediated by changes in myokines and immune cells.

Materials and methods

Study design

This study was a 12-week prospective, double-blind, randomized controlled trial involving OCS who had previously been treated for the disease. The study protocol was approved by the Institutional Review Board of Hanseo University (Approval No. HS22-11-01; approval period: 2 November 2022 to 1 November 2023) and registered with the Korean Clinical Research Information Service (ClinicalTrials.gov Identifier: KCT0008283; registration date: 10 March 2023). It was carried out in accordance with the principles of the Declaration of Helsinki and with the Consolidated Standards of Reporting Trials guidelines (Supplementary Table 1).

Participants

Participants were OCS who had been diagnosed and had completed their recovery between January 2021 and December 2023 at Seoul Songdo Hospital, and their ages ranged from 42 to 61 years. The overall experimental procedures were explained by the principal investigator. The inclusion criteria for this study were OCS under 65 years of age who had undergone surgery, radiotherapy, or chemotherapy, or whose survival duration was less than five years. Eligibility was further restricted to individuals who had not participated in any exercise program for at least six months prior to enrollment or who had received medical clearance to engage in exercise following cancer-related surgery. Exclusion criteria included individuals with deformities of the knee, hip, or spine; neurological conditions; use of medications such as steroids or intra-articular injections within the past six months; the presence of a pacemaker or internal metallic implants; and any history of major organ dysfunction or psychiatric

disorders. Participants were also excluded if they had undergone weight-loss treatments or had a previous history of cerebrovascular disease.

Participants were recruited from four hospital-based centers affiliated with the same medical institution. Individuals from one center were assigned to the control group (CON), while participants from the remaining three centers were allocated to the phytoncide-inhalation group (PHYT), resistance exercise group (EXE), and phytoncide-inhalation combined with resistance exercise group (PHYT + EXE), respectively. Random assignments were conducted using coded tags, which were drawn by representatives from each group. Sample size estimation was performed using G*Power (ver. 3.1.9.7; Heinrich-Heine-Universität, Düsseldorf, Germany), assuming an effect size of $f^2(V) = 0.25$, an alpha level of 0.05, a power of 0.95, four groups, and two measurement time points.

As shown in Fig. 1, a total of 102 participants were initially recruited from four independent sites to minimize intergroup interaction. Eighteen individuals were excluded for not meeting the inclusion criteria, and the remaining participants completed baseline assessments. During the intervention, attrition occurred as follows: 3 participants in CON, 2 in PHYT, 2 in EXE, and 1 in PHYT + EXE withdrew. All remaining participants were included in the final analysis.

Phytoncide and exercise interventions

Participants in the CON and PHYT groups visited the immune center at their scheduled times and performed meditation while lying on a mattress for 50–60 min, three days per week for 12 weeks. To ensure rigorous blinding, all pre- and post-intervention assessments followed standardized procedures. For PHYT and PHYT + EXE, olfactory stimulation was administered using phytoncide oil derived from *Chamaecyparis obtuse* [15]. The phytoncide oil was applied using a method previously validated for safety [6], and an oil burner made from cypress wood (Good Earth Lab, Seoul, Korea) was employed for its administration. The primary constituents of the oil were terpenes, predominantly monoterpenes and sesquiterpenes [16]. To facilitate diffusion, five drops of the oil were applied to the burner, allowing the wood to absorb and gradually release the fragrance. The intervention took place in a closed laboratory space measuring 66 m^2, with environmental conditions maintained at a temperature of 25–26°C and humidity of 50–60% to optimize scent dispersion [6].

Table 1
Resistance exercise programs for the EXE and PHYT + EXE

Items	Description	Duration (min)	Exercises
Warm-up	¨ Stretching to prevent an injury ¨ Low-intensity aerobic exercise to prepare working muscles	¨ 10–15	¨ Walking to brisk walking then standing stretching
Resistance exercise	¨ Start with low intensity and gradually increase ¨ Increase muscle mass ¨ Improve strength and endurance		
	¨ Phase I: 12 RM × 3 sets ¨ Phase II: 10 RM × 3 sets ¨ Phase III: 8 RM × 3 sets ¨ Phase IV: 6 RM × 3 sets	¨ 50–60 ¨ 50–60 ¨ 50–60 ¨ 50–60	¨ Lat-pull down; chest press; leg press; abdominal crunch; back extension ¨ Seated cable row; chest butterfly; deadlift; leg extension; leg curl
Cool-down	¨ Increasing resilience and flexibility	¨ 10–15	¨ Slow walking then floor stretching
RM, repetitions maximum			

The EXE and PHYT + EXE groups participated in a supervised resistance exercise program three days per week for 12 weeks. The exercise regimen was designed to align with the recommendations of the American Cancer Society and the American College of Sports Medicine [17,18]. The both groups began each session with a 10–15 min warm-up consisting of stretching exercises and low-intensity aerobic exercise as shown in Table 1.

Resistance exercise was performed on non-consecutive days, following established protocols for cancer survivors [14,19,20]. Exercise intensity progressed across four phases: 12 repetitions maximum (RM) in Phase I (Weeks 1–3), 10 RM in Phase II (Weeks 4–6), 8 RM in Phase III (Weeks 7–9), and 6 RM in Phase IV (Weeks 10–12). All resistance exercises were performed on weight machines to ensure participant safety. The EXE and PHYT + EXE performed the following exercise routines: on Tuesdays and Saturdays —lat pulldown, chest press, leg press, abdominal crunch, and back extension; on Thursdays—seated cable row, chest butterfly, deadlift, leg extension, and leg curl. The rating of perceived exertion scale was used to monitor individual fatigue levels and to determine appropriate rest periods between sets. Each resistance training session lasted 50–60 min and was followed by 10–15 min of stretching performed in seated and supine positions. Compliance and fidelity to the double-blind intervention were rigorously monitored by the principal investigator, who conducted scheduled and unannounced weekly visits to each of the four centers to verify that the intervention was being delivered as planned.

Outcomes

Food intake, physical activity, and body composition

First, participants were instructed to complete a diet diary, recording their food intake for three servings. A nutritionist entered the reported food types and quantities into CAN-Pro 5.0 (http://canpro5.kns.or.kr; Korean Nutrition Society, Seoul). Second, physical activity (PA) was assessed using the short-form version of the International PA Questionnaire by a trained researcher [21]. Participants recorded their PA for the previous seven days, and total energy expenditure was estimated in MET•min/week. Both measurements were assessed every four weeks, and the data from the first and final months were compared for analysis. Third, body composition was evaluated using a bioelectrical impedance analyzer (InBody 770; Biospace Co., Ltd., Seoul, Korea) following the measurement of height stadiometer. Before the assessment, participants removed all metal objects and were then instructed to stand on the device while holding the hand electrodes.

Blood sampling and analysis for myokines and immunocytes

After a 10-hour overnight fast, a clinical laboratory technician collected 10 mL of venous blood from the antecubital vein, which was then centrifuged at 3000 rpm for 15 minutes, and the resulting serum was stored at − 70°C until analysis. To evaluate the myokine responses, serum levels of IL-6 (Cat.#D6050) and IL-10 (Cat.#217-ILB) were quantified using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA) [22]. Cellular immune function was evaluated by analyzing lymphocyte subsets via flow cytometry. Antibodies (CD56-phycoerythrin, CD3-fluorescein isothiocyanate, CD4-BV510, CD8-PerCP-Cy5.5, and CD19) were obtained from BD Biosciences (Franklin Lakes, NJ, USA). Samples were incubated in the dark at room temperature for 15 min, followed by erythrocyte lysis with FACS lysing solution for 15 min. Data acquisition was performed using a FACS Canto II flow cytometer and analyses were conducted with FlowJo software (Tree Star, Ashland, OR, USA). Absolute lymphocyte subset counts were verified using an automated hematology analyzer. Optical density for ELISA measurements was read at 450 nm with a 540 nm reference wavelength using a Tecan Sunrise microplate reader (Tecan Group Ltd., Männedorf, Switzerland) [14,23].

Muscle function measures

Muscle function was assessed through measures of muscular strength and endurance. Strength was evaluated using a Smedley handgrip dynamometer (TKK 5401; Takei, Tokyo, Japan). Participants held the dynamometer with the proximal interphalangeal joint at a 90-degree angle, with the grip width adjusted to fit their hand size. While standing with their arms naturally positioned at their sides and ensuring the device did not touch their body, they performed two trials with each hand. The highest value from the trials was recorded, and the average of both hands was used for analysis [24]. Muscular endurance was assessed using a 60-second sit-up test, performed with arms crossed over the chest.

Participants lay on a mat with knees bent at a 90° angle and feet placed 30 cm apart, with ankles secured on footrests. Upon the examiner's signal, participants raised their upper body until their elbows touched their knees and then returned their back to the mat. Only repetitions meeting these criteria were counted [25].

QoL measure

Participants' overall health status related to QoL was evaluated using the EQ-SD, a standardized instrument developed by the EuroQol Group to quantify self-perceived health. After approval obtained from the EORTC QoL Group website (http://www.euroqol.org/), six initial dimensions were identified; however, these were subsequently refined to the current five dimensions. Consequently, the EQ-SD defines health across five domains: *Mobility, Self-care, Usual activities, Pain/Discomfort*, and *Anxiety/Depression* [7,13]. Each domain is scored on a three-point scale: no problems (1), some problems (2), and severe problems (3) by a researcher. Higher scores indicate lower QoL in the respective domain. In this study, the internal consistency of the QoL scale was confirmed with a Cronbach's α of 0.776. In this study, all 72 participants completed the EQ-SD at baseline and again after the 12-week intervention, enabling direct comparison of changes in perceived health status over time.

Data analysis

Data analysis and graphical visualization were conducted using GraphPad Prism 10.6.1 (La Jolla, CA, USA). All results are presented as mean ± standard deviation (SD). Analytical procedures followed the recommendations of Mansournia et al [26]. Categorical variables are shown as n (%) and compared using appropriate statistical tests, such as χ^2 or Fisher's exact test. To assess baseline differences prior to the comprehensive analysis, the Kruskal-Wallis test was applied to pre-level variables. For normally distributed data, a 4 × 2 repeated-measures ANOVA was applied, followed by Scheffé post hoc tests. Non-normally distributed variables were analyzed with the Kruskal–Wallis test, with adjustments for multiple comparisons. Delta (Δ)% values were calculated for detailed analysis at each time point. Effect sizes (η^2) were interpreted using established benchmarks, with values < 0.11 indicating a small effect, 0.53 representing a medium effect, and 0.93 indicating a large effect [27]. Statistical significance was set at $P \leq 0.05$.

Results

Demographic and anthropometric features

The participants had a mean age of 51.1 ± 5.3 years. Notably, based on the International Federation of Gynecology and Obstetrics staging system, participants presented with an average of 2.01 ± 0.9 comorbidities and had been diagnosed with ovarian cancer for 2.13 ± 0.6 years. Among those who had undergone surgery, the time elapsed since primary cytoreductive surgery was 46.7 ± 5.1 months, and 45.3 ± 4.4 months for those who received interval debulking surgery. In addition, lymph node metastasis

had occurred in an average of 1.6 ± 0.5 individuals, and organ metastasis in 1.9 ± 0.2 individuals. Meanwhile, among the participants, an average of 1.2 ± 4.1 individuals had received radiotherapy for ovarian cancer, and 1.1 ± 2.9 had undergone chemotherapy. Comparisons across the four groups revealed no statistically significant differences in these characteristics. Furthermore, no statistically significant differences were observed among the groups in any demographic or anthropometric characteristics prior to the intervention as shown in Table 2.

Table 2
Physical characteristics of the participants prior to the experiment

	Groups						
	CON (n = 18)	PHYT (n = 19)	EXE (n = 19)	PHYT + EXE (n = 20)	X^2	P	η^2
Age (y)	51.7 ± 5.3	51.1 ± 5.2	50.8 ± 5.6	50.9 ± 5.3	0.397	0.941	0.005
Height (cm)	155.1 ± 2.8	154.7 ± 3.4	155.5 ± 2.9	156.5 ± 4.3	3.804	0.283	0.036
Body weight (kg)	57.3 ± 5.7	56.9 ± 7.8	57.9 ± 9.4	58.5 ± 14.3	0.308	0.958	0.004
Body mass index (kg/m^2)	23.7 ± 2.8	23.6 ± 3.2	23.9 ± 3.8	23.9 ± 5.2	0.009	1.000	0.001
Married*	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.3	0.512	0.916	0.007
Employed*	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.9 ± 0.4	0.390	0.942	0.005
Medications' number*	1.9 ± 0.3	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.3	0.730	0.866	0.010
Supplements' number*	2.1 ± 1.1	2.1 ± 1.0	1.7 ± 0.8	2.2 ± 0.8	3.697	0.296	0.047
Comorbidities' number*	2.1 ± 0.7	2.1 ± 0.7	2.1 ± 0.7	2.2 ± 0.6	0.252	0.969	0.004
Ovarian cancer diagnosed year	4.1 ± 0.5	4.1 ± 0.5	4.0 ± 0.5	3.9 ± 0.5	3.610	0.307	0.026
Primary cytoreductive surgery (month)	46.5 ± 4.8	46.7 ± 5.4	47.7 ± 4.8	46.1 ± 5.6	1.281	0.734	0.014
Primary cytoreductive surgery*	1.2 ± 0.4	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.4	0.954	0.812	0.013
Interval debulking surgery (month)	44.3 ± 5.1	45.0 ± 4.7	45.1 ± 4.1	47.5 ± 5.3	0.626	0.890	0.072
Interval debulking surgery*	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	0.275	0.965	0.004
Lymph node metastasis*	0.7 ± 0.5	0.6 ± 0.5	0.6 ± 0.5	0.6 ± 0.5	0.594	0.898	0.008
Organ metastasis*	1.9 ± 0.2	1.9 ± 0.3	2.0 ± 0.0	2.0 ± 0.2	2.089	0.554	0.028

	Groups						
	CON (*n* = 18)	PHYT (*n* = 19)	EXE (*n* = 19)	PHYT + EXE (*n* = 20)	X^2	*P*	η^2
Radiation therapy*	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.5	1.2 ± 0.4	0.803	0.849	0.011
Chemotherapy*	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.2	1.2 ± 0.4	1.463	0.691	0.020
All data represents mean ± standard deviation. CON, control; PHYT, phytoncide; EXE, exercise; PHYT + EXE, phytoncide + exercise. The symbol * represents '1' indicating 'yes' or '2' indicating 'no'.							

As shown in Supplementary Table 2, calorie intake in CON increased from 1615.9 ± 181.3 to 1717.2 ± 265.8 kcal, reflecting an 8.6 ± 25.2% change. Similarly, PHYT showed an increase from 1627.2 ± 171.4 to 1739.4 ± 220.6 kcal, representing an 8.7 ± 21.3% change. EXE demonstrated a rise from 1584.1 ± 158.5 to 1720.9 ± 236.1 kcal, corresponding to a 10.2 ± 21.1% increase. A comparable increase was observed in PHYT + EXE, with intake increasing from 1560.4 ± 137.4 to 1738.9 ± 148.2 kcal, marking a 12.2 ± 13.0% change. The Δ% values showed no significant differences among the four groups ($P = 0.979$).

Although no significant differences in PA levels were observed among the groups at baseline, changes emerged following the 12-week intervention as shown in Fig. 2a. In CON, PA increased from 963.7 ± 121.4 to 995.6 ± 139.4 MET•min/week, reflecting a 4.8 ± 20.0% change. Similarly, PHYT showed an increase from 953.5 ± 139.0 to 986.9 ± 169.9 MET•min/week, representing a 5.1 ± 21.5% change. In contrast, EXE demonstrated a substantial rise from 954.7 ± 135.7 to 1458.2 ± 205.4 MET•min/week, corresponding to a 54.9 ± 27.8% increase. A comparable improvement was observed in PHYT + EXE, which increased from 946.4 ± 139.5 to 1435.5 ± 246.1 MET•min/week, marking a 53.7 ± 29.1% increase. The Δ% values showed significant differences among the four groups ($P = 0.001$, $\eta^2 = 0.506$).

In the body composition, there were no significant differences among the four groups before the intervention (Supplementary Table 3). After the intervention, body weight increased in CON (4.0 ± 9.2%) and PHYT (2.4 ± 9.7%), whereas it decreased in EXE (− 0.2 ± 9.0%) and PHYT + EXE (− 3.9 ± 6.0%), showing a significant interaction ($P = 0.014$, $\eta^2 = 0.136$). Muscle mass decreased in CON (− 7.5 ± 13.7%) and PHYT (− 4.7 ± 14.2%), whereas it increased in EXE (7.2 ± 9.8%) and PHYT + EXE (12.4 ± 6.5%), demonstrating a significant interaction effect (P = 0.001, $\eta^2 = 0.386$). The Δ% values also differed significantly among the four groups ($P < 0.001$, $\eta^2 = 0.356$), as illustrated in Fig. 2b. Fat mass increased in CON (21.5 ± 25.7%), PHYT (14.9 ± 27.0%), and EXE (7.7 ± 23.7%), whereas it decreased in PHYT + EXE (− 13.4 ± 13.9%), indicating a significant interaction effect ($P = 0.001$, $\eta^2 = 0.243$). The Δ% values also differed significantly among the four groups ($P < 0.001$, $\eta^2 = 0.258$), as shown in Fig. 2c. Similarly, BMI demonstrated a significant interaction effect ($P = 0.007$, $\eta^2 = 0.155$).

Changes in muscle function and QoL

As shown in Table 3, strength decreased in CON (− 10.2 ± 11.1%) and in PHYT (− 2.6 ± 24.1%), whereas it increased in EXE (4.1 ± 21.6%) and markedly in the PHYT + EXE (28.6 ± 14.9%), observing a significant interaction effect. Muscular endurance decreased in CON (− 24.1 ± 32.7%), increased in PHYT (14.5 ± 103.2%), and rose further in EXE (36.0 ± 83.8%). PHYT + EXE showed the largest improvement (140.3 ± 88.1%), indicating a significant group × time interaction effect.

Table 3
Comparative results of muscle function and quality of life

	Groups				P (η^2)		
	CON	PHYT	EXE	PHYT + EXE	G	T	G×T
Muslce function							
Strength (kg)							
Pre	31.3 ± 6.4	31.7 ± 6.1	32.0 ± 4.7	33.1 ± 2.7	0.001	0.026	0.001
Post	27.9 ± 5.7	30.6 ± 8.6	33.3 ± 7.9	42.4 ± 3.7	(0.267)	(0.067)	(0.432)
Endurance (reps)							
Pre	6.3 ± 2.0	6.2 ± 2.1	6.2 ± 2.1	6.1 ± 1.9	0.001	0.001	0.001
Post	4.8 ± 2.7	6.5 ± 4.5	8.4 ± 5.1	13.2 ± 2.2	(0.291)	(0.246)	(0.456)
Quality of life							
Mobility							
Pre	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	0.091	0.150	0.008
Post	1.7 ± 0.8	1.3 ± 0.5	1.1 ± 0.3	1.2 ± 0.4	(0.085)	(0.029)	(0.149)
Self-care							
Pre	1.3 ± 0.5	1.3 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	0.001	0.532	0.023
Post	1.8 ± 0.7	1.2 ± 0.4	1.1 ± 0.3	1.1 ± 0.3	(0.221)	(0.005)	(0.124)
Usual activity							
Pre	1.5 ± 0.7	1.7 ± 0.9	1.6 ± 0.8	1.7 ± 0.8	0.554	0.018	0.118
Post	1.7 ± 0.8	1.3 ± 0.5	1.2 ± 0.4	1.2 ± 0.4	(0.028)	(0.075)	(0.078)
Pain / discomfort							
Pre	1.6 ±	1.8 ±	1.8 ±	1.8 ± 0.4	0.070	0.001	0.001

	Groups				P (η^2)		
	CON	PHYT	EXE	PHYT + EXE	G	T	G×T
	0.6	0.4	0.4				
Post	1.9 ± 0.8	1.3 ± 0.5	1.2 ± 0.4	1.2 ± 0.4	(0.093)	(0.262)	(0.257)
Anxiety / depression							
Pre	1.7 ± 0.9	1.5 ± 0.7	1.6 ± 0.7	1.5 ± 0.7	0.001	0.027	0.046
Post	2.0 ± 0.8	1.2 ± 0.4	1.2 ± 0.4	1.1 ± 0.2	(0.212)	(0.066)	(0.104)
All data represents mean ± standard deviation. G, group; T, time; CON, control; PHYT, phytoncide; EXE, exercise; PHYT + EXE, phytoncide + exercise.							

As also shown in Table 3, in the changes of QoL, *Mobility* increased in CON (19.4 ± 34.9%) but decreased in PHYT (− 5.3 ± 32.9%), EXE (− 7.9 ± 44.9%), and PHYT + EXE (− 10.0 ± 20.5%), indicating a significant group × time interaction. *Self-care* increased in CON (58.3 ± 91.2%) and showed minimal change in PHYT but declined in EXE (− 7.9 ± 44.9%) and PHYT + EXE (− 7.5 ± 43.8%), revealing a significant interaction. No significant interaction was observed for *Usual activity*. *Pain/Discomfort* rose in CON (36.1 ± 80.1%) but decreased in PHYT (− 26.3 ± 25.6%), EXE (− 28.9 ± 38.4%), and PHYT + EXE (− 32.5 ± 24.5%). Finally, *Anxiety/Depression* increased in CON (39.8 ± 71.0%) but decreased in PHYT (− 4.4 ± 53.2%), EXE (− 9.6 ± 55.1%), and PHYT + EXE (− 19.2 ± 27.2%), with a significant interaction.

Changes in myokines and immunocytes

In Fig. 3a, IL-6 increased in CON (14.0 ± 37.9%) but decreased slightly in PHYT (− 4.2 ± 29.4%) and EXE (− 13.6 ± 17.3%), with a greater reduction in PHYT + EXE (− 20.9 ± 14.9%); a significant interaction was observed ($P = 0.011$, $\eta^2 = 0.143$). Figure 3b illustrates IL-10, which declined in CON (− 11.2 ± 21.5%) but increased in PHYT (8.6 ± 30.6%) and EXE (20.2 ± 32.4%), with a larger increase in PHYT + EXE (39.5 ± 22.5%); the interaction was significant ($P = 0.001$, $\eta^2 = 0.340$). The detailed patterns of these changes are further presented in Supplementary Table 4.

Figure 3c depicts neutrophil changes, showing a decline in CON (− 10.6 ± 28.3%), slight rises in PHYT (4.4 ± 24.5%) and EXE (7.7 ± 21.0%), and a larger increase in PHYT + EXE (13.1 ± 23.4%), with a significant interaction ($P = 0.002$, $\eta^2 = 0.181$). Figure 3d shows that lymphocytes decreased in CON (− 18.0 ± 16.8%) but increased in PHYT (4.5 ± 21.7%), EXE (8.3 ± 23.2%), and PHYT + EXE (16.4 ± 23.6%), the latter showing the largest change ($P = 0.001$, $\eta^2 = 0.266$). Figure 3e demonstrates that monocytes decreased in CON (− 16.0 ± 34.2%) but increased slightly in PHYT (5.5 ± 25.6%) and EXE (9.8 ± 39.7%), with a greater increase in PHYT + EXE (21.8 ± 34.2%); a significant interaction was observed ($P = 0.005$, $\eta^2 = 0.161$).

Figure 3f shows that eosinophil levels decreased in the CON (− 15.0 ± 22.3%) but increased slightly in PHYT (4.9 ± 25.0%) and EXE (10.1 ± 33.4%), and more markedly in PHYT + EXE (15.0 ± 34.7%), indicating a significant interaction effect ($P = 0.016$, $\eta^2 = 0.133$). However, basophils decreased in CON (− 12.1 ± 34.7%) but increased in PHYT (12.5 ± 48.1%) and EXE (15.8 ± 39.2%), with a greater increase observed in PHYT + EXE (20.9 ± 46.1%); however, no significant group × time interaction ($P = 0.182$) was observed. The detailed patterns of these changes are further presented in Supplementary Table 5.

Changes in lymphocytes subsets

In Fig. 4a, NK cells decreased in CON (− 17.6 ± 19.7%) but increased in PHYT (14.8 ± 47.4%) and EXE (12.2 ± 49.6%), with a larger increase in PHYT + EXE (66.5 ± 138.6%); a significant group × time interaction was observed ($P = 0.026$, $\eta^2 = 0.120$). Figure 4b illustrates $CD3^+$ T cells, which declined in CON (− 15.5 ± 22.8%) but increased in PHYT (7.5 ± 15.5%), EXE (8.2 ± 17.2%), and PHYT + EXE (11.8 ± 17.7%); the interaction was significant ($P = 0.001$, $\eta^2 = 0.273$). Figure 4c depicts $CD4^+$ T cells, showing a reduction in CON (− 17.7 ± 15.8%), modest increases in PHYT (2.8 ± 17.1%) and EXE (5.7 ± 24.5%), and a more pronounced rise in PHYT + EXE (15.5 ± 39.4%), with a significant interaction ($P = 0.001$, $\eta^2 = 0.195$). Figure 4d shows $CD8^+$ T cells decreased in CON (− 9.3 ± 30.2%) but increased in PHYT (6.2 ± 42.1%) and EXE (11.9 ± 48.6%), with a greater increase in PHYT + EXE (39.2 ± 50.7%) with a significant interaction ($P = 0.019$, $\eta^2 = 0.129$). Finally, Fig. 4e shows $CD19^+$ B cells decreased in CON (− 11.7 ± 20.3%) but increased in PHYT (8.1 ± 27.9%), EXE (13.6 ± 35.0%), and PHYT + EXE (19.9 ± 23.8%), the latter showing the largest change; a significant interaction was found ($P = 0.003$, $\eta^2 = 0.175$). The detailed patterns of these changes are additionally presented in Supplementary Table 6.

Discussion

To the best of our understanding, this may be the first study to suggest that combining phytoncide inhalation with resistance exercise could enhance muscle fitness and QoL in OCS by improving some myokine profiles and immunocytes responses. Among gynecological malignancies, ovarian cancer is the most fatal [1–3,28], and worries about recurrence manifest as fear and emotional distress—often cited as survivors' predominant concern—which negatively affects QoL. Like many other forms of cancer, OCS is commonly associated with sarcopenia and a decline in physical function [4]. The decline in physical function resulting from such muscle loss can lead to a cascade of adverse effects on the body. In cancer survivors, in particular, this deterioration may exacerbate psychological helplessness and stress related to fears of cancer recurrence, underscoring the need for appropriate and timely interventions [29]. Accordingly, several researchers have long proposed various lifestyle modifications to improve the physical and psychological functioning of cancer survivors, and to date, phytoncide inhalation and exercise are regarded as among the most economical and effective approaches [6,9, 29].

In this study, we found that phytoncide inhalation alone improved the psychological QoL domains of *pain/discomfort* and *anxiety/depression* compared with the CON group. However, the changes in the aforementioned variables appeared to be more pronounced with resistance exercise than with phytoncide inhalation. In this context, resistance exercise is increasingly recognized in academic

literature as an effective approach for improving not only muscle health but also QoL in cancer survivors [13,14,18,30]. Supporting this, Lee et al., who reported that a 12-week exercise intervention in OCS led to improvements of 28.3% in muscle strength and 126.5% in muscle endurance in the exercise group. Notably, their study also indicated that exercise-induced enhancements in muscular fitness facilitated beneficial changes across various physical parameters in OCS and additionally improved patients' efforts to overcome psychological limitations [20]. However, in this study, the combined application of phytoncide inhalation and resistance exercise led to substantial improvements in muscle function, as well as marked enhancements in psychological QoL domains, including *anxiety and depression*. Specifically, the present findings show that muscle strength and endurance declined in CON and PHYT but improved in EXE and PHYT + EXE, with the latter demonstrating a notably greater increase in muscle mass (12.4 ± 6.5%). In contrast, fat mass decreased significantly only in PHYT + EXE (− 13.4 ± 13.9%). The changes in muscle function and body composition observed in this study were attributable to increased PA volume and led not only to improvements in the *anxiety/depression* domain of QoL, but also to positive changes in *mobility, self-care*, and *pain/discomfort*. Specifically, even phytoncide exposure alone resulted in favorable changes in QoL domains; however, when resistance exercise was included—either alone or in combination with phytoncide—the effects became even more pronounced. These findings are similar with the report by Stevinson et al., who found that OCS who met the PA guidelines (at least 60 min of vigorous activity per week or 150 min of moderate-to-vigorous activity) reported substantially better QoL than those who did not (mean difference: 12.5; 95% CI: 9.1–16.0; $P < 0.001$; d = 0.75). They further noted that disease status was the only variable that moderated this association [31]. Schofield et al. even reported that relatively low-dose resistance exercise may be beneficial for survivors of advanced ovarian cancer [32].

In OCS with physical inactivity, the development of sarcopenia has been observed, whereas those who engaged in regular exercise demonstrated signs of sarcomegaly [20]. In this context, Pedersen and Hoffman-Goetz reported that moderate-intensity exercise provides a general enhancement of immunocytes, helping to establish a balance between pro- and anti-inflammatory myokines [33]. Based on the results of this study, IL-6 increased in CON but decreased in all intervention groups, whereas IL-10 showed the opposite pattern. Notably, IL-6 and IL-10 levels in PHYT + EXE were markedly improved compared with the other groups, suggesting that combining phytoncide inhalation with resistance exercise more effectively reduces pro-inflammatory responses. Such improvements in myokines may promote rapid recovery and create a more favorable physiological environment for subsequent resistance exercise, and the resulting enhancements in physical recovery and reductions in stress provide meaningful benefits for individuals with compromised health. These effects are likely attributable to the phytoncide essential oil used in this study, which suppresses sympathetic activity and activates the parasympathetic nervous system, thereby reducing fatigue and stress [9,34,35]. Moreover, when phytoncide inhalation was combined with resistance exercise, significant enhancements were observed not only in NK cells but also in adaptive immune cells. According to these preliminary studies, inhaling phytoncide fragrance not only helps prevent the decline of immune cells and activates the function of innate immune cells that destroy cancer cells but also alleviates psychological anxiety and

stress in cancer survivors through the stabilization of parasympathetic nervous activity [6,22]. These findings are consistent with previous reports and were similarly observed in the immune cell responses of this study. Specifically, OCS exposed to phytoncide showed improvements in neutrophil, lymphocyte, monocyte, and eosinophil. Moreover, when phytoncide exposure was combined with resistance exercise, significant enhancements were observed not only in NK cells but also in lymphocyte subsets, including $CD3^+$ T cells, $CD4^+$ T cells, and $CD19^+$ B cells. A similar pattern was reported by Park et al. who found that lymphocyte levels improved in the intervention groups, with NK and NKT cells showing further enhancement after 12 weeks of the combined intervention [36]. Although that study employed treadmill walking to improve aerobic capacity—differing from the resistance exercise used here—similar effects were observed, highlighting the influential role of phytoncide inhalation across different exercise modalities.

Ultimately, resistance exercise performed in a phytoncide-exposed environment appears to promote the recovery and development of muscle function in OCS, contributing to improvements in body composition and overall muscle health, which in turn positively affect quality of life. These findings suggest that the combined effects of phytoncide exposure and resistance exercise may further enhance the regulatory capacity of myokines and immune cells. While this study demonstrated synergistic outcomes of the combined phytoncide and exercise intervention, several limitations should be acknowledged. First, the sample size was relatively small and limited to OCS from a single medical network, which may reduce generalizability. Second, only a restricted set of myokines and immune cell subsets was measured; additional biomarkers could provide a more comprehensive understanding of the underlying mechanisms. Third, the effects of phytoncide were examined using a single type and dosage, limiting conclusions about dose–response relationships or other phytoncide formulations. Finally, the study did not include long-term follow-up, preventing assessment of the durability of the observed improvements. Future research should include a larger and more diverse cohort of cancer survivors and assess a broader range of myokines and immune cell subsets.

Conclusions

This study confirmed that muscle strength, endurance, and several QoL domains showed the greatest improvements in the group receiving both phytoncide exposure and resistance exercise. Moreover, the combination of phytoncide inhalation and resistance exercise elicited synergistic anti-inflammatory and immunomodulatory effects in OCS. In particular, the combined intervention produced more pronounced enhancements in NK cells, $CD4^+$ and $CD8^+$ T cells, and $CD19^+$ B cells than either intervention alone. This multimodal intervention may serve as a complementary strategy for post-cancer rehabilitation and underscores the value of integrating phytoncide with resistance exercise in survivorship care.

Declarations

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Author contributions

All authors jointly contributed to the study design. YSJ and SKP conducted the data collection. YSJ performed data analyses. All authors participated in interpreting the findings. The initial manuscript draft was written by YSJ, SKP and SJH, and subsequently revised by the other authors to enhance intellectual content. All authors reviewed and approved the final manuscript prior to submission. YSJ serves as the guarantor of the work.

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Data availability

The datasets generated and analyzed in this study can be obtained from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the Ethics Committee of Hanseo University (Approval No. HS22-11-01). Written informed consent was obtained from all patients. This study was registered with the Clinical Research Information Service of the Korea Centers for Disease Control and Prevention under Clinical Trials KCT0008283 on 10/03/2023.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Figures

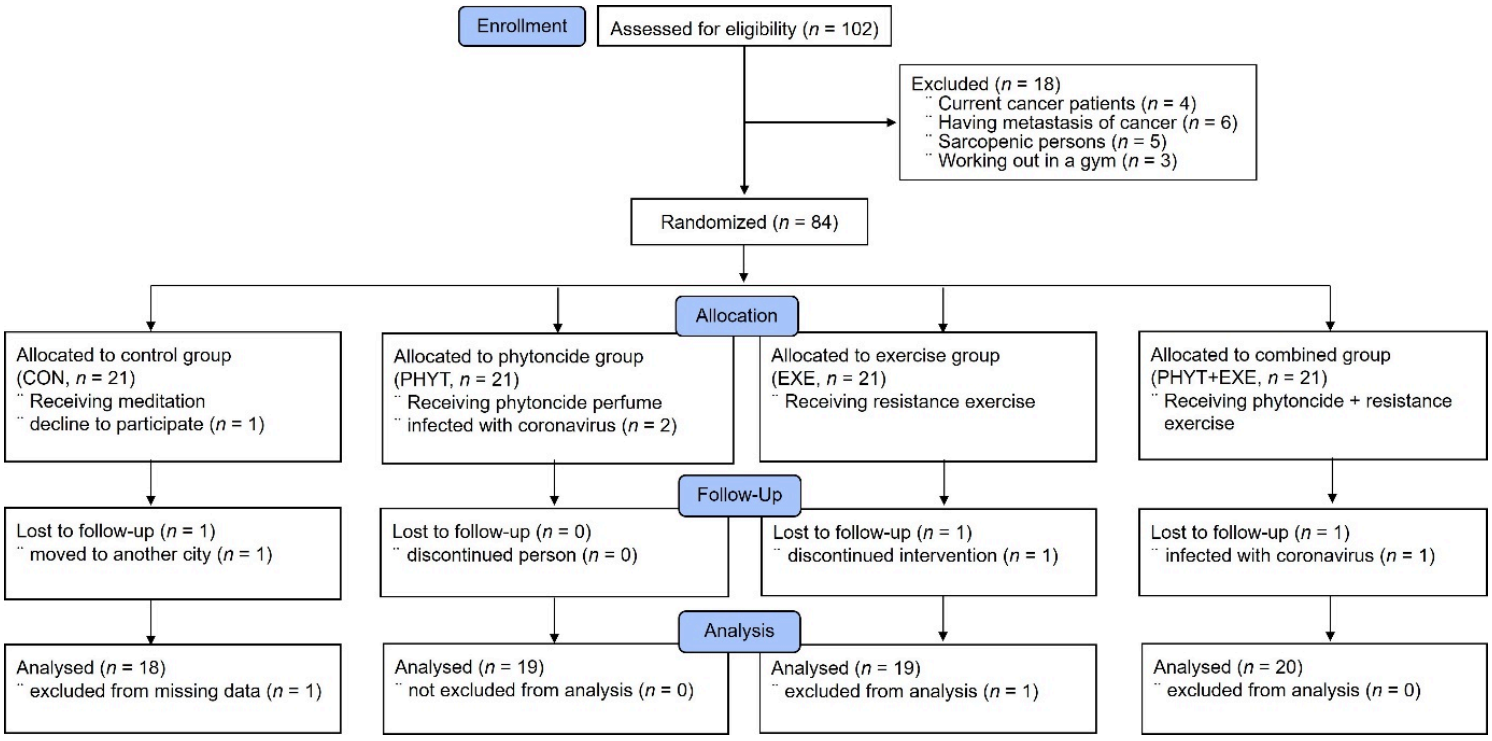

Figure 1

Consolidated Standards of Reporting Trials diagram

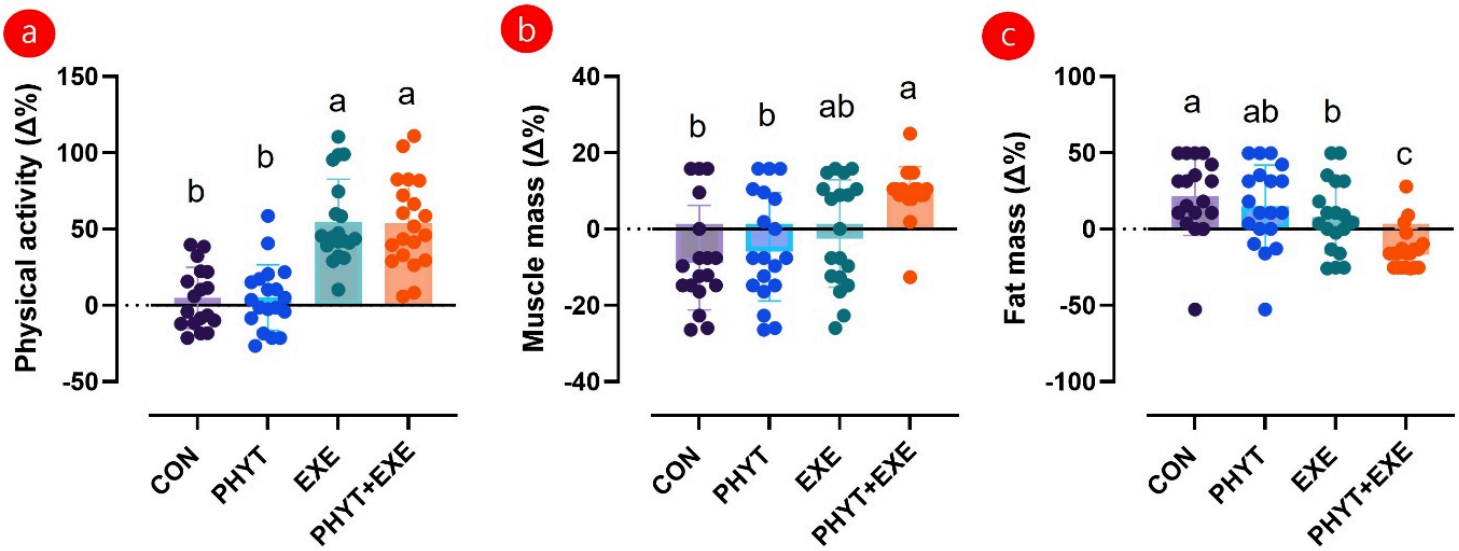

Figure 2

Delta (Δ) percentages' comparisons of physical activity, muscle mass, and fat mass. Symbols [a, b,] and [c] mean post-hoc results.

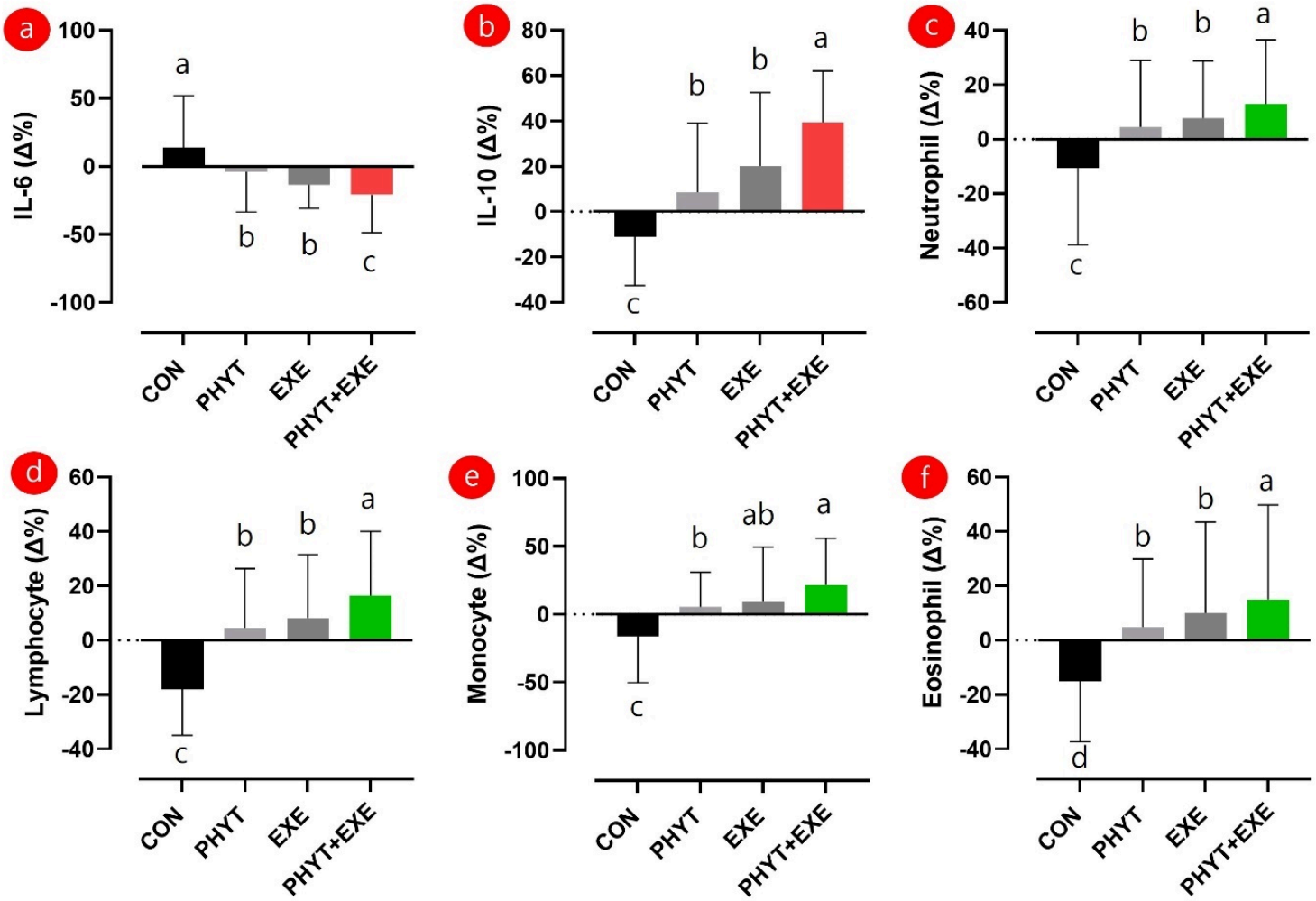

Figure 3

Delta (Δ) percentages' comparisons of myokines and immunocytes. Symbols [a, b, c,] and [d] mean post-hoc results.

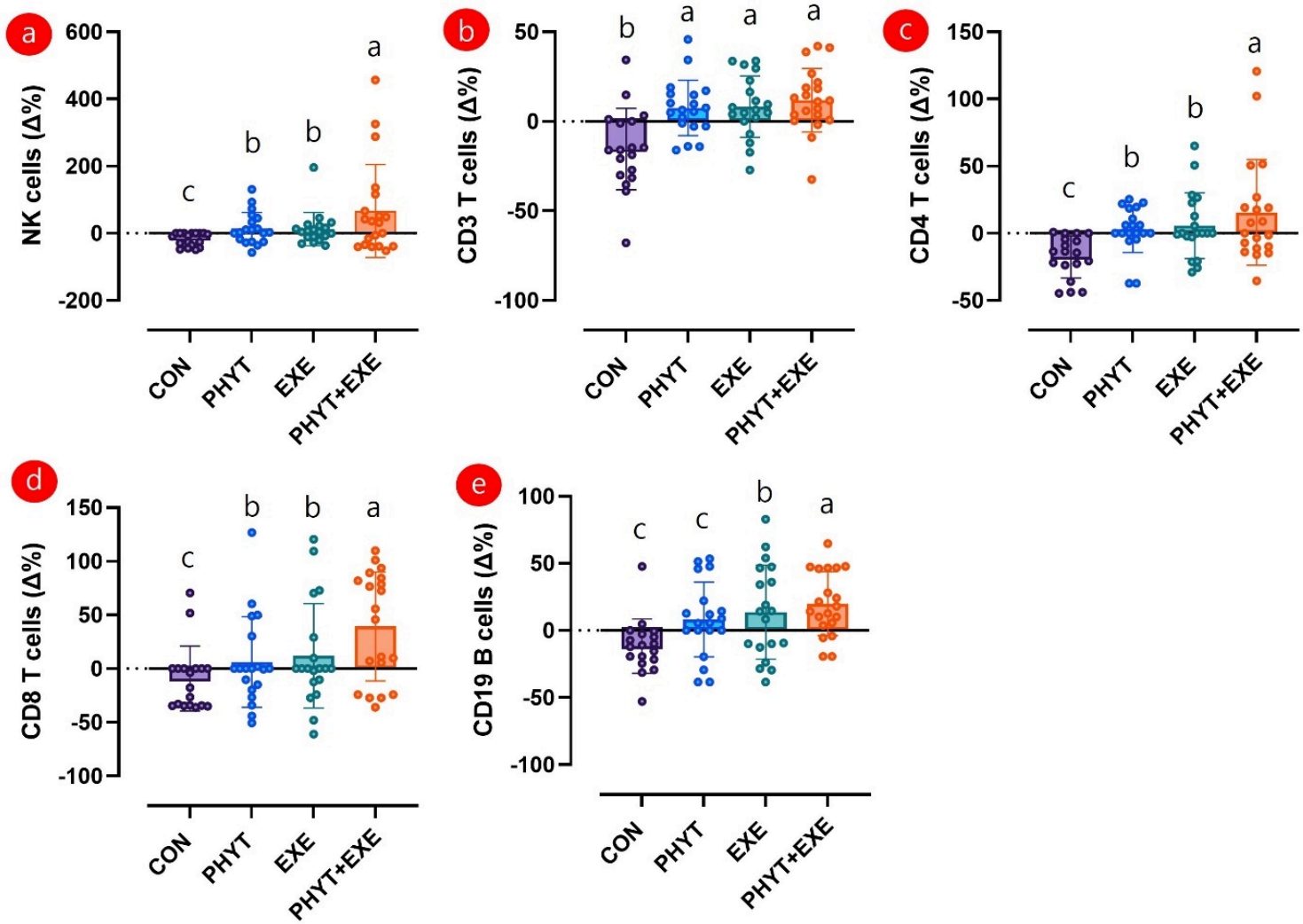

Figure 4

Delta (Δ) percentages' comparisons of lymphocytes. Symbols [a, b,] and [c] mean post-hoc results.

Supplementary Files

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- Suplementarytable1CONSORT2010Checklist.docx
- SUPPLEMENTARYMATERIALS.docx