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South American medicinal plants for the symptomatic treatment of benign prostatic hyperplasia: A systematic review

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ABSTRACT

Background & Aim: Benign prostatic hyperplasia (BPH) is one of the prevalent age-related medical conditionin men. In the last 20 years, alternative therapies, especially those based on herbs, are increasingly preferred. The most popularly consumed herb is *Serenoa repens*, a plant growing in the subtropical south-eastern United States which has shown very efficient results compared to pharmacological conventional treatments both in terms of cost and risks associated with them. Nevertheless, the same trial found no difference between *S. repens* and placebo according to the American Urological Association Symptom Score Index. As more and more consumers are turning increasingly towards natural therapies, it would be appropriate to promote the recognition of the value of other medicinal plants with potential applicability through comprehensive research. For this purpose, a descriptive comparison between several South-American plants little publicised in the pharmaceutical market is presented to slightly narrow the gap between the reliable evidence-based and popular information for consumers and the pharmaceutical industry.

Experimental: With this approach, a review of the literature was conducted through an electronic consultation of two databases, Science Direct and Google Scholar™.

Results: This narrative review highlights the wide range of natural medicines available for controlling the inflammatory symptoms of the lower urinary tract, which could be more explored from a pharmacological and chemical point of view.

Recommended applications/industries: The future use of natural products requires further investment in pre-clinical research and in clinical trials that investigate stability and a profitable pharmacokinetic/pharmacodynamic ratio. Although they are well tolerated and used daily by South American populations, the industry's proper commercial focus on these natural remedies cannot be separated from appropriate phyto-vigilance actions promoted by pharmaceutical companies.

1. Introduction

One of the most common ageing processes in men affecting the lower urinary tract is benign prostatic hyperplasia (BPH). BPH is pathologically characterised by a cellular proliferation of epithelial and stromal elements within the prostate gland. This prostatic enlargement partly obstructs the urethra causing clinical symptoms such as pollakiuria, dysuria, urinary retention, feeling of heaviness, and pain in the perineal region, sometimes associated with hematuria, cystitis, erection, impotence, and meteorism. The

incidence of BPH can be as high as 50% by the age of 60, and 90% by the age of 85 years, with a considerable impact on quality of life (Calvar González *et al.*, 2005; Klingler, 2003). The pathogenesis of BPHis not sufficiently clear, but has been mainly ascribed to elderlyage, genetics, endocrine status such as increase of estrogens, increased enzymatic activity of 5-α-reductase which is responsible for the transformation of testosterone into dihydrotestosterone (DHT), intra-prostatic inflammatory infiltration and, lifestyle (Ishiguro and Kawahara, 2014). Despite the decrease in testosterone levels in older men, the increase in oestrogen-induced DHT receptors, along with the increased synthesis of DHT and growth factors, would be sufficient to produce an inflammatory cascade and increase the prostate size. Furthermore, inflammation has been linked to the development and progression of prostate cancer (Calvar González *et al.*, 2005; Ishiguro and Kawahara, 2014; Klingler, 2003; Veiga Fernandez *et al.*, 2005; Wein *et al.*, 2004).

To date, pharmacotherapeutic pharmacological, surgical and alternative medicine therapies are adopted by several guidelines and statements (Lerner *et al.*, 2020). Several pharmacological classes are used, including alpha-adrenergic antagonists (alpha-blockers), 5-alpha-reductase inhibitors (5-ARIs), anticholinergics and botanicals (European Food Safety Authority, 2012).In essence: **i)** α-1 antiadrenergic agents (α1-blockers): as the first-line medical approach for treating bothersome lower urinary tract symptoms (LUTS). α1–blockers provoke the relaxation of the smooth muscle in the prostate tissue and relieve, as a consequence, urinary tension (Wilt and Macdonald, 2006). **ii)** 5-α- reductase inhibitors (5-ARIs): 5-ARIs is an enzyme that converts testosterone into DHT. Inhibitors lead to decreased proliferation of prostatic DHT-depending cells, thus, regulation of DHT levels in the prostate reduces its volume and risk of prostate cancer as well. Then DHT intercepts the ability of prostate cells to undergo TGF-β-induced apoptosis (Song *et al.*, 2008). Most 5-α-reductase inhibitors are steroid derivatives or compounds with a steroid-like structure such as finasteride and dutasteride. Finally, the treatment with a combination of α-1-antiadrenergic agents with 5-α-reductase inhibitors provides fast symptom relief and reduced prostate growth, such as doxazosin in combination with finasteride respectively (McVary *et al.*, 2011; Shrivastava and Gupta, 2012). **iii)** Among alternative medicines, numerous principles of natural origin are considered. For example, natural inhibitors such as penta- and tetracyclic triterpenes and aliphatic unsaturated fatty acids have been reported and α-linolenic acid is one of the most active. (European Food Safety Authority, 2012). Ellagitannins such as (-) epigallocatechin-3-gallate and certain phenolic compounds such as flavonoids, can directly interact with receptors or interfere with inflammatory mechanisms (Liang and Liao, 1992). Another group of effective naturally occurring inhibitors are phytosterols; among them, sitosterol is believed to be the most important agent. Various mechanisms of action have been proposed for sitosterol such as anti-inflammatory effects by interfering with prostaglandin metabolism, alteration of cholesterol metabolism, suppressor of prostatic growth, anti-androgen or anti-estrogenic effects (Lowe and Fagelman, 2002).

In Europe, in the last years, a number of natural treatments strongly influenced by Chinese and African traditional medicines, have gained popularity as symptomatic remedy for BPH and LUTS due to their accessibility, affordability, and reduced side effects representing an important source of financial gain for pharmaceutical companies (Bussmann, 2013; Schippmann *et al.*, 2002). In particular, *Pygeuma fricanum* Hook. f. bark, *Hypoxis rooperi*, *Agathosma betulina* (Lara *et al.*, 2017; Schleich *et al.*, 2006; Street and Prinsloo, 2013) come from Africa whereas many others come from China such as *Dendranthema morifolium*, *Saxifraga stolonifera*, *Anemarrhena asphodeloides*, *Phellodendron amurense*, *Scutellaria baicalensis*, *Ganoderma lucidum* (Chan and Chen, 2000; Shrivastava and Gupta, 2012; Ye *et al.*, 2002). Combinations of those plants can be found with *Secale cereale* pollen (Rye) and *Cucurbita pepo* seeds (Pumpkin) and the globally used *Serenoa repens* fruit (Saw palmetto), or *Urtica dioica* roots (Stinging nettle), (Russo *et al.*, 2016). *S. repens* lipid extract from Saw Palmetto contains fatty acids, mainly oleic, lauric, myristic, palmitic, linoleic, capric, stearic, and caprylic acids (>1.0%) and their esters, whereas plant sterols and higher aliphatic alcohols are minor components.

As far as natural remedies in South America, they are not yet widespread. However, it is worth mentioning that in many regions of South America, herbal medicines or “traditional medicine” practised by native populations are often the only available treatment. It is estimated that 50% of the population has limited or no access to medicines and that a large portion of these

people still uses medicinal plants (Bussmann, 2013). Currently, the most studied plant, and therefore the most used in BPH, is *S. repens*, of which the European Medicines Agency (EMA) has granted only the hexane extract as an established medicinal product (Nunzio *et al.*, 2020). Recently, great attention has been focused on the findings of clinical studies with the mentioned species as no difference was found when considering the American Urological Association Symptom Score Index comparing *S. repens* and placebo groups (Wilt *et al.*, 2009). As more and more consumers seek natural therapies, the evaluation of the clinical value of other medicinal plants should be promoted by more rigorous pre- and clinical studies. This paper, therefore, aims to review several South American plants that are scarcely promoted in the pharmaceutical market in order to reduce the knowledge gap between evidence-based and more conventional consumer and pharmaceutical industry information.

2. Materials and Methods

The study was conducted using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group, including PRISMA checklist, to ensure the inclusion of relevant information (Liberati *et al.*, 2009; Page *et al.*, 2021). A search was conducted through electronic consultation of two databases: Sciencedirect and Google Scholar™ through manual research considering the peer-reviewed literature such as observational studies, reviews, original research articles, comments, mini-reviews and opinion papers published in English until June 2020 with the combination of the following terms: "plant" OR "herbs" OR "South American plants", in combination through the operator AND "benign prostatic hyperplasia", "prostate inflammation", "traditional use", "Andes" or "phytotherapy". Lastly, the same research was performed for Google Scholar™ without considering the aforementioned operators.

The inclusion criteria were: 1) the study reviewed reporting symptomatic benefits on lower abdominal pain by medicinal plants from South America, 2) the use of medicinal plants (individually or in combinations) reporting at least one assay in vitro, in vivo, or in animals or humans3) the study investigated with chemical profile well described and/or compounds isolated/identified from the plants. The exclusion criteria were: 1) non-compliance with the three mentioned inclusion criteria; 2) the information obtained about plants with diuretic effects with no reports about the use for prostatic dysfunctions; 3) articles for which full text was not available since they were article abstracts and/or published posters, were not in English or were grey literature.

3. Results and discussion

Following the search criteria, we retrieved n=1016 literature articles. After removal of duplicate records, most full-text articles were excluded either due to reporting of a different outcome of interest or because Benign Prostatic Hyperplasia symptomatic treatment was not the primary topic (n=387). The records were again evaluated for any duplicates, during the eligibility screening based on title and abstract were obtained n=68 articles. Once all the inclusion/exclusion criteria had been applied, the number of full texts eligible for the project was n=13.

Mashua (Tropaeolum tuberosum Ruiz &Pavón)

It is a South American Andean tuber cultivated between 3000 to 4100 masl in Peru, Bolivia, Colombia, Venezuela, Ecuador, and northwest Argentina. Traditional use of mashua claims health improvement, related, among others, to kidney and liver pain, skin eczema and prostate disorders (Gade, 1992). Additionally, it has antifungal, insecticidal, nematocidal, antibiotic and diuretic properties. These biological effects are believed to be related to its active secondary compounds, the glucosinolates (GLs) and isothiocyanates ('mustard oils') responsible for its bitterness, as well as to the content of antioxidant phenolic compounds like proanthocyanidin, anthocyanin, gallic acid, gallocatechin, procyanidin B2 and epigallocatechin, hydroxycinnamic and hydroxybenzoic acid derivatives, rutin, myricetin derivatives and carotenoids, triterpenes and steroids(Chirinos *et al.*, 2013; Ortega *et al.*, 2006; Ramallo *et al.*, 2004). Proanthocyanidin fractions were the major contributors to the antioxidant activity reported for mashua tubers (Chirinos *et al.*, 2008). This tuber stands out from the other Andean roots because of its content of vitamin C and provitamin A and elevated quantity of polyunsaturated fatty acids (70.8%), among six varieties of mashua; the presence of linoleic acid n-6 (48.70%), α-linolenic n-3 (22.13%), palmitic (21.2%), and oleic acid n-9 (3.96%), stearic

(1.47%) and Cis-vacénico (1.30%).(Guevara-Freire *et al.*, 2018)

The GLs are found in many plant families such as Brassicaceae, Capparaceae, and Tropaeolaceae, they only become active when cell rupture occurs, and GLs are rapidly hydrolysed by the action of an enzyme called myrosinase. GLs are then converted to their bioactive form, known as isothiocyanates (Ramallo *et al.*, 2004).

The Andean locals prepare a traditional drink for prostate disorders consisting of boiled tuber blended with fruit juice and honey. Some people add leaves decoctions of "cashamarucha" (*Xanthium spinosum*) and/or "cola de caballo" (*Equisetum giganteum*) to increase the effect. It is popularly known that one or two tubers for 15 days relieve prostate symptoms. Regarding pre-clinical studies, several procedures in Mashua-treated rats showed a reduction in sperm number and quality (motility and morphology). No differences in serum testosterone levels were found between rats treated with vehicle and mashua after 42 days of treatment. This effect was reversible after 24 days after cessation of the treatment (Cárdenas-Valencia *et al.*, 2008; Leiva-Revilla *et al.*, 2012).

Cashamarucha (Xanthium spinosum)

Xanthium spinosum L. (Asteraceae) is a weed with a boreal tropical distribution. The plant is considered native to South America, and in Ecuador is known by the Quechua name Cashamarucha ("spiny chrysalis"). (Bader *et al.*, 2013; Cumanda *et al.*, 1991). The folk medicine based on Inca culture, suggests the decoction of roots for the treatment of arteriosclerosis and hypertension, leaf decoction for inflammatory conditions such as oophoritis "inflammation of the ovaries", hepatitis, dentalgia, cystitis, prostatitis, nephritis and, gastritis. The use of *X. spinosum* surpassed the limits of Incas practice due to its broad diffusion. For this reason, different medical indications are depending on the country. The principal components identified in cashamarucha are flavones and their derivatives (quercetin, pendulin, iocean, centaurin, and, patuletin), polyphenols (caffeic and chlorogenic acid and their derivates), sesquiterpene lactones (xanthinin, xanthatin-xanthanol-xanthumin derivates), diterpenes (atractyloside and derivates), and phytosterols (sitosterol, stigmasterol) (Cumanda *et al.*, 1991; Piacente *et al.*, 1996). The plant infusion and tincture had positive effects on induced benign prostate hyperplasia in pre-clinical studies in a rat model.

Red maca (Lepidium meyenii)

Lepidiummeyenii is a plant that grows exclusively above 4000 m in the Central Andes of Peru and it was widely used during the colonial and precolonial periods. Maca may be eaten fresh at the time of harvest but is more commonly dried for long-term preservation. It is prepared similarly for both food and medicine. The roots are dried in the sun, cooked in milk and/or water and served either in the cooking liquid with little sugar, or in a cocktail with aguardiente (Johns, 1981).

Nowadays in the local markets it is advertised as an aphrodisiac and fertility promoter probably attributed to the presence of aromatic isothiocyanates, like benzyl isothiocyanate and p-methoxybenzyl isothiocyanate, prostaglandins and, sterols (Dini *et al.*, 1994; Johns, 1981).

In comparison with other roots such as potatoes or carrots, maca tubers dried showed higher protein fraction (10.2%) and fibre content (8.5%). The lipid fraction (2.2%) contains important amounts of long-chain unsaturated fatty acids (linoleic, palmitic and oleic acids are the most prevalent) and sterols mainly sitosterol and campesterol. The hydrolyzable carbohydrates were 59.0 % compared to 61,4 and 79.8 for potatoes and carrots respectively. Maca is also rich in mineral content, in particular, Fe, Ca, and Cu (Dini *et al.*, 1994; Quirós and Aliaga, 1997).

Histological studies on the prostatic stroma, epithelium, and acini showed that hydroalcoholic or aqueous extract of red maca containing 0.1 mg of benzyl-glucosinolate can reduce prostate size in male rats in which prostatic hyperplasia had been induced by testosterone enanthate (Gonzales *et al.*, 2007, 2005). Red Maca reduced the prostate weight at 21 days of treatment, whereas the weights of seminal vesicles, testis, and epididymis were not affected. This study suggested that red maca was specific to prostate weight, whereas finasteride was able to reduce both prostate and seminal vesicle weight. Red Maca would have an anti-hyperplastic effect on the prostate of adult miceacting first at the prostatic stromal level (Gonzales *et al.*, 2008).

Vira-vira (Achyrocline bogotensis)

A. bogotensis (Kunth), known by the popular name "vira-vira", "cenizo", or "suso", is a native plant from Colombian Andes growing from 2.100 until 3.600 m.a.s.l. in the proximity to Bogota savannah (Sagawa *et al.*, 2005). Their leaves have aromatic essential oils with the smell of turpentine. It is used traditionally in decoction for inflammatory and infections of the skin, but mainly is employed for the respiratory tract, urinary tract and prostate disorders (Lara *et al.*, 2017).

Phytochemical screening of *A. bogotensis* extract revealed the significant presence of flavones (5-hydroxy-7,8-dimethoxyflavone, 3,5-dihydroxy-7,8-dimethoxyflavone, 3,5-dihydroxy-6,7,8-trimethoxyflavone), lignans (pinoresinol, syringaresinol) coumarin (scopoletin), triterpenes (ursolic acid and sitosterol) and, cyclobutane dimers (Lara *et al.*, 2017; Pombo, 2003; Sagawa *et al.*, 2005).

Flavones and cyclobutane dimers have shown *in vitro* antiviral, antineoplastic, and immunomodulatory actions. Regarding the anti-inflammatory effect, it has been ascribed to steroids, sterols, terpenes, phenols, flavonoids, and sesquiterpene lactones (Pombo, 2003; Sagawa *et al.*, 2005).

Babassu (Orbignya phalerata)

Babassu is the popular name of *O. phalerata* Mart. This palm is found in the North, Northeast, and Centre-west regions of Brazil and it has been used by Apinajè and Guajajara natives of north-eastern Brazil, yielding a variety of important products. Babassu palms provide food, fuel, shelter, fibre, construction materials, medicine, and other necessities of life for these people. For medicinal use, their kernels are commonly eaten entirely or as a grounded powder in parts of Brazil for the treatment of urinary disorders (Balick, 1988). Preclinical evaluation of the therapeutic effects of babassu mesocarp has shown antitumor, anti-inflammatory, and antimicrobial properties (Pereira da Silva and Paz Parente, 2001; Rennó *et al.*, 2008). In addition, mesocarp has a significant anti-thrombotic activity, which seems to be related to a slow coagulation process and an enhanced ability of macrophages to produce nitric oxide after stimulation (Azevedo *et al.*, 2007; Barroqueiro *et al.*, 2011). Since babassu oil is highly lipophilic, several nanoformulations for the prophylaxis of prostate pathologies were designed by using lipid nanocarriers. These babassu oil nanosystems were shown to reduce cell proliferation, as well as to induce necrosis/apoptosis in BPH cells and tissues (De Souza *et al.*, 2011).

Roystonea regia (D-004)

D-004 is the name ascribed to the lipid extract from the fruits of royal palm *R. regia*. Fruits were reported to contain a mixture of free fatty acids wherein oleic, lauric, palmitic, and myristic are the major constituents. Experimental studies demonstrated that D-004 induced smooth muscle contraction in vitro (Arruzazabala, 2005), D-004 at 800 mg/kg daily administered seemed to prevent prostatic hyperplasia induced by testosterone suggesting that one of the mechanisms could be the inhibition of prostatic 5c-reductase activity (Carbajal *et al.*, 2005; Perez *et al.*, 2006). D-004 200 and 400 mg/kg administered orally for 14 days prevented the increase of prostate size and the testosterone-induced histological changes in rats, its effects being comparable or mildly better than those of Saw palmetto (Noa *et al.*, 2005). D-004 (320 mg/day) for 4 months was as effective as *S.repens* (320 mg/day) for decreasing LUTS in men with moderate BPH, and was well tolerated (Guzmán *et al.*, 2013). Oral D-004 (320 mg/day) treatment for 6-8 weeks has been shown to increase total antioxidant status and catalase activity in healthy men. D-004 also inhibited phenylephrine-induced contractions of isolated vas deferens and prostate preparation and hence D-004 would act similarly to *S. repens* lipid extract (Arruzazabala *et al.*, 2011; Guzmán *et al.*, 2013)

With the attention of the world population for natural remedies, medicinal herbs are currently an important source of investigation and re-assessment in a significant number of pathologies. South America is an extensive area of natural medicinal resources, and reproductive health is part of it. Currently, the value of medicines and remedies of natural origin may acquire a significant dimension in many sectors of the pharmaceutical market, especially in the case of conditions that present a certain degree of discomfort and for which there are only symptomatic remedies to be taken continuously over time. We have therefore decided to focus our review on BPH because it is a very common pathology among the male population and whose approach mainly concerns the management of LUTS symptomatology which currently remains an unresolved clinical need with a significant burden for

the patients. Indeed, over the last 10 years, the production of phytopharmaceuticals, intended for the treatment of prostatic dysfunction, has largely increased and represents an open commercial supply line characterised by the constant introduction of innovations of natural origin.

Among the most traditionally used remedies, Andean tubers were largely found. Mashua tuber shows promise in the treatment of symptoms related to BPH and LUTS and has been used in some pre-clinical studies in rat animal models, demonstrating an effect on sperm quality and quantity but without lowering testosterone levels up to 42 days of treatment, an effect that is reversible 24 hours after cessation of exposure showed a reduction in sperm number and quality (Table 1).

Table 1. Full texts eligible after applying all the inclusion/exclusion criteria.

References	Plants	Models	Study Primary Objective	Principal Chemical Compounds
Cardenas, et al 2008	mashua (aqueous extract)	in rats	influence on prostate and testicular function	p-methoxybenzylglucosinolate, proanthocyanidin, anthocyanin, gallic acid, gallocatechin, procyanidin B2 and epigallocatechin, hydroxycinnamic and hydroxybenzoic acid derivatives, rutin, myricetin derivatives and carotenoids, triterpenes and steroids
Leiva-Redilla, et al 2012	mashua (aqueous extract)	in rats	effect dose-respond on prostate and testicular function	
Gonzales, et al 2005	red maca (aqueous extract)	in rats	proapoptotic and anti-proliferative effects in prostate	benzylglucosinolate, sterols, tannins, polyunsatured fatty acid, beta carboline,
Gonzales, et al 2007	red maca (aqueous and hydroalcoholic extracts)	in rats	a dose- response effect of different doses of benzylglucosinolates	benzylglucosinolate
Gonzales, et al 2008	red maca (aqueous and hydroalcoholic extracts)	in rats	effect on prostatic stroma	benzylglucosinolate
Lara, et al 2007	vira vira (ethanolic extract)	in rats	smooth muscle relaxant effect related to the alpha-1 antiadrenergic mechanism	Flavones cyclobutane dimmer, steroids, sterols, terpenes, phenols, flavonoids, and sesquiterpene lactones
De Souza, et al 2011	babassu (ethanolic extract nanoparticles)	in vivo	effect on BPH primary stromal cell and tissue cultures	main constituent is lauric acid, others capric acid, myristic acid, palmitic acid, stearic acid, oleic acid and linoleic acid
Carbajal, et al 2005	*Roystonea regia* (lipid extract or D-004)	in rats	effects of different doses of D-004	oleic, lauric, palmitic, and myristic acid
Arruzazabala, et al 2005	*Roystonea regia* (lipid extract or D-004)	in vitro, in rats	effects mediated by α-Adrenoceptors in Rats	
Perez, et al 2006	*Roystonea regia* (lipid extract or D-004)	in vitro	effects on Prostate Steroid 5 -Reductase Activity	
Noa, et al 2005	*Roystonea regia* (lipid extract or D-004)	in rats	effect on prostate size and the testosterone-induced histological changes	
Guzman, et al 2013	*Roystonea regia* (lipid extract or D-004)	human	effect on blood oxidative Variables in Men with Benign Prostate Hyperplasia	
Arruzazabala, et al 2011	*Roystonea regia* (lipid extract or D-004)	in rats	effect on α1-adrenoreceptors-mediated contractile responses	

The case of red maca tuber is particularly interesting because histological studies have been performed on the stroma of the prostate in model animals and its effects could translate downstream into lasting anti-hyperplastic action. Other tubers used traditionally for Andean people for prostate problems were found in literature during the screening process such as *Bomarea dulcis* Alstroemeriaceae (Gonzales *et al.*, 2014) but there is no information about in vitro, in vivo, animals or human assays. Yacon (*Smallanthus sonchifolia)* is another South-American tuber that reached greater diffusion in Europe as a source of dietetic nutrition and for the production of alcohol and inulin (Fernandez *et al.*, 2006). It was observed that yacon, in combination with *Torilis japonica* and *Acorus gramineus*, showed a significant reduction in BPH symptoms prostate

weights, dihydrotestosterone levels in the serum and proliferating cell nuclear antigen expression, compared to the non-treated group (Park *et al.*, 2014) but no full text in the English language was found.

However, it is important to note the lack of human trials in all of the mentioned tubers which limits the reliability of their properties. Despite this, an attribute that is worth highlighting is the chemical composition of mashua and red maca. Both of them contain particular components named GLs (glucosinolates), the same active principles present in broccoli. Broccoli has sulforaphane as the principal glucosinolate, which is found to be effective in preventing and treating various cancers such as prostate cancer (Sharoni *et al.*, 2012). This information led consequently to expanding the marketing of supplements and pills based on broccoli extract for promoting prostate health. In this regard, mashua besides presenting bioactive glucosinolates such as p-methoxybenzylglucosinolate, p-hydroxybenzylglucosinolate and benzylglucosinolate (Campos *et al.*, 2019; Nandini *et al.*, 2020) contains carotenoids. It has been shown that carotenoids such as lycopene and b-carotene, display ameliorative effects for prostatic hyperplasia due to their proapoptotic, anti-inflammatory, antiandrogen and antioxidant activity (Hałubiec *et al.*, 2021). Thus, mashua in terms of chemical composition could have more active ingredients for the therapeutic purpose.

Palm trees in America are other groups of plants that offer a wide variety of useful components for prostate hyperplasia. Among them lipophilic extract of *Roystonea regia* was the species that appeared to have more variety of essays and literature according to the research criteria, with great advances in the design of the pharmaceutical formulation design field and referring to effectiveness results compared to Saw palmetto. Babassu, in contrast, no information was found about human assays.

We acknowledge that a crucial point in the discussion of this review remains the availability of pre-clinical studies demonstrating a potential therapeutic effect in reproducible animal model even in the clinical phase with human subjects. However, we have also found that as of today there are a number of ongoing studies with well-conceived designs where the use of these NPs is arousing interest in several research groups.

4. Conclusion

The future of the use of natural products in pathologies that currently lack a conclusive therapeutic response appears very promising but requires further investment in pre-clinical research and clinical trials that can gather evidence of stability and a profitable pharmacokinetic/pharmacodynamic ratio in experimental models, and in the identification and study of possible adverse reactions. We do not exclude that some of the extracts may reach the clinical phase and may then be approved for BPH and other urinary diseases in addition to symptom management. Even though they are well tolerated and used daily by South American populations, the right focusonthese natural remedies for their positive impact on patients' quality of life must not be separated from safeguarding their safety: this must always be at the centre of our reflections.

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