



Erectogenic Effect of Thyme (*Thymus vulgaris*) Extract in Normal and 5-Fluorouracil induced Oxidative Stressed Adult Male Wistar Rats

O. Abimbola Akintemi^{a*}, R. O. Babalola^a and S. O. Babatunde^a

^a Department of Science Laboratory Technology, Rufus Giwa Polytechnic, Owo, Ondo State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Author OAA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author ROB managed the analyses of the study. Author SOB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

This study determined the effect of oral administration of aqueous extract from Thyme (*Thymus vulgaris*) extract (TVE) on the antioxidant status and activity of some penile function enzymes (acetylcholinesterase (AChE), phosphodiesterase-5 (PDE-5), adenosine diaminase (ADA), and arginase) activity in normal and 5- Fluorouracil- induced oxidative stressed rats. Sixty adult Wister rats (210-225g) were divided into ten (10) groups (n=6): Group 1: received oral administration of normal saline (NC), Group 2: received 100 mg/kg of thyme extract orally (TE 100 mg/kg), Group 3: received 200 mg/kg of thyme extract orally (TE 200 mg/kg), rats in group four were treated with 400 mg/kg of thyme extract orally (TE 400 mg/kg), Those in group 5: received 25 mg/kg of Vitamin C orally, while group 6 to 10 were induced with 150 mg/kg of 5-Fluorouracil solution (5-FLU, i.p), but group 7-10 were treated 100 mg/kg, 200 mg/kg, 400 mg/kg and Vitamin C (25mg/kg), respectively. After fourteen (14) days of treatment, the rats were sacrificed and the penile tissue was carefully isolated and prepared into homogenate, which was used for antioxidant and enzymes biochemical analysis. The result revealed that i.p induction of 5-FLU caused a significant increase in malondialdehyde level, as well as AChE, ADA, PDE-5 and arginase activities with concomitant

*Corresponding author: E-mail: bimbite4real@yahoo.ca;

decrease in thiol level when compared to control rats. However, the administration of TVE was found to reverse the effect of 5-FLU. The TVE was also found to reduce the MDA level and all the enzyme activities, but boosted the thiol level in the normal rats when compared to control rats. Interestingly the effect of the TVE was found dose-dependently, and 400 mg/kg TVE was found to be more potent among all the doses used in both normal and 5-FLU-induced oxidative stress rats.

Keywords: *Erectile dysfunction; thymus vulgaris; fluorouracil; penile enzymes.*

1. INTRODUCTION

5-Fluorouracil (5-FLU) has been regarded as one of the most frequently prescribed chemotherapeutic drugs for the adjuvant and palliative treatment of patients with cancers of the gastrointestinal tract, breast, head and neck [1] comparable to other chemotherapeutic agents, 5-FLU generates excess reactive oxygen species (ROS) and overpowers the antioxidant defense mechanism [2]. ROS interaction with cellular biomolecules including lipids, proteins and DNA, and alters the essential cellular functions. Thus, ROS caused mutations, result into malignant transformation and the development of cancer [3]. The use of cancer drug is allied with cognitive impairment and possibly called chemobrain. Chemobrain results in impaired learning, memory and altered processing speed. Thus, could be as a result of decline in proliferating new brain cells and decreased myelination of axon. Biomolecules structural changes due to medications by oxidants could lead to loss or dysfunction of activities of these biomolecules. This oxidative modification effects could be combated through mechanisms such as protein refolding or degradation, lipid turnover and DNA base excision and repair. Brain neuronal homeostasis is distressed when this mechanism is bridged, oxidative stress therefore ensues [4]. Oxidative stress is a major risk factor implicated in several human diseases such as cardiovascular disease, brain and learning dysfunction, kidney and heart failure, erectile dysfunction among others [1].

Erectile penile dysfunction (ED) is the inability of man to have strong penile erection, enough for sexual activity [5,6]. Studies have described ED as a common condition that becomes more prevalent as men age [5]. ED accounts for 45% of male sexual dysfunction in Nigeria and a larger population of men worldwide have also been predicted to be affected with ED in the future [7,8]. Penile erection involves neurovascular events modulated by psychological and hormonal factors [9]. Proper erection occurs when upon sexual stimulation,

there is a coordinated interplay between the penile vasculature, neural impulses, hormone level and cognitive behavior [10]. An important regulator of penile erection is nitric oxide (NO) and is released from both the endothelial cells as well as the neural tissue that supplies the corpora cavernosa [11]. NO is a gaso-transmitter which is involved in smooth muscle relaxation, promoting dopamine release and activating luteinizing hormone-releasing hormone thus controlling sexual behavior [12,5].

ED can arise from disturbances from vascular, neurologic, psychological or hormonal factors [13]. Medications and substances (such as tobacco, antidepressants) can also exacerbate ED [14]. As such, ED is a strong predictor for cardiovascular diseases (CVD), diabetes, testosterone deficiency, anxiety, Parkinson's disease, spinal cord disorder, multiple sclerosis, hyperlipidemia, and hypertension among others [15]. These mostly interrelated to lifestyle and endothelial dysfunction is prevalent in most instances [16]. Most of the antidepressant medications which includes the class of selective serotonin reuptake inhibitors (SSRI) such as paroxetine (Paxil), serotonin norepinephrine reuptake inhibitor such as venlafaxine have been associated to be common causes of ED [17,18].

The oral administration of phosphodiesterase-5 (PDE-5) inhibitors (for example sildenafil) is one of the first line therapies in the management of ED and is also part of the clinical approaches to mitigate sexual dysfunction associated with SSRIs [19]. PDE-5 inhibitors maintain erection by promoting the vasodilatory effects of NO [14]. The common adverse effects of PDE-5 inhibitors include headache, flushing, dyspepsia, hypotension, back pain among others [11, 5]. Sildenafil (viagra) is a potent PDE-5 inhibitor that is generically available and the first oral drug to be approved for the treatment of ED [14]. Studies have shown that it is effective within one hour of dosing and its usage can maintain sufficient erection for satisfactory sexual performance in both human and animal models [20]. Viagra when administered before sexual activity

produces reliable efficacy, good tolerability and rapid absorption that yields prompt onset of action [21]. In clinical trials, viagra has been shown to increase the duration and rigidity of penile erection in response to visual sexual stimuli thereby enhancing the ability to achieve erections, leading to successful completion of intercourse [22]. Arginase is also a key regulator of the production of NO [23]. L-Arginine is a substrate for both arginase and NO synthase, as such, the inhibition of arginase leads to an increased bioavailability of NO thus reducing oxidative stress and enhancing normal vascular function while an increase in the activity of arginase brings about reduced NO production because L-arginine is available for NO synthase [12]. Acetylcholinesterase (AChE) is an enzyme that acts on the neurotransmitter, acetylcholine. Acetylcholine carries signal from the nerve cells to the muscle cells while acetylcholinesterase is found in the synapse between the nerve cells to the muscle cells [24].

One of the most difficult hurdles for many men is admitting that they have a problem [13]. The stigma associated with ED prevents men from seeking help and an important component of overall wellbeing in sexual health is pleasurable sexual activity [13,14]. ED has been reported to lead to lower levels of physical and emotional intimacy which could further lead to reduced satisfaction in a relationship. Many men with ED have low self-esteem and feel isolated because they are unable to discuss this sensitive issue with their physician for fear of embarrassment [13]. As such, the likely worldwide increase in the prevalence of ED and the social stigma attached to the condition present a serious challenge for health care policy makers to develop and implement measures to manage ED [9].

Evidence have shown that ED has a significant negative impact on quality of life measures and that the successful treatment of ED can as such be associated with significant improvements of physical, psychological and emotional wellbeing [13,25]. Nevertheless, recent researches focus on cheap and natural sources having minimal or no side-effects with the aim of discovering a cure for ED and many spices/herbs have shown promising potential [26]. Dietary factors have been demonstrated over the years to play crucial role in the development of various human diseases [27]. Medicinal plant continues to provide valuable therapeutic agents in both modern medicine and traditional system [28]. In Nigeria and many other African countries,

several plants have been used for many years to improve sexual stimulation and performance [13].

Approximately 150 species of *Thymus* are abundantly found, mainly in Asia, Africa, and North America. Recently, its range has been widely extended to the Iberian Peninsula, with most of the species being endemic [29]. *Thymus vulgaris* L. (Lamiaceae) is a medicinal plant belonging to the Lamiaceae family. In folk medicine, some *Thymus* spp. are used for their anthelmintic, expectorant, antiseptic, antispasmodic, antimicrobial, antifungal, antioxidative, antiviral, carminative, sedative, and diaphoretic effects. They are usually administered by infusion or are used externally in baths to cure rheumatic and skin diseases [30]. Thyme contains high concentrations of phenols, including thymol (12-61%), carvacrol (0.4-20.6%), 1,8-cineole (0.2-14.2%), α -cymene (9.1-22.2%), linalool (2.2-4.8%), borneol (0.6-7.5%), α -pinene (0.9-6.6%), and camphor (0.7-3%). Carvacrol and thymol are the main phenolic components that are primarily responsible for its antioxidative activity [31]. In addition, thyme oil is widely used in phytotherapy, most notably to treat and offer protection from acne, hypertension, infections, and cancers [30]. The oil contains bioactive monoterpenes such as thymol, carvacrol, and linalool [29].

1.1 Justificaton

The effective control of ED has been of major interests, and the use of several conventional drugs is yet to have any distinctive stance. As such, there have been a current shift to the use of plant-based bioactive compounds, Report have described *T. vulgaris* to be useful in the management of several human ailments However, there is limited information on the effect of erectogenic properties *T. vulgaris*. Hence, this study is focused on the effects of *T. vulgaris* on antioxidant and enzymes activities linked with erectile function in 5-FLU-induced oxidative stressed male rats.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagent

Chemicals and reagents used: Acetylcholine Iodide, Gallic Acid and Folin-Ciocalteu reagent were obtained from Sigma-Aldrich (St Louis, MO, USA). Thiobarbituric acid (TBA), trichloroacetic acid (TCA), quercetin, 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2-deoxyribose were

procured from Sigma-Aldrich Chemie (Steinheim, Germany). Sodium carbonate, ferric chloride, aluminium chloride, potassium acetate, potassium ferricyanide, tris salt, ferric sulphate as well as other reagents used were of analytical grade; glass distilled water was also used.

2.2 Plant Materials

Thyme (*Thymus vulgaris L., Lamiaceae*) was gotten from Erekesan market, Oja Oba, Akure, Ondo State, Nigeria, and was authenticated at the department of science laboratory technology, Rufus Giwa Polytechnic Owo.

2.3 Animals Handlings

The handling and use of animals were in accordance with the NIH guide for the care and use of laboratory animals. The use of animal in this study was duly approved by the Animal Ethics Committee of our institution. In this experiment, sixty adults male Wistar rats weighing (210-225) g were purchased from the breeding colony of the Department of Biochemistry, Federal University of Technology Akure, Nigeria. Rats were maintained at 25 °C, on a 12-h light/12-h dark cycle, with free access to food and water. They were acclimatized under these conditions for 2 weeks before the commencement of the experiment.

2.4 Experimental Design

Sixty adults male Wistar rats weighing 210-225 g were randomly assigned to either normal (control) or 5-FLU groups (n = 6). The animals were further divided into different groups and different doses of thyme extract, and saline solution, were administered through oral gavage while 5-FLU was administered intraperitoneally (i.p) as follows:

- Group I: Normal control receiving saline (0.9% NaCl)
- Group II: rats were administered 100 mg/kg of thyme extract orally
- Group III: rats were administered 200 mg/kg of thyme extract orally
- Group IV: rats administered with 400 mg/kg of thyme extract orally
- Group V: rats were administered 25 mg/kg of Vitamin C orally
- Group VI: received 150 mg/kg of 5-FLU (i.p)

- Group VII: received 150 mg/kg of 5-FLU (i.p) and 100 mg/kg of thyme extract orally.
- Group VIII: received 150 mg/kg of 5-FLU (i.p) and 200 mg/kg of thyme extract orally.
- Group IX: received 150 mg/kg of 5-FLU (i.p) and 400 mg/kg of thyme extract orally.
- Group X: received 150 mg/kg of 5-FLU (i.p) and 25 mg/kg of Vitamin C orally.

The treatment lasted for 14 days; after which the rats were sacrificed penile tissue was collected and homogenized with cold sodium phosphate buffer (pH 6.9). The homogenate was centrifuge using refrigerated centrifuge. The supernatant obtained was used for biochemical analysis.

2.5 Biochemical Assays

2.5.1 Biochemical assays

Lipid peroxidation assay quantification of thiobarbituric acid reactive species (TBARS) followed the method of [32]. Total thiol (T-SH) and non- protein contents were determined according to the method previously described by [33]. Protein was measured by the Coomassie blue method according to [34] using bovine serum as standard. Phosphodiesterase-5 (PDE-5) activity was carried out using the previously described protocol of [35] with minor modifications. Arginase activity in the penile was assessed by the measurement of urea produced by the reaction of Ehrlich's reagent according to the method described by [36]. Acetylcholinesterase activity was assessed by a modified colorimetric method previously described by [37].

2.6 Data Analysis

The result of triplicate experiments was pooled and expressed as mean \pm standard deviation and the mean was compared using the one-way analysis of variance (ANOVA), followed by Duncan's multiple range tests. Statistical Package for Social Science (SPSS 17.0) for windows was used for the analysis. $P < 0.05$ was considered to represent a significant difference in both analyses used and IC_{50} was calculated using linear regression.

3. RESULTS AND DISCUSSION

3.1 Results

Fig. 1 below illustrates the effect of studied plant extract on the level of thiobarbituric reactive

species (TBARS) produced in the experimental rats. From the result, it was observed that the normal rat treated with 400 mg/kg TVE had reduced level of TBARS when compared to control. In the pre-treated group and induced, the entire induced group pre-treated with TVE extract had reduced TBARS level when compared to untreated 5-FLU induced group. Similar result was also observed in both total thiols (Fig. 2) and non-protein thiol level (Fig. 3).

Fig. 4, illustrates the effect of *thymus* extracts on the phosphodiesterase-5 activity in the penile tissue of 5-FLU-induced oxidative stress. The result depicts that normal rats treated with the extract and Vitamin C alone reduced PDE-5 compared to the control. Interestingly rats treated with 400 mg/kg extract of *Thymus* had the highest effect. It was also observed that the levels of activities of PDE-5 in the groups of rats induced with 5-FLU had the highest PDE-5 activity, but those that were pre-treated with the extract and Vit.C had reduced activity of PDE-5.

Fig. 5 described the effect of TVE on arginase activity in the penile tissue of normal and 5-FLU-

induced oxidative stress rats. The results depicted that the administration of TVE caused reduced arginase activity in normal rats but not ($p > 0.05$) significantly different from control, however there was significant increase in arginase activities in the rats induced with single dose of 5-FLU when compared to control rats. The result also showed that TVE pre-treated rats induced with 5-FLU had reduced arginase. Interestingly, 100 and 200 mg/kg TVE administered rats had reduced arginase activity ($p < 0.01$), while 400 mg/kg TVE and Vit C (25 mg/kg) had higher significant ($p < 0.001$) decrease arginase activity compared to 5-FLU induced rats.

AChE activity in the penile tissue of normal rats treated with TVE was also reduced but was not significant ($p > 0.05$) different except 400 mg/kg treated rat ($p < 0.05$) when compared to that of control rats. The result also revealed that single dose of 5-FLU caused significant ($p < 0.001$) increase in AChE activity compare to control rats, however, all the 5-FLU-induced rats pre-treated with TVE and Vit. C had reduced AChE activity ($p < 0.001$) when compared to the induced rats.

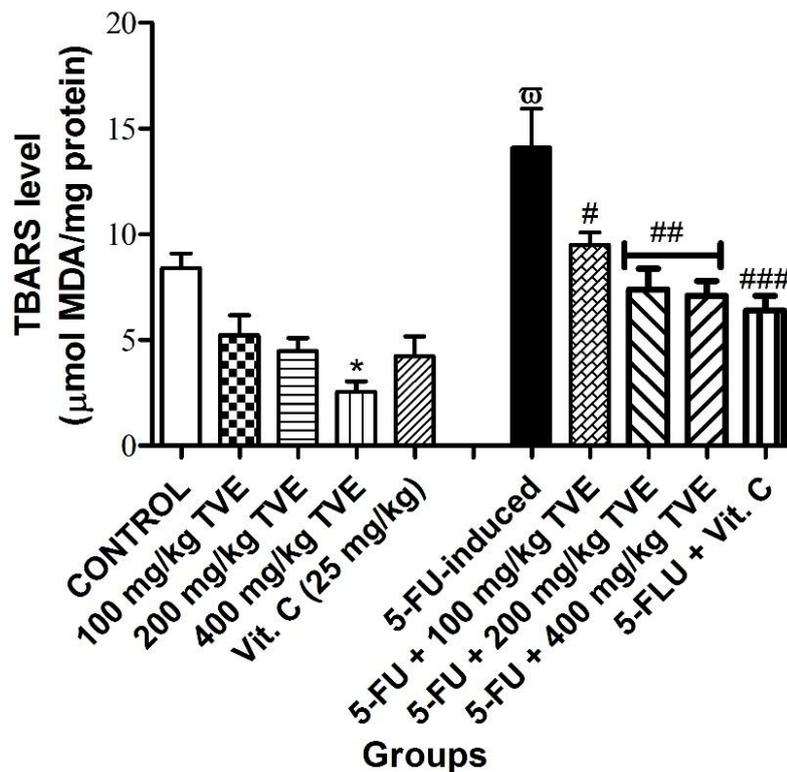


Fig. 1. Effect of *T. vulgaris* extract (TVE) on the thiobabaturic reactive acid species (TBARS) level in the penile of normal and 5-fluorouracil (5-FLU)-induced oxidative stressed male rats

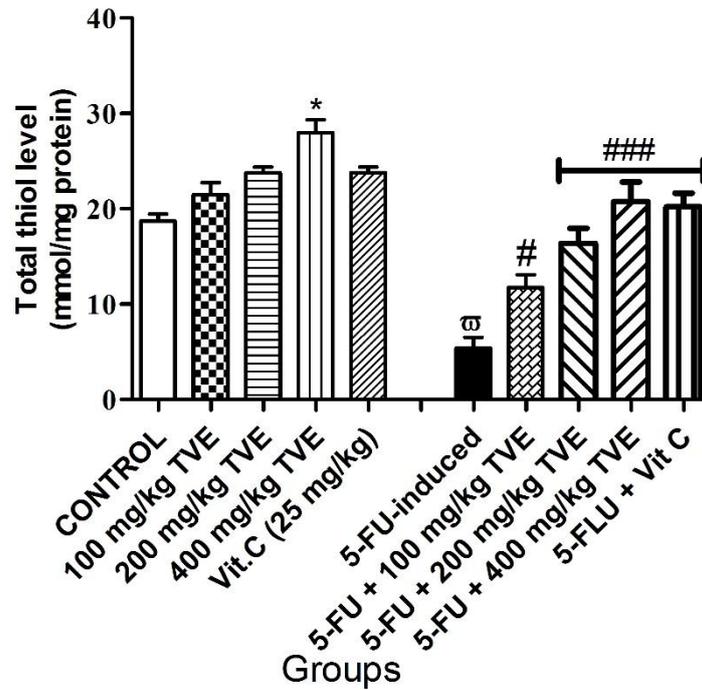


Fig. 2. Effect of *T. vulgaris* extract (TVE) on the total thiol level in the penile of normal and 5-fluorouracil (5-FLU)-induced oxidative stressed male rats

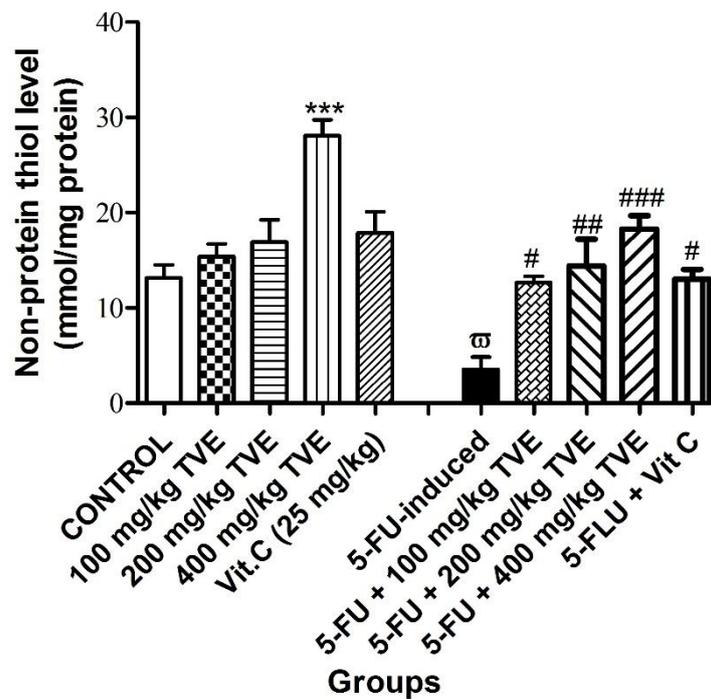


Fig. 3. Effect of *T. vulgaris* extract (TVE) on the non-protein thiol level in the penile of normal and 5-fluorouracil (5-FLU)-induced oxidative stressed male rats

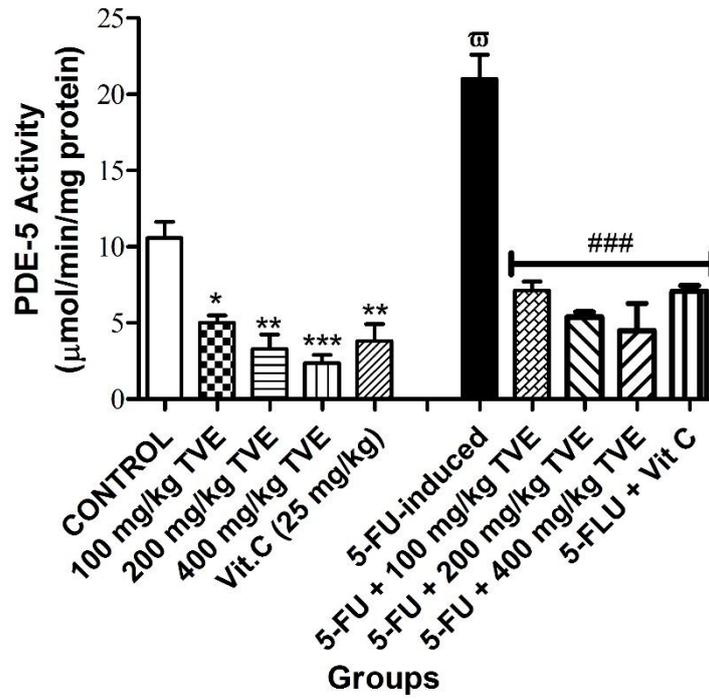


Fig. 4. Effect of *T. vulgaris* extract (TVE) on the penile phosphodiesterase-5 activity of normal and 5-fluorouracil (5-FLU)-induced oxidative stressed male rats

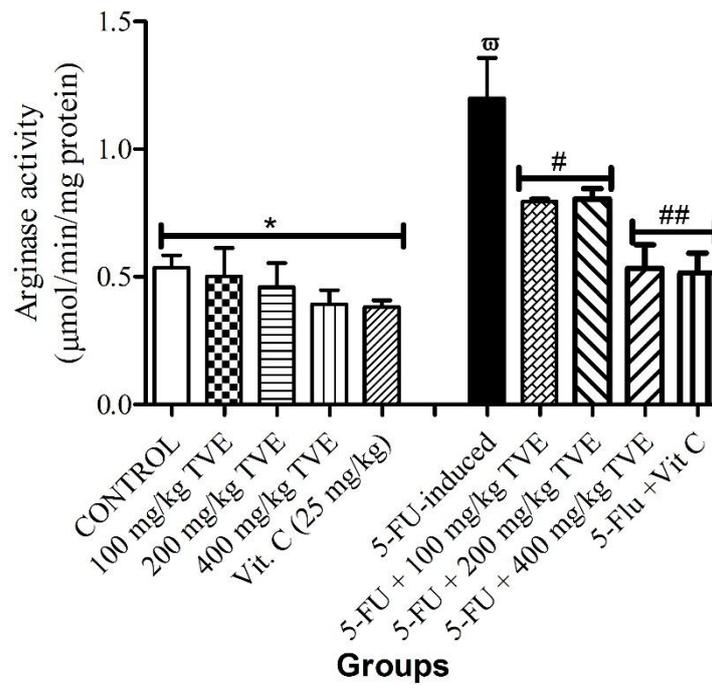


Fig. 5. Effect of *T. vulgaris* extract (TVE) on the penile arginase activity of normal and 5-fluorouracil (5-FLU)-induced oxidative stressed male rats

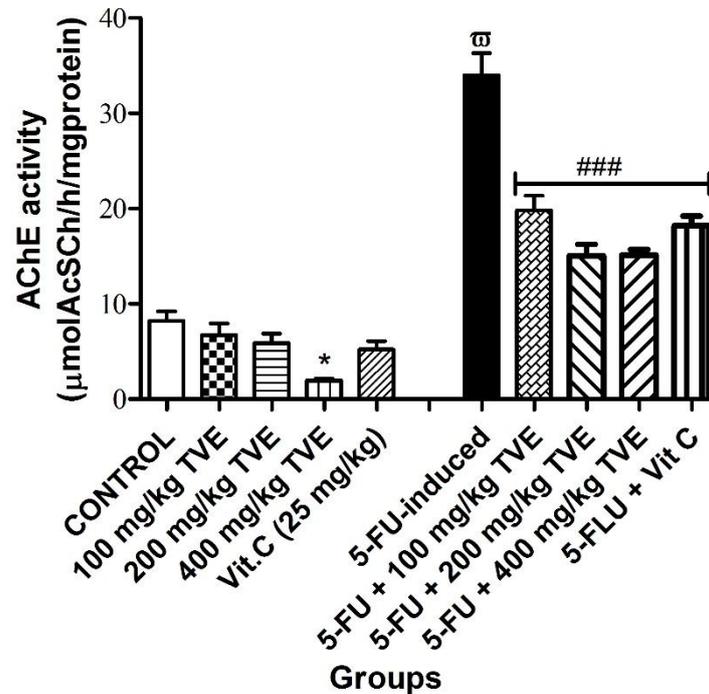


Fig. 6. Effect of *T. vulgaris* extract (TVE) on the penile acetylcholinesterase (AChE) activity of normal and 5-fluorouracil (5-FLU)-induced oxidative stressed male rats

3.2 Discussion

As popularly-known, the use of plant material as bankable sources for bioactive compounds for the medical treatment of various human diseases is from the time immemorial [27]. *Thymus vulgaris* (*T. vulgaris*) is among the most useful ancient medicinal plant, in the treatment of convulsions, respiratory diseases, among others, widely grown endemically in most part of the world, having the abilities to scavenge radicals [30]. The imbalance between pro-oxidants and the ability of antioxidants to scavenge free radicals bring about the occurrence of oxidative stress [38]. Free radicals catalyze the conversion of NO to peroxynitrite (ONOO*) thus limiting smooth muscle relaxation of the penile muscle [39]. Superoxide anion, a free radical, and peroxynitrite also impair endothelial function thereby causing ED [40]. The disruption of antioxidant imbalance in the body system can lead oxidative stress-induced ED via the initiation of lipid peroxidation and promoting the reduction of NO bioavailability. Hence, augmenting the body's antioxidant status could be a practical approach by which oxidative stress induced erectile dysfunction can be managed [41]. Results obtained from Figure 1 to 3, shows that *T. vulgaris* has great potential in the

management of oxidative stress. This could be as a result of some potential bioactive compounds such as phenolic compounds, essential oils such as thymol, carvacrol, 8-terpinene, p-cymene and α -pinene. Carvacrol and thymol, which have been reported as the major constituents *T. vulgaris* [42], which are capable to mitigate oxidative stress and enhancing its capability in the management/prevention of erectile dysfunction [43]. An important enzyme required for restoring basal smooth muscle tone, flaccidity and vaso-relaxation is phosphodiesterase-5 (PDE-5). PDE-5 regulates the activity of the second messenger in cells by cleaving to the phosphodiester bond of either cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP) or both. As such, the inhibition/reduced PDE-5 activity induces vasodilation, reduces systolic Ca^{2+} and stimulates erection by enhancing the accumulation of cAMP/cGMP. From Figure 4, a result obtained explains that PDE-5 activity was inhibited by administration of the Thymus extract in both normal and pre-treated rats. This finding is in line with [44] reports that bioactive compounds such as polyphenols of the extract as they have been reported to inhibit PDE-5 as such potentiating the activity of cGMP- a potent vasodilator [45]. Furthermore, literatures have

reviewed that polyphenols can cause endothelium-induced relaxation in vitro, as a result of inhibitory effects on phosphodiesterase, protein kinase as well as the influx of calcium ion [46]. A major predisposing factor of ED is decreased bioavailability of the vasoprotective endothelial NO which arises as a result of endothelial dysfunction or nerve injury [47]. Results obtained from Figure 5 explain that the studied extract reduced arginase activity in both normal and induced rats. Arginase is an important regulator of NO bioavailability and studies have explained that patients with ED commonly have increased arginase level due to decrease in the activity of the enzyme, nitric oxide synthase (NOS) thereby causing impairment in nitric oxide (NO) biosynthesis [48]. The utilization of L-arginine by arginase activity in vascular endothelia and smooth muscle cells of penile tissue can reduce NOS activity and consequently decrease concentration of NO: a major factor in erectile function [49]. Hence, the inhibition of arginase activity can be additional therapeutic targets for the management of ED as this could increase the bioavailability of L-arginine, contribute to the production of NO via reaction catalyzed by NOS, where overall result could facilitate penile erection [50]. Inhibition of arginase activity by the studied extracts is in line with some reports of plant extracts, which are rich in phenolics including epicatechin, quercetin, quercitrin and isoquercitrin and their arginase inhibitory potential [41,47]. The administration of TVE obtained shows that the concentration-dependent reduction of arginase activity in the penile tissue of the experimental rats is of importance as blood flow could be increased in the genitals during sexual arousal thus enhancing ED management. Interestingly, the inhibitory properties of the TVE could be associated to its phenolic components. This is because literatures by [51], have reported phenolics to have inhibitory effects on the activity of arginase. In addition, [52], explained flavonoids like quercetin and its derivatives (quercitrin and isoquercitrin) to be strong inhibitors of arginase activity and can be linked via the formation of hydrogen bond and hydrophobic interactions between these phenolic compounds and the hydrophobic active site of the enzyme. Acetylcholinesterase (AChE) is an enzyme that rapidly degrades the neurotransmitter, acetylcholine which enhances erection by acting on the vascular endothelium to release NO via the enzyme nitric oxide synthase thus increasing the cGMP level of the corpus cavernosum [53]. Hence, the cholinergic system

plays crucial role in the production of penile erection via the inhibition of AChE to maintain Ach- induced NO production from nitric oxide synthase. Figure 6 demonstrates that the extracts inhibited acetylcholinesterase in a concentration-dependent manner. This may also be attributed to its phytochemical constituents as studies have reported the AChE inhibitory effects of some compounds [54,55]. Other medicinal plants which also contain phytochemicals like flavonoids have been reported in literatures to enhance sexual activities [56,8]. Furthermore, because flavonoids are therapeutically potentials and are widely distributed in flowering plants, they possess antioxidant and hemodynamic activities. The antioxidant potential of *Allium cepa* provides protection against cellular damage to erectile tissues that can bring about ED due to oxidative stress [8] or leydig cells damage causing decrease in testosterone level and loss of libido [57]. Several studies had reported that the penile tissue is rich in cholinergic nerves, and for sexual activity.

4. CONCLUSION

The current study has established that 5-FLU can also be used to induce erectile dysfunction in male rats. Although, several reports have shown the medicinal values of bioactive compounds responsible for the various medicinal properties of thymus. As such, this study proves that the consumption of Thymus can be a safe and effective alternative remedy in sexual disorders by enhancing sexual activity. It may be concluded that the extract of thymus vulgaris has a significant effect on erectile dysfunction resulting in improved penile enzymes that stimulate sexual function.

Although, there exists a relationship between increased consumption of thymus extract and sexual function, However, it is apparent that more research is still needed to ascertain the medicinal benefits of sexual function of the extract in enhances sexual function.

DISCLAIMER

Products used for the research are commonly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products, hence the research is used for the advancement of knowledge. Also, the research work was funded by personal efforts of the authors.

CONSENT

It's not applicable.

ETHICAL APPROVAL

All procedures of this study described were reviewed and approved by the Institutional Animal Ethical Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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