Sisymbrium "Singers' Plant" Efficacy in Reducing Perceived Vocal Tract Disability

Abstract

Sisymbrium officinale is a plant used since Greeks Medicine in vocal tract diseases to reduce disability derived from dryness, sore throat, cough,... Modern Phytopharmacology is standardizing active principles in this plant, but still few works in literature describe results known in traditional medicine.

A small group of patients treated with Sisymbrium at recommended doses described the perceived physical disability pre and post treatment by VHI (Voice Handicap Index) scores. Analysis of the difference (delta) between VHI scores seems to prove Sisymbrium efficacy in reducing perceived disability, so facilitating voice use. In this way Sysimbrium results a choice to solve patients' discomfort, reserving "classical" treatments - NSAIDs and antibiotics - to major pathologies.

Keywords: Vocal tract; Erysimum; *Sisymbrium officinale*; VHI; Phytotherapy

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Introduction

Sisymbrium is an annual plant, spread mostly in the Eurasiatic Region and North Africa. It is very common in bare ground, on roadsides, dumps and edges of fields. Now is a weed plant in North America, too. There are many types of Sisymbrium: the most used in vocal tract diseases is *Sisymbrium officinale* (L.) Scop. (Brassicaceae).

Sisymbrium in medical history

The huge amount of popular nouns given to it (Table 1) reflects the described effects of this plant on vocal tract and other "catharral" diseases: indeed this millennial belief has but a few correlations in scientific literature.

Table 1: Sisymbrium Names.

Botanical Name	***Sisymbrium *Officinale (L.) Scop.* (*from an old Greek term for Cress)**
Botanical Synonim	*Erysimum officinale* (L.)
Pharmaceutical Name	Herba/Semen Sisymbrii (= Herba/Semen Erysimi)
Greek	*Ἐρύσιμον*: I save sing
	Chamaeplion
Latin	Erysĭmum
Italian	Erba cornacchia comune
	Erba dei cantanti
	Irione
	Erba crociona
	Lassanédda
	Sisimbrio
	Senape selvaggia
English	Hedge mustard
	Bank cress
French	Herbe aux chantre
	Velar officinale
	Tortelle
German	Rauken-Senfkraut
	Sangerkraut
	Weg-Rauke
	Wilder Hanf
	Wegesenf
	Kreuzkraut
Spanish	Allaria
	Hierba de los cantores
	Hierba de San Alberto
	Jaramago
Portuguese	Rinchao
Swedish	Vagsenap
Chinese	Ting-li

(http://www.infoerbe.org/site/scheda.php?ide=218&pg=SIN_BOT mod)

Dioscoride recommended it in "catharralis" diseases, so also in jaundice and in poisoning. In the XVII century, Jacques Dalechamps,

author of Historia generalis plantarum, wrote that his master Guillaume Rondelet "professeur royal de médecine à Montpellier" gave it to a young choir singer, who promptly regained his voice. Fernie [1] cited that, up to the time of Louis XIV, Racine wrote to Boileau to recommend him Erysimum syrup in order to be cured of voicelessness :"Si les eaux de Bourbonne ne vous guerissent pas de votre extinction de vois, le syrop d'Erysimum vous guerirait infalliblement. Ne l'oubliez pas, et a l'occasion vingt grammes par liter d'eau en tisane matin et soir". Tradition says that Racine gave this advice because he knew a singer, voiceless since 6 months, helped by erysimum to regain his voice and sing in front of the King in Notre Dame Cathedral.

In the International Plant Name Index 1, the plant name was given in 1772 by Giovanni Antonio Scopoli [2]. He wrote it in Flora Carniolica, a book to describe plants of his region (now in Northern Italy, between Trentino and Friuli regions). Scopoli was called "the Linnaeus of the Austrian

Empire": indeed he and Linnaeus were corresponding and Linnaeus named a solanaceous genus, Scopolia, the source of scopolamine, after him.

Traditional medicine recommends using the semi-fresh flowered aerial parts of *Sisymbrium officinale* in order to prepare an infusion having therapeutic effects to treat sore throats, coughs, and hoarseness (Benigni, et al. [3]. In his main text (1995) Font-Quer writes about S. officinale: "Se emplea principalmente contra las inflamaciones y catarros de la laringe, sobre todo para combatir la ronquera, así como contra la tos, los catarros pulmonares, etc., amen del escorbuto. Se usa de preferencia la planta fresca. Con la hierba recién colectada se prepara una tisana, como si se tratara de te, es decir, poniendo a hervir un cacito de agua y echando en ella cosa de 1 onza de la planta, tallos y hojas, por cada cuatro tazas; se toma cuando queda templada, y después de echar el azúcar que se desee". "It is used mainly against the inflammations and catarrhs of the larynx, especially to combat hoarseness, as well as against cough, pulmonary catarrh, etc., and scurvy too. The fresh plant is preferably used. The freshly harvested herb is prepared, as if it were tea, that is, putting a boil of water and throwing in it 1 ounce of the plant, stems and leaves, for every four cups; is taken when it is tempered, after pouring the desired sugar ".

Main active compounds

The chemical markers of *Sisymbrium officinale* are sulphated compounds, particularly glucosinolates, isothiocyanates and sulphated lactones, also found in mustard oil [4]; the main glucosinolate is glucoputranjivine [5]. Historically, the sulphated compounds are reputed to stimulate the mucosal secretion in the upper respiratory tract, so increasing expectoration [6].

Dried flowering aerial parts of *Sisymbrium officinale* (L.) Scopoli (= *Erysimum officinale L.*) contain respectively 3: 0.63% to 0.94% glucosinolates -where a minimum of 0.3% of total glucosinolates is expressed as sinigrin (C10H16KNO9S2; Mr397,5) and up to a 65% is isopropyl- glucosinolate -, 10.9% to 13.5% mucilages, 8.9% to 10.2% total itols, 0.50% to 0.56% flavonoids and 9.2% ash [7].

In the semen: cardenolide glycosides [8,9]. Essential oil: glucosinolates; thiocyanic glycoside. In the fresh plant: chiefly sinigrin (allylglucosinalates) and gluconapin (3-butenylglucosinolates) ascorbic acid (216.5 mg/100 g in fresh foliage) [10]. The tips of the foliage include among others corchoroside A (18.5 mg/100 g) and helveticoside (4.5 mg/100 g), cardioactive steroid glucosides.

Acqueous dried extract shows absence of sinigrin and presence of glucoputranjivin, isopropyl isothiocyanate and proline; putranjivine resulted to be 0.5 mg/g [11], adenine, 3 Calculated for the dried herbal substance [5] adenosine, and guanosine were present in significant quantities only in the traditionally prepared aqueous extract [7].

Volatile compounds of hedge mustard (*Sysimbrium officinale*) have been investigated. Forty-two compounds were identified after hydrodistillation (without or upon autolysis) with gas chromatography/mass spectrometry analyses [7].

Market available preparations

The Community herbal monograph refers only to two herbal preparations 4 from Sisymbrii officinalis herba: flos comminuted herbal substance and dry extract - extraction solvent ethanol 50% (V/V - volume to volume-) or water. The herbal substance is also available in combination products with other herbals or chemical substances, mainly codeine or sulfoguajacol and other herbal substances [12].

Indications

The pharmacological activity of Sisymbrium shows anti-inflammatory, analgesic, antitussive, myorelaxant and broad spectrum antimicrobial properties [13].

Politi et al. [7] Analyzed anti-inflammatory activity of *Sisymbrium officinale*. They found flavonoids, adenine, adenosine, guanine and oligosaccharides. They tested topical anti-inflammatory activity in the murine Croton oil-induced ear edema model but only a modest effect was observed at high concentrations.

Eccles hypotesized a generic "placebo-like" relaxing effect from sweet gustatory perception: gustatory afferences are mediated by cranial nerves VII, IX and X (vagus nerve) and gustatory fibers are localized in the rostral part of nucleus of solitary tract (NTS), so cough center is partially overlapped by gustatory afferences and sweet taste releases opioid peptides in NTS inhibit cough stimuli. But this effect should derive from sweeteners added to erysimum, which is a bitter plant.

European Medicines Agency (EMA) monograph "Assessment report on *Sisymbrium Officinale* (L) Scop. herba" states that "Sisymbrii officinalis herba has been in medicinal use for a period of at least 30 years as requested by Directive 2004/24/EC (European Community), thus the requirement for the qualification as a traditional herbal medicinal product is fulfilled (long-standing use) in the following indication: traditional herbal medicinal product for the relief of throat irritation such as hoarseness and dry cough. Since clinical studies with products

containing hedge mustard have not been found in the literature well-established use cannot be recommended. The mitigating effect of the herbal substance on the pharyngeal irritation might be due to the high mucilage's content (10.9%-13.5%) [5]. The benefit-risk balance can be considered positive." In the past, several combination products were on the market in Spain which included Erysimum Flos combined with Liquiritiae radix, Althaea radix, Marrubii herba, Anisi fructus and/or Thymi herba. For example in Euphon® syrup and pastille until 2004 in Belgium.

Products on the market in the EMA member states

Regulatory status overview: Marketing Authorisation only in Belgium and Portugal while Traditional Use Registration only in Germany and France. On the counter product in other countries.

Side effects - contraindications

As far as now, there are no known or proved side effects for Sisymbrium. The reported pharmacological effects are not considered contradictory to the traditional uses. Specific data on pharmacokinetics and interactions are not available.

EMA in 2013 specified "Non-clinical information on the safety of *Sisymbrium officinale* could not be retrieved. However, during the long-standing use in the Member States, no adverse effects or incidences were reported (Wolf 1992). Based on this it is concluded that there are no safety concerns relating to the use of the preparations in the given indication at the traditionally used doses."

2014 EMA monograph generally indicates contraindication in traditional use "in case of hypersensitivity to the active substance" (from the package leaflet of a Belgian product). About special warnings and precautions for use, recommend to avoid oromucosal use under 6yrs "because of the pharmaceutical form (solid dosage form) - from the package leaflet of a French product - and due to lack of adequate data". (The package leaflet of a German product shows "The use in children under 5 years of age is not recommended due to lack of adequate data.") The package leaflet Belgian product says "Syrup should not be used by children under 3 years of age and oral use under 3yrs , due to lack of adequate data and because medical advice should be sought."

No fertility data available nor about genotoxicity. Safety during pregnancy and lactation has not been established, even if the package leaflet of Belgian product says "The use of the syrup is not contraindicated during pregnancy and lactation." while in the package leaflet of a German product is written " In the absence of sufficient data, the use during pregnancy and lactation is not recommended."

No studies on the effect on the ability to drive and use machines have been performed. No undesirable effects known.

About pharmaceutical particulars, the content of cardenolides has to be specified in the herbal preparations and should be ≤1ppm. No case of overdose has been reported, even if information from the package leaflet of a German product: "Queasiness, vomiting, diarrhoea, headache and cardiac rhythm disorders have been reported." It is conceivable that over dosage would have digitalis-like effects. These should include queasiness, vomiting, diarrhoea, headache and cardiac rhythm disorders [14], PDR for Herbal Medicines [4]. Cases of poisonings, however, have not been recorded.

About pharmaceutical interactions, the package leaflet of a German product says " Potassium deficiency. Intake of cardiac glycosides". EMA report comments: This is only a theoretical assumption; no report is mentioned in the market overview. So no data available about pharmaceutical interactions.

Ema's overall conclusions on *sisymbrium officinale*'s clinical safety (2014)

a) The medicinal use of hedge mustard preparation is considered safe because no adverse effects have been reported during the long-standing use as a medicinal product in Belgium and Germany.

b) The known toxic cardioactive steroid glycosides have been documented as a minor component and their concentrations are too low to present any risk to human health.

c) The oromucosal use in children under 6 years of age is not recommended because of the solid dosage form and due to lack of adequate data.

d) The oral use in children under 3 years of age is not recommended due to lack of adequate data and because, for the proposed indication, medical advice should be sought for this age group.

e) Since there are insufficient data, the use during pregnancy and lactation is not recommended.

Aim of the Study

The vocal tract needs a high level of hydration to work properly, mostly at vocal folds edges level. The risk for friction and its derived lesions is directly related to relative humidity, amount of dusts, reduction of mucus lubrification from tissues hyperemia in case of flogosys.

The aim of this work is to observe perceived vocal tract disability and its variation after a short treatment with *Sisymbrium officinale*. As to World Health Organization, the consequences of a disease may be classified as impairment, disability and handicap. Disability is described as "a restriction or lack of ability manifested in the performance of daily tasks." Handicap is defined as, "a social, economic, or environmental disad-vantage resulting from an impairment or disability.".

A widespread used method to assess perceived Voice Handicap is Vocal Handicap Index questionnaire (VHI) by Jacobson et al. [15], where handicap is measured through three different scales measuring Physical, Functional and Emotional perceived disabilities. Perception of dryness and sore throat in the vocal tract is physically disabling. The scores delta, between pre and post treatment, in Physical Scale of VHI has been chosen to describe the perceived reduction in vocal tract disability.

Materials and Methods

Only France and Germany have products registrated for traditional use [16]. In this work the Authors used French product Sisymbrium. In random serie, patients claiming vocal tract discomfort were treated with Sisymbrium, 90 mg extract/day for 10-20 days, [16] alone or with treatment related to the diagnosed disease [17].

Diagnosis was described as: Functional Dysphonia (FD), Organic Dysphonia (OD), Laryngo Pharyngeal Reflux (LPR), Upper Airways Acute Flogosis (UAAF) or Upper Airways Chronic Flogosis (UACF), obtained through ENT objective evaluations. We tried to plan a "placebo control group", but the pharmaceutical firm did not accept to prepare it.

Patients filled a VHI - P scale before and after treatment

The Patients were 64 F and 40 M, aged 8-80 yrs -mean age 42,1yrs. They were 65 artists (A), 30 non artists (NA) and 9 Voice Professionals in spoken non artistic voice (VP). 3 of them did not submit to controls (NA) so the studied group was of 62 F, 39 M; 63 A, 30 NA, 8 VP. Their diagnosis distributed as 20 FD, 21 OD, 5 LPR, 14 LPR + OD, 32 UAAF, 13 UACF.

Results

i. The mean VHI-P pretreatment score was 27, 9 /40: pretty high level of perceived disability. The mean VHI-P post treatment score was 13, 2: a very low level of residual disability.

ii. The average DELTA VHI was around 14/40: this means the reduction of one third of the perceived disability in a short time.

iii. In FD the treatment with Sisymbrium obtained a mean reduction of disability of 13/40.

iv. In OD the result was 13, 6/40 in Sisymbrium alone treatment, while in 10 days complex treatment the reduction was 13/40 and in 20 days 14, 4/40.

v. In LPR the treatment with added Sisymbrium gave a mean reduction of 12/40 in a 10 days treatment and 13, 9/40 in a 20 days treatment.

vi. In UAAF treated with Sisymbrium the mean perceived reduction was 15/40, 14, 9/40 in 10 days combined and 15, 6/40 in 20 days combined.

vii. In UACF treated with Sisymbrium plus FANS for 20 days, the referred reduction of perceived disability was 13, 2/40 avg.

Discussion

Politi et al. [7] evaluated Sisymbrium anti-inflammatory effects in terms of edema reduction in mice ears (inners faces of auricular pavillon) measured as weight reduction of treated samples meaning edema's reduction. This choice might have been a limit, first because vocal tract tissues are at least of three different kinds (pseudostratified columnar, nonkeratinized and keratinized stratified squamous ephitelium) while mice ear has only a stratified squamous type, and second because Sisymbrium effect does not look similar to NSAIDs, like salycilates [18-20].

In our work the main claim is physical disabling effect of dryness, related to hyperemia and sticky secretions. The effect of Sisymbrium seems mostly "moisture enhancing", - and in this case tissues' weights should not change that much, or better increase than decrease.

The scores show a homogenous reduction around 30% (13/40) of perceived disability. The scores seem independent from different diagnosis or single or combined treatment. So the presence of Sysimbrium in the treatment seems the common factor facilitating reduction of perceived disability.

Conclusion

Vocal tract pathologies must be treated following Evidence Based Medicine protocols. But Biagi [13] pointed out that in some cases Phytoterapy mantains a pivotal role in the modern EBM. "Main peculiar features of medicinal plants may be compared to monomolecular drugs:

a. Pharmaco-toxicological profile

b. Multitarget mechanism of action

c. Synergistic mechanism of phytocomplex"

In our work a small group of patients with different diseases of the vocal tract, all resulting in perceived physical disability, a short treatment with Sisymbrium Officinalis, alone or combined with EBM drugs, resulted efficient in reducing disability. This observation seems coherent to traditional medicine expectations [21,22].

So we conclude that, in diagnosed absence of major diseases, when in a Patient the desired effect is simply prompt reduction of perceived disability to reduce resulting handicap, if prescribed under physician control and instrumental assessment, monitoring subjective perception of symptoms, phytotherapy may show efficacy and cost/effctiveness, where "main classical treatments" may be expensive, redundant or present undesired side effects.

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