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RESEARCH ARTICLE

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Suspected adverse reactions to medications and food supplements containing *Serenoa repens*: A worldwide analysis of pharmacovigilance and phytovigilance spontaneous reports

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Abstract

The safety of *Serenoa repens* (SR)-containing products was evaluated conducting a retrospective worldwide analysis of pharmaco- and phytovigilance report forms of suspected adverse reactions (SARs) collected up to 31 January 2022. Multivariate logistic regression was performed to estimate the odds ratios (ORs) of serious SAR. A total of 1810 report forms were analysed; 92% of subjects were males, with a median age of 69 years; 44% of cases were defined as serious. Subjects exposed to dietary supplements had a higher risk of developing serious SARs (OR: 1.60 [95% CI: 1.20–2.15]), as subjects exposed to 2–5 (OR: 1. 83 [95% CI: 1.30–2.58]) or more than 5 (OR: 3.45 [95% CI: 2.36–5.06]) suspect/interacting products. The probability of experiencing serious SAR was higher for subjects exposed to concomitant products (OR: 1.55 [95% CI: 1.15–2.08]), to more than four active compounds (OR: 4.38 [95% CI: 3.21–5.99]) and to SR for more than 14 days (OR: 1.89 [95% CI: 1.10–3, 22]), and lower for subjects exposed to higher doses of SR (OR: of 0.34 [95% CI: 0.20–0.58]). This evidence improves awareness on safety of SR containing products, suggesting the need of a further update of periodic reviews by national and international regulatory agencies.

KEYWORDS
drug, food supplement, pharmacovigilance, safety, saw palmetto, *Serenoa repens*

Giada Crescioli, Valentina Maggini, Fabio Firenzuoli, and Niccolò Lombardi are co-first and co-last authors.

1 | INTRODUCTION

The efficacy and safety of *Serenoa repens* (SR, also known as saw palmetto) have been assessed in several preclinical and clinical studies, and reviewed by regulatory agencies, such as the European Medicines Agency (EMA), in their assessment reports (European Medicines Agency, 2021; Laekeman & Vlietinck, 2013). In vitro, fatty acids (free fatty acids of caprylic, capric, lauric, myristic, palmitic, stearic, oleic, linoleic and linolenic acids) and phytosterols (β-sitosterol, campesterol and stigmasterol) containing SR extracts (Kwon, 2019) have demonstrated anti-inflammatory, anti-androgenic and estrogenic effects along with decrease in sexual hormone binding globulin; inhibition of 5 α-reductase, muscarinic cholinoceptors, dihydropyridine receptors and vanilloid receptors, as well as neutralisation of free radicals (Ye et al., 2019).

In clinical practice, the active constituents of SR extracted from the dried ripe fruit are currently used at the dose of 160–320 mg for the symptomatic treatment of benign prostatic hyperplasia (BPH), which are on the market as approved medications as well as dietary supplements (Tacklind et al., 2009). However, since SR extracts are generally sold without prescription, it is difficult to determine the numbers of subjects who take these products regularly, but it is estimated that the number of regular users is approximately 2.5 million adults in the United States (Avins et al., 2008). More recently, marketed products containing SR are also used for other therapeutic purposes such as androgenetic alopecia and acne (Dhariwala & Ravikumar, 2019), despite cumulated body of scientific evidence reports controversial results for these indications of use. A Cochrane systematic review performed in 2009 concluded that the long-term administration (more than 6 months) of SR extract is not superior to placebo in reducing lower urinary tract symptoms (LUTS) consistent with BPH (Tacklind et al., 2009). Furthermore, an updated review published in 2012 confirmed that SR, at double and triple doses, did not improve urinary flow measures or prostate size in men with LUTS consistent with BPH (Tacklind et al., 2012). Instead, a systematic review and meta-analysis of clinical studies published in 2016 showed that SR extract was effective for relieving BPH symptomatology as compared with placebo (Novara et al., 2016). Additionally, the authors reported that the hexanic lipidosterolic extract of SR (Permixon®) decreased nocturnal voids and increased maximum flow rate compared with placebo and had efficacy in relieving LUTS similar to tamsulosin and short-term finasteride. Permixon® had also a favourable safety profile with a very limited impact on sexual function, which is significantly affected by all other drugs used to treat LUTS/BPH, such as finasteride, tamsulosin or alfuzosin. Recently, a multicentre, randomised, double-blind, placebo-controlled trial confirmed that SR extract was effective, safe, well-tolerated and clinically and statistically superior to placebo in LUTS/BPH population (Ye et al., 2019). The Non-Neurogenic Male LUTS Guidelines from the European Association of Urology recommend only the use of hexane extract of *Serenoa repens* (HESr) although the clinical evidence on the efficacy of monotherapy is uncertain. Nevertheless, the combined use of SR and alfa1-blockers appears to be useful. With respect to safety and tolerability, HESr had a favourable safety profile, with gastrointestinal disorders being the most frequent adverse effects, with a very limited impact on sexual function (Oelke et al., 2013).

Overall, SR-containing products are generally well tolerated, and present specific contraindications in case of hypersensitivity and liver diseases (Laekeman & Vlietinck, 2013). A possible causal relationship with liver damage and pancreatitis has been reported anecdotally (Bruminhent et al., 2011; Jibrin et al., 2006; Lapi et al., 2010; Wargo et al., 2010). Clinical trials are generally not the optimal setting to investigate hepatic safety because patients with liver diseases are often excluded and clinical trials can point out only common and acute adverse events. Most minor adverse effects are related to the gastrointestinal system, especially when taken on an empty stomach (European Medicines Agency, 2021; Laekeman & Vlietinck, 2013). Biological plausibility for the association of SR and gynecomastia (European Medicines Agency, 2021; Laekeman & Vlietinck, 2013) and erectile dysfunction (Gallo et al., 2022) have been described, and also cases of allergy have been reported (European Medicines Agency, 2021; Laekeman & Vlietinck, 2013). Increases in blood pressure and ocular effects have been listed in the summary of product characteristics (SPCs) of some marketed products (European Medicines Agency, 2021; Laekeman & Vlietinck, 2013). Potential interactions with concomitant medications, such as anticoagulants (Yue & Jansson, 2001), are of particular concern, especially in frail populations (i.e., elderly, comorbidities, polypharmacy, etc.). Finally, considering that there is no therapeutic use in children, adolescents and women, the use of medications and food supplements containing SR should be avoided in these subsets (European Medicines Agency, 2021; Laekeman & Vlietinck, 2013). Considering the above-mentioned knowledge gaps and the growing use of medications and foods supplements containing SR in the general population, the aim of this present study was to investigate the safety profile of these products through a worldwide analysis of all pharmaco- and phytovigilance report forms, in relation to the indication of use, dosage and time of onset.

2 | METHODS

2.1 | Study design and data sources

This retrospective observational pharmaco- and phytovigilance analysis was performed on suspected adverse reaction (SAR) report forms collected up to 31 January 2022, from four National and International databases. The Italian Pharmacovigilance Network (RNF) was established in 2001 by the Ministry of Health (in 2003 by the Italian Medicines Agency, AIFA). RNF collects all suspected healthcare professionals' and citizens' SAR report forms from all Italian regions referring to drugs and vaccines (Crescioli, Bettiol, et al., 2021; Crescioli, Boscia, et al., 2021; Lombardi, Bettiol, et al., 2020; Lombardi, Crescioli, et al., 2020; Lombardi, Crescioli, Bettiol, Tuccori, et al., 2019; Lombardi et al., 2018, 2022; Mattioli et al., 2022; Pagani et al., 2021, 2022).

The Italian Phytovigilance system was set up in 2002 and it is coordinated by the Italian National Institute of Health (ISS). The

system collects all phytovigilance report forms referring to SARs occurring in subjects exposed to natural health products, such as foods supplements, herbal and homeopathic products, galenic preparations, traditional Chinese medicine and ayurvedic remedies (Crescioli et al., 2019; Lombardi et al., 2021, 2022; Lombardi, Crescioli, Bettiol, Menniti-Ippolito, et al., 2019).

VigiBase is the World Health Organization's (WHO) global pharmacovigilance database of safety reports of suspected SARs that was developed and maintained by the WHO-Uppsala Monitoring Centre (WHO-UMC). It collects report forms of suspected SARs from more than 170 national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring (WHO PIDM) (Noseda et al., 2022).

The Center for Food Safety and Applied Nutrition, CFSAN, Adverse Event Reporting System (CAERS) is a database maintained by the United States (US) Food and Drug Administration (FDA) since 2004. The CAERS database contains information on SAR reports and product complaint reports submitted for foods, dietary supplements and cosmetics. SAR report forms can be submitted by consumers, physicians and healthcare practitioners, and data are publicly available since 2016 (Monnot et al., 2021).

Each database was queried for SAR report forms reporting SR containing medications or CAM products as suspect/interacting agents. Considering the regulatory status of SR products, including medications and food supplements, and the expected heterogeneous scenario in the reporting of SARs, the use of different databases may allow to provide an overview of the safety profile of SR (Gatti et al., 2021; Raschi et al., 2018). Moreover, the Italian Phytovigilance system does not currently submit reports to WHO, thus no duplicates are not likely to be collected.

2.2 | Data management

Data from each queried source were merged and included in a single database created ad hoc for this analysis. The complete database with all SAR report forms was built using STATA v17 (StataCorp, USA).

Only pharmaco- and phytovigilance report forms reporting medications and CAM products containing SR as suspect/interacting agents were considered. Those containing medications and CAM products containing SR as concomitant agents were excluded.

Since Italy participates in the WHO PIDM, duplicate report forms from the RNF that were already present within VigiBase data were excluded from the analysis.

From each pharmaco- and phytovigilance report form the following demographic and clinical data were retrieved: country of origin, reporter's qualification, subject's age and sex. From each included report form, suspect/interacting and concomitant medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system (Lombardi et al., 2022; Mattioli et al., 2023). Suspect/interacting CAM products containing SR were described in terms of their content, listing each active compound reported in labels or within the description of the product available for customers.

For each SR suspect/interacting medication or CAM product, if available, the following parameters were considered: SR daily dose (mg), duration of treatment (days), indication/motivation of use and action taken with the suspect/interacting medication or CAM product after SAR occurrence (i.e., change of dosage, product withdrawal).

SARs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and reported as System Organ Class (SOC) and Preferred Term (PT) (Lombardi et al., 2022; Mattioli et al., 2023). SARs seriousness, defined according to the WHO classification (events leading to death, life-threatening, requiring hospitalisation, leading to significant disability or a congenital anomaly/birth defect, or other medically important condition), as well as SARs outcome (resolution with sequelae, still unresolved, complete resolution, improvement, death and not available) were also retrieved (Mattioli et al., 2022).

According to the information listed in each report form, the following variables were also analysed: presence of active compounds other than SR in the suspect/interacting agents, total number of suspect/interacting agents, total number of active compounds present within the suspect/interacting agents and total number of concomitant products.

2.3 | Statistical analysis

Descriptive statistics were used to summarise data. Categorical data were reported as frequencies and percentages, whereas continuous data were reported as mean and standard deviation (SD) or median values with the related interquartile ranges (IQRs). Multivariate logistic regression models were fitted to estimate the odds ratios (ORs) with 95% confidence intervals (CIs) of serious SAR according to age, sex, number of suspect/interacting drugs, presence of concomitant medications or other CAM products, SR daily dose (mg) and presence of active compounds other than SR in the suspect/interacting agents. All results were considered statistically significant at $p < 0.05$. Statistical analyses were performed with STATA v17 software (StataCorp, USA).

3 | RESULTS

A total of 1810 pharmaco- and phytovigilance report forms were included in the present analysis, of which 86.2% were from VigiBase, 9.3% from CAERS, 3.8% from ISS and 0.7% from RNF-AIFA (Figure 1). The majority of reports came from the European Union, in particular from Germany ($n = 451$), France ($n = 417$), Italy ($n = 161$) and Spain ($n = 131$), followed by United States ($n = 220$), Australia ($n = 48$), United Kingdom ($n = 24$) and Canada ($n = 23$). The trend of report forms by year (1986–2022) is described in Figure S1.

3.1 | Characteristics of subjects

Most subjects that experienced a SAR following the use of medications (34.0%) and/or CAM products (58.6%) containing SR were adult

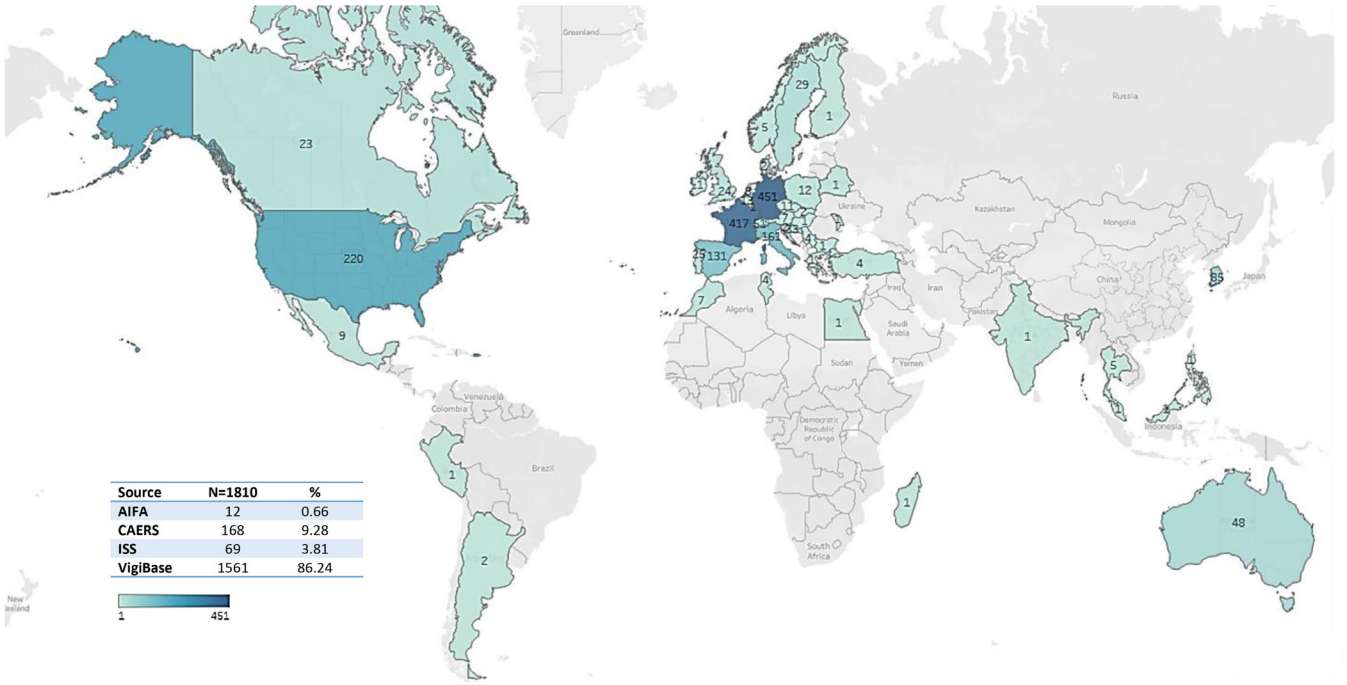

FIGURE 1 Suspected adverse reaction report forms provenience.

males (92.0%), with a median age of 69 years (IQR: 58–76; Table 1). Only 1.2% of them reported more than one product containing SR as a suspect/interacting agent, with a median daily dose of 320 mg. Approximately 30% of the products contained other active compounds in addition to SR. Overall, most of the report forms presented only one suspect/interacting product, without concomitant medications or CAM products.

Table S1 shows the most frequently reported suspected products, among which the first (33.4%) is represented by a registered medication (Permixon®, 320 mg of SR extract) and the second one (11.4%) by a dietary supplement (Prostagutt Forte®, 160 mg of SR extract and 120 mg of *Urtica dioica* extract). Of notice, all other reported commercial products belonged to the CAM.

3.2 | Characteristics of report forms

Of 1810 report forms, 30.7% were reported by physicians, followed by consumers (27.7%) and pharmacists (21.8%; Table 2). Forty-four percent of cases were defined as serious and, among them, 42.4% reported other medically important conditions, in 31.4% the SAR caused or prolonged the hospitalisation, and in 7.4% the SARs were life threatening, and some deaths were also reported. Outcome data were available for 67.2% of the report forms. Overall, 37.8% of cases had complete resolution of the SAR at the moment of reporting. Of notice, in 25.1% of report forms the outcome was unknown. A total of 33 (1.8%) subjects died.

Among males (Table 3), the main indication/motivation for use was prostatic hyperplasia (17.9%), urinary disorders (10.6%) and prostatic hypertrophy (9.2%). Among females, bladder and urinary (14.6%) disorders were the most frequently reported indication/motivation of use.

3.3 | Characteristics of suspected adverse reactions

Overall, a total of 3863 SARs were collected in the 1810 report forms (Table 4). Considering the most frequently reported SOCs, gastrointestinal disorders accounted for 19.3%, followed by skin and subcutaneous tissue disorders (10.5%), and nervous system disorders (10.4%). Observing in detail the individual PTs, those most described for the aforementioned SOCs were diarrhoea, pruritus and dizziness, respectively. Of notice, among the SOC Injury poisoning and procedural complication (5.0%), off label use accounted for 1.2%, incorrect product administration duration for 0.9%, product use in unapproved indication for 0.4% and medication error for 0.2%. More information on the SOCs, including those observed with lower frequencies and those reported by sex, are described in Table S2 and Figure S2.

3.4 | Risk of serious suspected adverse reactions

The multivariate logistic regression models (Table 5) showed that subjects exposed to food supplements had a higher probability of experiencing a serious SAR (OR: 1.60 [95% CI: 1.20–2.15]). Moreover, those exposed to 2–5 (OR: 1.83 [95% CI: 1.30–2.58]) or more than

TABLE 1 Characteristics of subjects.

	N = 1810 (%)
Sex	
Male	1665 (91.99)
Female	82 (4.53)
NR	63 (3.48)
Age (years)	
Mean ± SD	66.38 ± 14.43
Median (IQR)	69 (58–76)
Age classes	
<18	9 (0.50)
18–65	512 (28.29)
≥65	850 (46.96)
NR	439 (24.25)
Suspect/interacting product	
Medication	615 (33.98)
Food supplement	1061 (58.62)
Not assessable	134 (7.40)
More than one product containing SR	
Yes	21 (1.16)
No	1789 (98.84)
Serenoa repens reported daily dose (mg)	
Mean ± SD	373.35 ± 589.87
Median (IQR)	320 (160–320)
Suspect/interacting product containing only SR	
Yes	1279 (70.66)
No	531 (29.34)
Number of suspect/interacting products[a]	
Mean ± SD	2.15 ± 2.58
Median (IQR)	1 (1–2)
Number of concomitant products[a]	
Mean ± SD	0.90 ± 1.80
Median (IQR)	0 (0–1)

[a]Both medications and/or CAM products.
Abbreviations: IQR, interquartile range; NR, not reported; SD, standard deviation; SR, *Serenoa repens*.

TABLE 2 Characteristics of report forms.

	N = 1810 (%)
Reporter qualifications	
Physician	555 (30.66)
Consumer	502 (27.73)
Pharmacist	394 (21.77)
Other health professional	58 (3.20)
MAH	51 (2.82)
Lawyer	1 (0.06)
NR	249 (13.76)
Seriousness	
Serious	474 (26.19)
Other medically important condition	201 (42.40)[a]
Caused/prolonged hospitalisation	149 (31.43)[a]
Life threatening	35 (7.38)[a]
Death	27 (5.70)[a]
Disability	15 (3.16)[a]
Congenital anomaly/birth defect	1 (0.21)[a]
NR	46 (9.70)[a]
Non-serious	1018 (56.24)
NR	318 (17.57)
Outcomes	
Complete resolution	685 (37.84)
Unknown	455 (25.14)
Not recovered	251 (13.87)
Recovering	129 (7.13)
Hospitalisation	84 (4.64)
Death[b]	33 (1.82)
Recovered with sequelae	29 (1.60)
Disability	4 (0.22)
Congenital anomaly	1 (0.06)
NR	139 (7.68)

[a]Percentages out of 474.
[b]These cases of death included 27 cases with 'death' as seriousness criteria, and other 6 cases who presented different seriousness criteria at the moment of report forms drafting.
Abbreviations: MAH, marketing authorisation holder; NR, not reported.

5 (OR: 3.45 [95% CI: 2.36–5.06]) suspect/interacting products containing SR were more likely to experience a serious SAR. Furthermore, the probability of experiencing a serious SAR was significantly higher for subjects reporting concomitant products (OR: 1.55 [95% CI: 1.15–2.08]), for those exposed to more than four active compounds within the suspect/interacting products (OR: 4.38 [95% CI: 3.21–5.99]), and for subjects exposed to SR containing products for more than 14 days (OR: 1.89 [95% CI: 1.10–3.22]). Of interest, the probability of experiencing a serious SAR was significantly lower for subjects exposed to higher doses of SR. Specifically, an OR of 0.53 (95% CI: 0.30–0.92) and an OR of 0.34 (95% CI: 0.20–0.58) were estimated for 160–320 mg and ≥320 mg.

3.5 | Characteristics of serious suspected adverse reactions

A total of 474 (26.2%) report forms were defined as serious (Table S3). Similarly to the overall sample, subjects who experienced a serious SAR were mostly adult males (88.6%), with a median age of 69 years. Of them, 2.74% reported more than one product containing SR as a suspect/interacting agent, with a median daily dose of 320 mg. Approximately 22% of the products contained other active compounds in addition to SR. In this subset, a slightly higher median number of suspect/interacting products was observed. Most of these cases had a complete resolution of the SAR (24.3%), while 17.7% of

TABLE 3 Indication of use.

Males	Indication	$N = 1665$[a] (%)
	Prostatic hyperplasia	298 (17.90)
	Urinary disorders	176 (10.57)
	Prostatic hypertrophy	153 (9.19)
	Drug use for unknown indication	95 (5.71)
	Other prostatic disorders	88 (5.29)
	Prostatitis	36 (2.16)
	Bladder disorders	21 (1.26)
	Medication errors, suicide attempt and off-label use	13 (0.78)
	Hair and skin disorders	5 (0.30)
	Other indication of use	65 (3.90)
	NR	715 (42.94)
Females	**Indication**	$N = 82$[a] (%)
	Bladder disorders	12 (14.63)
	Urinary disorders	12 (14.63)
	Hair loss and hirsutism	5 (6.10)
	Other indication of use	10 (12.20)
	NR	43 (52.44)

[a]In a total of 63 report forms, the biological sex of subjects experiencing the SAR was not reported.
Abbreviation: NR: not reported.

subjects were hospitalised, and 5.3% died probably due to the SARs reported in the pharmaco- and phytovigilance report forms.

The most frequently reported suspect/interacting products and the indications of use were comparable to those observed for the primary cohort (Table S4). A case-by-case in-depth description of cases of death is depicted in Table S5.

4 | DISCUSSION

In the last decades, most of the evidence available in literature on SR concerns the evaluation of its efficacy as derived from clinical studies (Morgia et al., 2018; Rossi et al., 2018; Sudeep et al., 2020; Yamada et al., 2022; Ye et al., 2019; Zhang et al., 2021), in which safety is not exhaustively evaluated due to the well-known limitations of clinical trials (i.e., small and highly selected population, short follow-up, etc.). To the best of our knowledge, this is the first worldwide analysis evaluating safety of medications/dietary supplements containing SR using data from several national and international spontaneous reporting system databases. In particular, the present observational investigation underlined specific concerns regarding the use of medications and food supplements containing SR in terms of daily dose, number of active compounds and length of exposure.

As already described, there have been very few reported SARs associated with SR products. A systematic review of randomised and non-randomised trials and observational studies found that the SR

TABLE 4 Most frequently reported SOCs and PTs.

SOCs and PTs	Overall, $N = 3863$[a] (%)	Serious, $N = 1445$ (% in row)
Gastrointestinal disorders	745 (19.29)	185 (24.83)
Diarrhoea	119 (3.08)	19 (15.97)
Nausea	86 (2.23)	18 (20.93)
Abdominal pain	69 (1.79)	14 (20.29)
Upper abdominal pain	56 (1.45)	11 (19.64)
Dyspepsia	45 (1.16)	8 (17.78)
Vomiting	45 (1.16)	14 (31.11)
Skin and subcutaneous tissue disorders	406 (10.51)	101 (24.88)
Pruritus	92 (2.38)	19 (20.65)
Rash	63 (1.63)	15 (23.81)
Urticaria	36 (0.93)	7 (19.44)
Erythema	29 (0.75)	6 (20.69)
Maculo-papular rash	19 (0.49)	5 (26.32)
Nervous system disorders	400 (10.35)	211 (52.75)
Dizziness	75 (1.94)	29 (38.97)
Headache	75 (1.94)	17 (22.67)
Somnolence	23 (0.60)	8 (34.78)
Pain	22 (0.57)	14 (63.64)
Vertigo	18 (0.47)	4 (22.22)
General disorders and administration site cond.	338 (8.75)	137 (40.53)
Drug ineffective	45 (1.16)	12 (26.67)
Fatigue	38 (0.98)	14 (36.84)
Asthenia	33 (0.85)	16 (48.48)
Malaise	25 (0.65)	13 (52.00)
Hyperhidrosis	21 (0.54)	10 (47.62)
Investigations	284 (7.35)	135 (47.54)
Blood pressure increased	32 (0.83)	17 (53.13)
Blood urine present	15 (0.39)	6 (40.00)
ALT increased	14 (0.36)	6 (42.86)
AST increased	14 (0.36)	7 (50.00)
GGT increased	9 (0.23)	2 (22.22)
Hepatic enzymes increased	9 (0.23)	2 (22.22)
INR increased	9 (0.23)	4 (44.44)
Renal urinary disorders	237 (6.14)	71 (29.96)
Dysuria	34 (0.88)	6 (17.65)
Pollakiuria	33 (0.85)	10 (30.30)
Nocturia	23 (0.60)	2 (8.70)
Urinary retention	21 (0.54)	8 (38.10)
Chromaturia	15 (0.39)	2 (13.33)
Micturition urgency	15 (0.39)	1 (6.67)
Reproductive system and breast disorders	229 (5.93)	48 (20.96)
Gynaecomastia	50 (1.29)	6 (12.00)
Erectile dysfunction	43 (1.11)	8 (18.60)

(Continues)

TABLE 4 (Continued)

SOCs and PTs	Overall, $N = 3863$[a] (%)	Serious, $N = 1445$ (% in row)
Libido decreased	18 (0.47)	1 (5.56)
Pruritus genital	7 (0.18)	-
Testicular pain	4 (0.10)	-
Injury poisoning and procedural complication	192 (4.97)	45 (23.44)
Off label use	45 (1.16)	5 (11.11)
Incorrect product administration duration	36 (0.93)	6 (16.67)
Product use in unapproved indication	14 (0.36)	2 (14.29)
Medication error	8 (0.21)	3 (37.50)
Fall	7 (0.18)	4 (57.14)
Cardiac disorders	141 (3.65)	88 (62.41)
Palpitations	21 (0.54)	6 (28.57)
Heart rate increased	13 (0.34)	11 (84.62)
Tachycardia	13 (0.34)	3 (23.08)
Arrhythmia	10 (0.26)	4 (40.00)
Atrial fibrillation	9 (0.23)	6 (66.67)
Myocardial infarction	9 (0.23)	9 (100.00)
Respiratory, thoracic and mediastinal disorders	141 (3.65)	72 (51.06)
Dyspnoea	34 (0.88)	15 (44.12)
Cough	9 (0.23)	3 (33.33)
Epistaxis	9 (0.23)	4 (44.44)
Throat irritation	6 (0.16)	1 (16.67)
Sensation of foreign body	5 (0.13)	2 (40.00)
Musculoskeletal and connective tissue disorders	112 (2.90)	52 (46.43)
Myalgia	16 (0.41)	7 (43.75)
Arthralgia	14 (0.36)	3 (21.43)
Back pain	14 (0.36)	4 (28.57)
Muscle spasms	11 (0.28)	7 (63.64)
Contusion	2 (0.05)	1 (50.00)
Psychiatric disorders	103 (2.67)	62 (60.19)
Confusional state	10 (0.26)	4 (40.00)
Agitation	7 (0.18)	2 (28.57)
Anxiety	7 (0.18)	4 (57.14)
Feeling abnormal	6 (0.16)	5 (83.33)
Depression	5 (0.13)	3 (60.00)

[a]Total number of suspected adverse reactions recorded in 1810 report forms.
Abbreviations: PT, preferred term; SOC, system organ class.

containing supplements are generally well-tolerated and that SARs are rare (Agbabiaka et al., 2009). The most commonly reported SARs were gastrointestinal ones, and include stomach pain, diarrhoea and nausea. However, these SARs are generally mild, self-limiting and reversible.

TABLE 5 Serious suspected adverse reactions according to demographical and clinical characteristics.

	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (years)		
<18	1	1
18–65	0.80 (0.17–3.61)	0.52 (0.08–3.44)
≥65	0.76 (0.17–3.41)	0.56 (0.08–3.68)
Sex		
Male	1	1
Female	1.73 (0.97–3.08)	1.43 (0.68–3.02)
Type of suspect/interacting products		
Medication	1	1
Food supplement	1.13 (0.89–1.44)	1.60 (1.20–2.15)
Number of suspect/interacting products		
1	1	1
2–5	2.29 (1.74–3.01)	1.83 (1.30–2.58)
≥5	4.16 (3.01–5.74)	3.45 (2.36–5.06)
Presence of concomitant products[a]		
No	1	1
Yes	1.26 (1.00–1.59)	1.55 (1.15–2.08)
Suspect/interacting product containing only SR		
Yes	1	1
No	1.74 (1.35–2.24)	1.21 (0.86–1.71)
SR reported daily dose (mg)		
<160	1	1
160–320	0.60 (0.38–0.94)	0.53 (0.30–0.92)
≥320	0.55 (0.36–0.82)	0.34 (0.20–0.58)
Number of active compounds		
1	1	1
2–4	0.94 (0.71–1.24)	1.27 (0.87–1.86)
≥4	4.22 (3.19–5.58)	4.38 (3.21–5.99)
Length of exposure (days)		
<3	1	1
3–14	1.56 (0.85–2.85)	1.91 (0.99–3.70)
≥14	2.09 (1.30–3.39)	1.89 (1.10–3.22)

[a]Both medications and/or CAM products.
Abbreviations: CI, confidence interval; OR, odds ratio; SR, *Serenoa repens*.

Our results confirmed this evidence, with a majority of non-serious SARs (>50%), that completely resolved and/or improved in more than 40% of cases. Unfortunately, in more than 30% of cases information on the outcome of SARs was not reported or unknown at the time of the SARs reporting. The lack of quality and completeness of the information reported in pharmaco- and phytovigilance databases worldwide can make the evaluation of SAR more uncertain.

While SR use is generally considered safe, there are some concerns about potential risks associated to its high dosages. Products containing high doses of SR have been generally associated with a

greater number of SARs (Agbabiaka et al., 2009; European Medicines Agency, 2021; Laekeman & Vlietinck, 2013). However, we found that a higher daily dose of SR (≥320 mg) was associated with a lower risk of reporting of serious SARs as compared to lower dosages of SR. This is probably due to the fact that in our sample, most of the products with a high concentration of SR were represented by prescription medications, used under medical supervision and for shorter periods of time. On the contrary, food supplements, which generally contain a smaller quantity of SR (<160 mg) but often associated with other active compounds, are self-prescribed and used without medical supervision even for long periods of time. This consideration is also confirmed by the evidence of a higher risk of serious SARs observed for subjects exposed to food supplements compared to those exposed to medications. This may also explain why in our sample products with more than one active compound, used for a longer period of time, are associated with a higher risk of serious SARs. Of notice, to date, in specific clinical settings, such as BHP, the optimal dosage of SR has not yet been established, but, as reported in our sample and in most studies, doses commonly range from 160 to 320 mg per day (Agbabiaka et al., 2009; European Medicines Agency, 2021; Laekeman & Vlietinck, 2013).

Another important consideration concerns the use of products containing SR in combination with other pharmacological therapies (both medications and/or CAM products), which may indicate the presence of underlying comorbidities. These aspects are particularly relevant from a clinical point of view in terms of potential pharmacological interactions (SR product–drug, SR product–other supplement, SR product–disease interactions) (Crescioli et al., 2020; Lombardi, Crescioli, Bettiol, Menniti-Ippolito, et al., 2019). In fact, the pharmacovigilance and phytovigilance data analysed in this study showed that subjects even with only one concomitant therapy had an increased risk of serious SARs. This consideration is known not only for products containing SR but for all cases of polypharmacy, especially in presence of supplements. In this context, and considering the growing use of food supplements worldwide, greater attention should always be paid by healthcare professionals and customers to verifying the appropriate use of these therapeutic combinations, especially in frail subjects (i.e., elderly) (Lombardi et al., 2021, 2022). Another concern is related to the potential interaction between SR and certain medications. For example, SR may increase the risk of bleeding when taken in combination with blood-thinning medications like warfarin or acetyl salicylic acid (Bressler, 2005; Wang et al., 2015). Additionally, SR may interfere with the effectiveness of hormonal medications like birth control pills or hormone replacement therapy (Institute of Medicine (US) and National Research Council (US) Committee on the Framework for Evaluating the Safety of Dietary Supplements, 2005).

Although most of the subjects analysed in this study correctly use SR products, that is, male subjects for the treatment of urinary tract symptoms associated with BPH, a part of the sample seems to use these products inappropriately. In particular, from the analysis of the pharmacovigilance and phytovigilance report forms, we observed that a significant portion of females use supplements containing large amounts of SR, sometimes in combination with other active compounds and/or other CAM products, for unspecified indications. In our opinion, it is necessary to investigate the use of these products in females, to guarantee safety of SR even outside the urological field (i.e., androgenetic alopecia, androgenetic acne, etc.) (Evron et al., 2020; Grant & Ramasamy, 2012; Murugusundram, 2009).

Manufacturers of dietary supplements are not required to provide any dossier of clinical evidence of their products before their commercialisation. Health authorities only guarantee that any forbidden ingredient is listed within the label of the product (Lee et al., 2020; Saldanha et al., 2018). To date, all food supplements worldwide can be sold and bought online, even in countries where they are not currently marketed (Maggini et al., 2019). Healthcare professionals, especially community pharmacists, have a pivotal role in the counselling costumers, in particular with regard to CAM products (Brunelli et al., 2022; Harnett et al., 2019).

Another important aspect concerns the great difference that exists at a national and international level in the structure and functioning of databases that collect safety data of integrative medicines (such as Italian Phytovigilance and CAERS databases). Of note, all safety databases contain the fundamental information for the description of the clinical case (i.e., patient, suspect product, SAR and reporter's information, etc.). However, some databases lack important information such as: outcome, clear definition of seriousness, follow-up data, clear assessment of the causal relationship. As for pharmacovigilance systems, the harmonisation of phytovigilance systems at international level should be strongly encouraged to obtain a more efficient and comprehensive safety monitoring system for CAM. In this way, the observational analyses on the safety of any product could be carried out more efficiently, in terms of both completeness and execution times.

4.1 | Limitations and strengths

This study has several limitations. First, we have to consider the impact of underreporting a well-known issue that affects both medications and dietary supplements safety reporting systems. Furthermore, considering CAM products, this concern can be considered to a higher extent as compared to medications due to perceived better safety profile by both healthcare professionals and customers, who may also not always correlate suspected SARs to products containing SR (Gatti et al., 2021; Raschi et al., 2018). Additionally, post-marketing surveillance is not mandatory and is generally less well-known for dietary supplements, thus spontaneous reporting may further underestimate the real burden of SR-related SARs. Moreover, as already mentioned above, spontaneous report forms may lack important demographic and clinical data (i.e., concomitant medications and/or comorbidities, etc.). For these reasons, it is particularly challenging to perform the causality assessment. Similarly, residual confounders cannot be ruled out with certainty. In fact, several information was lacking, especially for report forms sent by customers. Moreover, information relating to the type of SR extract used is almost never available in the report forms. Therefore, although this information

could be very interesting, we were unable to evaluate whether different types of extracts are associated with different risk of ARs.

Notwithstanding the above-mentioned limitations, spontaneous reporting systems play a key role in exploring the safety profile of SR-containing products both from local and international perspective, thus increasing generalisability of our results. Furthermore, considering that data of CAM products use are not available (both in Italy and in other countries), neither in term of packages sold or in terms of population exposed, pharmacoepidemiological studies for risk estimates (i.e., case–control, cohort studies) are difficult, if not impossible, to be conducted. For this reason, only spontaneous reporting system can monitor safety of food supplements for possible regulatory actions (Gatti et al., 2021; Raschi et al., 2018). In particular, a further point of strength of this study concerns the in-depth research of the characteristics of each suspect/interacting product containing SR, which made it possible to estimate the risk of serious SARs considering several important covariates such as daily dose, number of active compounds and length of exposure.

5 | CONCLUSIONS

In conclusion, it is important to use caution when taking SR containing products, particularly in presence of other medications and/or CAM products. This evidence improves the healthcare professionals' awareness on the safety of SR containing products, suggesting the need of a further update of periodic reviews performed by the International regulatory agencies.

Moreover, it is also important for subjects to consult healthcare professionals (both general practitioner and community pharmacist) before taking SR supplements, especially if they are taking other medications or have an underlying medical condition.

The regulatory framework for the manufacture, sale and post-marketing surveillance of CAM products needs to be strengthened. A common centralised vigilance system, at least in Europe, could harmonise data collection and enhance the ability to timely detect safety signals, thus supporting regulators, in a public health perspective.

AUTHOR CONTRIBUTIONS

Giada Crescioli: Data curation; formal analysis; investigation; methodology; writing – original draft. **Valentina Maggini:** Investigation; methodology; writing – original draft. **Emanuel Raschi:** Investigation; methodology; supervision; validation; writing – review and editing. **Laura Augusta Gonella:** Data curation; methodology; resources; writing – review and editing. **Nicoletta Luxi:** Data curation; methodology; resources; writing – review and editing. **Ilaria Ippoliti:** Data curation; resources; validation; writing – review and editing. **Valentina Di Giovanni:** Data curation; methodology; resources; writing – review and editing. **Roberto Bonaiuti:** Writing – review and editing. **Niccolò Firenzuoli:** Visualization; writing – review and editing. **Eugenia Gallo:** Validation; writing – review and editing. **Francesca Menniti-Ippolito:** Supervision; validation; writing – review and editing. **Ugo Moretti:** Data curation; resources; supervision. **Gianluca Trifirò:** Supervision; validation; writing – review and editing. **Alfredo Vannacci:** Supervision; writing – review and editing. **Fabio Firenzuoli:** Funding acquisition; project administration; supervision; validation; writing – review and editing. **Niccolo Lombardi:** Data curation; investigation; methodology; project administration; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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