

Conference Paper

Antifatigue Activity of *Citrullus (Citrullus lanatus)* Genus Plant: A Review

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Abstract

Watermelon (*Citrullus lanatus*, the family of cucumber or *Cucurbitaceae*) is a vine that originates from a half-desert region in southern Africa. This plant is still close to pumpkin (*Cucurbitaceae*), melon (*Cucumis melo*) and cucumber (*Cucumis sativus*). Empirically this plant is useful for reducing fatigue. In addition, its health benefits can reduce fever, smooth urine, antihypertension, increase body immunity, etc. Watermelon is rich of electrolyte content, so that sweat, body fluids that have been lost during vomiting or during activity will be replaced by watermelon juice taken. Nearly 92% of the watermelon content is water, and the content of folate is 3 mcg / 100 g of watermelon which is needed during the early trimester of pregnancy for the formation of the brain and fetal nerves. Antioxidants and vitamin C help the body maintain health, can launch and stimulate urine, be good for the kidneys, reduce fever and prevent thrush, ward off carcinogenic free radicals because of its lycopene content. The purpose of this paper is to examine the anti fatigue activity of the citrullus genus plant bases on scientific data. The method used in this study is the literature's study. Searching for scientific data is done online (in the PubMed database, Science Direct and Google Scholar) and various books (Indonesian Herbal Pharmacopoeia and PROSEA).

Keywords: citrullus genus, anti fatigue Activity, invivo, invitro

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Received: 18 January 2019
Accepted: 26 February 2019
Published: 12 March 2019

Publishing services provided by
Knowledge E

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Selection and Peer-review under the responsibility of the 1st PANIHC Conference Committee.

1. Introduction

Fatigue is a normal and common thing it means a process of decreasing tolerance for physical work. The cause is very specific and depends on the type of work. It can be viewed from the anatomical aspects like central nervous system, neuromuscular and skeletal fatigue, and from the functional aspects like electrochemical fatigue, metabolic, reduced energy substrate, hyper / hypothermia and dehydration [1]

The emersion of muscle fatigue can be caused of several reasons, such as 1) The accumulation of lactic acid, 2) the result of free H⁺ accumulation from the results of ATP hydrolysis and anaerobic glycolysis in muscles that have exercised. The one and

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only energy source that be able directly used for muscle activity is ATP which must be available continuously so that muscle contraction activity can continue. In muscle tissue, available ATP is limited, however, there are three pathways that can supply ATP as needed during muscle contraction, namely system phosphagen, Anaerobic glycolysis and oxidative phosphorylation [1].

Natural products have proven that be a beneficial in the development of anti-fatigue drugs, especially from plant, namely watermelon (*citrullus lanatus*). Research was conducted in Spain in 2013, by using watermelon as 500 ml of juice with citrulline content which was known to be 1.17 grams before exercise was able to reduce anaerobic fatigue in athletes by 13-18% [2]. The study of Sirait, et al. (2015) was about the effect of giving 500 ml of watermelon juice to reduce muscle fatigue in weight lifters and reduce Delayed Onset Muscle Soreness Syndrome (DOMS). Other study was conducted on experimental rat which given 250 mg of citrulline supplementation before exercise for 7 days could suppress the increase / accumulation of ammonia levels in the blood and delay fatigue from occurring [3]

This *citrullus* genus is also useful for reducing fever, smoothing urine, antihypertensive, anti-fatigue and maintaining health [4]. All parts of this plant also have good potential for health. Utilizing this watermelon skin waste for diet and treatment can help health and protect the environment. Saponins have a bitter taste, can be related to pharmacological effects including hemolytic, bone health, lower blood cholesterol levels, cancer and stimulation of the body's immunity. Alkaloids can be as analgesic, antispasmodic and anti bacterial. Tannin is higher in watermelon than watermelon seeds. Tannin can be as an antimicrobial ingredient, also for treatment which includes inflammation, liver injury, kidney problems, arthrosclerosis, hypertension, gastric problems [5]. Emmanuel Research on 2014 stated that *citrullus lanatus* seed extract showed the potential to repair liver damage in albino's rat [6]. Besides that the effect of watermelon juice suppresses gastric acid secretion, for patients with gastritis and pregnant women whose emesis gravidarum is good news that watermelons are able to neutralize stomach acid levels thereby reducing the effects of bloating and nausea [7]. Research M. Pilian on 2014 stated that watermelon contained fiber and starch high so it was good for digestion and prevents constipation and other digestive complaints [8]

The chemical content of the *citrullus* genus consists of Citrulline that the most non-essential amino acid group contained in watermelon which is equal to 160 mg of citrulline in 100 grams of watermelon [2]. Citrulline supplementation helps enzymes involved in the *pathway glycogenolysis* process (breakdown of glycogen) and glycolysis (the process of glucose conversion to ATP) in *rat skeletal muscle*, which converts exchange shifts from

muscle aerobic energy metabolism (fatty acid based) to anaerobic. Besides that, the production of ATP from the Aerobic pathway helps the formation of energy to improve performance during exercise / activity. Citrulline is very effective in increasing muscle ATP, and increasing muscle strength to 23% with intake of 3g / kg per day (equivalent to 480 mg / kg in humans) [9].

A number of animal proteins are sources of arginine and citrulline such as dairy products; milk and yogurt, poultry, beef, and seafood, as well as vegetable proteins such as grains, vegetables, beans, nuts and seeds are also a source of protein and sources of citrulline and arginine, but citrulline is found in very small amounts in this type of food [10]. However, the very large content of citrullin is found in this *Citrullus lanatus* plant.

This paper aims to examine the role of the *Citrullus* genus as antifatigue based on scientific data collected.

2. Methodology

This study used a literature study method. Searching of scientific data was done from online sources and various books. Online sources were from in the *PubMed database*, *Science Direct* and *Google Scholar* using the keywords "*Citrullus*", "*Citrullus Lanatus*", "*Citrullus Lanatus + antifatique*" "*Citrullus Lanatus + fatigue*" "*Citrullus Lanatus + invivo*". There were no language and time limits for the cited article. Scientific articles from online databases included in the inclusion criteria are original research and used in vivo methods to test anticircular activity. Searching on books was done on Indonesian Herbal Pharmacopoeia (official literature) and Plant Resources of South-East Asia (PROSEA)

3. Results

3.1. What is the fatigue?

Fatigue is a common condition found in individuals that has a negative impact on individual performance, family life, and social relationships. Fatigue is a physiological phenomenon, a process of decreasing tolerance to physical work. The cause is very specific depending on the characteristics of the work. The causes of fatigue can be viewed from the anatomical aspects of central nervous system, neuromuscular and skeletal muscle fatigue, and from the functional aspects of electrochemical, metabolic fatigue, reduced energy substrate, hyper / hypothermia and dehydration [1].

Muscle fatigue is defined as a failure of the muscle to maintain or produce the strength needed in or the loss of the ability of the muscle to contract for producing the strength. Fatigue is caused by the disruption of homeostasis. This homeostatic disorder is caused by one or a combination of things such as the depletion of energy (energy), accumulation of metabolites consisting of lactates including H⁺ ions, organic phosphorus (Pi), adenosine diphosphate (ADP), inosine monophosphate (IMP) and intermediate substances from glycolysis, Disorders of Electrolyte Balance in Muscles, Disorders of Myosin-Actin Adhesion-Release Mechanism, Maximum Physical Activity, Source of Energy, Aerobic and Anaerobic Metabolism [12, 13]

Biochemical parameters of fatigue can be seen from the value of lactate levels in the blood, normal values Lactate levels in healthy individuals on 0.5 - 1 mmol / L [14]. Hyperlactatemia occurs during lactate on > 4 mmol / L [14].

Lactate is produced by many tissues in the human body and high levels of lactate are found in muscles. On normal conditions, lactate is quickly cleared by the liver with a small amount of additional cleansing by the kidneys. In aerobic conditions, pyruvate is produced through glycolysis and then enters the Krebs cycle, mostly through lactate production. In anaerobic conditions, lactate is the end product of glycolysis and returns to the Cori cycle as a substrate for gluconeogenesis.

In a tired condition, it occurs cumulation lactate in the muscles, when the intensity of physical activity is high, the body will produce energy quickly. Energy can be formed through aerobic and anaerobic metabolic pathways. Lactate production is the final glycolysis pathway where pyruvate is drawn into a form of energy. Lactate levels can increase by 10 fold in high physical activity but the increase can be in a short time depending on the supply of oxygen to the tissue. One consequence in some of these tissues will be forming lactic acid during this severe physical activity. In the condition of a muscle contraction (dysfunction), the ability to restore lactate becomes worse / not good, and the results of other metabolites will accumulate in the muscles. In this condition, the strength of muscle contraction will decrease and become easily tired [16]

3.2. What is watermelon?

It is a herbaceous plant that grows with name of *citrullus vulgaris* including into family of pumpkins (*cucurbitaceae*) which contains a lot of water. This shape is round and Spherical to rounded, large, varying in length from 20-30 cm, diameter 15-20 cm, with weights ranging from 4 kg to 20 kg. The skin of the fruit is thick and fleshy, slippery, the colors are vary like dark green, white yellow, or light green with white stripes. The flesh

of the fruit is red, pink (pink), orange (orange), yellow, and even white. Seed shape is elongated, flat, black, white, yellow, or reddish brown [4, 31]

3.3. Benefits of watermelon

In southern Africa, besides the flesh of the fruit consumed, leaves and young watermelon are also consumed as vegetables, as well as the seeds have beneficial nutritional value for health⁴ The benefits of watermelon are as follows [2, 17]

1. It can make full
2. Water and potassium can reduce blood pressure
3. Anti oxidants and vitamin C helps the body maintain health
4. It can stimulates urine that good for kidneys
5. It can reduce fever and prevent thrush
6. Lycopene can ward off carcinogenic free radicals

Red flesh of watermelon is richer in lycopene (an anti-oxidant compound which is a red pigment in fruit) while yellow watermelon is not. But the advantages of yellow watermelons are more rich in vitamins A and C more than red watermelons [8].

3.4. Nutritional content in watermelon

Watermelon is rich of citrulline, antioxidants, vitamins and other minerals in the flesh and skin. Citrulline is an amino acid formed in the urea cycle through condensation of ornithine and carbamoylphosphate that occurs in mitochondrial hepatocytes and enterocytes

3.5. Amino acid content in watermelon

Amino acid content in watermelon in 1 gram of wet watermelon weight (in mmol / gr wet weight) is: Phenylalanine 1.25; Histidine 0.24; Tryptophan 0.35; Lysine 0.82; Ornithine 0.32; Arginine 11.36; Aspartate Acid 0.97; Threonine 0.74; Serine 1.05; Glutamine 3.86; Glutamic Acid 1.38; Citrulline 23.68; Alanine 1.15; Valine 0.17; Isoleucine 1.24; Leucine 0.24 [18, 19]

TABLE 1: Watermelon (*Citrullus lanatus*), fresh, Nutritive Value per 100 g.

Principle	Nutrient value	Percentage of RDA
Energy	30 Kcal	1,5 %
Carbohydrate	7,6 g	6 %
Protein	0,6 g	1 %
Total fat	0,15 g	0,5 %
Cholesterol	0 mg	0 %
Dietary Fiber	0,4 g	1 %
Vitamin		
Folates	3 mcg	1 %
Niacin	0,178 mg	1 %
Panhotenic Acid	0,221 mg	4,5 %
Pyridoxine	0,045 mg	3,5 %
Thiamin	0,033 mg	3 %
Vitamin A	569 IU	19%
Vitamin C	8,1 mg	13,5 %
Vitamin E	0,05 mg	0,5 %
Electrolytes		
Sodium	1 mg	0 %
Potassium	112 mg	2,5 %
Mineral		
Calsium	7 mg	0,7 %
Copper	42 mcg	4,5 %
Iron	0,24 mg	3 %
Magnesium	10 mg	2,5 %
Manganese	0,038 mg	1,5 %
Zinc	0,10 mg	1 %
Phyto-Nutrients		
Carotene- β	303 mcg	-
Crypto-xanthine- β	78 mcg	-
Lutein-zeaxanthine	8 mcg	-
Lycopene	4532 mcg	-

(Source: USDA National Nutrient data base)

3.6. What is Citrulline?

Citrulline is a non-essential amino acid precursor of arginine and indirectly is a precursor of nitric oxide (NO), which is a vasodilator and increases mitochondrial respiration 20. Citrulline is an amino acid formed in the urea cycle through ornithine and *carbamoylphosphate* condensation that occurs in mitochondrial hepatocytes and enterocytes. Citrulline consists of 3 important metabolic pathways. Ammonia transformation into urea in the liver, synthesis of de novo from glutamine to arginine in the intestine

and kidneys, and synthesis of nitric oxide (NO). Two of the first pathway use the same enzyme, but the method of setting is different [19].

3.7. The role of Citrulline in the human body in overcoming the fatigue

Citrulline is an amino acid formed in the urea cycle through condensation of ornithine and *carbamoylphosphate* that occurs in mitochondrial hepatocytes and enterocytes. Now it is known that the role of enzymes that react to the synthesis of citrulline into arginine in endothelial cells is a group of enzymes called *nitric oxide synthases*. Citrulline is formed for the synthesis of arginine in almost all tissues and in the liver urea cycle. Citrulline can be found in plasma, and body physiological fluids such as urine, cerebrospinal fluid, amniotic fluid and sweat. The level describes the enzyme activity associated in citrulline synthesis and the use of citrulline in various networks [19].

The role of citrulline is as a precursor to the formation of NO (nitric oxide), where NO is directly involved in regulation of insulin secretion by causing membrane depolarization as well as an increase in intracellular Ca²⁺ concentration. NO inside the cell will cause intracellular K⁺ retention that causes membrane depolarization, then open Ca²⁺ channel so that Ca²⁺ influx increases, insulin secretion will occur, then stimulate glycogenesis in the liver thereby reducing blood glucose levels 21, and by increasing binding between insulin with insulin receptors which subsequently causes GLUT 4 translocation on the cell membrane surface which results in more optimal transport of glucose 22 Besides that Citrulline which is able to increase NO levels in the body will increase blood circulation, the effect can make the body more relaxed. Watermelon has Citrulline which is useful to make blood vessels relax and facilitate blood flow 23. Watermelon has high amounts of potassium and water content. The water and potassium content can help neutralize blood pressure. In addition, the benefits of watermelon can also strengthen the performance of the heart and strengthen the body's defense system because watermelon also contains antioxidants and vitamin C [2].

Citrulline supplementation helps enzymes involved in the process of *pathway glycogenolysis* (glycogen breakdown) and glycolysis (the glucose conversion process into ATP) in *rat skeletal muscle*, which convert exchange shifts from *muscle aerobic energy metabolism (fatty acid based)* to *anaerobic*. Besides that, the production of ATP from the Aerobic pathway helps the formation of energy to improve *performance* during exercise / activity. Citrulline is very effective in increasing muscle ATP, and increasing

muscle strength to 23% with intake of 3g / kg per day (equivalent to 480 mg / kg in humans [23].

Giving Citrulline before exercise can delay anaerobic fatigue experienced by athletes because Citrulline is able to reduce the accumulation or accumulation of lactic acid which is a by-product of anaerobic glycolysis. Citrulline accelerates decomposition of lactate in the muscles so that lactate can be metabolized again in the liver and kidneys to form energy through the cory cycle. Citrulline is also capable of detoxifying ammonia, which is one component of the urea cycle in the liver along with other amino acids such as arginine and ornitine. Ammonia in the blood is a product that accumulates in the muscle when Adenosine Monophospat (AMP) is deaminated during the formation of Adenosine Triphospat (ATP). Ammonia activates fosfo fructokinase which helps with lactate production. Because ammonia levels increase, lactate levels will also increase so that fatigue occurs [24]. Anaerobic fatigue can be reduced by consuming watermelon, because it contains citrulline. Citrulline is the most non-essential amino acid group contained in it which is equal to 160 mg of citrulline in 100 grams of it ². Citrulline is very effective in increasing muscle ATP, and increasing muscle strength to 23% with intake of 3 g / kg per day (equivalent 480 mg / kg in humans) [19].

3.8. The study of using watermelon as an antifatigue

TABLE 2: The Study of Using Watermelon as an Antifatigue.

Study	Sample	Dosage	Assessment	Research Result	Type	Researcher
Quasy experiment (2 group)	37 people / groups of Maternity's women	500 ml of watermelon juice	Identifying lactate levels	The treatment group had lower levels of lactate than the control group	Proceeding ICEST 2017	Wahyuni, dkk, 2017 ²⁶
Quasy experiment (2 group)	20 people / groups of weight lifters	500 ml of watermelon juice	Evaluating fatigue levels and DOMS symptoms	The treatment group had lower fatigue levels than the control group, and had a lower DOMS symptom	Thesis	Sirait, et.al, 2015 ³
Quasy experiment (2 group)	20 people / groups of soccer athletes	500 ml of watermelon juice	Evaluating fatigue level	The treatment group had lower fatigue level than the control group,	Thesis	Hasanah, 2014 ²⁷
invitro study of l-citrulline absorption in the intestine	7 athletes	500 ml of watermelon juice (1.17 mg of sitrullin)	Identifying potential watermelon juice as a functional drink for athletes	Giving watermelon juice before exercise can reduce anaerobic fatigue of athletes about 13-18%. And watermelon juice helped reducing heart rate and muscle pain after 24 hours.	Journal	Tarazona Diaz, et.al, 2013 ²

Study	Sample	Dosage	Assessment	Research Result	Type	Researcher
in vivo study of random crossover	19 athletes with 2x random treatment	Giving: - Watermelon juice enriched of pomegranate	Identifying the effects of L-Citrullin Juice with watermelon juice enriched with pomegranates on the physical endurance of athletes during Physical Exercise	Giving watermelon juice maintained muscle strength and avoids muscle damage, had significant strength during exercise and decreased muscle aches and pains after exercise.	Journal	Martínez, et.al, 2017 ²⁰
Article review	Athlete	L-citrulline supplement and watermelon	analyzing the potential of L-citrulline supplement and watermelon toward vascular benefits at rest and during exercise.	Decreasing blood pressure at rest and improving exercise performance in young healthy adults, with L-citrulline supplementation / watermelon	Journal	Figüeroa A, et.al, 2017 ²⁸
random crossover research, double-blind.	25 older adults (13 women and 12 men)	Giving; Citrulline (6 g of day 1) and placebo (maltodextrin) before and after 14 days	Identifying the effect of short-term supplementation of l-citrulline to increase l-arginine in improving blood flow and peripheral dilatation responses to exercise in older adults	l-Citrulline increased femoral blood flow by 11% and vascular conductance by 14% during lower limb exercise in the older male group and had implications for changing muscle metabolism which can lead to increase exercise tolerance in older men but it was not significant in the group of old women	Journal	Gonzalez et.al, 2017 ²⁹
study cross-over 2-way cross-random over double-blind	22 men trained in a 4 km long cycling trial	consuming 2.4 g / day of L-citrulline or placebo orally for 7 days. On day 8 they consumed 2.4 g of L-citrulline or placebo in 1 hour before the 4 km trial	Identifying the effects of oral l-citrulline supplementation in reducing the time needed by athletes to complete the ergometer cycle exercise trial	L-Citrulline supplementation significantly increased plasma L-arginine levels and reduced the resolution of the ergometer cycle by 1.5% (p <0.05) compared to placebo. In addition, L-Citrulline significantly improved the perception of muscle fatigue	Journal	Takashi, 2016 ²³

Study	Sample	Dosage	Assessment	Research Result	Type	Researcher
random crossover study 75 km cycling trial	20 people	consuming 280 mL / day of pure watermelon and drink carbohydrates 0.2 gm / kg or 6% carbohydrates every 15 minutes during the trial	Knowing the Comparison of Watermelon and Carbohydrate Drinks to Changes in Exercise Results, namely in Systemic Inflammation, Immune Disfunction, and Plasma Capacity Antioxidants	Exercise performance was not different between the trials of carbohydrate drinks and watermelon (p> 0.05), however, the level of effort felt was greater during the watermelon trial (p> 0.05). And it produced the same increase in blood glucose, but a higher increase in plasma antioxidant capacity post-exercise in l-citrulline, l-arginine, and total nitrate (all p <0.05)	Journal	R. Andrew, 2016 ³⁰
a placebo arginine crossover study	10 healthy adult men completed moderate and severe intensity cycling exercises on days 6 and 7	Supplement: of 7 days with Placebo Arginine (6 g / day), and Citrulline (6 g / day).	comparing the effect of l-citrulline (Cit) and l-arginine (Arg) supplementation on biomarkers of nitric oxide (NO), pulmonary O ₂ absorption kinetics (V (o ₂), and exercise performance	the results showed that l-citrulline supplementation but not Arginine supplementation could improve blood, V _{o2} kinetics, and exercise performance in healthy adults.	Journal	Bailey SJ 2015 ³¹
Clinical test with randomizati	22 people / groups of women maternity	1 gram of Sitruline malate	Identifying lactate levels	The treatment group had lower levels of lactate than the control group	Journal	Lestari, et.al, 2008 ²⁵

4. Conclusion

There were 11 articles that have been described which talked about the role of the citrullus genus plants which had anti-fatigue activity and be able to improve the performance of athletes and individuals, both in vitro and invivo getting easily.

Conflict of Interest

The writer had no problems or attachments to any party in this study.

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