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Review Article

Equisetum arvense: New Evidences Supports Medical use in Daily Clinic

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ABSTRACT

Relevant aspects to the clinical use of *Equisetum arvense* L. (common horsetail; *EA*) were reviewed and a search was conducted in the databases PubMed, LILACS, SciELO, Virtual Health Library, Cochrane and Scopus using the keyword "*Equisetum arvense*" for articles published from 2013 through 2017. So, eighty-eight articles that addressed the pharmacognostic aspects and *in vitro* and *in vivo* biological activity, clinical trials with *Equisetum arvense* (*EA*) combined with other plants or alone, case reports concerning possible drug interactions and review studies were selected. The most relevant reported pharmacological effects included antioxidant, anticarcinogenic, antimicrobial, vascular and ileum smooth muscle relaxant, analgesic, anti-inflammatory, antinociceptive, cytotoxic, antidiabetic, hepatoprotective, antilithiatic, dermatologic, wound healing, antileishmanial, diuretic, immunizing, platelet aggregation inhibitory, osteoblast response-promoting, remineralizing, anxiolytic, sedative, anticonvulsant and cognitive performance-stimulating activities. Five clinical trials demonstrated the efficacy of phytotherapeutic complexes containing *EA*, with three for treating benign prostate hyperplasia, one for chronic musculoskeletal pain and one describing the effects of a topical preparation on brittle nail syndrome. Three clinical trials tested *EA* alone; one analyzed its pharmacokinetics; another addressed the wound-healing effect of 3% *EA* ointment and a randomized double-blind clinical trial found that the diuretic effect of *EA* was superior compared to the negative control and equivalent to treatment with hydrochlorothiazide (25 mg/day) without changes in electrolyte excretion. Considering its long history of traditional use in several countries, *in vivo* and *in vitro* research and more recent clinical studies, *EA* meets the requisites for having well-defined medical applications with proven efficacy and acceptable safety.

Key words: Common horsetail, Diuretic, *Equisetum arvense,* Medicinal plants, Phytotherapy.

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INTRODUCTION

Equisetum arvense L. (*EA*) is in the family *Equisetaceae*. It is an herbaceous perennial plant native to the northern hemisphere that has long been used for medicinal purposes. The various species in this family are widely distributed all across Canada, the United States (except for the southeast), Europe, Africa and southern Asia, including Turkey, Iran, the Himalayas, China (except for the southeast), Korea and Japan.[1,2] *EA* is not native to Brazil, where common horsetail is popularly known as "cavalinha," and it was brought to the country to be grown for medicinal use.[3,4] Although the genus *Equisetum* is not yet included in the Brazilian pharmacopoeia, several species, including *EA*, are described in other official or non-official pharmacopoeias.[4] *EA* is listed in the Phytotherapeutic Memento of the 1st edition of Brazilian Pharmacopoeia and also in the Brazilian National List of Medicinal Plants of Interest to the Unified Health System (RENISUS, for its initials in Portuguese) as published by the Ministry of Health.[5] The Collegiate Board Regulation (RDC) nº 10 (2010) of the National Health Surveillance Agency (ANVISA, for its initials in Portuguese) addresses the reporting of drugs of plant origin and regulates the commercialization of *EA* as a plant-derived drug indicated for "swelling (edema) due to fluid retention" in the form of an infusion or a decoction.[6] A dry *EA* extract-based pharmaceutical preparation has been registered by ANVISA as a phytotherapeutic drug.[7]

According to the European Medicines Agency (EMA), the Evaluation of Medicines for Human Use Committee on Herbal Medicinal Products reported that the clinical data for the absorption, distribution and pharmacokinetics of *EA* are still insufficient.[2]

The aim of the present study was to review the literature on *EA* (common horsetail) to serve as a reference for phytotherapy researchers and legislators interested in data on this important medicinal plant.

MATERIALS AND METHODS

A literature search was performed in the databases PubMed, LILACS (Latin American and Carib-

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bean Health Sciences Literature), SciELO (Scientific Electronic Library Online), Virtual Health Library (BVS, for its initials in Portuguese), Cochrane and Scopus for the period from July 2013 to August 2017 using the keywords "*Equisetum arvense,* phytotherapy, medicinal plants, common horsetail and diuretic". Articles published in Portuguese, English, French or Spanish that addressed pharmacognostic, pharmacological, pharmacokinetic or *in vivo* toxicological aspects or those that reported clinical trials with *EA* or its extracts as a plant-derived medicine as the primary subject or together with other species were considered. All the available articles were evaluated and the ones that analyzed issues related to the clinical use of *EA* were selected for review. Studies on agronomic aspects or those that were focused on the analysis of the chemical structure of substances isolated from *EA* were excluded.

RESULTS

The literature search retrieved 181 articles. Eighty-six articles that analyzed several aspects of *EA* were included for systematic review, in addition to the ANVISA and EMA documents. The articles were categorized according to their primary topics as follows: pharmacognostic aspects (8), *in vitro* (36) and *in vivo* (28) biological activity, clinical trials of *EA* combined with other plants (6) or alone (3), case reports relative to possible drug interactions (1) and review studies (5) (Figure 1).

Pharmacognostic aspects

Equisetum arvense L. belongs to the family *Equisetaceae*, genus *Equisetum* L. and subgenus *Equisetum*. The genus *Equisetum,* which belongs to the phylum Sphenophyta, appeared at the end of the Paleozoic Era, approximately 300 million years ago. It appears that this is the single extant genus from class *Equisetopsida* and it is considered the oldest extant genus on Earth. It comprises more than 30 species, most of which are small plants that ordinarily do not reach one meter high. The fact that these plants are uniformly distributed across the world might be due to having appeared prior to the continental drift, as indicated by the dating of fossil records, which might explain their easy adaptation to the most disparate climates. They are considered the terrestrial plants with the highest silica content, which might account for their many medical applications.[4,8]

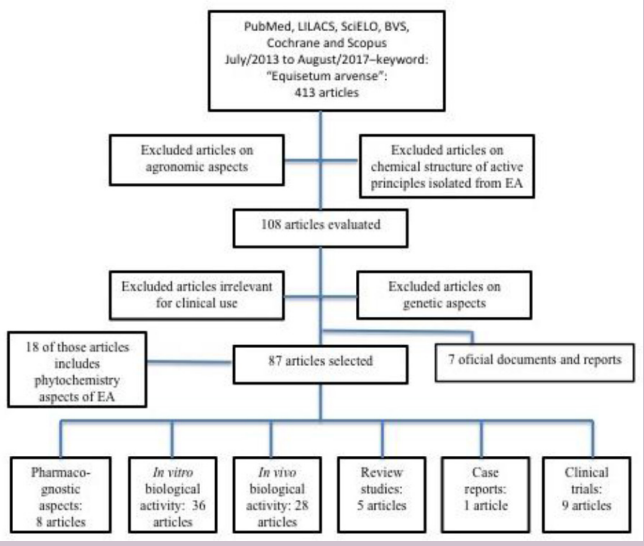

Figure 1: Flowchart representing the search of articles for review.

The name *Equisetum* derives from Latin (*equi* = horse and *setum* = tail) and may be explained by the botanical description of the plant. The leaf-free stems resemble asparaguses and when desiccated, they become hollow, rough and strong; their many fine branches with small, scale-like leaves resemble a horsetail (Figure 2).[9] The term "*arvense*" in turn comes from the overall tree-like appearance of the plant. *EA* is a perennial plant with a peculiar appearance that reaches up to 20 to 65 cm high. It is characterized by primary branched aerial stems with whorls.[10] The stems have two types, sporiferous (fertile) and sterile. Fertile stems are simple and have a reddish hue, loose brown sheaths and an oblong spike that disappears in the summer. The reproductive structure, which is known as a strobilus and is where spore production occurs, is located on the terminal end and the branches. Sterile stems are green, furrowed and hollow; the branches are thin and arranged in pairs. These simple, light green branches exhibit four angles and they are rough and articulate. The deep rhizome reaches down to 2 meters deep.[10,11]

The parts used for medicinal purposes are the shoots, which are primarily desiccated sterile stems.[2,12]

The sterile stems are composed of the cortex, parenchyma, stomata and silica granules. The parameters that characterize the plant-derived drug are its water content (15.45%), total ash (22%), acid insoluble ash (11%), water soluble ash (8%) w/w and foaming index (100).[12]

Chemical components

A broad review study reported the presence of alkaloids, carbohydrates, proteins, amino acids, phytosterols, saponins, sterols, ascorbic acid, silicic acid, phenol, tannin, flavonoids, triterpenoids and volatile oils, among many other biologically active components.[13] *EA* is quite rich in minerals and it stands out for its silicon (Si) content, especially in the

Figure 2: Illustration of the botanical characteristics of Equisetum arvense.

Source: Tropicos.org[9]

form of SiO_2 (5% to 10%) and a small portion as water-soluble silicates.[2,14] Si is known to be beneficial for plants; its absorption by transporters has a protective effect against biotic and abiotic stresses. *EA* is a valuable model for studying the absorption and deposition of this important mineral.[15,16] Phenolic acids, such as di-E-caffeoyl-meso-tartaric acid (0.008%) and methyl esters of protocatechuic and caffeic acid were detected, in addition to silicic acids, silicates, polyenoic acids, dicarboxylic acids and styryl-pyrone.[12] Potassium, calcium and phosphorus ions were identified, as were sodium, magnesium, zinc, aluminum and manganese, albeit in lower proportions.[12] Flavonoids including luteolin, quercetin, apigenin, isorhamnetin and kaempferol[17] were found at percentages ranging from 0.2% to 0.09%; quercetin and kaempferol primarily appear as glucosides (quercetin 3-glucoside and its malonyl esters).[12] The steroid fraction is essentially composed of beta-sitosterol (60%), campesterol (32,9%), isofucosterol (5.9%) and cholesterol (traces).[18] Isoprenoid flavor precursors, i.e., 3-oxo-alpha-ionol (spicy odor) and (E,E)-pseudoionone (balsamic odor) as well as odorous benzenic derivatives, i.e., phenylethanal (hyacinth and lilac notes) and 2-phenylethanol (rose odor) contribute to the odor of *EA*(Fons, 2013 #30;Fons, 2013 #30).[19] Traces of alkaloids (nicotine, palustrine and palustrinine) were detected.[12,20]

A complex that was initially categorized as having a saponin nature (equisetonine) was later identified as a sugar and flavonoid mixture.[2] With regards to the dry weight of the *EA* extract, a study published in 2013 reported a total phenol content of 18.67%, 125 mg gallic acid/g, a total antioxidant capacity of 1608 μM TEAC/mg and 0.0049 mg silicic acid/mg.[21]

Considering the significant growth of the global market for phytotherapeutic products in recent years, their regulation is crucial from a public health viewpoint. *EA* is used in countless plant-based products, but it might be adulterated with the closely related species *E. palustre* L., which might contain toxic alkaloids. Because morphology-based identification is often difficult, if not impossible, molecular techniques might be useful for the certification of processed materials. A study analyzed two molecular identification techniques as methods for testing the purity of these products. One method is based on thin-layer chromatography (TLC), in accordance with European Pharmacopoeia and the other is based on DNA barcoding, which has been used in recent years to identify materials in plant-derived products. Although TLC is more cost- and time-effective, DNA barcoding is more powerful for determining the identity of adulterant species.[22] Regarding quality control, Gallo *et al.* applied two chromatography methods (HPTLC and HPLC) to fingerprint *EA* and related species. For *EA*, HPLC might be useful for identifying and evaluating the quality of plant materials derived from related species and to investigate the presence of individual components.[23] The specific markers for *EA* identified by TLC were rutin, chlorogenic acid, kaempferol and caffeic acid.[24] Brune *et al.* described the applicability of "inter-simple sequence repeats" (ISSR)-PCR for the differentiation of *Equisetum* species with a special focus on the detection of hybrids. According to these authors, the ISSR banding patterns were highly typical for each of the most common species in the *Equisetum* genus.[25] Table 1 shows de list of phytochemicals present in *E. arvense*.

In vitro pharmacological activities

References on the antioxidant, anticarcinogenic, antimicrobial, vascular and ileum smooth muscle relaxant, anticonvulsant, sedative, anxiolytic, dermatologic, immune, antinociceptive, anti-inflammatory, antidiabetic, antileishmanial, diuretic, platelet aggregation inhibitory and osteoblast response-promoting activities of *EA* are shown in Table 2.

Table 1: List of phytochemicals present in *E. arvense.**

Sn No.	Groups	Compounds
1	Flavonoids	Kaempferol-3-O-sophoroside-7-O-glucoside, kaempferol-3-O-(6"-O malonylglucoside)-7-O-glucoside, kaempferol-3-O-sophoroside, quercetin-3-O-glucoside, apigenin, apigenin-5-O-glucoside, luteolin, luteolin-5-O-glucoside, genkwanin-5-O-glucoside and isoquercitrin
2	Triterpenoids	Isobauerenol, taraxerol, germanicol, ursolic acid, oleanolic acid and betulinic acid
3	Phenolic Glycosides	Equisetumoside A, equisetumoside B, equisetumoside C, onitin and onitin-9-O-glucoside
4	Styrylpyrone	Equisetumpyrone, 3'-deoxyequisetumpyrone and 4'-O-methylequisetumpyrone
5	Alkaloids	Nicotine, palustrine and palustrinine
6	Phytosterols	Cholesterol, epicholestanol, 24-methylenecholesterol, isofucosterol, campesterol and β-Sitosterol
7	Minerals	Silicic acid, silicates, potassium, calcium, aluminium, sulphur, magnesium and manganese

*Source: Badole and Kotwal, 2014.[43]

Table 2: Summary of the *in vitro* pharmacological activities of *EA*.

Activities	References
Antioxidant	Myagmar and Aniya, 2000;[48] Nagai *et al.* 2005;[49] Štajner *et al.* 2006;[50] Milovanović *et al.* 2007;[51] Mimica-Dukic *et al.* 2008;[52] Da Silva and Do Carmo, 2009;[53] Štajner *et al.* 2009;[54] Četojević-Simin *et al.* 2010;[55] Huh and Han, 2015[56]
Antimicrobial	Husson *et al.* 1986;[57] Suganda *et al.* 1983;[58] Guerin and Reveillere, 1984;[59] Heisey and Gorham, 1992;[60] Radulović *et al.* 2006;[61] Milovanović *et al.* 2007;[51] Brune *et al.* 2008;[25] Geetha *et al.* 2011;[62] Pereira *et al.* 2012;[63] Wojnicz *et al.* 2012;[64] De Oliveira *et al.* 2013;[65] Garcia *et al.* 2013[66]
Anti-platelet aggregation	Mekhfi *et al.* 2004;[67] Goun *et al.* 2002[68]
Cytotoxic and anticarcinogenic	Yoshinobu, 1992;[69] Goun *et al.* 2002;[68] Alexandru *et al.* 2007;[70] Četojević-Simin *et al.* 2010;[55] Al Mohammed *et al.* 2017[71]
Vasorelaxant	Sakurai *et al.* 2003[72]
Hepatoprotective	Oh *et al.* 2004[73]
Remineralization	Ferraz *et al.* 2008;[74] Raczuk *et al.* 2008;[75] Bye *et al.* 2010;[76] Law and Exley, 2011;[77] Pereira *et al.* 2012[63]
Anti-inflammatory	Gründemann *et al.* 2014;[30] Saeed *et al.* 2014[78]
Antileishmanial	Saeed *et al.* 2014[78]

In vivo pharmacological activities

Literature evidences on anxiolytic, antidiabetic, analgesic and anti-inflammatory, benign prostate hyperplasia, wound healing, remineralizing, antilithiatic, bladder myorelaxant and diuretic *in vivo* activities of *EA* are summarized in Table 3.

Review studies

References and scopes of review studies on *EA* found in the literature are shown in Table 4.

Table 3: *In vivo* activities of *EA*.

Activities	References
Anxiolytic	Dos Santos Junior *et al.* 2005;[42] Rezaie *et al.* 2011;[20] Singh *et al.* 2011;[79] Sarris *et al.* 2013[80]
Antidiabetic	Safiyeh *et al.* 2007;[81] Soleimani *et al.* 2007[82]
Analgesic and anti-inflammatory	Monte *et al.* 2004;[83] Sandhu *et al.* 2010[12]
Benign prostate hyperplasia	Oka *et al.* 2007;[34] Tamaki *et al.* 2008[36]
Wound healing	Ozay *et al.* 2010;[84] Hayat *et al.* 2011;[85] Ozay *et al.* 2013[86]
Remineralizing	Kotwal and Badole, 2016[29]
Antilithiatic	Grases *et al.* 1994;[87] Crescenti *et al.* 2015[88]
Bladder myorelaxant	Zhang *et al.* 2015[89]
Diuretic	Rebuelta *et al.* 1978;[90] Franck Bakke and Hillestad, 1980[91]

Table 4: Summary of the review studies activities of *EA*.

Scope of review	References
Systematic review on *EA*	Mello and Budel, 2013[4]
Pharmacological aspects of EA	Al-Snafi, 2017[13]
Ethanopharmacological and Phytochemical review on *EA* with reference to osteoporosis	Badole and Kotwal, 2014[43]
Pharmacology and phytochemistry of *EA*	Sandhu *et al.* 2010[12]

Case Report

A recent study described a possible interaction between *EA* and antiretroviral therapy in two HIV-positive patients. This interaction might have triggered a virological breakthrough in the patients, who maintained the same regimen for many years that included lamivudine, zidovudine, efavirenz, emtricitabine and tenofovir. Given the scarce data on the pharmacological properties of *EA* regarding potential drug-herb interactions, the authors concluded that these interactions might occur when these agents are taken simultaneously and thus advise clinicians to avoid this combination until further data become available.[26]

Summary for medical use in daily clinic

Dosage form

According to the Phytotherapeutic Memento in the 1st edition of Brazilian Pharmacopoeia, the primary pharmaceutical preparations are as follows:[27]

- Tincture: (1:4-5) in 31.5% hydroethanolic solution (w/w)
- Tincture: (1:4-5) in 96% hydroethanolic solution (v/v)
- Capsules and tablets containing dry extract (4-7:1) via aqueous extraction
- Capsules and tablets containing dry extract (7.5-10.5:1) via extraction with 70% hydroethanolic solution (v/v)[1]
- Medicinal tea (infusion)

Dose

Single doses by oral route are used by adults as follows:[27,28]

a) Infusion of leaves or shoots: 2-3 g in 250 mL of boiling water (teacup)

b) Coarsely fragmented plant matter: 570 mg

c) Tincture (1:4-5) in 31.5% hydroethanolic solution (w/w): 20 drops

d) Tincture (1:5) in 96% hydroethanolic solution (v/v): 30 to 40 drops

e) Dry extract (4-7:1) via aqueous extraction: 185 mg

f) Dry extract (7.5-10.5:1) via extraction with 70% hydroethanolic solution (v/v): 200-225 mg.[2]

The average dose is three *single doses* per day; the maximum daily dose is four *single doses*.[2]

Uses based on folk medicine

For generations, *EA* has been used in folk medicine for the treatment of several conditions, including tuberculosis, kidney and bladder infections; as a hemostatic for profuse menstruation, nose, lung and gastric bleeding; rheumatic conditions; gout; wounds and ulcers; swelling, bone fractures and burns; brittle nails; and hair loss.[1] *EA* is traditionally indicated primarily as a mild diuretic, for swelling, inflammation and remineralization.[2,29] There is a long tradition of *EA* use in Europe for treating inflammatory problems.[30]

Uses based on traditional medicine

In Ayurveda, *EA* is traditionally used for treating prostate inflammation and hypertrophy, urinary incontinence and nocturnal enuresis in children.[31] Nicholas Culpepper, a 19th century English botanist, used *EA* juice or decoctions to make bleeding stop as well as for treating skin ulcers, wounds and inflammation, kidney stones and cystitis.[14]

Uses based on preclinical studies

In many countries, the corresponding legislation is based on the long history of use in traditional medicine, ethnopharmacological studies, phytochemistry research and pharmacological studies.[14]

A report published by the EMA Committee on Herbal Medicinal Products (CHMP)[2] lends support to the use of *EA* by oral route to promote the kidney excretory function, the treatment of post-traumatic and stasis edema, irrigation therapy in bacterial and low urinary tract inflammatory diseases and kidney and bladder stones. The dose recommended by EMA is 220 to 225 mg of dry extract 3 or 4 times per day.[2] The maximum daily dose used in clinical studies was 900 mg of dry extract.[32]

German Commission E approved the use of *EA* as an herbal medicine (in the form of powder or tea) at an average daily dose of 3 to 6 g or the equivalent amount of other preparations in 2 or 3 daily intakes for treating post-traumatic or stasis swelling and as a diuretic in cases of bacterial and inflammatory lower urinary tract diseases with the presence of urinary sediment. *EA* was also approved for topical use as a decoction (50 g/L) in compresses or baths or as a liquid extract at a dose of 50 drops diluted in water as an adjuvant for treating hard-to-heal wounds.[2,14,33]

In Brazil, ANVISA's RDC no. 10 recommends using *EA* in the form of an infusion or a decoction at 3 g/150 mL of water, 2 to 4 times per day to treat edema (swelling) due to fluid retention.[6]

Uses based on clinical studies

Three studies evaluated the usefulness of Eviprostat®, a commercial preparation containing *Chimaphila umbellata*, *Populus tremula*, *Pulsatilla pratensis and EA* extracts and wheat germ oil for treating Benign Prostate Hyperplasia (BPH). The effects of each individual component on the Reactive Oxygen Species (ROS), namely superoxide anion (O^{2-}) and hydroxyl radical (OH*), were assessed. The results suggest that ROS suppression might partially contribute to the anti-inflammatory action of Eviprostat®, which might be involved in its therapeutic effect in BPH.[34] The clinical efficacy of Eviprostat® was assessed in two studies. One was an open-label multicenter clinical trial in which 100 patients with BPH took 2 tablets of Eviprostat® 3 times per day over 12 weeks. The primary parameters for efficacy were the International Prostate Symptom Score (IPSS), maximum urinary flow rate (Q_{max}), Residual Urine (Ru) and prostate Volume (V). All the parameters exhibited

significant improvement. The rate of clinical adverse events was 1%.[35] The other study compared the usefulness of Eviprostat® and EVI-F, a new formulation of Eviprostat® containing two times more active ingredients. Patients with BPH were randomly allocated to the Eviprostat® group (6 tablets/day) or the EVI-F group (3 tablets/day). The clinical efficacy of these two drugs was evaluated by means of the IPSS and the Quality of Life (QOL) score and their safety was evaluated based on the incidence of side effects. Based on guidelines for clinical studies on dysuria, the changes in the total IPSS and the QOL score were comparable to the previously reported data for classical BPH treatment agents and these parameters showed gradual improvements over the course of the treatment period. Both treatments were well tolerated. The clinical usefulness of monotherapy with EVI-F or Eviprostat® was reasonably demonstrated in this study. Furthermore, both treatments reduced nocturia, which has an impact on the QOL of patients with BPH.[36]

A clinical trial assessed the efficacy of *EA, Urtica dioica, Boswellia serrata, Allium sativum* and *Apium graveolens* for treating chronic musculoskeletal pain. Combined with Vitamin B1, a mixture of the five plants promoted a significant reduction in the score on the pain scale and significantly improved the functional mobility of body sites affected by chronic joint, back and muscle pain. No adverse effect was reported.[37]

The efficacy of topical *EA* ointment application was tested for wound healing and the reduction of inflammation and pain relief after episiotomies in nulliparous mothers. A double-blind clinical trial analyzed 54 women in the *EA* group and 54 women in the placebo group. Five and 10 days after childbirth, the primary outcomes (wound healing and pain intensity) were assessed based on the Redness, Edema, Ecchymosis, Discharge and Approximation of the edges (REEDA) scale and a Visual Analog Scale (VAS). In addition, the number of painkillers used and adverse events experienced during the 10-day period of the study were analyzed. The mean scores were significantly lower in the treated group compared to the controls at both evaluation times. The difference in the pain score was significantly lower in the treated group and the mean number of acetaminophen tablets used over the 10-day period was higher for the control group. The 3% *EA* ointment promoted wound healing and relieved pain during the 10-day period after the episiotomy.[22]

To assess the topical effect of *EA* on brittle nails, a clinical, blind, crossover and controlled study randomly allocated 38 female patients to two groups. The groups alternately received treatment with a cosmetic nail polish that contained *EA*, methyl sulfonyl methane and Hydroxypropyl Chitosan (HPCH) that was indicated for treating brittle nail syndrome. The tested preparation was more effective at controlling the signs of the syndrome compared to not using it.[38]

The effect of a water-soluble nail polish containing *EA* on nail psoriasis was tested. A randomized, double-blind, placebo-controlled, parallel-group trial was performed to evaluate the efficacy and tolerability of a nail polish containing HPCH, *EA* and methyl sulfonyl methane on nail psoriasis. The test product or a placebo was applied once daily for 24 weeks. The clinical cure rate showed the statistically significant superiority of the tested nail polish compared to the placebo (Fisher's exact test, P=0.0445). This superiority was already present after 16 weeks of treatment. In addition, an analysis of the Nail Psoriasis Severity Index showed statistically significant clinical improvement after 12 weeks of treatment in comparison to the results obtained after 8 weeks.[39]

The efficacy of Urox®, a proprietary combination of phytomedicine extracts including, *Crataeva nurvala* stem bark, *Equisetem arvense* stem and *Lindera aggregata* root, in reducing a variety of bladder symptoms, compared to an identical placebo, was documented in a randomised, double-blind, placebo-controlled trial. Data were collected at baseline, 2, 4 and 8 weeks, with the primary outcome being self-reported urinary frequency. One hundred and fifty participants (59% female, aged) took part in the study. At week 8, urinary day frequency was significantly lower in response to treatment compared to placebo. Similarly, episodes of nocturia were significantly fewer after 8 weeks of treatment versus placebo. Symptoms of urgency and total incontinence were also lower (all p<0.01) in the treatment group. Significant improvements in quality of life were reported after treatment in comparison to placebo. No significant side effects were observed resulting in withdrawal from treatment.[40]

In filling a considerable gap in the clinical studies on the diuretic effect of *EA*, a double-blind, randomized clinical trial randomly distributed 36 healthy male volunteers into 6 groups (n=6) that underwent a three-step intervention. *EA* dry extract (900 mg/day), placebo (900 mg/day) or hydrochlorothiazide (25 mg/day) were alternately administered for 4 consecutive days and separated by a 10-day washout period. The diuretic effect was assessed based on the 24-h water balance and serum electrolytes. Each volunteer served as his own control and the results were compared between the 3 groups. *EA* exhibited a diuretic effect that was stronger than that of the negative control and was equivalent to that of hydrochlorothiazide (25 mg) without causing significant changes in the excretion of electrolytes. There was no significant increase in the urinary elimination of the catabolites. Rare minor adverse events were reported. All the laboratory parameters remained within the corresponding normal range. The clinical, electrocardiographic and laboratory data did not change before and after the experiment, which suggests that the drug is safe for acute use. Further research is needed to better clarify the mechanism of the diuretic action and the other possible pharmacological actions of this phytomedicine.[32]

Toxicity, contraindications, adverse effects and interactions

In assessment of acute hepatotoxicity in rats, no anatomical pathology changes were found in the liver tissue or in the liver enzymes.[3]

No toxic effect was detected with respect to clinical, hematological, urinary or serum biochemical parameters, body weight or internal organ weight when 0.03% to 3% *EA* hydroalcoholic extract was added to the food given to male and female rats for 13 days.[41]

A hydroalcoholic *EA* extract in doses of 2 and 5 g/Kg (IP) was associated with 12% and 37.5% mortality in rats, respectively. As the LD_{50} was > 5 g/Kg, the extract was rated practically non-toxic.[42]

EA is contraindicated during pregnancy and breastfeeding as well as for children under 12 years old due to a lack of specific studies[2] and the presence of nicotine.[43]

Individuals with kidney or heart failure should avoid *EA* because its diuretic effect might cause potassium loss, which might particularly affect patients with heart failure who were treated with digitalis medicines or other drugs that reduce serum potassium.[6]

According to considerations based on pharmacological inferences, *EA* might cause a Vitamin B1 (thiamine) deficiency due to the presence of the enzyme thiaminase.[44]

Luengo does not recommend *EA* for patients with active gastroduodenal ulcers because the presence of tannins and silicic salts and acids might irritate the gastric mucosa.[45]

Rare cases of allergies might develop among patients sensitive to *EA*'s chemical components. Prolonged use and abuse might cause exudative edema, dysphagia, headache, tenesmus and loss of appetite and when high doses are used, gastric and urinary irritation may occur due to the presence of nicotine.[6]

Pharmacological interactions with lithium and digitalis medicines have been described.[14] Since a possible interaction between *EA* and antiretroviral therapy might have triggered a virological breakthrough in two patients and given the scarce data on the pharmacological properties

of *EA* regarding potential drug-herb interactions, clinicians should avoid this combination until further data become available.[26]

Although nicotine in high doses might cause tolerance and dependence, it might aid in smoking cessation in low doses.[46]

Precautions during the use of Equisetum arvense

Individuals taking *EA* are recommended to take Vitamin B complex supplements. Chronic alcoholics should avoid *EA* due to a propensity for Vitamin B1 deficiency. The concomitant use of nicotine-containing substances, diuretics or lithium medicines should be avoided. Supervision by a healthcare specialist is recommended while taking *EA*.[43]

Absorption, distribution, metabolism, elimination

A clinical study on *EA* alone analyzed the excretion of urinary metabolites of flavonoids and hydroxycinnamic acids, which are polyphenolic compounds present in our daily diet in the form of tea and vegetables as well as in herbal remedies used in phytomedicines. *In vivo* data on absorption, bioavailability and metabolism after the oral intake of these compounds are scarce and contradictory. To examine their metabolism and renal excretion, a standardized *EA* extract was administered to 11 volunteers following a flavonoid-free diet for 8 days. Twenty-four-h urine samples were collected and analyzed by HPLC-diode array detection (DAD). The putative quercetin metabolites (3,4-dihydroxyphenylacetic acid or 3,4-dihydroxytoluene) were not detected in any of the urine samples. The endogenous amount of homovanillic acid, which is generally regarded as one of the primary quercetin metabolites, did not increase significantly. However, hippuric acid (the glycine conjugate of benzoic acid) increased twofold after drug intake. Thus, the degradation to benzoic acid derivatives rather than phenylacetic acid derivatives seems to be a predominant metabolic route.[47]

DISCUSSION AND CONCLUSION

EA is a medicinal plant that has been used for millennia in the traditional medicine of India, China and Greece and in the folk medicine of many countries. The traditional knowledge about *EA* and scientific studies conducted since the beginning of the 20th century led to its approval as a medicine in several countries, including Brazil.

In this systematic review, unlikely other review studies, we have compiled all the clinical studies that include *EA* alone or in associations, with the aim of supporting its safe clinical use in various situations at daily medical clinic. In addition, we showed its main pharmacological actions and indicate the safe doses, along with the care that should be taken regarding toxicity issues, adverse effects and medicinal interactions. Three studies showed the usefulness of a preparation containing *Chimaphila umbellata*, *Populus tremula*, *Pulsatilla pratensis* and *EA* extracts and wheat germ oil for treating benign prostate hyperplasia.[34-36] The results suggest that ROS suppression might partially contribute to the anti-inflammatory action. The flavonoid isoquercitrin (quercetin-3-*O*-glucoside) present in the extracts of *EA* may interfere with the polyfunctionality of immunocompetent cells, thereby providing an anti-inflammatory mode-of-action.[30]

A clinical trial demonstrated the efficacy of *EA, Urtica dioica, Boswellia serrata, Allium sativum* and *Apium graveolens* for treating chronic musculoskeletal pain, combined with Vitamin B1. The authors claims that *EA* contains β-sitosterol, campesterol and isofucosterol, which provide anti-inflammatory steroidal effects and, thus, may explain the success of the therapeutic effect.[37]

The efficacy a combination of phytomedicine extracts including *Crataeva nurvala*, *EA* and *Lindera aggregata* in reducing a variety of bladder symptoms, was documented in a randomised, double-blind, placebo-controlled trial. Symptoms of nocturia, urgency and total incontinence were lower in the treatment group. *EA* is a genito-urinary astringent for urinary incontinence and enuresis in children. Its silica content likely contributes to this effect, besides its anti-inflammatory, anti-bacterial and anti-lithogenic effects.[40]

In a randomized, double-blind clinical trial, the diuretic effect of *EA* was superior compared to that of the negative control and equivalent to that of hydrochlorothiazide (25 mg), without significant changes in electrolyte excretion, signs of toxicity or significant adverse effects, suggesting that *EA* is an effective diuretic and safe for acute use.[32] The flavonoids and the high potassium content may contribute to this effects.[2]

A topical *EA* 3% ointment application promoted wound healing and relieved pain during the 10-day period after the episiotomy.[22] The authors of the studies discussed that the positive effects on wound contraction may have resulted from silicea, silicic acid, silicon and saponin content in the extracts. The results support the traditional topical use of the water decoct in wound healing.[2]

The topical effect of *EA* on brittle nails was more effective at controlling the signs of the syndrome compared to not using it.[38] In another clinical trial, the effect of a water-soluble nail polish containing *EA* on nail psoriasis showed superiority, when compared to the placebo.[39] *EA* is a source of organic silicon and since nails contain 16 mg of silicon dioxide per 100 g, it seems to contribute to their strength and hardness while maintaining stability among keratin fibrils.[38]

Recent clinical evidences and the testing of preparations and products containing *EA* for therapeutic purposes at a large scale are paving the way for new research (including phase IV and drug surveillance studies).

The scientific studies that support the validation of *EA* by EMA, Commission E and the Brazilian Ministry of Health are based on its traditional use, preclinical pharmacological studies and more recently, on clinical studies. The applied criteria also serve to assess the toxicity and safety of the use of this plant; however, they do not rule out the possibility of still unknown toxicity-related factors. For this reason, *EA* should not be used by children under 12 years old or by pregnant or breastfeeding women. Aqueous preparations should be avoided by patients with health problems that demand fluid restriction (heart or kidney failure).

The final report of the EMA/CHMP concludes that the toxicology data on *EA* are still insufficient and thus the committee-maintained *EA*'s classification as a traditional medicinal product in Europe. However, considerable advances in research indicate that the status of *EA* as a phytotherapeutic agent is becoming more likely.

Due to its age-long and almost cosmopolite use and the available studies in addition to its use as a traditional and folk medicinal agent, *EA* is emerging as a phytotherapeutic drug that is potentially useful in several medical fields. For this reason, new studies on its pharmacokinetics, pharmacodynamics and toxicology are needed, as is evidence on its therapeutic effects, with special emphasis on its potential as an effective and safe diuretic.

One might thus conclude that as a function of its long history of traditional use in several countries, *in vivo* and *in vitro* research and more recent clinical studies, *EA* meets the requisites for well-defined medical application with proven efficacy and acceptable safety. However, large-scale clinical trials are needed to confirm this hypothesis.

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CONFLICT OF INTEREST

Due to the strictly academic nature of this publicly funded scientific review, the authors declare no conflicts of interest.

ABBREVIATIONS

ANVISA: National Health Surveillance Agency of Brasil; **BPH:** Benign Prostate Hyperplasia; **BVS:** Virtual Health Library, Brasil; **CHMP:** Committee on Herbal Medicinal Products; **EA:** *Equisetum arvense*; **EMA:** European Medicines Agency; **FAPEG:** Fundação de Amparo à Pesquisa do Estado de Goiás; **HPCH:** Hydroxypropyl chitosan; **HPLC:** High performance liquid chromatography; **HPLC-DAD:** HPLC coupreld winth diode array detector; **HPTLC:** High performance thin-layer chromatography; **IP:** Intraperitoneal administration route; **IPSS:** International Prostate Symptom Score; **ISSR-PCR:** Inter-simple sequence repeats; **LD_{50}:** Lethal median dose; **LILACS:** Latin American and Caribbean Health Sciences Literature; **Q_{max}:** Maximum urinary flow rate; **QOL:** Quality of life; **RDC:** Collegiate Board Regulation of Brasil of the National Health Surveillance Agency; **REEDA:** Redness, Edema, Ecchymosis, Discharge and Approximation of the Edges Scale; **RENISUS:** Brazilian National List of Medicinal Plants of Interest to the Unified Health System; **ROS:** Reactive Oxygen Species; **Ru:** Residual Urine; **SciELO:** Scientific Electronic Library Online; **TEAC:** Total antioxidant capacity; **TLC:** Thin-layer chromatography; **V:** Prostate volume; **VAS:** Visual Analog Scale.

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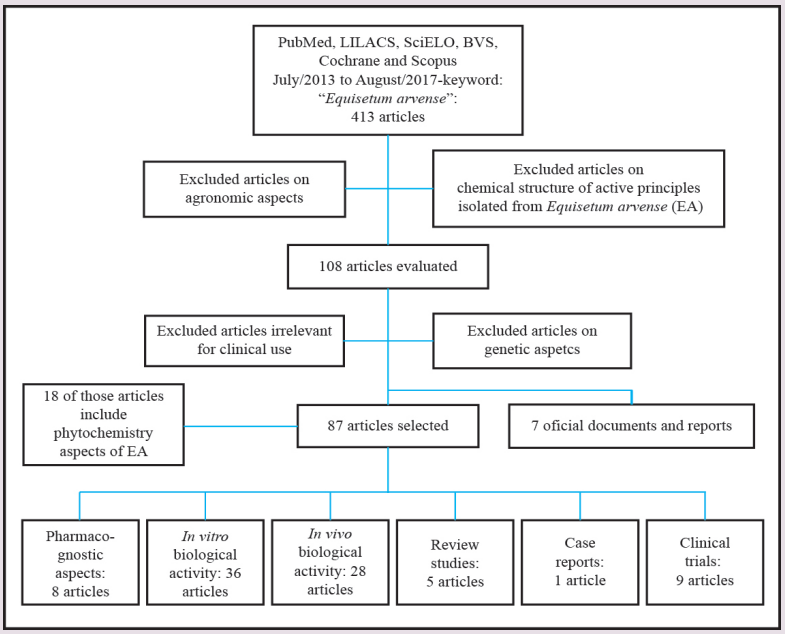
GRAPHICAL ABSTRACT



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