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Potential of Curcumin to Reduce Serum Nuclear Factor-Kappa B (NF-kB) Levels After High-Intensity Exercise

Potencial de la curcumina para reducir los niveles séricos del factor nuclear kappa B (NF-kB) después del ejercicio de alta intensidad

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Abstract. The study aimed to analyze the effect of curcumin on serum NF-kB levels after high-intensity exercise. This experimental research uses a pre and post-control group design. Research subjects were selected using a purposive sampling technique. Following this, the subjects were divided into two groups: Group K1 with a placebo and Group K2 with a dose of 400 mg of curcumin. A total of 20 healthy men aged between 20-30 years participated in this study. On the first day, Data on the characteristics of the research subjects were collected. The subjects warmed up and did high-intensity training in squad exercises and leg presses with an intensity of 80-90% of maximum ability. The intensity of each research subject was determined using the one repetition maximum (1RM) test. 1RM is the maximum weight that can be lifted in one repetition of a movement. The exercise is performed in four sets of 10 repetitions with a recovery time of approximately 60 seconds between set. On the second day, 24 hours after high-intensity exercise, all subjects took blood samples (pre-test) and then were given intervention based on their respective groups. On the third day, 48 hours after high-intensity exercise, all subjects took blood samples (post-test). Blood samples were analyzed in the laboratory using the ELISA method with catalog numbers Human NF-kB ELISA kit E0690Hu. The results of this study reported that the group given curcumin after high-intensity exercise reduced serum NF-kB levels significantly (*$p<0.05$) compared to the placebo group. It can be concluded that the administration of curcumin at 400 mg after high-intensity exercise can reduce serum NF-kB levels. Reducing NF-kB levels is believed to lessen pro-inflammatory cytokines such as TNF-a and is closely related to muscle pain after exercise. We recommend using curcumin as a natural ingredient that can potentially reduce NF-kB. In future research, we strongly recommend examining other inflammatory biomarkers, such as TNF-a and Interleukin.
Keywords: Curcumin, Inflammation, Cytokines, Exercise, Health

Resumen. El estudio tuvo como objetivo analizar el efecto de la curcumina sobre los niveles séricos de NF-kB después del ejercicio de alta intensidad. Esta investigación experimental utiliza un diseño de grupo de control pre y post. Los sujetos de investigación fueron seleccionados mediante una técnica de muestreo intencional. A continuación, los sujetos se dividieron en dos grupos: el grupo K1 con un placebo y el grupo K2 con una dosis de 400 mg de curcumina. En este estudio participaron un total de 20 hombres sanos de entre 20 y 30 años. El primer día se recogieron datos sobre las características de los sujetos de la investigación. Los sujetos calentaron y realizaron entrenamiento de alta intensidad en ejercicios de equipo y prensas de piernas con una intensidad del 80-90% de la capacidad máxima. La intensidad de cada sujeto de investigación se determinó mediante la prueba de una repetición máxima (1RM). 1RM es el peso máximo que se puede levantar en una repetición de un movimiento. El ejercicio se realiza en cuatro series de 10 repeticiones con un tiempo de recuperación de aproximadamente 60 segundos entre series. El segundo día, 24 horas después del ejercicio de alta intensidad, a todos los sujetos se les tomaron muestras de sangre (prueba previa) y luego se les administró una intervención basada en sus respectivos grupos. Al tercer día, 48 horas después del ejercicio de alta intensidad, a todos los sujetos se les tomaron muestras de sangre (post-test). Las muestras de sangre se analizaron en el laboratorio mediante el método ELISA con números de catálogo Human NF-kB ELISA kit E0690Hu. Los resultados de este estudio informaron que el grupo que recibió curcumina después de un ejercicio de alta intensidad redujo significativamente los niveles séricos de NF-kB (*$p<0,05$) en comparación con el grupo de placebo. Se puede concluir que la administración de curcumina a 400 mg después del ejercicio de alta intensidad puede reducir los niveles séricos de NF-kB. Se cree que la reducción de los niveles de NF-kB disminuye las citoquinas proinflamatorias como el TNF-a y está estrechamente relacionado con el dolor muscular después del ejercicio. Recomendamos utilizar curcumina como ingrediente natural que potencialmente puede reducir el NF-kB. En futuras investigaciones, recomendamos encarecidamente examinar otros biomarcadores inflamatorios, como el TNF-a y la interleucina.
Palabras clave: Curcumina, Inflamación, Citoquinas, Ejercicio, Salud

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Introduction

High-intensity exercise such as resistance training is an important component of an overall fitness regimen for athletes and recreationally active people (Akbulut et al. 2021; Brar, Bhardwaj, and Prabu 2021; Maciel et al. 2021). High-intensity exercise is good for increasing lean muscle mass, but Exercise Induced Muscle Damage (EIMD), Delayed Onset Muscle Soreness (DOMS), can limit performance after a training session (Owens et al. 2019; Romero-Parra et al. 2021; Viribay et al. 2020; Xin and Eshaghi 2021).

Several studies have reported that muscle pain reaches its peak 24 hours after exercise (Ayubi et al. 2022; Chang et al. 2021; Hung et al. 2021; Muljadi et al. 2021). In connection with this phenomenon, currently, around 30 million people worldwide who experience DOMS are usually treated with non-steroidal anti-inflammatory drugs (NSAIDs) (Ayubi and Sastika Putri 2021; Kyriakidou et al. 2021). Giving NSAIDs after exercise has the effect of inhibiting hypertrophy and muscle strength. As a result, giving NSAIDs will actually negate the results of the exercises carried out (Schoenfeld 2012). High-intensity exercise will increase Nuclear Factor-kappa B (NF-κB) signaling so that it will trigger inflammation (Jung et al. 2018). Meanwhile, muscle pain is caused by increased levels of pro-inflammatory cytokines, namely Tumor Necrosis Factora-alpha (TNF-a) in the blood in response to muscle damage (Ayubi et al. 2023).

Other alternative solutions need to be sought to reduce complaints of muscle pain, but still not interfere with the response of muscle growth after exercise. One of the natural ingredients contained in turmeric is curcumin. Curcumin is known for its active compounds that have anti-inflammatory activity (Boarescu et al. 2022). Curcumin is able to inhibit inflammation by modulating NF-κB signals and blocking TNF-α signals by activating protein responses in muscles (Srivastava et al. 2017; Venkata et al. 2012). The anti-inflammatory activity of curcumin also inhibits the production of pro-inflammatory eicosanoids which include prostaglandins and leukotrienes (Han, Zhang, and Li 2021; Petrone-Garcia et al. 2021; Zhu et al. 2019). Curcumin has been widely used to increase endurance and Maximal oxygen uptake VO2 max (Hamidie, Ali, and Masuda 2017). In addition, curcumin has been widely used in the medical world to accelerate wound healing (Sharma et al. 2018). Until now, curcumin has never been reported to cause post-exercise side effects, but the effect of curcumin in reducing NF-κB signals after high-intensity exercise in untrained people is unknown.

The purpose of this study was to analyze and prove the effect of curcumin on serum NF-κB intensity after high-intensity exercise.

Methods

Study Design

This experimental research uses pre- and post-control group design. Research subjects were selected using a random sampling technique, then the subjects were divided into two groups, namely a group which was given a placebo (K1) and a group which received curcumin (K2).

Subjects

A total of 20 healthy men participated in this study (subject characteristics are shown in Table 1). The inclusion criteria in this study were men aged 20 to 30 years, with normal Body Mass Index (BMI), and subjects not trained in sports. The exclusion criteria in this study were subjects under 20 years of age and abnormal blood pressure before exercise. This study's drop-out criteria were consuming coffee, turmeric foods, and non-steroidal anti-inflammatory drugs (NSAIDs). Next, research subjects received instructions about the research mechanism and signed a written agreement willing to become research subjects.

Procedure

1. In the beginning, we prepared administration such as ethical eligibility permits and permits for borrowing facilities and infrastructure
2. We screened respondents who were used as research subjects based on inclusion and exclusion criteria and filled out the form willing to become research subjects (Informed Consent) by research subjects.
3. The subjects were divided into two groups, namely the group that received a placebo, and the group that received curcumin. The placebo was provided in a form of empty capsules and curcumin was given in a form of natural supplement capsules at a dose of 400 mg. The 400 mg dose of curcumin was chosen based on our previous literature studies (Ayubi et al. 2023).
4. On the first day, all subjects collected data on the characteristics of the research subjects, then did a warm-up, and then the subjects did exercises in the form of squad exercises and leg presses with an intensity of 80-90% of their maximum ability. The intensity of each research subject was determined using the one repetition maximum (1RM) test. 1RM is the maximum weight that can be lifted in one repetition of a movement. The exercise is performed in four sets of 10 repetitions with a recovery time of approximately 60 seconds between set.
5. On the second day, 24 hours after high-intensity exercise, all subjects had their pre-test blood samples taken to measure serum NF-kB levels, then they were given intervention according to their group.
6. On the third day, 48 hours after high-intensity exercise, post-test blood samples were taken from all subjects to measure serum NF-kB levels.
7. Blood samples were analyzed in the laboratory using the ELISA method with catalog numbers Human NF-kB ELISA kit E0690Hu.

ELISA Procedure

1. Add 100μL standard or sample to the wells. Incubate for 90 min at 37°C.
2. Discard the liquid, immediately add 100μL Biotinylated Detection Ab working solution to each well. Incubate for 60 min at 37°C.
3. Aspirate and wash the plate for 3 times.
4. Add 100μL HRP conjugate working solution. Incubate for 30 min at 37°C. Aspirate and wash the plate for 5 times.
5. Add 90μL Substrate Reagent. Incubate for 15 min at

37°C.

6. Add 50μL Stop Solution.

7. Read the plate at 450nm immediately. Calculation of the results.

Figure 1. ELISA Procedure

CONSORT flowchart

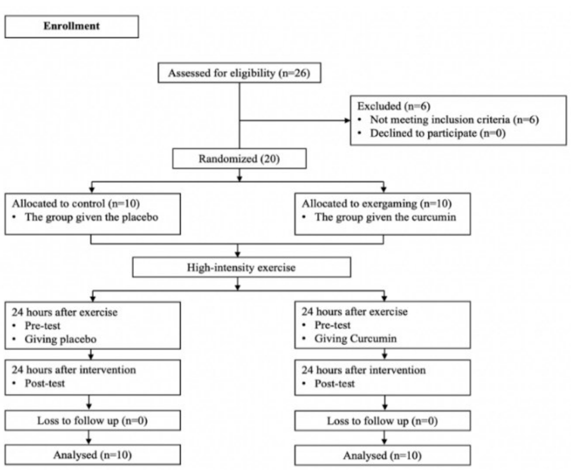

Figure 2. The CONSORT flowchart

Statistical analysis

Statistical analysis in this study used the IBM SPSS version 27 application, a descriptive test was performed to obtain the mean, standard deviation and standard error. Furthermore, the normality test was carried out using the Shapiro-Wilk method, if the data were normally distributed the different test was carried out using the paired t-test, but if the data was not normally distributed, the difference was carried out using the Wilcoxon signed rank test.

Ethics

Declaration of ethics was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga with registration number (No.118/EC/KEPK/FKUA/2022).

Results

Data on the characteristics of the research subjects are shown in Table 1-5.

Table 1.
Characteristics of research subjects

Data	Group	N	x̄±SD	Shapiro-Wilk	p-value
Age (y)	K1	10	22.60±1.83	0.149	0.389
	K2	10	23.30±1.70	0.850	
Height (cm)	K1	10	166.95±4.46	0.891	0.179
	K2	10	169.80±4.64	0.243	
Weight (kg)	K1	10	63.55±9.11	0.823	0.938
	K2	10	63.20±10.68	0.386	
BMI (kg/m^2)	K1	10	23.13±4.20	0.046	0.173
	K2	10	21.70±3.17	0.477	

In the table above, only BMI K1 data is not normally distributed, so the Wilcoxon Signed Ranks Test is used for different tests. All data from the table above did not differ significantly in each group.

Table 2.
Characteristic subject: body temperature, blood pressure and pulse before exercise

Data	Group	N	x̄±SD	Shapiro-Wilk	p-value
Body temperature (°)	K1	10	36.56±0.26	0.184	0.619
	K2	10	36.47±0.49	0.523	
Systolic blood pressure (mmHg)	K1	10	123.00±6.27	0.475	0.355
	K2	10	119.80±8.62	0.987	
Diastolic blood pressure (mmHg)	K1	10	75.30±6.66	0.100	0.385
	K2	10	71.60±11.31	0.385	
Pulse (mmHg)	K1	10	84.70±5.45	0.053	0.165
	K2	10	88.70±6.83	0.779	

Table 3.
Characteristic subject: body temperature, blood pressure and pulse after exercise

Data	Group	N	x̄±SD	Shapiro-Wilk	p-value
Body temperature (°)	K1	10	36.16±0.32	0.065	0.168
	K2	10	36.39±0.41	0.193	
Systolic blood pressure (mmHg)	K1	10	117.80±2.70	0.550	0.655
	K2	10	116.90±5.64	0.251	
Diastolic blood pressure (mmHg)	K1	10	74.40±4.90	0.992	0.320
	K2	10	75.80±5.57	0.220	
Pulse (mmHg)	K1	10	80.80±6.16	0.951	0.947
	K2	10	80.60±7.18	0.140	

Table 4.
Characteristic subject: body temperature, blood pressure and pulse before curcumin treatment

Data	Group	N	x̄±SD	Shapiro-Wilk	p-value
Body temperature (°)	K1	10	36.14±0.39	0.688	0.825
	K2	10	36.18±0.40	0.960	
Systolic blood pressure (mmHg)	K1	10	125.90±6.52	0.099	0.143
	K2	10	120.20±9.80	0.198	
Diastolic blood pressure (mmHg)	K1	10	70.90±4.22	0.421	0.948
	K2	10	70.70±8.57	0.930	
Pulse (mmHg)	K1	10	83.00±7.84	0.533	0.785
	K2	10	84.10±9.81	0.466	

Table 5.
Characteristic subject: body temperature, blood pressure and pulse after curcumin treatment

Data	Group	N	x̄±SD	Shapiro-Wilk	p-value
Body temperature (°)	K1	10	36.26±0.32	0.398	0.231
	K2	10	36.08±0.32	0.884	
Systolic blood pressure (mmHg)	K1	10	129.90±14.27	0.553	0.247
	K2	10	122.60±12.98	0.321	
Diastolic blood pressure (mmHg)	K1	10	72.10±4.84	0.391	0.647
	K2	10	70.50±9.73	0.208	
Pulse (mmHg)	K1	10	83.90±9.38	0.947	0.484
	K2	10	80.90±9.38	0.251	

All data from Tables 2-5 are not significantly different in each group

Curcumin Reduces Serum NF-kB Levels

Table 6.
Results of the Normality Test for serum NF-kB Levels

Data	Group	Shapiro-Wilk	
		n	p-value
NF-kB Levels (Pre-test)	K1	10	0.461
	K2	10	0.988
NF-kB levels (Post-test)	K1	10	0.272
	K2	10	0.990

Information:

P>0.05 = Data is normally distributed

The results of the analysis of serum NF-kB levels between the pre-test and post-test in each group are presented in Figure 3.

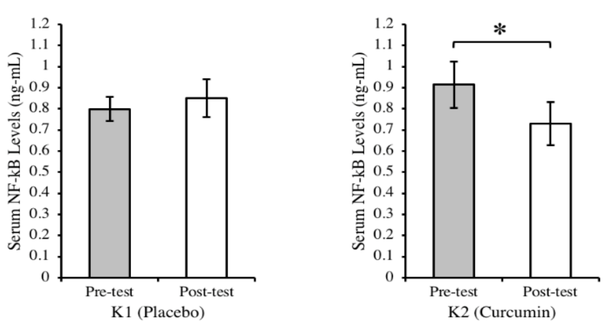

Figure 3. Group (K2) that was given curcumin after high-intensity exercise was able to reduce serum NF-kB levels significantly (*$p<0.05$) compared to group (K1) that was given placebo. Data presented as Mean ± Std Error. The P-value was obtained using a paired t-test to compare the pre-test and post-test of each group.

Table 7.
Serum NF-kB Level Different Test Results

Difference Test Method	Group	P
Paired t-test	K1 (pre-test and post-test)	0.593
	K2 (pre-test and post-test)	0,030*

Information

*There is a significant difference in the Paired test ($p<0.05$)

Discussion

This study was conducted to analyze the effect of curcumin on serum NF-kB levels after high intensity exercise.

We observed that the placebo group did not significantly decrease serum NF-kB after high-intensity exercise, while the 400 mg curcumin group significantly reduced serum NF-kB. Our research answer and confirm a literature study reported findings that curcumin has a positive effect on inflammatory responses (Ayubi et al. 2023; Dias et al. 2021). High-intensity exercise, especially with eccentric movements, will result in muscle damage and inflammatory response (Markus et al. 2021; Nanavati et al. 2022). Eccentric movements contribute to high mechanical stress and produce bone extracellular matrix fragments that are recognized by receptors expressed by innate immune cells (Nanavati et al. 2022). Cell activation mediated by this process stimulates NF-kB activation (Jameson et al. 2021).

A theory reports that NF-kB plays a role in controlling inflammation, especially in the secretion of pro-inflammatory cytokines such as TNF-a and IL-6 (Nanavati et al. 2022). In this regard, we believe that the main cause of muscle pain is due to an uncontrolled increase in pro-inflammatory cytokines such as TNF-a for several days after high-intensity exercise. In the case of exercise-induced muscle damage, a histological study showed that neutrophils enter the muscles and accumulate in the damaged area from 1 to 24 hours after exercise (Paulsen et al. 2010). In addition, muscle damage is characterized by ultrastructural disturbances of the muscles which increase the release of inflammatory cytokines by macrophages (Nanavati et al. 2022). Neutrophils and pro-inflammatory cytokines that interact with each other aim to control the pro-inflammatory response when muscle damage occurs (Hody et al. 2019). On the other hand, while pro-inflammatory cytokines increase, macrophages also release anti-inflammatory cytokines that contribute to muscle recovery and regeneration (Nonnenmacher and Hiller 2018).

We believe the role of NF-kB is the therapeutic goal of curcumin in inflammation because of the importance of NF-kB in the regulation and expression of TNF-a which is a cause of muscle pain. Our research findings are supported by an experimental study on the effect of curcumin on NF-kB expression in rats induced by drinking ethanol (Fatolahi et al. 2020). In that study, curcumin can significantly reduce NF-kB levels. In addition, a study reported that curcumin is able to attenuate osteoarthritis through the NF-kB pathway (Buhrmann et al. 2021). Curcumin is one of the natural ingredients that have anti-inflammatory activity (Dias et al. 2021; Yan et al. 2021). A recent literature study reported that curcumin works by suppressing the secretion of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-17, and TNF-a (Peng et al. 2021). Research on the effect of curcumin on TNF-a levels after exercise is perhaps limited. However, on the other hand, we found a study that reported that there was no significant reduction in TNF-a levels given curcumin at a dose of 1500 mg/day for 28 days after aerobic exercise in trained men (MS et al. 2020). We analyzed from this study that the ineffective effect of curcumin is probably due to aerobic exercise which is classified as moderate exercise intensity so it does not trigger post-exercise inflammation. In this regard, what distinguishes this research is that the subjects involved are people who are not trained and the exercises are carried out with high intensity. This is a strong foundation that exercise performed at high-intensity results in muscle damage and triggers an increase in pro-inflammatory cytokines in the blood (Ayubi et al. 2023; Dias et al. 2021).

In summary, interesting new findings in this study report that curcumin administered at a dose of 400 mg/day can reduce serum NF-kB levels. Based on the laboratory tests we conducted, we believe the reduction in pain intensity occurred due to the anti-inflammatory effect of curcumin which is able to modulate NF-kB signals and block TNF-a signals. Meanwhile, we paid close attention to all aspects of research and measurement during the research. For future studies, we hope to test the effects of curcumin on other inflammatory biomarkers such as IL-1B, IL-2.

Conclusion

It can be concluded that the administration of curcumin at 400 mg after high-intensity exercise can reduce serum NF-kB levels. Reducing NF-kB levels is believed to lessen pro-inflammatory cytokines such as TNF-a and is closely related to muscle pain after exercise. We recommend using curcumin as a natural ingredient that can potentially reduce NF-kB. In future research, we strongly recommend examining other inflammatory biomarkers, such as TNF-a and Interleukin.

Conflict of interest

The authors declare no conflict of interest

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