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Effect of Curcumin (Turmeric) Supplement on Maximal Oxygen Uptake (VO_{2max}) and Lactate Threshold in Human

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ABSTRACT

Many studies have reported on the antitumor, antioxidant, antiarthritic and anti-inflammatory properties of curcumin. The present examined effects of curcumin together with exercise to increase VO_{2max} and lactate threshold in human. In a study on animals, 10 -week-old male Wistar rats were divided into non-eTR and eTR groups. We used low (50 mg/kg-BW/day) and high doses (100 mg/kg-BW/day) of curcumin dissolved in dimethyl sulfoxide (DMSO). These doses were injected intraperitoneally into all animals for two hours before swimming exercise using Western blot (WB) analysis. In the study on humans, the sample was divided into two groups and the duration who were asked to consume two capsules (@ 550 mg) per day for 6 weeks. Aerobic exercise (jogging) was scheduled 4 times a week during the period, at vigorous intensity (60-90% maximum heart rate). The level of VO_{2max} and lactate threshold was examined pretest and posttest. Results showed that low doses and high doses curcumin treatment significantly increased COX-IV protein expression. Furthermore, 1.1-gram curcumin/day for 6 weeks significantly increased VO_{2max} and lactate threshold on human. The results showed that curcumin treatment can optimise human performance through its ability to increase VO_{2max} and lactate threshold.

Keywords: Aerobic exercise, curcumin, lactate threshold, VO_{2max}

INTRODUCTION

Excellent physique and good psychological health are important for performance in sport. Previous study have reported the use of ergogenic aids combined with training, mechanical device, nutritional practice, pharmacological approach, or physiological technique to improve sports performance which is (Porrini & Del Bo, 2016). Ergogenic

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aids refer to use of amino acid, blood doping, manipulating exercise methods and, equipment, and drugs or hormone to enhance performance. However, performance can be impaired by some alleged use of ergogenic substances or phenomena (Porrini & Del Bo, 2016). A study in Italy showed that almost 94% of coach and trainers provided their athletes with nutritional supplements (Porrini & Del Bo, 2016) to increase sports performance. Ergogenic aids can be in the form of food source too (Silver, 2001).

Polyphenols has attracted the attention of researchers and food manufacturers for over a decade. This is due to the antioxidant properties of polyphenols, their abundance in our diet, and their probable role in the prevention of various diseases associated with oxidative stress, for example cancer, cardiovascular and neurodegenerative diseases.

Furthermore, in many medicinal plants, polyphenols modulate the activity of a wide range of enzymes and cell receptors (Manach, Scalbert, Morand, Remesy, & Jimenez, 2004); (Middleton, Kandaswami, & Theoharides, 2000). Some plants contain several thousand molecules of a polyphenol structure (i.e., several hydroxyl groups on aromatic rings), and edible plants have been identified as consisting of several hundred compounds classified into different groups based on the function of phenol rings they contain and the structural elements that bind these rings to one another. The phenolic acids, flavonoids, stilbenes, and lignans are different in each plant. Oxygenated heterocycle (ring C) is formed by the flavonoids. This substance share a common structure consisting of 2 aromatic rings (A and B) are bound together by three carbon atoms. These may be divided into 6 subclasses as a function of the type of heterocycle involved: flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols (catechins and proanthocyanidins). In addition to this diversity, various carbohydrates and organic acids may be associated with polyphenol.

Turmeric is a spice belonging to the ginger family (Zingiberaceae) and has a component called Curcuma longa (Nandiyanto et al., 2016). This is described as horizontal underground stems with shoots and leaves called rhizomes. The spice is notable for its vibrant yellow colour. Curcuminoids is largely derived from fat-soluble polyphenolic pigments. The yellow pigment is segregated from the rhizomes of Curcuma longais termed curcumin, or turmeric, as it is the natural phenol curcuminoid. The safe consumption of curcumin is easily confirmed by the fact that for hundreds of years it has been part of the diet of people in a number of countries. Several previous studies have reported the antitumor, antioxidant, antiarthritic and anti-inflammatory properties of curcumin. This correlation was shown using GOLD and AutoDock analysis as well as validated targets of anticancer therapy (COX-2, PhenolsulphoTransferases, Matrix metalloproteinases (MMPs), P450 and TNF-alpha). It was observed in the binding affinity of BDC against the targets that these derivatives are potent procarcinogen activating enzyme inhibitors (Figure II-8). Curcumin, a hydrophobic natural product, comprises two phenolic rings. Each ring is replaced with methoxy ether functionality in the ortho-position and attached to each other by an aliphatic unsaturated heptane linker in the para-position with an α, β diketonic functionality on carbon-3 and -5. The electrophilic α, β-unsaturated carbonyl groups are capable of reacting with a nucleophile such as glutathione (Scapagnini et al., 2002). Results from a number of studies suggest that the diketone functionality is able to go through reversible tautomerisation between enolic- and ketonic-forms (Payton, Sandusky, & Alworth,

2007). Commercial curcumin characteristically comprises three main curcuminoids: curcumin (~77%), dimethoxy curcumin (~17%) and bisdemethoxycurcumin (~3%). Findings of earlier studies have shown that curcumin have ability to increase mitochondrial biogenesis through increased cAMP (Hamidie, Yamada, Ishizawa, Saito, & Masuda, 2015). Furthermore, Japanese researchers have suggested that curcumin treatment regulated exercise-induced oxidative stress (Takahashi et al., 2014). Both results indicated that curcumin treatment have the ability to increase performance via regulated activity on mitochondria.

An increase in muscle mitochondrial content is one of the most important factors responsible for improved endurance-exercise performance in response to training. These typical doubling of muscle mitochondria that occurs during training plays an important role in the increase in maximal Oxygen uptake (VO_{2max}). The utilisation of this substrate has the ability to increase oxidation of fat relative to carbohydrate, increase lactate threshold, and fatigue resistance (Calvo et al., 2008; Davis, Carlstedt, Chen, Carmichael, & Murphy, 2010; Holloszy & Coyle, 1984). Indeed, these studies have shown that treatment with polyphenol quercetin increases VO_{2max} and endurance capacity.

Earlier studies have also reported on the correlation between the exercise and anti-inflammation and antioxidant properties of curcumin effects (McFarlin et al., 2016). However, there is no proven effect of curcumin treatment in increasing VO_{2max} on human. Therefore, this study examines first, effect of curcumin treatment on VO_{2max} and lactate threshold on humans, and second, effect of single bout curcumin treatment on mitochondrial marker COX IV expression. The findings point to the effectiveness of curcumin treatment combined with exercise in increasing COX-IV protein expression, VO_{2max} and lactate threshold and ultimately to improve sports performance.

MATERIALS AND METHODS

Animals Study

The study used 10-week male wistar old rats weighing 282-375g. The animals were exposed to a 12h light dark photoperiod. A standard diet and water were provided *ad libitum* (Oriental Yeast, Tokyo, Japan). The Ethics Committee on Animal Experimentation of Kanazawa University (Protocol #: AP-10187) had approved all procedures. The animals were randomly divided into two groups: the first group was fed 50mg curcumin /kg-BW/day with eTR while the second group =was fed 100mg 100 mg/kg-BW/day with eTR and eTR group. Low doses of curcumin (50 mg/kg-BW/day) or high doses of curcumin (100 mg/kg-BW/day) were dissolved in dimethyl sulfoxide (Sigma-Aldrich, New Jersey, USA). All animals were injected intraperitoneally with curcumin once daily two hours before the swimming exercise.

Exercise Training

The rats swam for two hours. They swam in four 30-min bouts separated by 5 min of rest. A weight that was equal to 2% of body weight was tied to the body of the rat after the first 30-min bout. All the rats swam in a barrel filled to a depth of 50 cm. The swimming area was 200 cm^2/rat.

Western Blotting. Animals were anesthetised (50 mg of pentobarbital sodium per 100 g of body weight). For biochemical studies, gastrocnemius (Gas) was quickly isolated. Then, the tissues were washed in ice-cold saline mixture. Next, the tissues were removed from the connective tissues and nerves, and then frozen in liquid nitrogen. Nuclear proteins were isolated using a modification of the protocol by Blough, Dineen and Esser (1999). Approximately 40 mg of muscle was homogenised in 500 µl of ice-cold buffer A (250 mmol/l sucrose, 10 mmol/l NaCl, 3 mmol/l $MgCl_2$, 1 mmol/l dithiothreitol (DTT) (Wako, Tokyo, Japan), 1 mmol/l PMSF (phenylmethylsulphonyl fluoride) (Wako, Tokyo, Japan), and 2 µl/40 mg tissue protease inhibitor cocktail (Wako, Tokyo, Japan), on ice for ~30 s. The homogenate was then spun in a centrifuge for 5 minutes at 500*g* at 4°C. The supernatant, representing a crude fraction, was used as the total tissue fraction in the immunoblots. The remaining pellet was resuspended in 500 µl of ice-cold buffer B (50 mmol/l Tris (Wako, Tokyo, Japan), pH 7.5, 1 mmol/l EDTA (Wako, Tokyo, Japan), 1 mmol/l EGTA (Wako, Tokyo, Japan), 1 mmol/l DTT (Wako, Tokyo, Japan), 50 mmol/l NaF (Wako, Tokyo, Japan), 5 mmol/l Na pyrophosphate (Wako, Tokyo, Japan), 50 mmol/l $MgCl_2$ (Wako, Tokyo, Japan), 10% glycerol (Wako, Tokyo, Japan), 1% Triton X-100 (Wako, Tokyo, Japan), 1 mmol/l PMSF (Wako, Tokyo, Japan), and 2 µl/40 mg tissue protease inhibitor cocktail and placed on ice for 10 minutes, with occasional mixing. The resuspended pellet was spun in a centrifuge for 5 minutes at 3,000*g* at 4°C. The supernatant, representing the nuclear fraction, was extracted and stored.

Western blot analysis was performed as previously described (Furuichi, Sugiura, Kato, Shimada, & Masuda, 2010). In brief, equal protein amounts (4.5 µg/lane) of samples were loaded onto SDS-PAGE gels 12.5% and proteins were transferred to a polyvinylidene fluoride (PVDF) membrane. The membrane was incubated in a blocking buffer. Then, with a COX-IV (1:1000 dilution, Abcam, Cambridge, England) A GAPDH (1:100 dilution, Abcam, Cambridge, England), it was then reacted with the secondary antibody. Finally, the signals were visualised by enhanced chemiluminescence (ECL) (GE Healthcare, Piscataway, NJ, USA). The signal intensity was quantified with imaging software (Image J, NIH, USA).

Human Study. Generally, randomized pretest-posttest comparison group was used as research design, but this study also used 2 x 2 crossover design in order to compare the effect of treatment within the sample. All samples received two treatments, then the results were compared. The study also avoided the variances of the sample which may affect to the results if it compared both the experiment and control group only.

Sample. Twelve students from the programme of sport science, Universitas Pendidikan Indonesia, were recruited for the study.

Instrument. Cardiopulmonary exercise test (Cosmed T 150, Rome, Italy) with a gas analysis method was utilised as the instrument to obtain the data.

Protocol. $_xVO_{2Ma}$ was measured using 12 km/h protocol, while LT was predicted using modified v-slope.

VO_{2Maa} Procedure. The Sample was divided into two groups randomly. Group 1, the experiment group, received aerobic exercise and curcumin as treatment. Group two, the control group only received aerobic exercise without curcumin. This study was divided into 2 periods, each period completed in six weeks. Curcumin (Borobudur, Semarang, Indonesia) was orally consumed in form of 2 capsules (@ 550 mg) per day during the treatment period. Aerobic exercise (jogging) was scheduled 4 times in a week during the period, using vigorous intensity (60-90% maximum heart rate) based on American College of Sport Medicine Guidelines (Heyward & Gibson, 2014). This study applied 4-weeks-wash-out-phase. In order to avoid the carry out effect from previous period in the next period, the group which previously was the experiment group, switched and then became the control group. At the beginning of each period, the sample performed underwent level of VO2Max and lactate threshold.

RESULTS

Animal Study

Figure 1 shows curcumin treatment together with exercise increases COX-IV expression. Values are means ± SD, n = 6. *: (asterisk shows significant difference from DMSO ($P < 0.05$)). CD 50 = curcumin 50 mg/kg-BW/day in DMSO, CD 100 = curcumin 100 mg/kg-BW/day in DMSO. These results indicate that curcumin treatment together with exercise increased the mitochondrial marker (COX-IV) in musculus gastrocnemius.

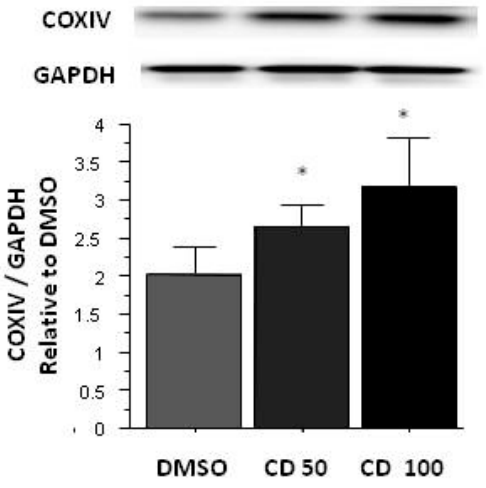

Figure 1. Curcumin treatment together with exercise increase COX-IV expression

Based on our hypothesis, single bout curcumin treatment may have the potential for an additive or synergistic effect on mitochondrial biogenesis. Content of mitochondrial in skeletal muscle was tested using COX subunit IV (COX-IV) protein expression. Single bout curcumin treatment together with exercise increase mitochondria marker COX-IV in skeletal muscle for low doses (50 mg/kg-BW/day. Furthermore, high doses (100 mg/kg-BW/day) curcumin treatment

indicated increased COX-IV protein expression 1.5-fold (Figure 1). This result indicated that curcumin has ability to be addictive effect of exercise to increase mitochondrial marker COX IV.

Figure 2 shows curcumin treatment increases VO_{2max}. Values are means ± SD n = 12. *: (Asterisk show significant difference from Pre- Test ($P < 0.05$)). These results indicated that 6 weeks curcumin treatment increased VO_{2max}.

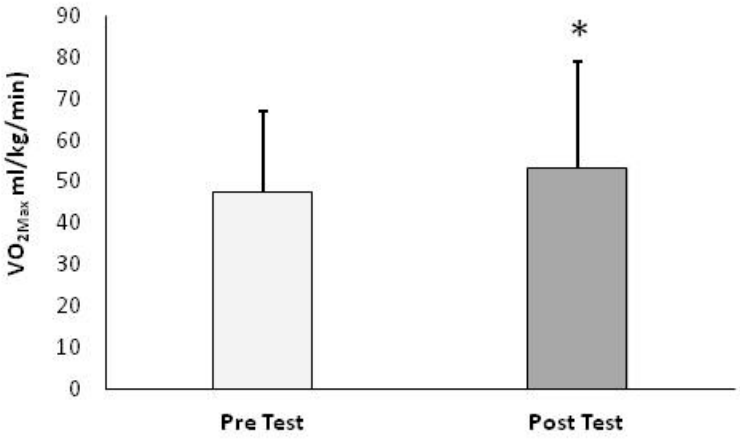

Figure 2. Curcumin treatment increases VO_{2max}

Curcumin Treatment Increase VO_{2max}

To know the effect of curcumin treatment effect on human and we interested to determine effect curcumin on 6 weeks aerobic exercise. Our result showed that means of VO2 max pretest is 47,44 ml/kg/min compare with VO_{2max} posttest is 53,41 ml/kg/min, our result indicated that 6 weeks curcumin treatment increase $VO_{2\,max}$ (Figure 2).

Figure 3 shows curcumin treatment increases lactate threshold. Values are means ± SD n = 12.*: Asterisk shows significant difference from Pre- Test ($P < 0.05$). These results indicated that 6 weeks curcumin treatment increased lactate threshold.

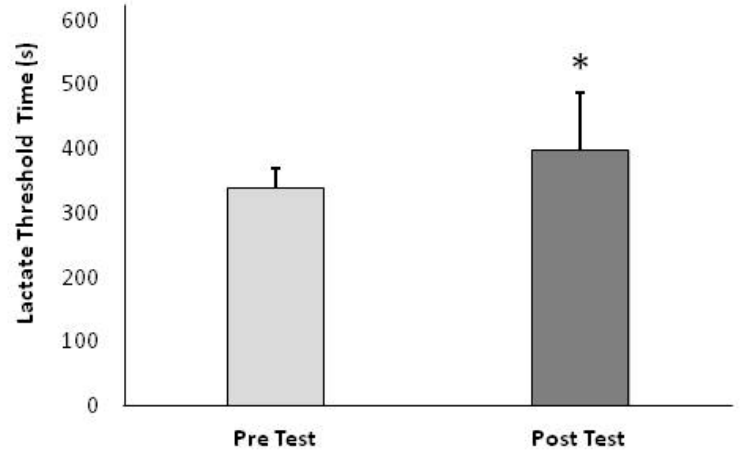

Figure 3. Curcumin treatment increases lactate thresholds

Curcumin Treatment Increases Lactate Threshold

We were interested to see the effects of 6 weeks curcumin treatment on lactate threshold. Our results showed that means of lactate threshold pretest is 338,75 while the second and curcumin treatment increase means of lactate threshold posttest be 398,66 second or increase around 59,91 second. This result indicated that curcumin has the ability to increase lactate threshold (Figure 3).

DISCUSSIONS

Similar with our previous study which indicated that curcumin treatment increases addictive effect of endurance training to increase mitochondrial marker COX-IV protein expression (Hamidie et al., 2015), the current study also showed that single bout curcumin treatment increases mitochondrial marker COX-IV protein expression. One study also indicated that curcumin has ability to inhibits PDE (Phosphodiesterase) which regulated cAMP to convert AMP (Abusnina, Keravis, & Lugnier, 2009). The result was support by our previous study which showed that curcumin increased cAMP. Based on this result we speculated that indeed curcumin has ability to increase mitochondrial biogenesis on cell environment. Furthermore, our result showed low dose curcumin treatment (50 mg/kg-BW) has significant effect to increase mitochondrial marker COX-IV (Figure 1).

Based on result above, the researchers determined the effect of curcumin treatment on human study, in particular, to know its effect on aerobic capacity, including VO_{2max} and lactate threshold. Several human studies evaluated effect of polyphenol on aerobic performance and also maximal oxygen capacity (VO_{2max}) (Davis et al., 2010) (Malaguti, Angeloni, & Hrelia, 2013). However, no study has determined effect of curcumin on maximal oxygen uptake on human. Previous studies have suggested that exercise induced oxidative stress in human cell (Santos et al., 2016) (Powers & Jackson, 2008). Under normal conditions, oxidative stress is biological pathway which has important roles in the body. Commonly, overproduction of reactive oxygen species (ROS) or a defect in endogenous antioxidant defence system, including enzymatic and non-enzymatic antioxidants, has been defined as oxidative stress (Yavari, Javadi, Mirmiran, & Bahadoran, 2015). In order to suit skeletal muscle, this conditions promote oxygen flux, which finally leads to increased production of ROS and free radicals (Kelkar, Subhadra, & Chengappa, 2008). Exercise increases the oxygen uptake 10 to 20 fold and pushes the generation of ROS and free radicals and correlation to attack biological macromolecules, especially DNA, polyunsaturated fatty acids, amino acids and active proteins (Lambertucci, Levada-Pires, Rossoni, Curi, & Pithon-Curi, 2007). During exercise, in metabolic rate and consumption of oxygen is increased due increases=d temperature and decreases in PH of cellular muscle which accelerate the production of free radicals. Debates are ongoing on the origins of the ROS production. However, the skeletal muscle has been thought as the major source of ROS generation (Cooper, Vollaard, Choueiri, & Wilson, 2002; Powers & Jackson, 2008).

The ROS activates muscles during exercise such as eosinophils, neutrophils, phospholipase A2 dependent processes, mitochondria, and some immune cells including macrophages, nicotinamide, xanthine oxidase adenine dinucleotide phosphate (NADPH) oxidase, and monocytes. (Cooper et al., 2002). Thus, mitochondria is shows the correlation of production

of ROS and free radical and indeed previous studies have suggested this (Zorov, Juhaszova, & Sollott, 2014). Some dietary antioxidants have been identified. These could contribute to protection against free radicals production and oxidative damage, induction of antioxidant signalling pathways, promotion of the endogenous antioxidant defence system, and attenuation of oxidative stress and consequently, prevention of related disorders. Turmeric is a spice from the rhizomes belonging to a ginger family (Zingiberaceae) component. This is called Curcuma longa. Curcumin was reported to have antitumor, antiarthritic, antioxidant, and anti-inflammatory properties. Previous studies have shown the anti-inflammatory properties y of curcumin and its ability to reduce muscle damage (McFarlin et al., 2016). Furthermore, curcumin as a supplement has strong antioxidant capacity (Landeros et al., 2017), even stronger than resveratrol (Aftab & Vieira, 2010). An increase in muscle mitochondrial content is one of the most important factors responsible for increasing endurance-exercise performance. These typical doubling of muscle mitochondria occurs during exercise. These plays an important role for increasing maximal Oxygen uptake (VO_{2max}). The utilisation of this substrate has ability to increase oxidation of fat relative to carbohydrate, fatigue resistance, and increase lactate threshold. Indeed, the current study has shown that curcumin increases protein mitochondrial marker COX-IV (Figure 1) in animal study. Our results prove that curcumin increase oxygen maximal capacity and lactate threshold (Figure 2 and 3). Based on above evidence we can surmise that curcumin potentially can increase human performance with its ability to be have strong antioxidant capacity and furthermore its ability to decrease mitochondrial ROS production.

CONCLUSION

In conclusion, single bout curcumin increases mitochondrial marker COX-IV protein expression on animals study; furthermore, oral consumption of curcumin oral at 1,1 gram / days for 6 weeks has the potential to increase maximal oxygen uptake VO_{2max} and lactate threshold. Taken together, the study suggests that curcumin can increase human sports performance through its ability to increase $VO_{2max}$and lactate threshold.

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