REVIEW ARTICLE

Drug Safety 2009; 32 (8): 637-647
0114-5916/09/0008-0637/$49.95/0

Serenoa repens (Saw Palmetto)
A Systematic Review of Adverse Events

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Contents

Abstract

Serenoa repens (W. Bartram) Small, also known as saw palmetto, is one of the most widely used herbal preparations for the treatment of lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH). Although a number of randomized controlled trials (RCTs) and systematic reviews of the efficacy of *S. repens* for the treatment of LUTS and BPH have been published, no systematic review on its drug interactions or adverse events currently exists. This review assesses all available human safety data of *S. repens* monopreparations.

Systematic literature searches were conducted from date of inception to February 2008 in five electronic databases; reference lists and our departmental files were checked for further relevant publications. Information was requested from spontaneous reporting schemes of the WHO and national safety bodies. Twenty-four manufacturers/distributors of *S. repens* preparations and four herbalist organizations were contacted for additional

information. No language restrictions were imposed. Only reports of adverse events in humans from monopreparations of *S. repens* were included. Data from all articles, regardless of study design, reporting adverse events or interactions were independently extracted by the first author and validated by the second.

Forty articles (26 randomized controlled trials, 4 non-randomized controlled trials, 6 uncontrolled trials and 4 case reports/series) were included. They suggest that adverse events associated with the use of *S. repens* are mild and similar to those with placebo. The most frequently reported adverse events are abdominal pain, diarrhoea, nausea, fatigue, headache, decreased libido and rhinitis. More serious adverse events such as death and cerebral haemorrhage are reported in isolated case reports and data from spontaneous reporting schemes, but causality is questionable. No drug interactions were reported.

Currently available data suggest that *S. repens* is well tolerated by most users and is not associated with serious adverse events. The majority of adverse events are mild, infrequent and reversible, and include abdominal pain, diarrhoea, nausea and fatigue, headache, decreased libido and rhinitis. We found no evidence for drug interactions with *S. repens*. However, higher quality reporting of adverse events is essential if safety assessments are to be improved in future.

Serenoa repens (W. Bartram) Small [Arecaceae], also known as saw palmetto, scrub palmetto, American dwarf palm tree and cabbage palm, is a small, low-growing, dwarf-palm tree native to the West Indies and south-eastern America.[1] It is also known by synonyms such as *Sabal serrulata* and *Serenoa serrulata*. American Indians in Florida, USA, in the early 1700s, first used berries of *S. repens* to treat testicular atrophy, erectile dysfunction, and prostate swelling and inflammation. The medicinal value of *S. repens* for the relief of prostate swelling has been reported in the medical literature since the 1800s.[2] Traditionally, the berries also served as a staple food and medicine for the treatment of stomach ache and diarrhoea as well as being used as a diuretic and sexual tonic.[3]

There is a considerable demand on our healthcare services for treating lower urinary tract symptoms (LUTS), which are common in older men. Obstructive voiding (weak urine flow, hesitancy, straining and incomplete emptying) and bladder storage problems (frequency, urgency and nocturia) are the most prominent symptoms of LUTS. Often LUTS are considered to be due to benign prostatic hyperplasia (BPH). These symptoms are also experienced by women, as well as in men with prostates that are not enlarged.[4,5]

Currently, *S. repens* is one of the most widely used phytotherapeutic preparations for the treatment of BPH/LUTS.[6] Commercial extracts of the dried ripe berries and blends are widely available as prescription drugs or sold over the counter.[7] The German Commission E (a governmental regulatory agency established to evaluate the usefulness of herbs and publish monographs) approved the use of *S. repens* for BPH in stages I and II.[8] The main constituents of the berries are fatty acids and phytosterols (β-sitosterol, stigmasterol, cycloartenol, lupeol, lupenon and methylcloartenol).[1] The pharmacologically active components are believed to be the steroidal compounds and sitosterol.[1] *S. repens* is reported to possess anti-estrogenic activities,[9] to decrease residual urine[10] and to decrease painful urination.[11] *Serenoa repens* may act to increase the metabolism and excretion of dihydrotestosterone through inhibition of cellular and nuclear receptor binding.[12]

S. repens is often assumed to be free of adverse effects; in particular, it does not seem to interfere with sexual function as some other BPH medications.[3] In view of the widespread use of *S. repens*, it is important to ascertain its safety. Therefore, the aim of this review is to assess the available human safety data on *S. repens* monopreparations.

1. Literature Search Methodology

Systematic literature searches were conducted in the following electronic databases, all from their respective inception until February 2008 and without any language restrictions: PUBMED via Medline, AMED, EMBASE, CINAHL and the Cochrane Library – the Cochrane Central Register of Controlled Trials (CENTRAL). The search terms were the common names(s), scientific names(s) and synonyms for *S. repens* {'Saw palmetto' OR '*S. repens*' OR 'Serenoa' OR 'Serenoa' AND ('Permixon' [Substance Name] OR 'herbal preparation PC-CARE' [Substance Name] OR 'Prostamol-Uno' [Substance Name] OR '1-monomyristin' [Substance Name]) OR '*Sabal serrulata*' OR 'Sagezahnpalme' OR 'Permixon'}. No limits were placed on the search function. Further relevant data were retrieved by hand searching the reference lists of identified papers and searching our files at the Complementary Medicine department, Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, UK.

Additional data were requested from the following reporting schemes: Adverse Drug Reactions Advisory Committee (ADRAC), Australia; Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Germany; US Food and Drug Administration (FDA); and the Medicine and Healthcare products Regulatory Agency (MHRA), UK. The WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden (WHO-UMC) was also requested to provide the total numbers of adverse events reports received up until September 2007 involving the use of *S. repens*. Twenty-four manufacturers/distributors of *S. repens* preparations were identified from a review,[13] standard text[14] and from Internet searches. They were contacted and asked for adverse event reports and any other safety information held on file. Four herbalist organizations (British Herbal Medicine Association, UK; European Herbal & Traditional Medicine Practitioners Association, UK; European Scientific Cooperative on Phytotherapy, UK; National Institute of Medical Herbalists, UK) were also contacted for relevant information.

The review includes all relevant data from clinical trials (randomized and non-randomized), uncontrolled studies, case reports/series, surveys and postmarketing surveillance studies of *S. repens*. Only human studies assessing monopreparations are included. Data from reports and studies with combination preparations of *S. repens* or investigations in animal or *in vitro* models were excluded.

The screening, selection of articles and data extraction were carried out by the first author (TBA) and verified by the second (MHP). Data from papers published in German were extracted by the second author (MHP) and verified by the third (BW). Other non-English papers were extracted by the third author (BW). Disagreements were resolved through discussion between co-authors. Data on adverse events or adverse effects associated with *S. repens* treatments were extracted according to predefined inclusion criteria using pre-designed data-extraction sheets. An adverse event is any unfavourable and unintended sign (including abnormal laboratory results), symptom or disease associated with the use of a medicinal product. A 'serious adverse event' is any untoward occurrence relating to a medicinal product that is life threatening, disabling or which might result in, or prolong, hospitalization or morbidity. No formal assessment of the statistics of the primary data was performed.

2. Findings

One hundred and forty potentially relevant articles were located, 100 of which were excluded for the following reasons: the product was a combination preparation of *S. repens* (n = 14); the article did not include any information on adverse events (n = 13); the preparation used was not *S. repens* (n = 6); they were *in vitro* studies (n = 11); they were animal studies (n = 3); or they

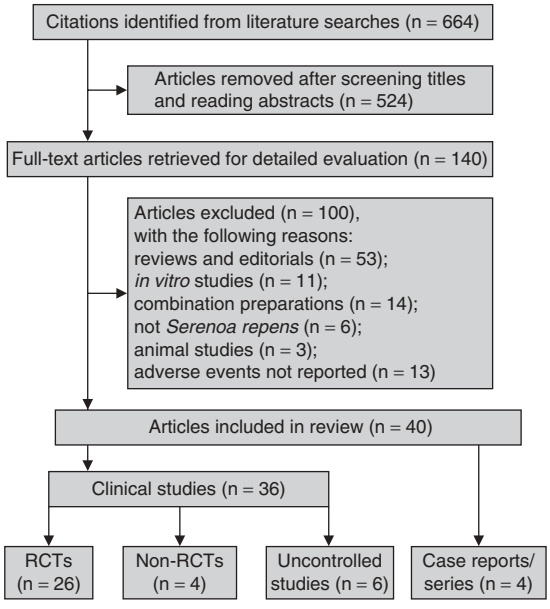

Fig. 1. Flow chart of the study-selection process. **RCTs** = randomized controlled trials.

were reviews, commentaries or editorials (n = 53). The remaining 40 papers were included in the review (figure 1). The majority of the included studies were published in English (n = 29). The rest were as follows: Italian (n = 5); German (n = 1); Russian (n = 2); and one paper each in Slovak, Spanish and French.

The study population were mostly men diagnosed with BPH (n = 25), men with stages I–II prostatic adenoma (n = 5) and LUTS (n = 4). Healthy volunteers were investigated in three studies, pelvic pain or discomfort (n = 1) and patients with androgenetic alopecia (AGA) were assessed in two studies. All except two studies[15,16] involved only men. *S. repens* was administered for ≤6 months in 68% of the studies (n = 27), for 6 months to 2 years in 20% (n = 8) and for >2 years in 5% (n = 2) of the studies, duration of treatment was not specified in 8% of the studies (n=3).

In 15 studies,[17-31] Permixon® (a commercial standardized extract of *S. repens*, Pierre Fabre Médicament, Castres, France) was used. One study[32] used three different standardized extracts of *S. repens*: Prostagutt uno® (Dr Willmar Schwabe GmbH, Karlsruhe, Germany), Prostess uno® (Tad Pharmazeutisches Werk, Cuxhaven, Germany) and Talso uno® (Sanofi Winthrop, Morrisville, PA, USA). Prostaserene®,[33,34] Prostagutt mono®[35,36] and Prostamol uno®[37,38] were each used in two studies; Libeprosta was used in one study.[5] The brand name of the *S. repens* preparation administered to participants was not reported in 17 studies.[6,15,16,36,39-51] *S. repens* extract was administered orally in daily doses ranging from 100 to 480 mg except in one study[39] where rectal application was compared with oral administration.

2.1 Evidence from Clinical Trials

2.1.1 Randomized Controlled Trials

Twenty six randomized controlled trials (RCTs) reporting adverse events from *S. repens* preparations were located; 14 of these were placebo-controlled (table I; see Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A13);[6,18,20,21,24,25,27,30,32,33,40-43] the remaining 12 studies (table II; see Supplemental Digital Content)[16,17,19,22,23,28,29,34,39,44,45,52] had active controls of either finasteride, tamsulosin and alfuzosin (all three are synthetic drugs used to treat BPH) or no treatment controls. The 14 placebo-controlled trials (table I; see Supplemental Digital Content) reported the following adverse events: headache (6), diarrhoea and other gastrointestinal disorders (18), fatigue (6), nausea (1), vomiting and vertigo (1), cardiovascular complaints (2), common cold (3), gastrointestinal bleeding (3) and urinary problems (2). Stomach upset and diarrhoea were the most commonly reported symptoms.

Of the non-placebo-controlled studies (table II; see Supplemental Digital Content), six studies[19,22,23,29,44,45] compared the effect of *S. repens* with finasteride, tamsulosin and alfuzosin. One study[16] compared *S. repens* with a herbal combination preparation of *Citrus aurantium, Echinacea purpurea and Silybum marianum*. One study[17] compared the effect of *S. repens* extracts with watchful waiting (no treatment) while the remaining four studies[28,34,39,52] were dose-finding studies. Adverse events reported in these studies were gastralgia, abdominal discomfort,

hypertension, decreased libido, impotence, ejaculation disorder, gastrointestinal disorders, rhinitis, headaches, fatigue, dizziness and skin disorders.

2.1.2 Non-Randomized Controlled Trials

Four non-randomized controlled trials[37,46-48] were included (table III; see Supplemental Digital Content). In a double-blind study,[47] the effectiveness of an extract of *S. repens* was compared with mepartricin (an antibiotic used in the treatment of BPH). Twenty men were treated with either *S. repens* (320 mg daily) or mepartricin (50.000 U every 12 hours). Nineteen men were included in the final analysis; the duration of treatment was not reported. One patient developed an allergic reaction, which did not lead to his withdrawal from the study.

In a study of 45 men with BPH,[46] 25 patients received prazosin, an α_1-adrenergic receptor antagonist (1 mg on days 1–4, 2 mg on days 5–9 and 4 mg thereafter), while 20 men were treated with *S. repens* (brand and dosage not reported) for 12 weeks. Only adverse events that led to withdrawal from the study appear to have been reported: four in the prazosin group (arterial hypertension and gastric intolerance) and none in the *S. repens* group.

An open-label, prospective, study with three parallel groups[48] assessing the effects of three treatment regimens of *S. repens* and tamsulosin involved 60 men with BPH treated for 6 months. One group (n = 20) was treated with *S. repens* extract (320 mg daily), another group (n = 20) received tamsulosin (0.4 mg daily) and the third group (n = 20) received *S. repens* plus tamsulosin (320 mg + 0.4 mg daily). No adverse events were reported in the *S. repens* group, 34 adverse events were observed in the tamsulosin and S. *repens* plus tamsulosin groups (table III; see Supplemental Digital Content).

Aliaev et al.[37] described the results of an open-label prospective study with 54 men with stage III prostatitis. One group of men (n = 30) was treated with *S. repens* (Prostamol uno®, 320 mg daily) and compared with a group of men (n = 24) receiving no treatment. One patient in the *S. repens* group had moderate dyspepsia, which resolved without stopping the drug.

2.1.3 Uncontrolled Studies

Six uncontrolled studies involving *S. repens* monopreparations were included[26,31,35,36,38,53] (table IV; see Supplemental Digital Content). No adverse events were observed in three studies.[31,38,53]

Three reports[26,35,36] provided details of adverse events. In one study,[35] 60 men with stage I–II BPH were treated with Prostagutt mono® (Dr Willmar Schwabe GmbH, Karlsruhe, Germany), 320 mg daily for 12 weeks. Seven adverse events were reported, of which only intolerance to the drug seemed related to the treatment; two deaths of unrelated causes were recorded. Stomach upset and dizziness, which existed before treatment, also persisted in one patient.

The remaining two studies[26,36] were open, multicentre, uncontrolled assessments of the tolerability of *S. repens* preparations. In one study,[26] 155 men with clinically diagnosed BPH were treated with permixon (160 mg twice daily) for 2 years and adverse events recorded every 3 months. Ten adverse events were reported by nine patients. Unspecified 'cardiovascular problems' were the most frequently reported adverse events (n = 4). One adverse event was reported in three of the patients and, in each case, this led to discontinuation of the treatment. One of these patients also withdrew from the study. Details of the remaining three adverse events were not provided. In the other study,[36] 109 patients were treated with a *S. repens* extract (WS 1473, two capsules containing 160 mg each administered once daily) for 12 weeks and 93 men completed the treatment. Five adverse events were recorded; one of them was serious (a 67-year-old patient who had coronary heart disease died of myocardial infarction). Mild conjunctivitis and gastrointestinal complaints were other adverse events reported in this study.

2.2 Data from Case Reports/Series

Three case reports[15,49,50] and one case series[51] were located (table V; see Supplemental Digital Content). Prolonged bleeding was observed in a

53-year-old male with cavernous sinus and left petroclavial meningioma who was using *S. repens* to treat his BPH.[49] The authors of this report considered that the prolonged bleeding was possibly caused by platelet dysfunction due to cyclooxygenase inhibition by the *S. repens* extract. No mention was made of the dosage or registered name of the *S. repens* preparation involved.

Acute dermatitis on the scalp with secondary generalization to the rest of the body was observed in a 24-year-old woman with AGA.[15] Further information on the *S. repens* solution or the dose was not provided. Jibrin et al.[50] reported severe non-radiating epigastric pains associated with nausea and vomiting in a 55-year-old, reformed-alcoholic male who had been abstinent for over 15 years. The dosage or registered name of the *S. repens* preparation was not provided but the patient had been taking the drug for the treatment of BPH for about 4 years. Based on the results of a de- and rechallenge, the authors believed that the acute hepatitis and pancreatitis were probably induced by *S. repens*.

The only case series located[51] implicated *S. repens* in the loss of iris tone and intraoperative floppy-iris syndrome (IFIS) in two patients who were using *S. repens* while undergoing cataract surgery. The report provided no information on the particular *S. repens* preparation used or the dose suspected. Patient A, a 49-year-old man, demonstrated moderate IFIS during the cataract surgery without any further complications. Patient B, a 74-year-old man who had not taken any drugs other than *S. repens* for about 5 years also experienced moderate IFIS during surgery. Although the surgical outcome was excellent, a segmental loss of iris pigment epithelium visible only by transillumination was reported.

2.3 Data from National Reporting Schemes

2.3.1 Medicine and Healthcare products Regulatory Agency (UK)

Nineteen reports of adverse events suspected to be associated with the use of *S. repens* were received by the MHRA prior to May 2007 (table VI; see Supplemental Digital Content); seven of these were for *S. repens* monopreparations and twelve for combination products. All cases except one involved men aged between 35 and 84 years. The adverse events reported for monopreparations of *S. repens* were artrial fibrillation (1), hypertension (1), liver abscess (1), chest pain (1), gynaecomastia (1), increased blood pressure (1) and headache (1). For the other 12 cases, *S. repens* was taken in combination with other herbs such as *Chrysanthemum parthenium* and other substances like glucosamine. Two drug interactions were reported for two combination products of *S. repens*; no further details were provided.

2.3.2 Federal Institute for Drugs and Medical Devices, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) (Germany)

A total of 39 cases concerning the *S. repens* preparations Talso®, Sita®, Permixon®, Prostagutt mono®, Prostagutt uno® and Sabalvit uno® were reported to the BfArM between 1990 and September 2007. Case reports were mainly from companies but also from physicians, pharmacists and patients. Of these reports, 11 were for combination products and 28 cases reporting 40 adverse events were for monopreparations. Spontaneous reports (n = 21), clinical trials (n = 17) and post-marketing surveillance (n = 1) were received. The majority of patients were men (n = 37) aged between 49 and 91 years. Gastrointestinal disorders, including stomach discomfort and nausea, were the most common adverse reactions reported (table VII; see Supplemental Digital Content). In 21 cases, a monopreparation of *S. repens* was the only drug taken by the patient.

Although *S. repens* was taken in combination with other drugs in 18 cases, it was the only suspected agent in 15 cases. In only three cases was there another suspected agent. In one case of delirium in a 91-year-old man, three agents were suspected (olanzapine, valproate sodium and *S. repens*). In the case of a 16-year old female taking a monopreparation of *S. repens* along with four other agents (verapamil, ferrous sulfate, ibuprofen and *Cynara scolymus*), dizziness, depression and suicidal tendencies were reported.

In the third case, the patient was taking Prostagutt forte® (*S. repens* and *Urtica* extract) with seven other agents (pravastatin, ramipril, carvedilol, aspirin (acetylsalicylic acid), insulin, a number of herbal extracts and amlodipine). The patient presented with depression, increased blood creatine phosphokinase and myalgia; the *S. repens* preparation, pravastatin, ramipril, carvedilol, aspirin and insulin were all suspected to be responsible for the observed adverse event.

2.3.3 Adverse Drug Reactions Advisory Committee (Australia)

Prior to April 2007, 19 reports of adverse events associated with *S. repens* in 14 patients were received by the ADRAC (table VIII; see Supplemental Digital Content). In six cases, *S. repens* was the only drug taken by the patient. Even though *S. repens* was taken with other drugs in eight cases, it was the only suspect in six of these cases.

In the case of a 64-year-old patient, profound hypokalaemia leading to cardiac arrest and eventually death was reported; eight agents were suspected (*S. repens*, perindopril, atorvastatin, aspirin, metoprolol tartrate, prazosin, hydrochlorothiazide, lercanidipine). In another case, a patient taking a *S. repens* product together with a homeopathic remedy reported flatulence and stomach pain. Both drugs were suspected as a cause.

2.3.4 Food and Drug Administration (USA)

Seventy-two reports of patients who had taken *S. repens* preparations were received by the FDA within a 10-year period (from November 1997 to November 2007). Of these reports, 90% were from manufacturers; the remaining 10% were directly from healthcare professionals and consumers. *S. repens* was a secondary suspect in all of these reports as the patients had taken one or more other drugs. A total of 169 adverse events were reported, all the cases except one involved men. The most frequent adverse events were cerebral haematoma, fall, jaundice, anaemia, cholestatic hepatitis and Parkinson's disease (table IX; see Supplemental Digital Content).

2.4 Data from the WHO Collaborating Centre for International Drug Monitoring

By September 2007, 287 reports of 512 adverse events had been received by the WHO-UMC from the national drug safety bodies of participating countries, including those above. Of these adverse events, 389 were related to monopreparations of *S. repens* (table X; see Supplemental Digital Content), 59 to *S. repens* in combination with other herbs including *Cucurbita pepo*, *Urtica* spp and *Echinacea purpurea*, 5 to *S. repens* in combination with vitamins and minerals and 59 to *S. repens* in combination with other substances including trospium chloride and tocopheryl acetate. However, the WHO-UMC cautions that the information from the database may not be homogenous with respect to the sources or the likelihood that the pharmaceutical product is responsible for the suspected adverse reaction. No additional information was provided with these reports.

2.5 Data from Manufacturers of *Serenoa Repens* Preparations

Only three of the 24 manufacturers of *S. repens* preparations who were contacted responded. Two manufacturers provided additional safety data. One company (Dr Willmar Schwabe GmbH, Karlsruhe, Germany) provided information on adverse events from its *S. repens* preparations, Prostagutt mono® reported in uncontrolled trials.[35,36] The adverse events were myocardial infarction, conjunctivitis, gastrointestinal disorders, urinary retention and dizziness.

2.6 Data from Herbalist Organizations

Only one of the four herbalist organizations contacted responded. The National Institute of Medical Herbalists, UK, informed us that our request would be dealt with by its Director of Research, but we received no further correspondence. No response was received from the other three organizations despite two reminders.

3. Discussion

We identified 40 articles (26 RCTs, 4 non-RCTs, 6 uncontrolled trials and 4 case reports/series) reporting adverse events from *S. repens*; no serious adverse events were observed in 3 reports.[31,35,36] In the studies that reported adverse events, the incidence rates were comparable to those of placebo. In the comparative trials, the number of adverse events for *S. repens* was similar to that of the controls. Adverse events reported were gastrointestinal disorders, headache, fatigue, decreased libido and rhinitis.

A total of 533 adverse events following treatment with *S. repens* extracts were reported by the spontaneous reporting schemes of the MHRA, BfArM, ADRAC and FDA. No information on patient history, dose and treatment duration was provided in the majority of these reports. Additional numbers were requested for adverse event reports involving *S. repens* received by the WHO-UMC, which receives reports from over 80 participating National Centres, including the above. An overlap of reports between the data from the spontaneous reporting schemes and those held by the WHO-UMC is likely and this could have lead to an overestimation of the number of cases.

Adverse events reported were generally mild to moderate; although one report of hypokalaemia leading to fatality was received by ADRAC. The most frequent adverse events reported to the spontaneous reporting schemes were gynaecomastia, abdominal pain, diarrhoea, dyspepsia, nausea and erectile dysfunction. Although case reports and case series are interpreted as spontaneous reporting or 'passive surveillance', they are useful in demonstrating the type and nature of adverse events but lack information on the incidence of adverse events.[54] Conclusive attribution of causality is not possible in the majority of these reports.

No report of drug interactions with *S. repens* was found among the clinical studies located. Two spontaneous reports of drug interactions with two combination products of *S. repens* were located but further details were not provided. However, the severity and number of adverse events reports from the use of *S. repens* extracts seems small compared with the extent to which the product is consumed. This may indicate that the herb is relatively safe, otherwise it may suggest that adverse events are under-recognized.

Reports of adverse events resulting from herbal treatments are frequently neither reported nor documented; when documented, the reports are usually of low quality, often lacking adequate information for any meaningful cause-effect evaluations. We did not assess the internal validity of the included studies. For questions of safety, internal validity seems less important than for questions of effectiveness. For example, already a number of case reports with low internal validity are sufficient to prompt regulators to take products off the market as in the case of kava products. Thus, it is not always necessary to have evidence from studies with high internal validity (e.g. RCTs) for regulatory action. We only indicated internal validity in our manuscript by categorizing the data into evidence from RCTs, uncontrolled studies, case reports etc. In addition, safety evaluations of herbal preparations are particularly problematic since herbal medicines are a mixture of more than one active ingredient coupled with the uncertainty of which or how many of the constituents are pharmacologically active.

Commercially available herbal medicinal products may vary in contents and concentration of their active ingredients. This largely depends on the geographical source of the plant, the time of harvest, plant parts used, type of extract (aqueous, alcoholic, glycerine) as well as delivery forms.[55] Therefore, considerable differences may be observed in the results of clinical trials of heterogeneous products even when the same botanical species are used. Habib and Wyllie[13] reported significant proportional differences in constituents among 14 different brands of *S. repens* extracts analysed despite their common origin. The concentrations of fatty acids, methyl and ethyl esters, long chain esters and glycerides differed considerably and may have had an impact on the clinical efficacy and safety of the extracts. Hence, there is a need for plant extracts

to be analysed and assessed individually despite their common origin.

Systematically reviewing adverse events of a therapy is far from straightforward. It requires combining data from very different types of reports, such as clinical trials, postmarketing surveillance and case reports. A standard methodology to evaluate the totality of the evidence available does not exist. Statistical pooling is rarely an option, due to the heterogeneity of the primary data. Our approach to conduct a purely descriptive review seems reasonable and should perhaps be considered as the gold standard for future evaluations of that type.

Clearly, different types of reports have different strengths and weaknesses. Clinical trials are less open to bias than observational data. They allow us to compare adverse event rates of one treatment with those of another (e.g. placebo), and are a reliable tool for detecting common and early adverse events. Unfortunately, the quality of reporting adverse events in clinical trials is variable and frequently not good. Because clinical trials are always limited in terms of sample size, they are less useful for the identification of rare adverse events. Observational data and case reports may be essential for that purpose. We suggest that the combination of experimental studies (clinical trials) and observational data will generate the complete evidence that is necessary for any critical evaluation of therapeutic safety.

With the use of herbal medicines increasing substantially in the last two decades, documenting and preventing adverse events and drug interactions from the use of these products has become of utmost importance.

4. Conclusion

Currently available data suggest that *S. repens* is well tolerated by most users and is not associated with serious adverse events. The majority of adverse events reported were mild, infrequent and reversible. The most frequently occurring adverse events were abdominal pain, diarrhoea, nausea and fatigue, headache, decreased libido and rhinitis. There is currently no human evidence to suggest drug interactions with *S. repens*. Improved reporting of adverse events is needed for more reliable safety assessments.

Acknowledgements

Edzard Ernst was awarded a grant for a research fellowship by Dr Willmar Schwabe GmbH, Karlsruhe, Germany. Taofikat Bisola Agbabiaka was supported by this research fellowship. None of the other authors have any conflicts of interest that are directly relevant to the content of this review to declare. The authors wish to thank Myeong Soo Lee, PhD, Department of Medical Research, Korea Institute of Oriental Medicine, Daejeon, South Korea, for assistance with retrieving relevant articles.

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