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Research Article

Effect of *Gynerium sagittatum* methanol extract on testosterone-induced benign prostatic hyperplasia in rats compared with finasteride.

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Abstract

Gynerium sagittatum (Caña Brava) is used in ethnomedicine to treat benign prostatic hyperplasia without any scientific information on its safety profile after its administration. Evaluate the possible curative effect of methanolic extract of *Gynerium sagittatum (GS)* on testosterone-induced benign prostatic hyperplasia in rats. 36 male rats with an average weight of 300 g ± 50 g and 2.5 months of age were used, 6 random groups of 6 rats each were formed; Group I, blank: with physiological serum 2 mL / Kg every 24 h. for Per Orally (PO), control group II: with olive oil subcutaneous 0.5 mL + testosterone 25 mg (TA), group III: with olive oil subcutaneous 0.5 ml + testosterone 25 mg + extract of *Gynerium sagittatum* 50 mg/kg PO, group IV: olive oil subcutaneous 0.5 mL + testosterone 25 mg + extract of *Gynerium sagittatum* 250 mg/kg, Group V: olive oil subcutaneous 0.5 mL + testosterone 25 mg + extract of *Gynerium sagittatum* 500 mg/kg, Group VI: olive oil subcutaneous 0.5 mL + testosterone 25 mg + Finasteride 0.6 mg/kg. weighed subsequent treatments, and prostate, kidneys, and liver were measured, and a pathological study determined prostate-specific antigen and serum determination of toxicity markers by liver profile. A 99% decrease in the comparative prostate index was observed in control group I, and a better effect was observed at a dose of 500 mg/kg (P <0.004). This study has shown that GS has a beneficial effect on induced benign prostatic hyperplasia in rats.

1. Introduction

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm of aging men and is present in approximately 8% of men in the fourth decade of life but up to 90% of men in the ninth decade [1]. Hyperplasia is observed globally in almost 50 percent of patients aged 60 years and 90 percent of patients aged 80 years and under 30, respectively. Population studies indicate that from the age of 40, common uropathy symptoms secondary to benign prostatic hyperplasia differ from 13% and exceed 60% in older patients. Let us consider that with age, the incidence of lower urinary tract symptoms (LUTS) increases. The population is aging in most European countries, and the number of men seeking medical attention for LUTS/BPH will rise dramatically over the next 20 years [2]. Mortality due to BPH is low, and patient's quality of life is conditioned by its evolutionary attitudes, evolutionary attitude, and the formation of evacuation symptoms with varying severity effects on the patients of life on the patient's

quality of life. The prevalence of histological BPH is estimated to occur in 8% of men aged 31 to 40 years, up to 50 % of men aged 51 to 60 years, and more than 80% of men. It is more than 80 years of age and it is uncommon among young men. Symptoms are measured using scales of symptom scoring.

Approximately 80% of those over 50 have BPH in a greater or lesser degree, so 33% of those over 50 have a well-formed adenoma already. Ninety-five percent have BPH at 80 years of age. The possibility that an 80-year-old man wants prostate surgery has been reported to be 30 percent [3]. We can see from other foreign sources that the anatomical or histological evidence of BPH present in autopsy studies has been estimated at 50 to 60 years (40%), 60 to 70 years (60%), and 70 to 80 years (80%) [4].

The disorder becomes a clinical entity linked to subjective symptoms, with lower urinary tract symptoms being the most common manifestation. However, it must be believed that not all men with BPH histology will develop severe LUTS, while LUTS will develop in other men who do not have BPH histology. The incidence of symptoms and signs of BPH in men may be associated with other prostate disorders. It may be a risk factor for the development of prostatitis or prostate cancer, other causes of sub-ventricular obstruction (urethra), stenosis, bladder neck sclerosis, bladder conditions (in situ carcinoma, inflammation, stones, or other conditions leading to a non-specific disease like lower urinary tract infections. Another critical factor is state propensity to expand [5, 6]. The pharmacological options that we currently have are the following:

- Alpha-adrenergic receptor blockers
- 5-alpha reductase inhibitor
- Inhibitor of the enzyme phosphodiesterase 5
- Anticholinergic agents

However, the ever-increasing interest in flavonoid-based natural products increases interest in flavonoid-based natural products due to the recognition of their broad pharmacological activity. Due to this fact, pathologies such as diabetes mellitus, cancer, heart disease, viral infections, and stomach protective effects have been identified like ulcer duodenal, and inflammatory diseases. Other activities that should be highlighted include their antiviral and antiallergic properties and their anti-thrombotic and anti-inflammatory properties [7]. According to the available evidence, extracts from various plants used in the treatment of BPH have a mild beneficial effect, like that of a placebo, to improve symptoms and urinary flow measurements. However, it will be essential to have sufficient length and good design studies to determine its role in the disease's progression and minimize complications. We chose the ethanolic extract for the pharmacological properties that it offers us at the time of carrying out the phytochemical march, which provides us with obtaining better results in the presence of various molecules. At the moment there are no previous studies for this plant where the ethanolic extract has been carried out or obtained to carry out other studies. It is the first time that this procedure is being carried out for said plant.

The 5-alpha-reductase inhibitors represented: finasteride and dutasteride; finasteride is a selective inhibitor of the type II isoenzyme, and dutasteride, a non-selective inhibitor of type I and II isoenzymes, have relevant adverse effects such as decreased libido, erectile dysfunction and ejaculation disorders, gynecomastia. Combined alpha-blocker therapy with 5-alpha reductase inhibitors is an effective method, care must be taken in treatment lasting less than a year due to suspicion of intravesical obstruction and high residual urine volume [8]. Currently, there is a growing interest in flavonoids because they present a broad pharmacological activity, possibly a consequence of their antioxidant capacity. Due to this fact, there have been described protective effects in pathologies such as cancer and inflammations, viral infections, ulcers, stomach, duodenal, and heart disease. The components of the root of *Gynerium sagittatum* would inhibit the enzymatic process that converts testosterone to DHT, which is the main androgen responsible for stimulating prostate growth. That is the aqueous extract of the root of the "caña brava" decreases the DHT concentration in the prostate and decrease of the tumor of the prostate [9, 10].

The pathophysiological evolution of BPH occurs with processes of an inflammatory or infectious nature that affect the prostate gland; in addition, the inflammation process can independently affect the development of BPH [11]. In different countries of the world and in Peru, specifically, there are medicinal plants that contain flavonoids, tannins, which show

an anti-inflammatory and antioxidant effects. This is the case of *Moringa oleifera*, whose leaves and roots have shown a greater antioxidant and anti-inflammatory effect than the seeds [12, 13]. On the other hand, phytochemical knowledge of the *Gynerium sagittatum (caña brava)* species is not well described. Thus, more studies are necessary to validate its traditional use. In this context, we have evaluated the possible curative effect of the methanolic extract of *Gynerium sagittatum* on induced BPH by testosterone in rats. Considering the magnitude of the problem, this research aims to contribute to the therapy of BPH to be able to take it into account in the future, which will help reduce costs, giving an alternative to conventional drugs which have a high price. The justification of the study is based on the analysis of a qualitative phytochemical march, since we do not have the technology to carry out a quantitative phytochemical march. However, our study is based on qualitative results with the results of the presence of substances such as flavonoids, alkaloids, etc; which allows us to analyze the study and give theoretical support to its results.

2. Materials and methods

2.1 Plant materials

The guide for the *Gynerium sagittatum (caña brava)* plant was sent to the Natural History Museum of the National University of San Marcos for its taxonomic study, Constancy N ° 12-USM-2018.

2.2 Animals

Adult Holtzman rats were obtained from our Animal House at the National Institute of Health and used for the present study. Rats were kept 6 per cage at room temperature (22 °C) with a 12:12 hr light / dark cycle. They have also fed them Purina laboratory food and tap water ad libitum. The "Guide performed all animal experiments for the Care and Use of Laboratory Animals" of the US National Institutes of Health, 08. The Institutional Review Board of the Office of Scientific Research of the "Universidad Nacional Mayor de San Marcos" approved the study.

2.3 Preparation of aqueous ethanol extract of Gynerium sagittatum (Caña Brava)

The plant guide was dried in the sun within the temperature range of 30–42 °C for five days before being reduced in size to a coarse powder with an electric grinder. The uncultivated plant powder weighing 1000 g was extracted with 90% aqueous ethanol in three cycles using a Soxhlet extractor. The crude extract was filtered with Whatman No. 4 filter paper and the filtrate was concentrated in vacuo at 30 °C to obtain 80 g of the residue's weight (8.7% w/w). The residue was stored in an airtight bottle and kept in a refrigerator at 4 °C until use.

2.4 Phytochemistry of Gynerium sagittatum (Caña Brava)

For this procedure, the methanol extract was dissolved in physiological saline solution, separated, and reserved to carry out the phytochemical march. The sample had a content of 5 mg of the section that was dissolved in physiological serum at volumes of 3 to 5 ml in tubes and test 8 of 5 mL. The phytochemical examination of the aqueous extract of *Gynerium sagittatum (Caña Brava)* was carried out using standard phytochemical procedures, 9, 10, 11, 12, and 13. The aqueous extract of *Gynerium sagittatum (Caña Brava)* was lyophilized before the extraction procedures. After extraction in methanol, the presence of flavonoids (Shinoda test), anthraquinones (Bornträger reaction), tannins (gelatin / ferric chloride test), phenolic compounds (ferric hydroxylate test), free amino acids (trial of ninhydrin), and glycosides (Polish test) were evaluated, [14-17].

2.5 Benign prostatic hyperplasia induction

Two weeks before the start of therapy, BPH induction was performed. The model was induced by subcutaneous injection of testosterone enanthate twice at a dosage of 25 mg (0.1 mL, 250 mg / 1 mL presentation) on day one and day 7; this procedure was performed daily in all rats (Wang R, 2015). Testosterone enanthate, diluted in 0.5 ml of extra virgin olive oil for home use (this oil olive was chosen for the experience with other studies in our Pharmacological department and also we do not have oil olive pharmacological), was prepared at a dosage of 25 mg (0.1 mL). Being prepared corresponds to the benign prostatic hyperplasia caused by the agent for the groups II, III, IV, V, and VI from the experimental study. Experimental groups III, IV, and V were administered daily: testosterone enanthate in 25 mg of oil solution subcutaneously plus the methanolic extract of the *Gynerium sagittatum* (caña brava) guide prepared as mentioned above, in the following doses:50 mg/ kg, 250 mg/kg and 500 mg/kg orally for

30 days, this was done with a metallic orographic cannula.

The experimental group VI was administered testosterone enanthate in 25 mg oil solution subcutaneously plus 0.6 mg/kg of finasteride; this was used as a comparator for the treatment with the extract of *Gynerium sagittatum (caña brava*), [18]. It should be noted that a pilot study was carried out before the start of the trial, with two rats per group, which allowed the administration of the times and the adjustment of the administration and induction techniques of the disease in the animals.

2.6 Experimental design

Male rats with a mean weight of 300 g ± 50 grand and a mean age of 2.5 months, randomly distributed into six groups of 6 animals each, were selected for this research. At Bioterium, they were conditioned for seven days. Faculty of Human Medicine, National University of San Marcos; 6 metal cages with animal capacity were then housed. It was set at a temperature between 19 °C- 22 °C, 40-50 percent humidity, with alternating 12-hour light/ dark cycles starting at 8 a.m. Water and a nutritious diet were given to them ad libitum. The experimental groups are described below

i. White group (I): with physiological saline 2 mL/kg every 24 hours orally for 30 days.
ii. Control group (II): with 0.5 mL subcutaneous olive oil + 25 mg of testosterone (TA) for 30 days.
iii. Experimental group (III): extract of TA + *Gynerium sagittatum (caña brava)* 50 mg/kg orally for 30 days.
iv. Experimental group (IV): extract of TA + *Gynerium sagittatum (cane brava)* 250 mg/ kg orally for 30 days.
v. Experimental group (V): extract of TA + *Gynerium sagittatum (caña brava)* 500 mg / kg orally for 30 days.
vi. Experimental group (VI): TA + Finasteride 0.6 mg /Kg orally for 30 days.

2.7 Method of obtaining blood samples and extraction of the prostate, kidney, and liver glands.

On day 31, with an overdose of 100 mg/kg sodium pentobarbital, animals in all research groups were euthanized. By intracardiac puncture with a 21G needle, approximately 5 ml of blood was drawn from each of the rats after expiration; the blood was then deposited into labeled test tubes (5 ml) containing 0.01 mL of 100 mg / 5 mL sodium heparin. Both samples were immediately moved to "Dos de Mayo Hospital" biochemical analysis laboratory calculation. The measure often calculated total prostate-specific antigen (serum PSA), urea, TPG, alkaline phosphatase, total bilirubin and was analyzed according to the institution's methodology.

The prostate glands were surgically removed from each of the animals after blood collection and fixed with 10 percent formaldehyde. The following measurements were taken for each of the prostate glands and with the regular forceps clamp holder: Length (ventral length), width, and height.

• Weight in grams, using a high precision analytical balance, with a sensitivity of 0.1 mg. All measurements were recorded on some cards created to collect this information.

Kidneys and liver were removed from each of the rats for histopathological evaluation. We sent the samples for the anatomopathological study of the tissues designed for tiny review: also comparative method was used with the tissue samples of the rats of the control group (White group). The pathological study was performed with a high-resolution Nikon binocular microscope (40x magnification) with built-in light, which allows the review of morphological alterations in tissues and cells.

2.8 Histopathological examination

The prostate samples from the rats were set for 24 hours with Bouin's fixative. The samples were dehydrated, rinsed with xylene, and embedded in paraffin using graduated alcohols. Hematoxylin and eosin were produced in six-micron thick sections and stained with (H&E). Using a light microscope, histological observation was prepared (Olympus BX41). The magnitude of the prostate histopathological changes was measured, while the glandular cavity diameter and height of the glandular epithelium were measured.

The prostate anatomy pathology research was also conducted at the macroscopic level: it was performed by measuring prostate measurements (length, width, and height) compared to the white group (I). It was considered that when the prostate was found to be smaller than that of the target group's experimental animals or the like, there was a curative effect.

2.9 Determination of the prostate index (PI)

PI was calculated from the ratio of prostate weight

(PW) to body weight (BW) of each rat as follows:

% inhibition=100- [(normal/negative treatment control -normal control) x 100]

2.10 Statistical analysis

The SPSS version 21 statistical package for Windows was used to conduct all statistical analyses; the data will be interpreted as an average ± standard deviation at a confidence level of 95 percent; variable tests will be analyzed by ANOVA, and a p-value <0.05 will be considered relevant compared to Dunnett's C. Multiple comparison comparisons will be evaluated by ANOVA using Fisher's LSD test, and a p-value <0.05 will be considered suitable appropriate compared to Dunnett's C.

3. Results and discussion

3.1 Phytochemistry of Gynerium sagittatum (Caña Brava)

The *Gynerium sagittatum (Caña Brava)* guide methanolic extract has an extraction yield of 50 percent by weight. Its organoleptic features include its brown, crystallizable, and hygroscopic, oily appearance. Qualitative phytochemical research showed that the methanolic extract contains abundant free amino acids, phenolic compounds, glycosides, and anthraquinones in the *Gynerium sagittatum* guide (Table 1).

Table 1. Results of the phytochemical march of *Gynerium sagittatum (cane brava)*

Metabolite	Reagent	Results
Tannins	Jelly	-
Phenolic compounds	Ferric chloride	++
Free Amino Acids	Ninhydrin reaction	+++
Alkaloids	Dragendorff reaction	-
Glycosides	Mayer's reaction	-
Anthraquinones	NaOH	++
Flavonoids	Shinoda reaction	++++

The secondary compound identification tests have detected free amino acids, phenolic compounds, glycosides, anthraquinones, and flavonoids. Absent (-), Little quantity (+), Regular quantity (++), Abundant quantity (+++).

3.2 Evaluation of serum PSA levels associated with the curative effect of the methanolic extract of Gynerium sagittatum (caña brava) guide.

Effects of serum PSA levels when determining the curative effect of the methanol extract according to the recommendations of *Gynerium sagittatum (Caña Brava)* indicate a higher decrease in serum PSA values with an extract dose of 500 mg/kg compared to the second extract dose and compared to finasteride above the 3-dose guidance methanol extract results (Fig. 1 & 2).

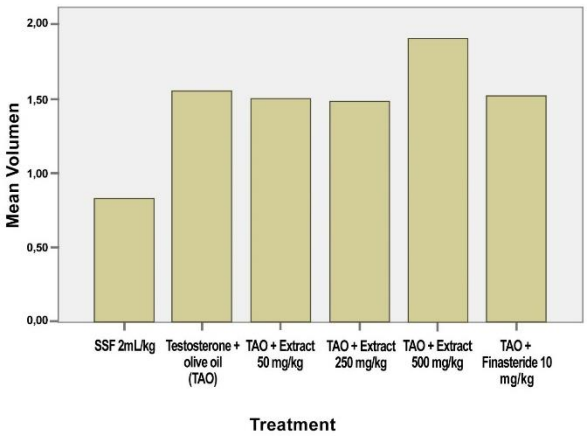

Figure 1. Comparison to evaluate the volume of the prostate gland when assessing the beneficial effect of the methanolic extract of *Gynerium sagittatum* (wild cane) in benign prostatic hyperplasia induced in rats. Values are mean ± SD (n = 6); mean values within the same column with different lowercase superscripts are significantly different (P <0.05) according to Duncan's multiple range test to evaluate the with ANOVA technique. SD = standard deviation.

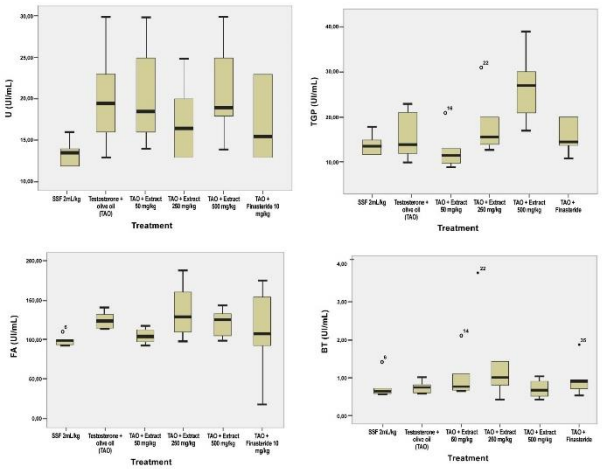

Figure 2. Comparison to evaluate the results of urea, TGP, FA, and BT when assessing the beneficial effect of the methanolic extract of *Gynerium sagittatum* (caña brava) in benign prostatic hyperplasia induced in rats. Values are mean ± SD (n = 6); mean values within the same column with different lowercase superscripts are significantly different (P <0.05) according to Duncan's multiple range test to evaluate with the ANOVA technique. SD = standard deviation.

3.3 Evaluation of the prostate index

The findings of the Prostate Index assessment of the curative effect of the methanol extract of the *Gynerium sagittatum (caña brava)* guide show a reduction of the PI with the extract dose to 500 mg/kg (p<0.004)

relative to other extract doses and compared to finasteride, which is below 500 mg/kg dose of the *Gynerium sagittatum* extract methanol (Fig. 3).

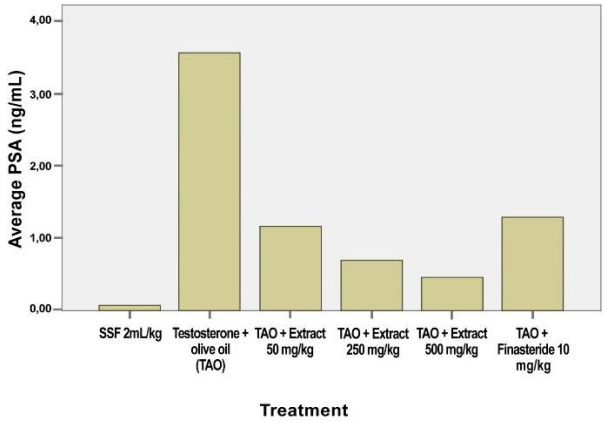

Figure. 3. PSA level evaluates the curative effect of the methanolic extract of the *Gynerium sagittatum* (wild cane) guidelines in benign prostatic hyperplasia in rats. Statistical analysis: the test of multiple comparisons using the Tukey test shows that p<0.0001. We can identify that Average PSA decreases with the extract of the *Gynerium sagittatum* at 250 mg/kg

3.4 Evaluation of the dimensions of the prostate.

The measurement of prostate gland measurements indicated a decrease in prostate gland dimension with an extract dosage of 50 mg/kg when assessing the curative effect of the methanolic extract of the *Gynerium sagittatum (caña brava)* guide. There is also evidence of a drop in prostate and height with a 250 mg/kg dose of the extract (Fig. 4).

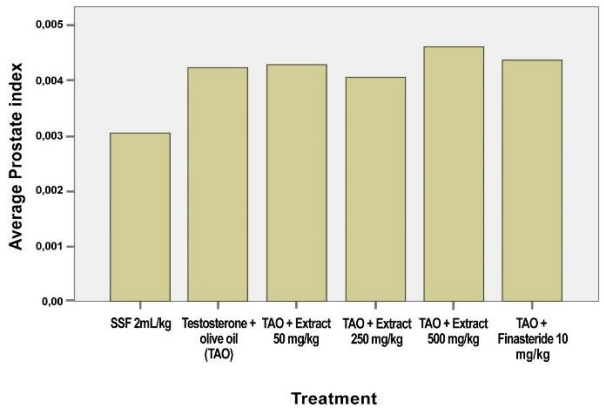

Figure 4. Prostate index evaluated the beneficial effect of the methanolic extract of the *Gynerium sagittatum* (caña brava) guidelines in benign prostatic hyperplasia in rats. Statistical analysis: the test of multiple comparisons using the Tukey test shows that p<0.051. We can identify that the Average Prostate index decrease with the extract of the *Gynerium sagittatum* at 250 mg/kg.

3.5 Evaluation of the volume of the prostate gland.

The findings of the assessment of the prostate gland volume when assessing the curative effect of the methanol extract indicated in the *Gynerium sagittatum (caña brava)* guide shows a decrease in the prostate gland volume with an extract dose of 250 mg/kg compared to the other extract doses and compared to the finasteride dose of less than 500 mg/kg of the methanol extract of *Gynerium sagittatum*.

3.6 Evaluation of the weight of the prostate.

The findings of the prostate gland weight assessment when measuring the curative effect of the methanol extract of the *Gynerium sagittatum (caña brava)* guide indicate a similar decrease with the extract dose of 250 mg/kg, accompanied by doses of 50 mg/kg, respectively

3.7 Weekly assessment of body weight.

The findings of the weekly body weight evaluation during the 30 days of the trial to test the curative effect of the *Gynerium sagittatum (caña brava)* methanol extract recommendations indicated a reduction in the dosage of 500 mg/kg extract relative to the other doses of the extract and compared to finasteride, which is higher than the results of the three doses of methanol extract. Such findings agree with the bodyweight averages (Fig. 5).

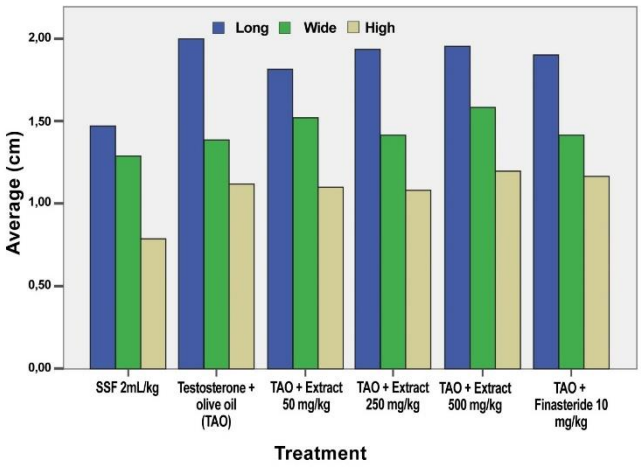

Figure 5. dimensions of the prostate gland when evaluating the curative effect of the methanolic extract of *Gynerium sagittatum (wild cane)* guidelines in benign prostatic hyperplasia in rats. Statistical analysis: the test of multiple comparisons using the Tukey test shows that p<0.001. We can identify that the average of long, comprehensive, and high decrease of the extract of *Gynerium sagittatum* at 250 mg/kg.

3.8 Evaluation of serum biochemical analyses of urea, TGP, FA, and BT.

The findings of the biochemical analysis evaluation to evaluate the serum levels of urea, TGP, FA, and BT when assessing the curative effect of the *Gynerium sagittatum (caña brava)* methanol extract is as follows: urea (mean value: 17 - 42 mg/dL) shows values within the normal range but with a better outcome at the 250 mg/kg extract dose; TGP (mean value: 17 - 42 mg/dL) shows values within the normal range but with a better outcome at the 250 mg/kg extract dose (Fig. 6).

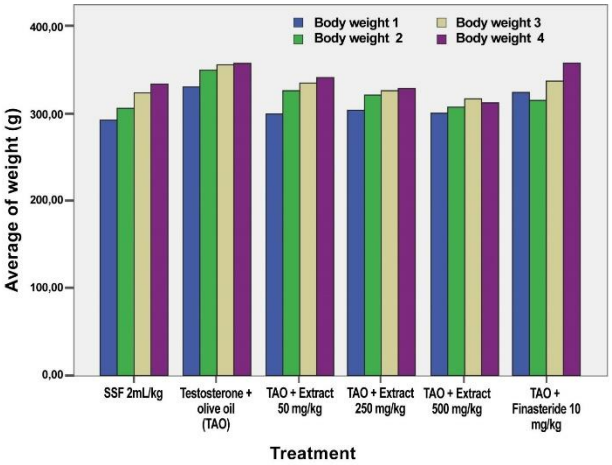

Figure 6. weekly body weight when evaluating the curative effect of the methanolic extract of the *Gynerium sagittatum* (wild cane) guidelines in benign prostatic hyperplasia in rats. Statistical analysis: the test of multiple comparisons using the Tukey test shows that p<0.243. We can identify that the effect curative evaluating the weekly bodyweight decrease with the extract A of *Gynerium sagittatum* at 50 mg/kg.

3.9 Effect of the extract on the histopathology of prostate tissue.

The findings of microscopic (pathological) observations of histological parts of the prostate gland in all experimental groups show the following: 500 mg/kg oral extract of *Gynerium sagittatum (Caña Brava)* if it has a curative effect in rat-induced benign prostatic hyperplasia (Figure 7 B). The findings of microscopic analyses of the histological parts of the liver in all experimental groups indicate that no cellular alterations and histopathological alterations related to the toxicity of the extract and comparators have been found, indicating the safety of treatment with *Gynerium sagittatum (caña brava)* extract at the level of the liver. The findings of microscopic (pathological) studies of the histological parts of the kidney indicate cellular congestion with 500 mg/kg of *Gynerium sagittatum extract (Caña Brava)* and 0.6 mg/kg of finasteride, suggesting that there is no evidence of cellular toxicity in the 50 and 25 mg/kg doses of *Gynerium sagittatum extract (Caña Brava)* experimental classes (Fig. 7 A, B, C, D, E). It is noted that the vascular contours of the acini and muscle fibers are still formed in Experimental Group V (40X). A 500 mg/kg extract of *Gynerium sagittatum (Caña Brava)* was orally administered.

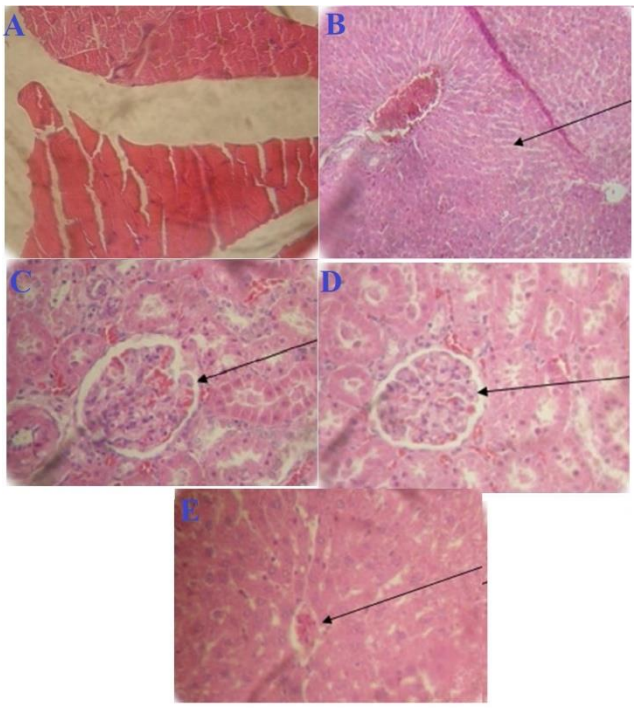

Figure 7. A- Liver without histological alterations (40X). B- Liver without histological alterations (40X). *Gynerium sagittatum (Caña Brava)* extract 50 mg/kg was orally administered. C- Liver without significant histological alterations (40X). *Gynerium sagittatum (wild cane)* extract was administered orally, 250 mg/kg extract. D- Kidney with euro typic standard histological structure (40X). *Gynerium sagittatum (wild cane)* extract 50 mg/kg was orally administered. E- Kidney with a preserved histological system (40X). *Gynerium sagittatum (wild cane)* extract was administered orally, 250 mg/kg extract.

The antecedents of the conventional usage of the *Gynerium sagittatum (Caña Brava)* guide suggest the use in the form of oral infusion [19]. However, because of the partial polarity of the methanol solvent before chains of different lengths and contradictions of the solutes, because of the partial polarity of the methanol solvent before chains of various sizes and polarities of the solutes, a higher extraction coverage of all the substances and beneficial metabolites of the plant was suggested for this examination, resulting in

a robust carrying capacity of the metabolites linked to the content.

The presence of phenolic compounds, free amino acids, glycosides, anthraquinones, and flavonoids detected by the phytochemical march of the methanolic extract, which agrees with the findings of researchers [19, 20], who also identified these compounds, as well as new phenolic compounds ((2R, 3R)-2,3-trans-7, 40-dimethoxy-dihydro flavanol, (2R, 3S, 4S)-2,3-trans-3,4-cis-7,40-dimethoxy-3,4-dimeth-oxy-3,4-flavandi). All these plant metabolites have been used as an anti-inflammatory, analgesic, and diuretic treatments in the Peruvian Amazon. In comparison, asthma and anemia were treated with leaf infusion. Therefore, the process used in this trial to induce the benign prostatic hyperplasia model is that it increases serum testosterone levels that produce an exclusively exogenous induction of benign prostatic hyperplasia, [20,21], which indicates that the same effect occurs molecularly. By disease induction, this description shows us the precise and scientific effect of the production of exclusively exogenously induced benign prostatic hyperplasia, at the end the disease's process was also demonstrated once again [21].

According to a study conducted with plants with a high percentage of flavonoid content and using high-performance liquid chromatography (HPLC), it was found that the flavonoids present in the vast majority of plants with the presence of flavonoids have the substances baicalin and gentiopicroside that provide phytotherapy treatment that acts on BPH-1 cells and has been found to suppress cell viability As far as their mechanisms are concerned, they inhibit cell growth by decreasing endogenous cyclin D1 protein levels and preventing the S step during the progression of the cell cycle. The flavonoid treatment of BPH-1 cells suppressed the development of prostaglandin E2 and protein levels of cyclooxygenase-2 (COX-2). Secretion of proinflammatory cytokines, interleukin-8 and interleukin-6; this hypothesis of action is also applied to the findings of the assessment of prostate gland measurements (Fig. 4) in the evaluation of the beneficial impact of the methanol extract of the *Gynerium sagittatum* (caña brava) guidelines, showing a decrease in prostate gland dimension with a dose of *Gynerium sagittatum*. There is also evidence of reducing prostate gland width and height at the dosage of 250 mg/kg of the extract [23].

The results of the assessment of the prostate index, the volume, and weight of the prostate gland (Fig. 7) indicate a decrease in the extract dose at 250 mg/kg when assessing the beneficial effect of the methanolic extract of the *Gynerium sagittatum* (caña brava) guide; this effect may be due to the inhibitory effect of 5 alpha-reductase, a suggestion that leads us to the guide utilization of the extract. Significant inhibition of Type I and Type II 5 alpha-reductase was demonstrated in a specially formulated 5-day model of co-cultured human prostate cell therapy with 10 mg/mL of permixon (a plant containing flavonoids as the study extract in this trial) [23, 24].

A decrease in the amount of the extract to 500 mg/kg compared to the other doses of the extract and other differences with finasteride mentioned above when evaluating the weekly body weight during the 30-day trial. The results of the three doses of the *Gynerium sagittatum (caña brava)* methanolic extract guide also showed a gradual increase in weekly body weight in the group that induces benign prostatic hyperplasia in rats. These findings agree with bodyweight averages. The mechanism by which this outcome occurs is that testosterone acts with an anabolic effect and acts on the genes that activate growth factors, stimuli of actin, and myosin, and culminates in an increase in muscle mass, increasing by increasing body weight [23-25].
Based on the results obtained from the evaluation of the biochemical analysis to determine the serum levels of urea, TGP, FA, and BT, it is shown that extract of GS does not produce any toxicity in the organs producing these markers, such as the liver and kidney when evaluating the beneficial effect of the methanolic extract on the *Gynerium sagittatum (Caña Brava)* guide. Overall, flavonoids are considered good scavengers of free radicals. To investigate the effect of xenobiotics and phytochemicals (flavonoids) on medicine, the liver is an essential functional model. For which this research looks especially promising. They inhibit the detoxification of CYP450 pathways when flavonoids are present and prevent harmful components' metabolism, including tetrachloride, paracetamol, and thioacetamide. The study of plant-derived flavonoids as detoxifying agents should encourage this evidence. Through the

antioxidant/electrophile response element (ARE/EPRE) in the promoter domain, polyphenols could activate the detoxification enzyme [24, 25].

In this study, glandular proliferation with altered fiber-muscular stoma and without matrix complications was demonstrated by control group histopathology. However, a contrast was observed at a dose of 500 mg/kg orally after thirty days of treatment with *Gynerium sagittatum (Caña Brava)* extract when it had a curative effect on rat-induced benign prostatic hyperplasia. Although therapeutic agents' mechanisms for BPH treatment have been reported, antioxidant/free radical imbalance or oxidative stress is postulated to be a critical, crucial essential factor in BPH development and the overproduction of process species reactive oxygen. The cause of oxidative stress contributing to tissue damage and the pathogenesis of diseases related to oxidation is inflammation. The section seems to have had its curative effect on benign prostatic hyperplasia; other researchers' studies confirmed this information [23, 25, 26].

The methanol extract of the *Gynerium sagittatum (caña brava)* guide shows, in Figure 6, a more significant decrease in serum PSA values with an extract dose of 500 mg/kg, as shown in other studies where flavonoids may inhibit the production of PSA, including isoflavones (genistein, biochanin A), flavones (luteolin, chrysin) and flavonoids (naringenin), which may hinder the production of PSA. Not well studied is the ability of flavonoids and other polyphenols to regulate androgenic effects. The various mechanisms through which these compounds inhibit PSA and other androgen-regulated proteins have been demonstrated by those studies. In the presence of resveratrol, androgen-induced decreases in PSA and human glandular kallikrein (hK2) production. Similar outcomes were seen with polyphenols from green tea (GTP). It was found that before treatment with testosterone, 20-60 mg/ml of GTP incubated with LNCaP cells significantly reduces the production of ornithine decarboxylase, another androgen-regulated protein leading to the production of PSA [27].

One of the most common urological disorders affecting older men is benign prostatic hyperplasia (BPH). It is non-cancerous prostate gland hyperplasia caused by the urethra-surrounding epithelial and stromal cell tissue of the prostate that obstructs urine flow. Although there is no clear evidence for the pathogenesis of BPH, significant critical factors related to the development and progression of BPH appear to be aging and testicular androgens. The prevalence of BPH is found in 50 percent of men at 60 and more than 80 percent of men older than 80. Androgen-dependent growth of the prostate [6].

The 5-alpha reductase enzyme catalyzes testosterone's conversion within the prostate to be the more potent androgen, dihydrotestosterone (DHT), and this enzyme interacts with androgen receptors (AR) to control average development. Therefore, the excessive production of DHT in the prostate cause's hyperplasia of prostate epithelial and prostate stromal cells, contributing to BPH development in older men. Oxidative stress was postulated as a critical essential factor for the production and progression of BPH [28, 29,1], considering the androgen imbalance. Testosterone-induced benign prostatic hyperplasia (BPH) is related to the androgen receptor signaling pathway, to promote epithelial cell proliferation; testosterone by the action of 5α reductase is converted into dihydrotestosterone (DHT), this is a more potent androgen than testosterone to stabilize and activate the transcriptional activity of the androgen receptor (AR), thus significantly increasing tissue BPH compared to the normal prostate, also increase PSA [1, 30, 29].

Androgens affect gene expression in various tissue and cell types by binding to androgen receptors (AR), dihydrotestosterone (DHT) has a higher affinity for AR than testosterone; in the prostate, the interaction between DHT and AR induces the synthesis of proteins, such as prostate-specific antigen (PSA). PSA, which is a glycoprotein in humans, is encoded by the kallikrein-related peptide 3 (KLK3) gene and is secreted by prostatic epithelial cells; when PSA rises in the blood, it is used as a clinical marker for the prognosis of the disease. The hyperplasia of the stromal cells and the prostatic epithelium would have as a mechanism an imbalance between cell proliferation and death, favoring cell proliferation and inhibiting apoptosis [31]. Sinomenine hydrochloride (SIN) is the main bioactive alkaloid isolated from the root of the traditional Chinese

medicinal plant. In BPH-1 cells, SIN therapy significantly decreased Bcl-2 protein expression, significantly increased Bax protein expression, and significantly decreased PCNA protein expression. These results indicate that SIN therapy inhibited the proliferation of BPH-1 cells through the apoptotic pathway. SIN therapy significantly reduced protein expression of Bcl-2 and PCNA in the PG tissues of mice with TP-induced BPH in vivo, indicating that SIN treatment alleviated BPH via the apoptotic pathway, which was consistent with in vitro data. These findings suggest that SIN treatment may improve BPH via the apoptotic pathway [32, 33].

Inflammation is another mechanism for the development of BPH, which is also an important clue. In about 90 percent of the samples taken during transurethral resection of prostate BPH, histological evidence of prostate inflammation is present. The metabolites of arachidonic acid (AA) are generated by cyclooxygenase (COX) lipoxygenase (LOX), and cytochrome P450 monooxygenase (CYP450) pathways, respectively. They have been acknowledged to play a crucial and essential role in inflammatory processes and BPH pathogenicity. Many eicosanoid compounds derived from the COX and LOX pathways can determine the degree of inflammation and pharmacological response as biomarkers related to diseases in a biological system. This principle of action is also applicable to the findings of the assessment of prostate gland measurements (Fig. 4) when the beneficial effect of the *Gynerium sagittatum (Caña Brava)* methanol extract is assessed showing a decrease in prostate gland length with an extract dose of 50 mg/kg, and there is also evidence of a reduction in prostate gland length with a dose of 50 mg/kg [19, 20] (Fig. 6). The mechanisms of treatment of benign prostatic hyperplasia)

4. Conclusions

This experimental study allowed us to face a current public health problem and make and use the effectiveness of the natural resources that we have at our disposal, such as the *Gynerium sagittatum (Caña Brava)* guide. Likewise, given that the experiment had favorable results in rats it is important to promote further research so that this treatment can be applied in humans, since it is a highly accessible resource for the community. We can observe that a 99% decrease in the comparative prostate index was observed in control group I, and a better effect was observed at a dose of 500 mg/kg ($P < 0.004$). This study has shown that GS has a beneficial effect on induced benign prostatic hyperplasia in rats.

Authors' contributions

Al authors contributed equally

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Availability of data and materials

All data are available in the main text. Additional data will be made available on request according to the journal policy.

Conflicts of interest

Authors declare no competing interests.

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