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Research Article

Effect of Watermelon (Citrullus Lanatus) Extracts on Testosterone Levels a Systematic Review and Meta-Analysis

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Abstract

Testosterone levels have been declining 1% every year in the world. Natural alternatives have recently been sought through plants, teas and natural extracts that may aid in pharmacological treatments that usually have several adverse symptoms. One fruit that has aroused interest in this area is the watermelon (Citrullus lanatus), which appears to promote increased testosterone levels. This study was carried out by searching the main databases available through the keywords "Citrullus lanatus" and "testosterone". After the exclusion of articles that did not meet the inclusion criteria, 6 articles were analyzed. Of these, all presented higher levels of serum testosterone after the period of treatment with alcoholic extract of different parts of the fruit. The concentration predominantly used in the studies was 200 mg/kg, and although the effect is dose dependent, at 30 mg/kg of body weight there already appears to be an effect. The letal dose of consumption of the extracts was found at concentrations higher than 2 g/kg. More studies should be done using forms of non-alcoholic extraction. Since all studies were performed on animals, supplementation in humans is necessary to evaluate the applicability of this substances, and the effects on human physiology.

Keywords: Citrullus lanatus; Testosterone; Meta-analysis

Introduction

On the meeting about the ambient challenges of the reproductive health in 2007, it was reported a global decrease in the testosterone levels of 1% each year during the last 50 years, leading to a worsening in the global male health and high rates of infertility. Currently one in each 6 men could be considered infertile, these scenario is more common in the urban area [1]. Testosterone is formed in the Leydig cells at the testicles, rates of normality for a healthy men ranges between 300 and 900 ng/dL. Testosterone finds receptors in practically all tissues, and promotes diverse effects in the development of the masculine sexual characters, among which, one of most important consists of the development of muscle and strength. Due to this effect, frequently, this hormone or its synthetic analogues are used by athletes to improve its muscular performance [2]. The consumption of synthetic anabolic steroids is related to a series of adverse effects to its chronic use, among which cardiovascular alterations (arrhythmia, dislipidemia, thrombosis, hypertension and myocardium hypertrophy leading to ventricular insufficiency), psychological alterations (impulsive and aggressive behavior, anxiety, sleeplessness and eventually personality disorders), testicular atrophy, hepatic peliosis, acne, folliculitis and renal injury [3]. Therefore, it comes of great importance the study of natural plants and extracts that are capable to increase testosterone levels without presenting deleterious effects.

The watermelon (Citrullus lanatus) is a tropical fruit from a ground plant of same name from the Curcubitaceae family [4]. It presents great economic importance, being produced in the whole world and is very appreciated by its nutritional value, refreshment and low caloric value [5]. The interior part of the watermelon is generally colored and presents great amounts of beta carotene and lycopene which possesses recognized antioxidantt activity. Its extracts are used for diverse purposes as antihypertensive, anti-inflammatory and antimicrobials [6]. Each part of the watermelon possesses distinct characteristics on its composition. The seeds for example are excellent protein sources, being able to be used in the feeding for preparations and alimentary plans [7]. The extracted oil of the seeds is composed mainly by linoleic acid, palmitic acid and estearic acid. It also contains phytochemicals as the lycopene, saponins, flavonoids alkalis, oxalate and tannin [8].

Materials and Methods

Researches were performed in the databases Scielo, Web of Science, Google scholar, OVID, PubMed, SCOPUS and BVS at July, 2019, through the key words "Citrullus lanatus" and "testosterone". A total of 178 articles were found, of which 27 were selected through the title. At this point, all articles in english or portuguese were selected if the title showed some correlation with both keywords used. Of the selected articles, 1 could not be accessed for complete reading and was excluded. After the reading, 8 were excluded due to the experimental model that did not fit the election criteria, 3 didn't present or didn't control of the dosage of supplied C. lanatus, and 6 articles didn't detailed the dosage of testosterone used. Other 3 articles were removed for repetition in the different databases. Figure 1 presents a summary of the research processes and selection. The inclusion criteria for the articles to our meta-analysis were: be written in English or portuguese; use only extracts of Citrullus lanatus at the

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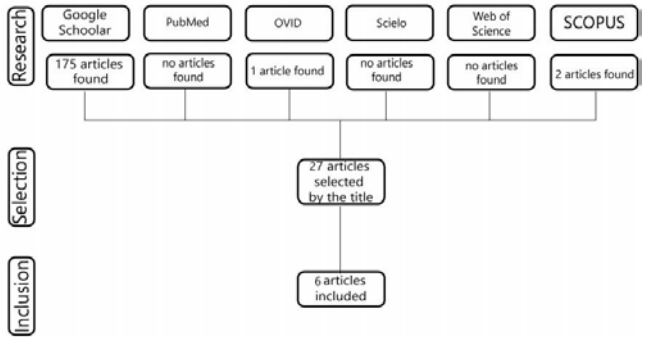

Figure 1: Summary of the selection process.

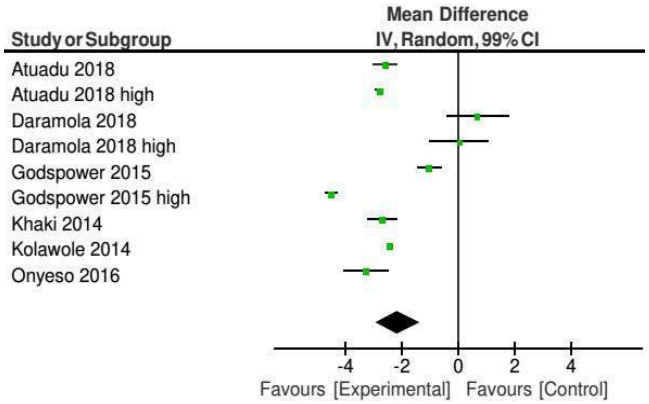

Figure 2: Meta analysis.

treatment; specify the concentrations of the solutions used; specify the testosterone levels before and after treatment, or present a control group exposed to the same conditions as the treated group so the comparison between them were possible. Give the solution exclusively orally to the subjects. The risk of bias of the six studies included, were scored through QUADAS-2 questionaire and showed low risk of bias at all parameters (table not shown). The meta- analysis was analyzed using the software Review Manager 5.3 (2014).

Results

The six articles that fitted the inclusion criteria and were analyzed in this review were longitudinal studies, with periods of treatment varying from 21 to 35 days, they all used male rats. Three articles used extracts from the seeds [7,9,10], two used the extract from the rind [11,12], and one used the extract from the pulp [13]. The researchers in the studies measured the testosterone levels before and after the treatment period, the treated group was compared with the control group, in order to observe the effect of the treatment. The studies that treated animals with different concentrations were considered as different studies to the meta analysis (Figure 2) to consider the importance of the dosage. Presents a summary of the data of these studies (Table 1).

Discussion

In the study of Khaki et al. [9], the administration of an alcoholic extract from the C. lanatus seeds at a concentration of 30 mg/kg, daily, during 28 days was able to significantly increase the total serum

Table 1: Summary of the data of the 6 articles included in the meta-analysis.

References	Animal Model	Parts Used	Dose	Treatment	n
Khaki A, et al. [9]	male rats	Hydro Alcoholic Extract Seeds	30 mg/kg	28 days	10
Onyeso GI, et al. [10]	diabetic male rats	Hydro methanolic Extract Seeds	200 mg/kg	21 days	5
Godspower O, et al. [7]	male rats	Hydro Alcoholic Extract Seeds	100 mg/kg (Low Dose) 200 mg/kg (High Dose)	30 days	5
Kolawole TA. et al. [12]	male rats	Methanolic Extract Rind	200 mg/kg	35 days	5
Atuadu VO, et al. [11]	male rats	alcoholic Extract Rind	100 mg/kg 1000 mg/kg	21 days	6
Daramola OO, et al. [13].	Male rats	Aqueous Extract pulp	100 mg/kg (Low Dose) 200 mg/kg (High Dose)	30 days	5

levels of testosterone of adult male rats. On an experiment published by Godspower et al. [7], 20 adult male rats were divided into four groups: a control group that didn't receive any treatment, a group that received 100 mg/kg of a methanolic seed extract, a group that received 200 mg/kg of this methanolic extraction, both treated groups received also 2.25 mg/kg of lead acetate to stimuli oxidative stress. The last group received lead acetate only. All groups were treated for 30 days. This study shows a significantly impact on the values of serum testosterone when the animals were exposed to a high oxidative situation. On the other hand, an increase in the testosterone levels was observed in the treated groups. Demonstrating not only that the beneficial effect of the seeds extract consumption occurs via antioxidant capacity, but also demonstrated a concentration related effect, observing a greater response to the group that received 200 mg/kg in comparison with the group receiving 100 mg/kg. Kolawole et al., [12] also used the lead acetate at a dose of 2.25 mg/kg to stimuli oxidative stress on the animals, and observed a decrease of 50% at the testosterone levels of the animals receiving lead acetate compared to the control group. The treatment with 200 mg/kg of C. lanatus rind was able to increase testosterone above the levels observed at the control group and also increased significantly the testosterone levels of the lead acetate group, confirming the results showed by Godspower et al., [7].

At another study using rind extract, [11] were tested 500 mg/kg and 1000mg/kg in rats. They showed values of testosterone almost 10x higher compared to the control group in both treated groups, and there was no difference between groups. We can speculate that migth be a saturation point were higher concentration protocols, does not correspond to higher testosterone levels. Kolawole et al., [12] tested what would be the letal dose of the rind extract consumption and determined that this value should be higher than 2000 mg/kg. So even if the high value used by Atuadu et al., [11], 1000 mg/kg, is apparently a safe dose it might be unnecessary. At a similar study the animals received one single dose of an injection with alloxan at 150 mg/kg to induce diabetes. The hidroalcoholic extract of C. lanatus seeds was administered at a dose of 200 mg/kg during three weeks and was capable to reduce the glicemia of the diabetic animals and to raise the

testosterone levels [10]. Testing a different extration, Daramola et al., [13] used an aqueus extract of the pulp of the fruit. His group treated the animals for 30 days with 100 mg/kg and 200 mg/kg and observed no statistical difference between groups. So it is possible that the extraction protocol influences the results on testosterone levels, given that even been observed the antioxidant effect, the expected rise on testosterone levels was not present. It could also be explained by the lower levels of antioxidants found on the pulp of the fruit, as showed by [14] in her master's degree thesis. She compared the antioxidant activity and influence on testosterone levels on rats treating them with an alcoholic extraction of different parts of the fruit. She showed that the animals treated with pulp extractions presented the lower increases on testosterone levels, and the animals treated with an extraction of the seeds showed the greatest increase compared to the other groups.

In general, the authors had credited this hormonal increase to the antioxidant activity of the components of the fruit, as the flavonoids and the minerals that would have acted in the testicles stimulating the testosterone production. The Citrullus lanatus extractions of seeds and rind were able to increase serum testosterone levels on healthy animals treated or restored the levels on animals under oxidative stress induced treatments. Although we still have just a few studies about on this area, the results presented here seems promising, as after an analysis of the data showed in this review, it is possible to affirm that the alcoholic extract of Citrullus lanatus seeds and rind was capable to increase the levels of serum testosterone in healthy rats, or reestablish the levels of animals under induced stress treatments. This effect seems to be dose dependent reaching a plato stage at higher concentrations 500 mg/kg or higher doses doesn't seem to cause higher effect. It is possible that doses higher than 2 g/kg have a letal effect, although the mechanisms to that negative effect should be investigated. More studies are necessary to determine the most effective treatment dosage and to describe the molecular pathways that results on this effect of Citrullus lanatus components on serum testosterone levels.

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