Research Article

Response of serum C-reactive protein, tumor necrosis factor-α, and heat shock protein 70 levels to trachyspermum copticum and selected swimming training

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Abstract

Regular physical activity is the best defense against many diseases, illnesses, and abnormalities. Aerobic exercise and the consumption of herbal supplements strengthen the body's immune and defense systems. This study aimed to investigate the effect of a period of swimming endurance training with trachyspermum copticum (Ajwain) consumption on serum levels of some inflammatory factors in young men in a randomized clinical trial. The statistical population included all male students less than 25 years of age at the Islamic Azad University of Varamin Phishva, Iran. Among them, sample sizes of 60 people were selected by simple random sampling and were divided into four groups of 15 people each: trachyspermum copticum + training, trachyspermum copticum, training, and control. The training program included endurance swimming for 10 weeks either with or without the addition of trachyspermum copticum. Serum concentrations of tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and heat shock protein 70 (HSP70) were measured in two-time stages before and after the study period. The level of CRP inflammatory index, TNF-α cytokine, and HSP70 were lower among the training + trachyspermum copticum than in the control group and other experimental groups. Endurance swimming training and trachyspermum copticum with anti-inflammatory properties strengthened the immune system, increased antioxidant defense, and decreased inflammatory markers. Also, the level of physical activity has improved this condition by improving endothelial function.

Key Words: **Exercise training, Inflammation, Trachyspermum copticum, Immune system**

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Introduction

Physical activity is effective in regulating pro-inflammatory markers and may have a dual effect on the immune (Kashef et al., 2012). Inflammation affects the production of TNF-α (tumor necrosis factor-α) and IL-6 (interleukin 6). Some studies have shown that exercise can modulate these risk factors (Ambrósio et al., 2018) and other studies point to the lack of direct effect of physical activity on inflammatory parameters (Beavers et al., 2013). Heat shock proteins (HSPs) are also a group of protected molecules produced by the mechanical and physiological stress of exercise. Increases in these molecules can be detected in plasma, muscle, and other tissues. Jiang and colleagues reported that exercise with trimetazidine improves anti-fatal stress capacity by increasing autophagy and 70-myocardial heat shock protein in mice (Jiang et al., 2021). Szyller and Bil-Lula showed that heat shock proteins are produced during oxidative stress and physical activity (Szyller and Bil-Lula, 2021). But several researchers believe that with continued exercise and supplementation, heat shock protein levels will decrease (Karami et al., 2015).Gray et al. (2009) reported swimming training and garlic consumption in obese male rats modulated serum TNF-α levels, increased IL-10, and had a positive effect on reducing inflammation. The combination of two intervention methods can have a better effect (Asgari et al., 2015). In a study, the effect of walking on markers of insulin resistance and systemic inflammation in middle-aged men was researched. The results showed this intervention did not affect the markers of systemic inflammation (Gray et al., 2009). Another study showed that sesame improved blood sugar control, decreased serum lipids, and lipid peroxidation (Mohammadshahi et al., 2016). So, medicinal plants are considered due to the lack of side effects, greater availability, and lower cost (Heidari et al., 2015; Firoozi et al., 2019). In this regard, Moein and Zarghami Khameneh investigated the effect of silymarin supplementation on serum levels of IL-6 and CRP following a period of aerobic activity in healthy men, which had reduced inflammatory markers (Moein and Zarghami Khameneh, 2015). The plant compounds affected the antioxid-

-ant, anti-inflammatorys, and spasmodic (Burt, 2004). Trachyspermum copticum (known as Ajwain) as an herbal supplement may improve and modulate the production of inflammatory or oxidative markers (Alavinezhad and Boskabady et al., 2014; Chahal et al., 2017). However, the effects of endurance swimming training with the use of trachyspermum copticum are not known (Haghiroalsadat et al., 2012). The purpose of this study aimed to investigate the effect of a swimming endurance-training course with supplementation of trachyspermum copticum on serum levels of some inflammatory factors in young men.

Materials and Methods

Subjects

This research was a quasi-experimental study with pre-test and post-test design. The sample size estimates for each group of 15 people based on previous studies and using the available statistical population. Among all male students under 25 years old, Islamic Azad University - Varami Pishva, 222 people were randomly selected as a statistical sample. After explaining the method and purpose of the study, written consent was obtained from the subjects to participate in the study. First, the medical history of all subjects was reviewed and subjects with a history of a specific disease (such as diabetes, heart disease, and hypertension) were excluded from participating in this study. Simple random method 60 people were selected as a statistical sample (Figure 1 - Consort Flow Diagram). Subjects were divided into four groups of 15 people each: trachyspermum copticum + swimming endurance training, trachyspermum copticum, swimming endurance training, and control.

Anthropometric measurements

The first blood samples were taken 24 hours before the start of the study and their anthropometric measurements (height, weight, body mass index, Vo2max) were recorded. First, anthropometric indices of the research samples were measured and recorded separately by groups (Table 1).

Then 10 ml of blood was taken from the brachial vein of each person in a sitting position. The blood sample was immediately poured into anticoagulant tubes containing EDTA and sodium/heparin and transferred to a reference laboratory. Blood samples were stored at 4°C and then centrifuged at 3000 rpm for 15 minutes. Plasma and serum were then poured separately into the labeled tubes and transferred to a freezer at -20°C for measurement of blood variables. After that, the research subjects were divided into their groups and performed the research protocol, and took supplements.

Intervention and Exercise protocol

Table 1. Some descriptive characteristics and anthropometric indices of participant characteristics.

Variables	Groups	Mean± mean
Weight (kg)	Ajwain ± Training	74.87±8.53
	Ajwain	74.73±7.01
	Training	75.67±8.47
	Control	72.80±5.99
Height (cm)	Ajwain ± Training	1.74±2.27
	Ajwain	1.75±3. 9
	Training	1.79±2.13
	Control	1.74±4.00
Body mass index (kg/m^2)	Ajwain ± Training	24.55±1.68
	Ajwain	24.41±1.34
	Training	24.63±1.67
	Control	23.79±1.46
Vo2max (ml.kg.min)	Ajwain ± Training	43.18±1.45
	Ajwain	44.52±0.43
	Training	43.87±1.67
	Control	44.12±0.32

The supplement group + endurance swimming training and the supplement group consumed 4 trachyspermum copticum capsules daily. Each capsule contained 500 mg of trachyspermum copticum (Shafiezadeh et al., 2020). The capsules were taken 4 times a day and the study period was 10 weeks. In addition, the training group and the trachyspermum copticum group + swimming endurance training performed the research training protocol. To control the interfering factors, the study sample followed the same designed diet and physical activity during the study with maximum accuracy (Mohammadshahi et al., 2016). The designed exercise program included one selected endurance swimming training (Table 2). The training program was designed based on the execution protocols of previous research.

Assessment of TNF-α, CRP, HSP70

After the end of the training and supplementation protocol, the second blood sample was taken and transferred to the laboratory to check for inflammatory markers. To measure and evaluate TNF-α in human, the ELISA kit from the French company Diaclone and the immunoassay method based on sandwich ELISA was used. In this method, two monoclonal antibodies were used against two separate antigen sites on the human TNF-α molecule and a streptavidin-biotin system. This kit has no cross-reactivity or interference with similar molecules. TNF-α, known as cachectin and TNF-SF1A, is an adipokine that is involved in systemic inflammation and stimulates the acute phase response. This product is mainly produced by active macrophages, CD4 + lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons. The human ELISA kit was used with high sensitivity of 0.16 pg/ml with SDS-EK182HS, and ELISA sandwich test.

Latex Agglutination test (CRP) was used to measure and evalua-

Table 2. Selected endurance swimming training program.

Variable	Specification
Weeks	**10**
Sessions	**3 days per week**
Stretching exercises	Forward shoulder rotation with one arm only. Backward shoulder rotation with one arm only. Forward rotation using both arms. Backward rotation using both arms. Lateral arm rises. Alternating arm raises moving on arm forwards and one arm backwards. Lateral arm raises Alternating arm raises moving on arm forwards and one arm backwards. Lateral arm raises finishing with the movement with straight arms Straight-leg hamstring stretch with one leg resting on a starting block or box As above, but with your foot flexed 'Roll' your back forwards and then 'unroll' again until you are back in an upright position Standing with your legs apart, bend your upper body sideways, first in one direction and then the other Twist your upper body, first in one direction and then the other, making sure you are standing
Main protocol	**Warm up**: 300 easy swim, 4×50's freestyle (breathing every 3, 5, 7, 9 by 50), 100 choice drills. **Pre-set**: 8×50's IM order (15 seconds rest). **Main set**: 2 Rounds- 5×100's freestyle breathing every 5 strokes (20 seconds rest).
Cool down	500 easy alternating backstroke and freestyle swimming

-te CRP. This test is based on inactive agglutination of mucus. First, CRP-specific antibodies are prepared by injecting CRP into laboratory animals, and then these specific antibodies are attached by the Fe particles of latex polystyrene particles. Therefore, the addition of serum-containing CRP to the above particles causes agglutination of latex particles. This method is very sensitive. In this study, the sensitivity of the kit was up to 1 microgram/milliliter CRP serum.

To measure and evaluate the serum level of HSP70, a special human laboratory kit was used by ELISA method, cobs Mira auto-analyzer (Roch), Bender Med System factory-made in Germany and the coefficients of intra- and extra-assay changes were <5% and <13%, respectively. Standard curve the range was 0.78-50-50 ng/ml.

Statistical analysis

In this research, descriptive statistics methods of means, tables, standard deviations, and graphs were used. IBM SPSS statistical software version 21 (Armonk, NY: IBM Corp.) and Microsoft EXCEL were used to calculate and submit reports. Normality of data was assessed using Shapiro-Wilks and using the Levin test, and the homogeneity of variance was determined. Differences between TNF-α, CRP, and HSP70 among the 4 groups were determined using a one-way analysis of variance followed by Tukey's post hoc test. $P \leq 0.05$ was considered statistically significant.

Results

The mean and standard deviation of CRP were measured and compared among four research groups. The results showed that the rate of CRP was lower among the swimming endurance training group + trachyspermum copticum supplementation than the other groups (Figure 2).

Mean and standard deviation of TNF-α were measured and compared among four research groups. The results showed that the rate of TNF-α was lower among the swimming endurance training group + trachyspermum copticum supplementation than in the other groups (Figure 3).

The mean and standard deviation of HSP70 was measured and compared among four research groups. The results showed that

Table 3. Results analysis of variance of inflammatory markers in research groups.

Variables	Groups	Groups	sig
CRP	Ajwain ± Training	Ajwain	**0.013**
		Training	**0.213**
		Control	**0.000***
	Ajwain	Training	**0.028**
		Control	**0.012**
	Training	Control	**0.000***
TNF-α	Ajwain ± Training	Ajwain	**0.145**
		Training	**0.408**
		Control	**0.000***
	Ajwain	Training	**0.237**
		Control	**0.000***
	Training	Control	**0.000***
HSP70	Ajwain ± Training	Ajwain	**0.321**
		Training	**0.000***
		Control	**0.243**
	Ajwain	Training	**0.000***
		Control	**0.651**
	Training	Control	**0.126**

*: $P \leq 0.05$; Ajwain (trachyspermum copticum)

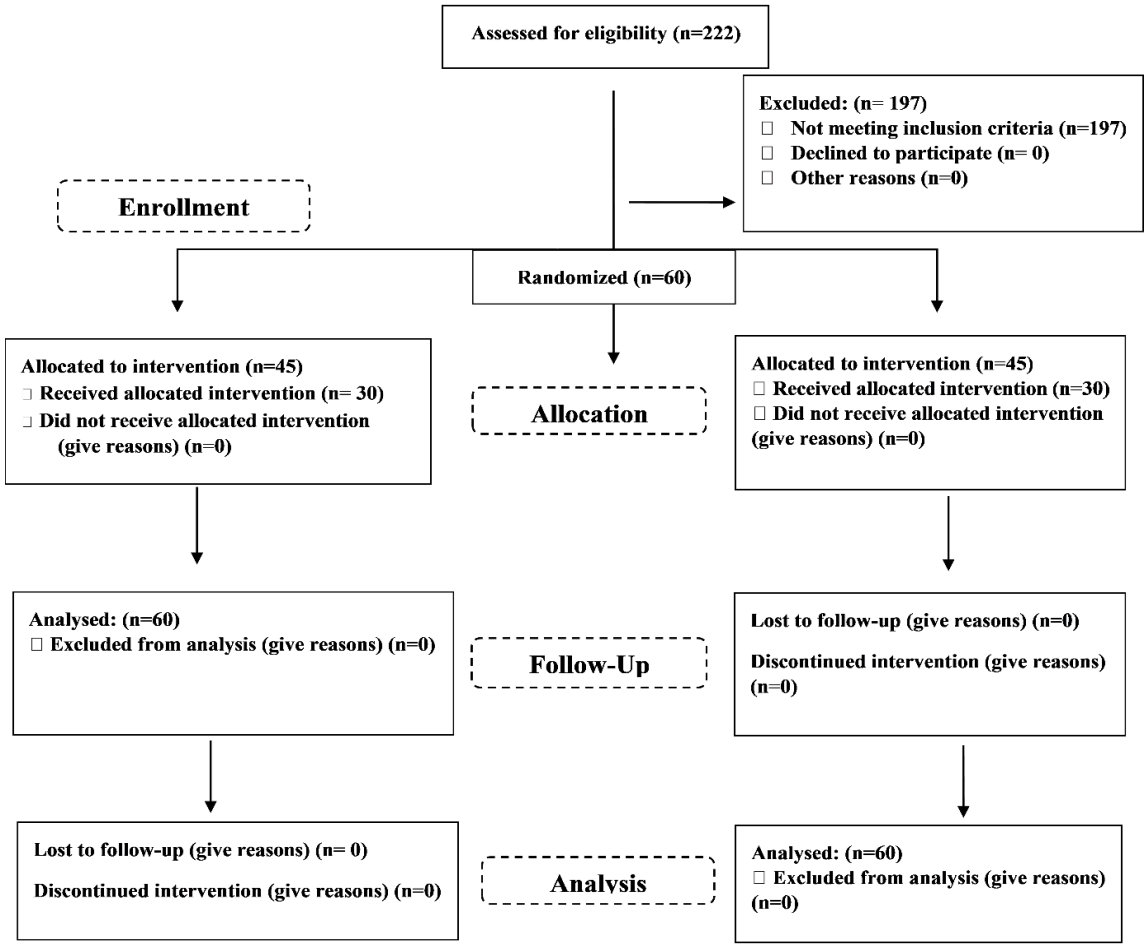

Figure 1. Consort flow diagram

the rate of HSP70 was lower among the swimming endurance training group + trachyspermum copticum supplementation than in the other groups (Figure 4).

Descriptive and inferential analysis (inter-group) ANOVA and Tukey posthoc was applied (Table3). The mean serum of CRP index of the subjects in the group trachyspermum copticum + swimming endurance training group and the group swimming endurance training was significantly lower compared to the control group ($P<0.05$).

The mean serum TNFα of the subjects in the group of trachyspermum copticum + swimming endurance training group and the trachyspermum copticum group was significantly lower compared to the control group ($P<0.05$). The mean serum HSP70 of the subjects in the group of trachyspermum copticum + swimming endurance training group and the trachyspermum copticum group was significantly lower compared to the training group ($P<0.05$).

Discussion

The results of the present study showed that endurance training and the addition of trachyspermum copticum can affect the serum level of CRP and the researcher's hypothesis was confirmed. Post-workout HS-CRP levels were significantly lower in the experimental groups compared to the control group (Figure 2). Based on this, it seems that the decrease in CRP levels was due to the effect of endurance swimming training and trachyspermum copticum, which is consistent with the studies of Church et al. (Church et al.,2002). A 6-month combined aerobic-resistance training program has also reduced CRP levels in obese women. But the results of another study showed that 18 months of combined aerobic-resistance exercise had no significant effect on serum CRP in men, obese and elderly women (Beavers et al.,2013). Also, a study of middle-aged people showed that 12 months of intermittent aerobic exercise for 60 minutes and six days a week with an intensity of 60-85% of maximum heart rate had no significant effect on CRP. The findings of these two studies are in contradiction with the results of the present study. This difference is probably due to the age difference, physical and training condition of the subjects, and the relationship between CRP and fat percentage. Performing endurance training through the CRP resting mechanism has reduced it. The body responds depending on endurance swimming training in the form of cardio-

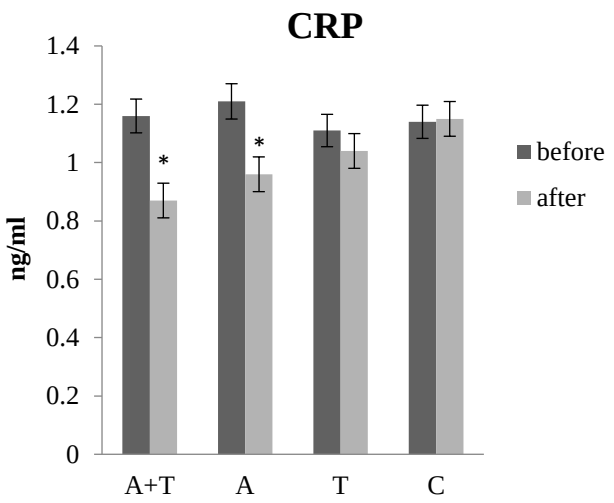

Figure 2. Comparison of mean and significance level of C-reactive protein (CRP) in 4 research groups. *: Significant difference compared to control group; Ajwain ± Training (A+T), Ajwain (A); Training (T); Control (C).

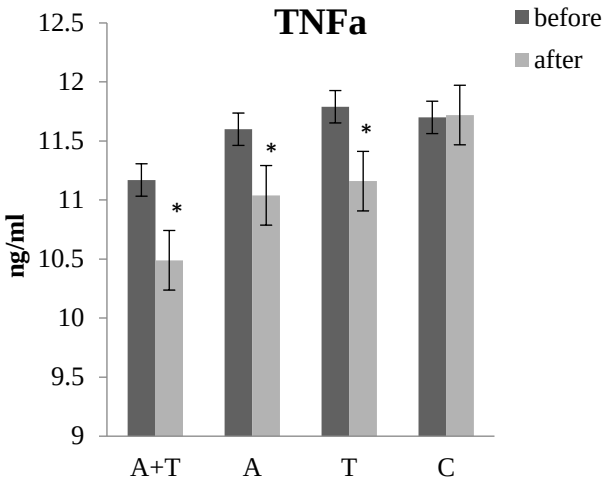

Figure 3. Comparison of mean and significance level of tumor necrosis factor-alpha (TNFa) in 4 research groups. *: Significant difference compared to the control group; Ajwain ± Training (A+T), Ajwain (A); Training (T); Control (C)

-vascular adaptations (de Moraes et al.,2018). Resting and the submaxillary heart rate will decrease due to decreased sympathetic effect and increased parasympathetic activity. These mechanisms will reduce the pressure and stress on the immune system. Serum CRP levels are greatly increased, especially during an inflammatory response, which is affected by disruption of endothelial homeostasis and decreased expression of nitric oxide synthesis. Physical activity reduces peripheral inflammatory markers associated with endothelial dysfunction, improves endothelial function in nitric oxide availability, and reduces oxidative stress (de Moraes et al.,2018). The findings of the present study also showed that endurance training combined with the consumption of trachyspermum copticum reduced serum TNF-α levels and the researcher's hypothesis was confirmed (Figure 3). The intensity of exercise affects TNF-α change, and training duration (4-18 months) will reduce TNF-α. Dabidy Roshan and Jolazadeh reported that the decrease in TNF-α level after 6 weeks of training was not significant in rats, but with its continuation up to 12 weeks, the decrease was significant (Dabidy Roshan and Jolazadeh,2009). Studies have shown that obese people have a high synthesis of inflammatory markers from fat cells, and a weight loss program in obese women reduces inflammatory markers through lifestyle changes, such as a low-calorie diet and increased physical activity (Safarzade et al.,2012). Physical activity may also relieve inflammation by improving endothelial function. Physical activity reduces environmental inflammatory markers in relation to endothelial dysfunction (Kazemi et al.,2019).

Some studies show that exercise reduces the production of HSP70 by cells and tissues, which is in line with the results of the present study. Some results support the reduction of HSP70, and have been reported to regulate heat shock proteins and the researcher's hypothesis was confirmed (Figure 4) (Avenatti et al.,2018). According to this research, exercise and physical stress may have little effect on HSP70 production. However, strenuous aerobic activity has caused more changes in HSP70 (de Moraes et al.,2018). A significant increase in HSP70, after training, marathon, and ultra-marathon has been reported (Xu et al.,2008). Fisher et al. have observed changes in HSP70 in their study. Some reporting an increase in HSP70 in eccentric contractions, rowing training, high-intensity resistance, and unusual training (Paulsen et al.,2007; Cumming et al.,2021). The

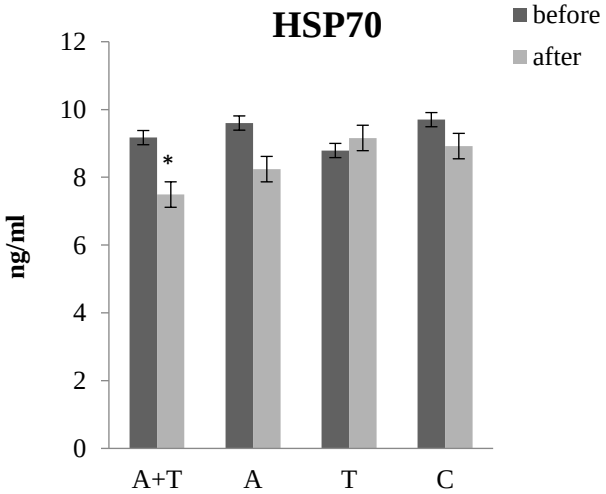

Figure 3. Comparison of mean and significance level of heat shock protein 70 (HSP70) in 4 research groups. *: Significant difference compared to the control group; Ajwain ± Training (A+T), Ajwain (A); Training (T); Control (C)

effect of exercise on inflammatory immune activity is not clear, but one of the physiological benefits of exercise is an increase in the anti-inflammatory effect. HSP70 can also be related to the type of physical activity, intensity, and duration of exercise (Cumming et al.,2021). Of course, the expression of heat shock proteins in human leukocytes is usually modulated by adaptation to aerobic and endurance training (Krüger et al.,2019). Trachyspermum copticum also has antioxidant properties, metabolic effects, and recall of fat sources and effects on the respiratory system. It also reduces muscle-bruising, strain and reduces inflammation of joints and tendons. Protein, fat, minerals, fiber, carbohydrates, calcium, thiamine, riboflavin, phosphorus, iron, and niacin are significant in trachyspermum copticum (Alavinezhad and Boskabady et al.,2014; Chahal et al.,2017). Therefore, the role of trachyspermum copticum and its function in the body has caused the synergy of the effects of endurance swimming training and the reduction of inflammatory factors, TNF-α, CRP, and HSP70 in the research samples (Table 3).

Conclusion

Consumption of trachyspermum copticum and swimming endurance training have synergistically reduced levels of inflammatory markers and strengthened the immune system. Gender, age, smoking, body fat reserves, underlying diseases such as diabetes, physical activity, and cardiovascular fitness are also effective in producing inflammatory factors and are probably conflicting factors in the results of research with others. Further controlled studies are required to confirm the presented results.

What is already known on this subject?

The use of trachyspermum copticum and the training method to strengthen the immune system have already been studied alone and other factors and cells of the immune system were examined. Of course, most research has had animal specimens.

What this study adds?

In this research, trachyspermum copticum and swimming exercises have been used simultaneously. . Another point is that an acute phase protein, a heat shock protein and an inflammatory cytokine were examined as research variables.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The experimental research procedures were all performed according to the approval of the Research Ethics Committee of Islamic Azad University - Varamin-Pishva Branch, Iran (ethical code: IR.IAU.VARAMIN. REC.1398.007). Also, this clinical trial is approved by the Iranian Registry of Clinical Trials site (IRCT20180805040704N1).

Informed consent All participants and the research sample had complete information about the research process and cooperated with satisfaction and awareness. Written consent was obtained from all of them before the investigation began.

Author contributions

Conceptualization: F.N., M.A.; Methodology: F.N., M.A.; Software: F.N., M.H.; Validation: F.N., M.A., M.H.; Formal analysis: F.N., M.A., M.H.; Investigation: F.N., M.A.; Resources: F.N., M.A., M.H.; Data curation: F.N., M.A., M.H.; Writing - original draft: F.N., M.A., M.H.; Writing - review & editing: F.N., M.H.; Visualization: F.N., M.A., M.H.; Supervision: F.N.; Project administration: F.N.; Funding acquisition: F.N. All authors read and approved the final manuscript.

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