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HERBAL TREATMENTS FOR CHRONIC RHINOSINUSITIS – A NARRATIVE COMPARISON OF WESTERN KNOWLEDGE TO EASTERN EUROPEAN TRADITIONAL REMEDIES AND ORIENTAL TRADITIONAL MEDICINE

Adela-Ioana Mocanu[1,2], Horia Mocanu[3,4*], Mihai Lupaşcu[5,6*], Alexandra-Cristina Neagu[7§], Mihaela Andreescu[8,9§] and Roxana Maria Nemeş[1,10,11§]

[1]Doctoral School, Faculty of Medicine, "Titu Maiorescu" University, 031593 Bucharest, Romania.
[2]Department of ENT&HNS, Polimed Medical Center, 040067 Bucharest, Romania.
[3]Department of ENT&HNS, Faculty of Medicine, "Titu Maiorescu" University, 031593, Bucharest, Romania.
[4]Department of ENT&HNS, Găeşti City Hospital, 135200, Găeşti, Dâmbovița, Romania.
[5]Department of ENT&HNS, Faculty of Medicine, "Ovidius" University, 900527, Constanța, Romania.
[6]Department of ENT&HNS, Constanța County Clinical Emergency Hospital, 900591, Constanța, Romania.
[7]Department of ENT&HNS, "Marie Sklodowska Curie" Emergency Children's Hospital, 041434, Bucharest, Romania.
[8]Department of Hematology, Faculty of Medicine, "Titu Maiorescu" University, 031593, Bucharest, Romania.
[9]Department of Hematology, Colentina Clinical Hospital, 01171, Bucharest, Romania.
[10]Department of Physiopathology, Faculty of Medicine, "Titu Maiorescu" University, 031593, Bucharest, Ro-mania.
[11]Department of Special Respiratory Functional Explorations, "Marius Nasta" Institute of Pneumophtisiology, 050159, Bucharest.

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***Corresponding Author**
Horia Mocanu
Department of ENT&HNS, Faculty of Medicine, "Titu Maiorescu" University, 031593, Bucharest, Romania.

ABSTRACT

Chronic rhinosinusitis (CRS) is an affliction of significant prevalence, closely connected to allergic disorders and acute rhinosinusitis, which mainly benefits from classical treatment (CT) including corticosteroids, antibiotics and surgery. However, a large number of patients reports poor or disappoining results of classical wester medicine and therefore seek for complementary and alterna-tive medicine (CAM). The most common type of CAM used for sinus inflammation are herbal treatments (HM), known in Chinese traditional medicine for millennia for their resistance to foreign pathogens, anti-inflammatory, antibacterial and immunomodulatory effects and increasingly popular with European and North American patients and physicians. Apparently, one-third of U.S. population uses some form of CAM for treating CRS with estimated expenses of $23 billion is spent annually on these therapies. Most patients do not inform their physician on the use of herbal or alternative treatments. Most studies regarding plant extracts or mixtures come from China and South-East Asia and are usually scientifically performed, as the use of HM is done on a large scale within this geographical area. Western Europe has oriented the knowledge towards scientific research and rationally proven effects which automatically led to developing industrial products (extracts and mixtures of extract) that are safe to use and currently present in CRS management protocols. Eastern Europe remains the unknown quantity of the equation, as the herbal use, although ancient, hasn't been properly documented and organized. The plants are not widely spread and their use remains somewhat traditional, even mystical and confided to regions. Although certain plant families seem to be common in use for all continents and regions, the actual common plants are few. This is explainable by geographical and biological differences. The influence of folklore and spirituality in this regard remains to be studied further. We performed a literature survey between July 2021 and July 2023, using a variety of Romanian and East-European ethnobotanical books as well as well-established databases, to find the most relevant articles. Articles were not limited to those published in the English and Romanian languages, as the purpose of our work was to present exhaustive data related to an array of cultural inheritance. We attempted a narrative presentation of the material instead of a systematic re-view in order to make it easier and more pleasant to read and also to bring a sense of folklore and tradition to this topic, as these two parameters play an important role in the use of herbal therapies.

KEYWORDS: chronic rhinosinusitis, herbal; plants, medicinal; phytotherapy; extracts; traditional, Romanian, East-European, Balkans, complementary, Chinese, Asian, oriental.

1. INTRODUCTION

Chronic rhinosinusitis (CRS) is an affliction of significant prevalence (10.9% in Europe and 13% to 17% in the United States according to current statistics).[1,2,3] which can be diagnosed after 12 weeks of presence of at least two main symptoms which include: nasal obstruction, nasal drainage, facial pain/pressure, hyposmia/anosmia, accompanied by objective clinical or radiological evidence.[2] On top of significant prevalence in the general population, the association with significantly increased costs of healthcare services due to the severe morbidity and poor quality of life (QoL) have been frequently reported.[2,4,5,6,7,] Rudmik et al estimate for the United States alone, the total costs associated to CRS to be 10 to $13 billion per year and total indirect costs resulted from reduced labor productivity to exceed $20 billion per year.[8] A statistic from 2006 reports 257,000 sinus surgeries, most of which due to CRS, with an average loss of 5.67 workdays per year in the United States.[3,9,10] Other authors associate CRS to chronic debilitating conditions such as depression, olfactory dysfunction, fatigue, sleep disorders, and sexual dysfunction.[11] We should also note the frequent association of CRS to allergic disorders, rhinitis, acute sinusitis etc.

Extensive research and continuous acquired knowledge on CRS led to developing a number of protocols for so called conventional treatments (CT) which include topical intranasal corticosteroids, antihistamines and saline irrigation. If a positive result is not obtained, oral corticosteroids, antibiotics, and surgical treatment may be applied[2,4,12] with their entire array of risks and complications including adverse reactions and antibiotic resistance.[4,13,14] If we also consider that many patients do not report significant improvement in quality of life after surgery for CRS, we can easily understand the need to seek complementary and alternative methods of treatment including the very old and popular herbal medicine (HM).

HM is by no means a new occurrence in the treatment of CRS especially in East Asian traditional medicine which emphasizes the holistic approach and uses an array of herbs known for their resistance to foreign pathogens, anti-inflammatory, antibacterial and immunomodulatory effects.[15]

Although large-scale surveys on the usefulness of HM and complementary and alternative medicine (CAM) to treat CRS are lacking, this type of approach has grown in popularity in many western countries. It is believed that use of CAM is particularly prevalent among patients with allergic disorders or rhinosinusitis.[3,16,17]

Complementary and alternative medicine can be defined as "diagnosis, treatment, and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine" [18]

Apparently, one-third of U.S. population uses some form of CAM for treating CRS with estimated expenses of $23 billion is spent annually on these therapies. Up to 75% of patients do not inform their physician on the use of herbal or alternative treatments, although physicians must be aware of any use of herbal products by patients, due to their possible adverse side effects and interactions with other medications.[19] This type of attitude has also been reported by other studies - up to 69% of patients admit-ting to using CAM but most of them failing to reveal this usage to their physicians, and oftentimes using it instead of their conventional prescribed medications.[21-25] Amongst all CAM methods which also include homeopathy, acupuncture, massage, osteopathic manipulation, the use of HM seems to be the most common. A North American study by Blanc et al[26] surveyed the alternative medicine use of 175 individuals with rhinosinusitis, and found that 26% of the respondents reported using at least one herbal remedy. Some 9% of respondents were taking a traditional Chinese herbal remedy. Some of these responders did not use any form of western medication (CT).[27]

The use of CAM is gaining popularity in West-European countries as well, with an estimated £1.6 billion being spent on it annually in the UK alone.[25] The current UK prevalence of CAM use is reported at 25% and rising, and the number of CAM practitioners is within the region of 50,000.[25]

Tradition and folklore, especially in East-European countries, play an important role in perceiving and using phytomedicine (nearly 80% of the population of developing countries according to the World Health Organization).[28,29] In the Western world and developed countries, phytomedicine is perceived more as a holistic and natural approach to treatment and gains popularity with patients that are increasingly unsatisfied by the poor results of CT in CRS. Clinicians from western countries have always raised concerns over HM efficacy, some of them even expressed concern for the reversion to irrational approaches to medical practice[18,30] which emphasizes the need of understanding the mechanisms of action of common plant extracts and dominant compounds. Many of these products and treatments do not have scientifically validated results but become popular through press, social media and transmission of Eastern cultural heritage (extensive immigration from South-East Asia, Middle-East, Balkans etc.).

2. MATERIALS AND METHODS

A literature survey was performed between July 2021 and July 2023, using a variety of Romanian and East-European (Bulgaria, Macedonia, Greece, Russia, Ukraine etc.) ethnobotanical books as well as well-established databases, such as PUBMED, WEB of SCIENCE, SCOPUS, EMBASE, COCHRANE LIBRARY (Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register), CINAHL, and AMED to find the most relevant articles. Articles

were not limited to those published in the English and Romanian languages, as the purpose of our work was to present exhaustive data related to an array of cultural inheritance. We focused on the most recent works between 2010 and 2021 (75% of the cited material) but not neglecting any older relevant materials. Materials pertaining to Romanian information are also available in the Romanian Academy Library (https://biblacad.ro//eng_index.html) and/or in the Romanian National Library (http://www.bibnat.ro/).

We attempted a narrative presentation of the material instead of a systematic re-view in order to make it easier and more pleasant to read and also to bring a sense of folklore and tradition to this topic, as these two parameters play an important role in the use of herbal therapies. We searched the aforementioned databases using the general structure of the search strategy "search terms for condition" AND "search terms for intervention." Both MeSH terms and TEXT terms were used for the condition as well as the intervention.

The MeSH terms for the condition were: sinusitis.

The TEXT terms for the condition were: chronic rhinosinusitis, CRS, chronic rhinitis, chronic sinusitis, allergic rhinitis, allergic sinusitis, sinus inflammation.

The MeSH terms for the intervention were: Medicine, herbal; Plants, Medicinal; Drugs, Chinese Herbal; Phytotherapy; Plant, Extracts; Medicine, Traditional.

The TEXT terms for the intervention were: herb, herbs, herbal, plant, plants, phytomedicine, botanic, extract, traditional, Romanian, East-European, Balkans, natural, alternative, complementary, Chinese, Asian, oriental.

Despite the lack of well-founded data, we thought it was important to include as many herbal therapy variants with adjacent active compounds as possible to underline the variety of plants known as active in CRS and also the differences and similarities between various geographic areas of the world. We did not exclude studies that were specifically performed on acute rhinosinusitis or even rhinitis since we considered the anti-inflammatory effect of HM to be more important than the pathogenic form of the disease and also not to overlook the undeniable pathogenic link between acute rhinosinusitis, allergies and CRS. However, many studies did not specify a subtype of disease, and we included these in our discussion for the sake of completeness. We also included articles in which rhinitis and multiple subtypes of sinusitis, including CRS, were mentioned (e.g., CRS with allergic rhinitis). We considered the close relationship between the acute and chronic form of the affliction and the pathogenic link to rhinitis. The anti-inflammatory, antibacterial and antiallergic properties of the presented plant extracts should have corresponding results in all types of rhinosinusitis.

3. RESULTS

The aim of the study is to document as much information as possible on herbal therapies known to be used in the treatment of sinusitis and present it in an organized and exhaustive manner. We would also like to comment on differences and similarities between this folkloric, sometimes archaic knowledge from various geographic regions and conclude if the flora is the only factor involved or if any other factors related to spirituality and believes are also at play.

South-East Asia and the Middle East

The use of HM is a common practice in South-East Asian medicine, as shown by Lee et al. in their extensive review[4], that reports that most studies concerning HM from Asia come from China (79/80). where HM is actively used. Other sources include Taiwan, Korea, Vietnam, Mongolia, Iran. This article by Lee et al. comprises of 80 studies and reports that a wide range of HM modalities is known and currently documented as used in South-East Asia.

Bi Yuan Shu (BYS) is an herb mixture used in various forms: *Biyuan tongqiao* granule the most often (13 studies), *Biyuan* decoction and *Biyuanshu* oral liquid (4 studies each). As for the dosage form, the decoction was the most common (47 studies), followed by granules (19 studies) and capsules (6 studies). The actual plants used in these traditional Chinese mixes are:
Magnolia denudata Desr., Encycl. [J. Lamarck & al.] [Magnoliaceae; Magnoliae Flos] (63 studies),
Xanthium strumarium L., Sp. Pl. [Asteraceae; Xanthii Fructus] (61 studies),
Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Enum. Pl. Jap. [Apiace-ae; Angelicae Dahuricae Radix] (57 studies),
Glycyrrhiza uralensis Glycyrrhiza uralensis (Fisch. ex-DC.) L.Duan, J. Syst. Evol. [Le-guminosae; Glycyrrhizae Radix] (51 studies),
Scutellaria baicalensis Georgi, Bemerk. Reise Russ. Reich [Labiatae; Scutellariae Radix] (43 studies),
Mentha arvensis var. piperascens (Malinv. ex-Holmes) H.Hara, J. Fac. Sci. Univ. Tokyo, Sect. 3, Bot. [Lamiaceae; Menthae Herba] (33 studies),
Ligusticum chuanxiong S.H.Qiu, Y.Q.Zeng, K.Y.Pan, Y.C.Tang & J.M.Xu, Acta Phytotax. Sin. [Apiaceae; Ligustici Rhizoma] (31 studies),
Poria cocos (Schw.) Wolf [Polyporaceae; Poria (Hoelen)] (29 studies),
Astragalus membranaceus Bunge, Gen. Astragali [Leguminosae; Astragali Radix] (27 studies),
Ephedra sinica Stapf Bull. Misc. Inform. Kew [Ephedraceae; Ephedrae Herba] (24 stud-ies),
Platycodon grandiflorus (Jacq.) A.DC., Monogr. Campan. [Campanulaceae; Platycodi Radix] (23 studies),
Atractylodes macrocepha-la Koidz Fl. Symb. Orient. -Asiat. [Asteraceae; Atractylodis Rhizoma Alba] (22 studies),
Saururus chinensis Hort. ex-Loudon, Hort. Brit. [Loudon] [Saururaceae; Houttuyniae Herba] (21 studies).[4]

The effects of *Bi Yuan Shu* have been studied in combination with classical treatment (intranasal steroid and antibiotic therapy) for patients recovering from FESS surgery. These patients experienced significantly less pain, discharge, and breathing difficulty than did those taking the standard treatment alone.[4] In a multi-center RCT, Liang et al[31] assessed BYS for its adjunctive effect on clinical symptoms and signs in 340 patients with CRS and nasal polyps who had undergone FESS. Half the patients received additional antibiotics and topical steroids (n 170) whilst the other half only received antibiotics and topical steroids (n 170) for 20 days. Significant improvements in individual symptoms that favored BYS were seen for pain, breathing difficulty, purulent nasal discharge, hyposmia, and halitosis, but not for fever and cough, which showed only a positive trend. Analysis was by intent-to treat.

Ge Gen Tang (GGT) is a traditional Chinese medicine made up of many herbs. GGT formulations typically contain *Puerariae radix* (Pueraria lobata (Willd.) Ohwi, Bull. Tokyo Sci. Mus.), *Ephedrae Herba* (Ephedra sinica Stapf Bull. Misc. Inform. Kew), *Cinnamomi Ramulus* (Cinnamomum cassia Nees ex Blume, Bijdr. Fl. Ned. Ind.), *Paeoniae Radix* (Paeonia lactiflora Pall., Reise Russ. Reich.), Glycyrrhizae *Radix preparata* (Glycyrrhiza uralensis (Fisch. ex-DC.) L.Duan, J. Syst. Evol.), *Zingiberis Rhizoma* (Zingiber officinale Roscoe, Trans. Linn. Soc. London), and *Zizyphi Fructus* (Ziziphus jujuba Mill., Gard. Dict.). It is described as being useful for treating upper respiratory tract infections.[27,32] Yen et al report *Ge Gen Tang* use as common[3] whilst Chang et al experiment with multiple in vitro cell lines to demonstrate that *Ge Gen Tang* exerts antiviral action against respiratory syncytial virus (RSV).[33] The conclusion was that exposure of RSV to *Ge Gen Tang* resulted in a significant reduction in TNFa expression. There are at this time no clinical data to suggest that *Ge Gen Tang* has any efficacy in the treatment of CRS.

Nigella sativa L., Sp. Pl. [Linnaeus], a member of Ranunculaceae family, commonly known as black seed, used for centuries in the Middle-East and India for treating various ailments such as : cough, colic, lactation, eye infections, anorexia, diarrhea, dyspepsia and fever, it is also enriched by a significant religious importance (Ayurvedic medicine), probably due to its antiseptic, local analgesic and anti-inflammatory properties.[34,35]

The biochemical content includes: amino acids, proteins, carbohydrates, 0.4-1.49% essential oil, 30-44.21% fixed oil, sterols (cholesterol, campestrol, stagmasterol, -spinasterol, -sitosterol) 12, alkaloids (nigellidine, nigellimine, nigellicine), saponins and crude fiber, minerals (calcium, iron, sodium, potassium).[35,36] The essential oil and the fixed oil both contain similar active agents but in different concentrations: Thymoquinone (2-isopropyl-5-methyl-1,4-benzoquinone) at 26.8-54.8% for essential oil vs 3.5-8.7mg/g in fixed oil.[35,37,38] Linoleic acid makes up 50% of fixed oil, followed by oleic acid (25%), palmitic acid (18%). p-cymene (14.7-38.0%), longifolene (1.2-10.2%), -thujene (1.3-10.1%), carvacrol (0.5- 4.2%). Essential oil also contains cubebene (0.4-3%), -pinene (0.2-2.4%), limonene (0.7-2.3%), -pinene (0.4-3.0%), sabinene (0.2-1.6%).[39]

The presence of thymoquinone, nigellone, thymohydroquinone is associated with anti-inflammatory and antioxidant effects[34,38,40] that correlate to reducing the inflammation of sinuses and respiratory airways, significant suppression of nasal mucosal congestion and improvement of allergic rhinitis symptoms. In other studies, *N. sativa* seed fixed oil, thymoquinone and nigellone dose dependently inhibited the formation of 5-lipoxygenase products and 5-hydroxy-eicosa-tetra-enoic acid (5-HETE) from polymorphonuclear leukocytes.[41] Scientific data has been obtained in animal model experiments in which *N. sativa* fixed oil reduced cyclooxygenase and 5-lipoxygenase pathways of peritoneal leukocytes[42], improved lung inflammation and decreased peripheral blood eosinophil count.[43,44]

Beneficial effects in sinusitis may also include enhancing humoral immune responses by reduction in IgA, IgM and C3 levels 27. Action against pathogenic micro-organisms should not be neglected. The antiviral effects of thymoquinone, against avian influenza virus (H9N2)[45] and murine cytomegalovirus infection model[46] were confirmed by its stimulatory effects on CD4+ T lymphocytes in murine BALB/c cytomegalovirus model.[47] Thymoquinone also exhibited strong antimicrobial properties against fungi, Gram negative and positive bacteria.[48]

N. sativa has been traditionally used for curing headache due to its analgesic effects as an opioid principle with an antagonizing effect on naloxone.[49] This could also extend to analgesic effects in CRS. Thymoquinone and *N. sativa* seed fixed oil de-creased the antinociceptive effect of morphine, therefore, the antinociceptive effects of *N. sativa* seed fixed oil and thymoquinone is via indirect activation of k-opioid and supra-spinal 1 receptor subtype.[50]

Ageratum conyzoides Sieber ex Steud., Nomencl. Bot. [Steudel] is an herbaceous plant, belonging to the Chrysanthemum family, found in Southeast Asia and Central America. Known in Oriental medicine as treatment for respiratory infections, pharyngitis and used for detoxifying, eliminating swelling, hemostasis and increasing secre-tion for a decongestant effect on the nose and sinuses.[51,52] The main ingredients in *Ageratum conyzoides* are essential oil (g-cadinen, caryo-phyllen, ageratocromen, de-methoxy-ageratocromen) accounting for about 2%, alkaloids and saponins. The whole plant contains 0.16% essential oils whilst leaves and flowers contain 0.2% essential oil. Leaves contain stigmast 7-en-3-02, quercetin, kaempferol, fumaric acid, and cafeic acid, carotenoids, low phytosterols, tannins, saponins and uronic compounds. The rough saponin content in stems and leaves (dried herbs) is 4.7%.

Pharmacological effects of *Ageratum conyzoides* include resistance to bacteria such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*. In South-East Asia it is usually used for treating sinusitis and chronic rhinorrhea in the form of freshly squeezed plant juice (50gr).[53]

Heliotropium indicum L., Sp. Pl. is a wild-growing hard herbaceous Asian plant from the Boraginaceae family, used as anti-inflammatory and antalgic in support for treatment of sinusitis.[34,54] It is used as instillations of plant juice for 10 days. Although *Heliotropium indicum* contains hepatotoxic xyanhydric acid and alkaloids it does not immediately affect the body.[34,55] The World Health Organization has advised against using it as a drug because it can cause liver toxicity, hemorrhage and even cause cancer to users.

Xanthium strumarium L., Sp. Pl. also a tropical plant, belonging to the Asteraceae family containing fat, alkaloids, iodine and saponins, which have analgesic, antibacterial and anti-inflammatory properties, traditionally used in South-East Asia (Vietnam) for the treatment of CRS, in conjunction with other plants (*Ageratum conyzoides* 30g, *Honeysuckle* 20g, *Xanthium strumarium* 12g).[34,35]

Urtica dioica L., Sp. Pl. [Linnaeus] has been reported to have anti-inflammatory and anti-allergenic properties.[56,57] The active components include adenine, nicotinamide, synephrine and osthole. Also, alkaloids (Synephrine) in its composition are known to work as nasal decongestants[56,58] and is used in traditional Chinese medicine for treatment of seasonal allergy and other inflammatory disorders.[56,59] *Urtica dioica* extract has been studied in-vitro and proven as inhibitor of several key inflammatory events. Its effects include: antagonist and negative agonist activity against the Histamine-1 (H1) receptor which blocks histamine production and release; inhibition of mast cell tryptase hindering mast cell degranulation and consequent release of a host of pro-inflammatory cytokines and chemokines that lead to the appearance of allergy symptoms; inhibition of Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) both key enzymes involved in the induction of many inflammation events associated with allergic rhinitis and therefore prevention of prostaglandin formation; Hematopoietic Prostaglandin D2 synthase (HPGDS) inhibition, that specifically deters Prostaglandin D2 production, a primary pro-inflammatory mediator in allergic rhinitis.[56,60] A more recent study deals with investigating the efficacy of supportive therapy of allergic Rhinitis by Urtidin® Tablet.

Artemisia afra Jacq. ex Willd. is one of the most widely used herbal remedies in South Africa to treat an entire array of ailments manifested with inflammation and pain.[61,62] These include coughs, colds, asthma, fever, influenza, diabetes and malaria[62], and sometimes rhinitis.[61,63] Related plants such as *A. ordosica* Krasch. have been proven by use of in vivo models to have effects in controlling allergic inflammatory response in rhinitis.[61,64] Clinical trials with nasal spray preparations of A. abrotanum containing its essential oils and flavonols have been performed with good results.[61,65]

Chelidonium majus L., Sp. Pl. – also used for its proven anti-inflammatory potential and modulation of immune response (in vitro cellular models, in vivo experiments). Chelidonic acid was efficient in mouse models of ovalbumin-elicited allergic rhinitis.[66,67]

Zingiber officinale Roscoe, Trans. Linn. Soc. London (Ginger) – the antiallergic effect of 6-gingerol, the major compound of ginger, has been studied in mouse allergy model and primary/cell line culture systems. Oral administration of ginger reduces the severity of sneezing and nasal rubbing by nasal sensitization of ovalbumin and suppressed infiltration of mast cells in nasal mucosa and secretion of ovalbumin specific immuno-globulin-E in serum. Accordingly, 6-gingerol suppressed in-vitro differentiation of both Th1 cells and Th2 cells from naive T-cells.[68]

The study by Kawamoto, et al., 2015 shows that 6-gingerol suppresses cytokine production for T-cell activation and proliferation, thereby not causing β-cell and mast cell activation and resulting in prevention or reduction of allergic rhinitis symptoms. 6-gingerol significantly inhibited the phosphorylation of mitogen activated protein kinases, calcium release and nuclear localization of c-fos and nuclear factor-κβ by phorbol 12-myristate 13-acetate and ionomycin stimulation.[68,69]

Echinacea is a well-established traditional treatment for CRS, with its most common species: *Echinacea pallida* (Nutt.) Nutt., Trans. Amer. Philos. Soc., *Echinacea purpurea* (L.) Moench, Methodus (Moench), and *Echinacea angustifolia* DC., Prodr. [A. P. de Candolle].[27,70] The plant extracts appear to have antiviral action through activation of the immune system (upregulation of the proinflammatory cytokines IL-1b, IL-6, IL -10, and tumor necrosis factor alpha (TNFa) in human macrophages).[27,71] Asher et al. states that there are more than 350 studies to date on the herb *Echinacea* and those have indicated that *Echinacea* activates T and B cell lymphocytes in vitro,[19, 72-74] although this has recently been called into question.[19,75] Several metanalyses on *Echinacea* for the common cold have suggested a positive effect,[19,76,77] whilst other studies have shown no clear effect of these extracts.[19,78,79] A meta-analysis of 16 trials yielded overall better results for *Echinacea* preparations than placebo. The large number of *Echinacea* preparations (over 200 on the current market) make comparative study and recommendations quite difficult.[19,80,81]

Regarding herbs, Shea butter placed on the upper lip (from the seed of the African shea butter tree, *Butyrospermum parkii* Kotschy, Sitzungsber. Acad. Wien,

Math. -Nat. l. Abth. I.) was found to be an effective nasal decongestant in an extremely small study.[19,82]

Ma huang is a dietary supplement containing *Ephedra sinica* Stapf. (ephedra alkaloids), often used as a nasal decongestant. The plant is also commonly found in BYS and GGT. Adverse reactions associated with *Ma huang* use include hypertension, palpitations, tachycardia, stroke, and seizures.[19,83]

Western Europe

Compared to Asian herbal treatments, the substances used on a large scale in Western cultures are by far more scientifically studied and based on classical experimentation. That is the reason why a number of them is already used as recognized treatment and part of various protocols. Another difference would be that wester used substances tend to be industrially extracted (phytoneering) whereas East-Asian plants are used in their physical form, usually as decoction.

Sinupret® (Bionorica SE, Neumarkt, Germany) is by far the most popular form of HM used in Western medicine. It is a trademarked herbal preparation developed in Germany which has been developed using phytoneering processes and contains ex-tracts of five herbs: elder (*Sambucus nigra* L., Sp. Pl. [Linnaeus], Caprifoliaceae) flowers, primrose (*Primula veris* L., Sp. Pl., Primulaceae) flowers with calyx, common sorrel (*Rumex acetosa*, L., Sp. Pl., Polygonaceae), European vervain (*Verbena officinalis* L., Sp. Pl., Verbenaceae) and gentian (*Gentiana lutea* L., Sp. Pl., Gentianaceae) root. All these plants are known for their mucolytic effect and sometimes for anti-inflammatory activity. In a randomised, double-blind, placebo-controlled trial by Richstein and Mann, conducted on 31 patients with CRS, the radiological evaluation showed that 12/16 of them experienced considerable improvements or total recovery compared with 6/15 placebo-treated patients (p value not reported).[84,85] Another randomized, open-label, comparative study conducted on 46 patients with exacerbation of CRS, concluded that treatment for 21 days (2 tablets, 3 times per day) resulted in improvement for 23.5% (4/17) and lack of pathologic findings in 41.7% (10/24). The authors concluded that phytoneering synthetized drugs were equivalent in effect to N-acetylcysteine therapy.[84,86] However, we must note that the researchers permit-ted the use of associated drugs, which could have modified the outcome.

A number of other trials[87-90] tested the effect of *Sinupret* as adjunctive treatment to antibiotics and/or nasal decongestant in patients with acute rhinosinusitis. In a randomized study by Zimmer et al.[90], 90 patients suffering from acute bacterial sinusitis received either *Esberitox* (see below) or *Sinupret* (5 tablets 2/d) as adjunctive treatments to doxycycline, or doxycycline alone for 20 days. Both herbal preparation groups had a significantly higher responder rate (*Sinupret* 85.7%, *Esberitox* 86.7%) compared with control (50%). Berghorn et al[88] treated 140 patients with acute bac-terial sinusitis with either *Sinupret* liquid (50 drops 3/d) or placebo as adjunctive treatment to antibiotics and nasal decongestant. The duration of the treatment was 14 days. The results were assessed by combined clinical score and ultrasonogram findings and showed better results in the *Sinupret* group, without statistical significance. Neubauer and März[89] randomized 160 patients with acute bacterial sinusitis into two groups to receive either *Sinupret* sugar-coated tablets (2 tablets 3/day) or placebo as adjunctive treatment to antimicrobial and decongestant therapy for 2 weeks. Evaluation was done radiologically and via patient questionnaire. *Sinupret* was found to be significantly better than placebo.

This extract combination has been evaluated through in vitro and animal models and proven to poses significant activities against various microbe and virus, secretolytic and anti-inflammatory activity.[91] This herbal mixture was perceived through these studies to be effective and well tolerated.[92]

Cyclamen europaeum L., Sp. Pl. extract (Nasodren®) is a product with surfactant activity through its rich saponins content. It is reported to ease intranasal drainage of fluid from the sinuses through a physical mechanism. Cyclamen is a member of the primrose family (Primulaceae) and its use as medicine can be traced back to ancient Greece where Theophrastus (4th−3rd centuries BC) recommended inserting a mixture of cyclamen extract and honey into the nose to treat nasal catarrh and headaches ("to clear the head").[84]

Cineole is a terpenoid oxide extracted from eucalyptus oils. *Eucalyptus globulus* Labill., Voy. Rech. Pérouse is part of the Myrtaceae family and is known for the an-ti-inflammatory, antiseptic and decongestant properties. Its traditional uses include asthma, nasal congestion, runny nose, cough, sore throat and sinusitis. Used in a double-blind, placebo-controlled RCT as adjunctive treatment to a nasal decongestant in the treatment of 152 patients with ARS. (*Cineole* capsules 100 mg/d) vs. placebo for 7 days, the improvement of clinical symptoms (eg, headache, nasal obstruction, and impairment of condition) was significant in favor of *Cineole*.[87]

Bromelain is a proteolytic enzyme extracted from the stem and the fruit of the *Ananas comosus* (L.) Merr., Interpr. Herb. Amboin. (pineapple). Its physiological effects appear to include interactions with inflammatory, immune, cell signaling, coagulation molecules and related pathways as it inhibits nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB) and cyclooxygenase-2 (COX-2), and it stimulates the production of proinflammatory cytokines IL-1b, IL-6, TNFa, and IFNg.[19,93] The enzyme's anti-inflammatory action is due to its inhibition of bradykinin production at the inflammatory site. As such, it has also been extensively studied and used. Most studies are randomized and similarly designed around the use of *Bromelain* (2 tablets 4/d) or placebo for 6 days, in a double-blind fashion. All patients also re-

ceived some form of CT (antibiotics, antihistaminic decongestants, and analgesics). In a cohort of 49 patients, Seltzer et al. 24 reported significantly better results in the Bromelain group for overall rating, breathing difficulties, and nasal discomfort with trends of improvement towards subsidence of edema, inflammation, headache, and pain.[94] Taub et al. on the other hand 26 observed improvements in the bromelain group in nasal mucosal inflammation, nasal discharge, breathing difficulty, headache, and overall rating, but only nasal mucosal inflammation and overall rating reached statistical significance.[95] These three double-blind placebo-controlled studies from the 1960s showed statistically significant improvement in the symptoms of sinusitis over control subjects. In all studies, the patients were also taking antibiotics and did not benefit from radio-graphic documentation of sinusitis.[94-96]

However, the debate on the benefits of pineapple extract in CRS is still opened and the research has been continued in recent years and concluded that *Bromelain* could represent a therapeutic option due to its anti-inflammatory properties and its pharmacokinetics and pharmacodynamics characteristics as well as safety of use. Some forms of intranasal administration have also been suggested.[97 -98]

Andrographis paniculata (Burm.f.) Wall. ex Nees, Pl. Asiat. Rar. (Wallich) is an annual herbaceous plant of the family Acanthaceae, native of India and Sri Lanka. The herb is useful for treating upper respiratory tract infections, ulcerative colitis and rheumatic symptoms although limited. The preparation *Kan Jang*® contains *Andrographis paniculata* and *Eleutherococcus senticosus* (Maxim. & Rupr.) Maxim., Prim. Fl. Amur. and may shorten the duration and lessen the symptoms of common cold.[84]

Angocin® Anti-Infekt N contains mustard oils (isothiocyanates) that inhibit the growth of bacteria and viruses. It also contains natural antibiotics from *Tropaeolum majus* L., Sp. Pl.(nasturtium) and *Armoracia rusticana* G.Gaertn., B.Mey. & Scherb., Oekon. Fl. Wetterau (horseradish), which make it effective in the treatment of respiratory and urinary tract infections.[84]

Esberitox is an herbal mixture with immune stimulating properties, composed of three herbs, *Thuja occidentalis* L., Sp. Pl., *Echinacea angustifolia* DC., Prodr. [A. P. de Candolle], and *Baptisia tinctoria* (L.) R.Br. in W.T.Aiton, Hort. Kew., ed. 2 [W.T. Aiton]. One of the studies described above[87,90] tested *Esberitox* (3 tablets 3/d) as well as *Sinupret* as an adjunctive treatment to doxycycline for acute sinusitis.

Myrtol is a plant extract (distillate) that consists mainly of three monoterpenes: alpha-pinene, d-limonene and 1,8-cineole extracted from *Pinus spp* (Pine), *Citrus aurantiifolia* (Christm.) Swingle, J. Wash. Acad. Sci. (lime) and *Eucalyptus globulus* Labill., Voy. Rech. Pérouse. It has been reported as reducing symptoms of acute sinusitis in a double-blind, placebo-controlled study run on 330 patients that received *Myrtol* (300 mg/d, n 109), another unidentified essential oil licensed for this indication (300 mg/d, n 110), or placebo (n 111). The total symptom score (headache, pain at bending over, general well-being, fever, pain upon pressure, nasal secretion, and nasal obstruction) has been used as assessment method and the mean decrease was 10.3 in the *Myrtol* group, 10.4 in the other essential oil group, and 9.0 in the placebo group. The author reported no difference between *Myrtol* and the other essential oil group and that both groups were superior to placebo group.[87]

Capsaicin is the pungent principal ingredient of *Capsicum frutescens* L., Sp. Pl. [Linnaeus] (red chili pepper) and is a direct stimulant of the sensory-C-fibers, producing the release of CGRP[99,100] and other tachykinins.[99,101] Tissue depletion of CGRP is the result of systemic pre-treatment of adult guinea-pigs with capsaicin as well as destruction of sensory-C fiber terminals.[99,102] In the pig nasal mucosa, local intra-arterial (i.a.) injection of capsaicin induces CGRP-LI release with concomitant vasodilatation of both capacitance and resistance blood vessels[99,103]; capsaicin probably does not stimulate mast cell histamine release directly.[11, 12] The intensity of rhinosinusitis symptoms seems to be well correlated to the concentration of sensory neuropeptides. This concentration has been found to be reduced by repeated intranasal applications of *Capsaicin*.[99,104]

A study conducted by Snider et al. (1992) found that rhinitis, sneezing, and con-gestion were alleviated in patients who received repeated nasal sprays of capsaicin.[105,106] In a placebo-controlled study, intranasal capsaicin was shown to be effective in reducing nasal symptomatology in nonallergic, noninfectious perennial rhinitis without affecting cellular homeostasis up to 9 months after treatment.[105,107] Fokkens et al., (2016) mentioned the activity of capsicum against rhinitis but it is not effective for elderly patient on rhinitis.[108] Other scientists have also determined activeness of capsicum against rhinitis.[105,109,110] Effect in CRS and rhinitis is based on a polypeptide named activity is Bradykinin (BK) which is involved in nociception, vasodilatation and capillary permeability augmentation. BK receptors have been found in the nasal mucosa where they may produce CGRP- and possibly SP-release from primary sensory-C fibers via capsaicin-independent mechanisms.[105,111] The molecular mechanisms involved in effective Capsaicin treatment have been described in detail by several authors[105,112- 131] and summarized in the extensive reviews by Asher et al, Masud-Parvez et al. respectively.[19, 105]

Dictamnus is the popular name for a group of medicinal herbaceous plant species of the Rutaceae and Lamiaceae families, which have been use for millennia to treat chronic rhinitis, nasopharyngitis and pharyngitis but also cough, jaundice, anorexia, eating disorders, and toxic effect of contact with venomous animals. *Dictamnus albus* L., Sp. Pl., and *D. hispanicus* Webb ex Nyman,

Consp. Fl. Eur., are generally used for medicinal purposes with specific indications which relate exclusively to the use of a specific part of the plant. Roots and root bark are the plant part more frequently used. The use of *D. albus* presents notable differences between Western Europe and Eastern Europe with only thirteen common uses of the 42 analyzed.[132]

Petasites hybridus (L.) G. Gaertn., B. Mey. & Scherb., Oekon. Fl. Wetterau (Butter-bur), a member of the sun-flower family, is purported to be effective in treating allergic rhinitis and have nasal decongestant effects.[27,82, 133,134] In CRS, evidence sup-porting its use is negligible.[27]

Eastern Europe

Plants have been used traditionally for centuries for the symptomatic treatment of respiratory tracts diseases (e.g. cough, rhinitis, bronchitis, throat infection, fever, influenza) in Eastern Europe. These substances are potential inhibitors of chemotaxis of neutrophils in inflammation by inhibition of IL-8 secretion. Selected extracts from the Asteraceae family such as roots of *Inula helenium* L., Sp. Pl., flowers of *Helianthus annuus* L., Sp. Pl., flowers of *Achillea ptarmica* L., Sp. Pl., roots of *Anacyclus pyrethrum* (L.) DC., Fl. Franc. [de Candolle & Lamarck] and aerial parts of *Grindelia squarrosa* (Pursh) Dunal, Mém. Mus. Hist. Nat. are believed to have just such an effect of suppression of production of cytokines/chemokines and of expression of adhesion molecules located on cell surface.[28]

Mentha x pipperita L., Sp. Pl. [Linnaeus] (Peppermint) is an important plant, which contains 0.20-0.25% essential oil, of which menthol menthone are the main volatile components. The most important chemical components of peppermint oil are: menthol (40.7%), menthone (23.4%), menthyl acetate,. 1,8-cineole, limonene, beta-pinene, beta-caryophyllene. The other ingredients include tannins 6-12%, triterpenes and bitter substances. Rosmarinic acid and a number of flavonoids, such as eriocitrin, luteolin and hesperidin are also phenolic components of the peppermint leaves. The essential oil is also used for inhalation purposes, as an ingredient in creams, and to cure rhinitis, bronchitis and rheumatic diseases.[135]

Berberis vulgaris L., Sp. Pl. is used to ease inflammation and infection of the respiratory tract such as pharyngitis (sore throat), sinusitis, rhinitis (nasal congestion), bronchitis and traditionally tuberculosis as well as candida (yeast) infections of the skin or vagina.[136] The effects on psoriasis requires further studies.[136-139]

Geranium robertianum L., Sp. Pl. (aerial parts) is documented as traditional treatment (herbal tea) for sinus inflammation in Montenegro[140-142]

A number of plants are traditionally used in Romanian HM for treating upper air-way pathology such as pharyngitis, laryngitis, rhinitis. These include: *Allium cepa* L., Sp. Pl. (bulb) via organosulfur compounds, flavonoids, and phenolcarboxilic acids[143-147]; *Allium sativum* L., Sp. Pl. (bulb) via organosulfur compounds, flavonoids, and phenolcarboxilic acids[143-147]; *Juniperus communis* L., Sp. Pl. (shoots, berries) via polyphenols, essential oils (monoterpenes)[143-145, 147]; *Salvia officinalis* L., Sp. Pl. (leaves) via flavonoids, phenolcarboxilic acids, essential oils (monoterpenes)[143-147] and *Verbascum phlomoides* L., Sp. Pl. (flowers) mucilages, flavonoids, iridoids.[143,145,147,148]

Origanum majorana L., Sp. Pl. is widely used in the Balkans to treat colds and rhinitis.[149-151] Sideritis scardica Griseb., Spic. Fl. Rumel, also, from the Lamiaceae fam-ily, is an aromatic plant very popular in Greece, Bulgaria, Albania, and North Macedonia where it is largely used in local cuisines. The species, together with several related Sideritis species, is known as "mountain tea", and use as decoction in folk medicine of the Balkan countries to strengthen the immune system, and treat cold, flu, and allergies.[149,152,253] It is also employed against shortness of breath, sinus conges-tion, and even pain and mild anxiety.[149,153-155]

Artemisia vulgaris L., Sp. Pl.- Researchers from Romania investigated the chemical composition and the antifungal activity of the essential oil extracted from the *Artemisia dracunculus* L., Sp. Pl. [Linnaeus], *A. abrotanum* Savi, Mat. Med., *A. absinthium* L., Sp. Pl. and *A. vulgaris* L., Sp. Pl. (Asteraceae) herbs against *Candida albicans*. The disk-dilution method was used in the in vitro experiments. The observed inhibition zone measured 12.5 mm. The zone of the positive control, carried out with nystatin, measured 15.0 mm, while that of the negative control, carried out with an empty paper disc, measured 6.0 mm. The results thus confirmed the antifungal activity of the essential oil of the herb against *C. albicans*.[156,157]

Swedish researchers have studied the effect of a nasal spray containing the essential oil and flavonoids derived from *Artemisia abrotanum* Savi, Mat. Med. on the course of allergic rhinitis and reported that relief of symptoms is possible. The essential oil contained large amounts of 1,8-cineole, davanone and linalool, with centaureidine di-methylether, casticin and quercetin dominant among the flavonoids. The study took place on a cohort of 12 patients with known allergic rhinitis and/or bronchial obstruction, or with allergic rhinitis with coexisting allergic conjunctivitis or with exercise-induced asthma. The preparation was applied immediately after noticing the characteristic allergic symptoms of the nose. The effects were assessed based on a questionnaire filled in by the patients. Five minutes after application of the spray, the patients reported alleviation of nasal symptoms similar to the use of an antihistamine medication or chromoglycan. The results of the study indicate that a nasal spray with a mixture of essential oils and flavonoids present in *A. abrotanum* can be effective in the treatment of allergic rhinitis but also for allergic conjunctivitis and obstructive bronchial disease.[65,158,159]

Sambucus nigra L., Sp. Pl. [Linnaeus]-The creamy-white flowers and glossy, purplish-black berries have been used for therapeutic purposes in acute and chronic rhinosinusitis and respiratory viral infections such as cold and herpes.[160,161] According to different studies, both elderberry fruit and flower are high in polyphenols.[161,162] Its high antioxidant and antiviral activity has been recognized by the use of *S.nigra* extract in the commercially available product *Sinupret*.

Bryophyllum pinnatum Lam. Oken, Allg. Naturgesch. (Crassulaceae) in the form of sap drink and *Leonurus cardiaca* L., Sp. Pl. (Lamiaceae) as aerial parts tea have been documented as part of the ethnobotany of Hutsuls living in the Carpathian Mountains of Bukovina (SW) Ukraine and NE Romania.[163] This border area suggests that the knowledge is common to both Romanian and Ukrainian population and by extension to other nationalities inhabiting the area such as Polish, Russian, Tartar etc.

Medicinal Plants of Russian Pharmacopoeia Russian traditional medicine infusion of aerial part of *Bidens tripartita* L., Sp. Pl. is widely used in the treatment of catarrhal rhinitis, angina, acute respiratory infection, and as an anti-inflammatory in co-litis, gout, and infantile rickets.[164] The efficacy of mixtures with *Tussilago farfara* L., Sp. Pl., also from the Asteraceae family, has been shown in the complex treatment of rhinosinusitis in miners with chronic bronchitis.[164] But no further details are pro-vided by the author.

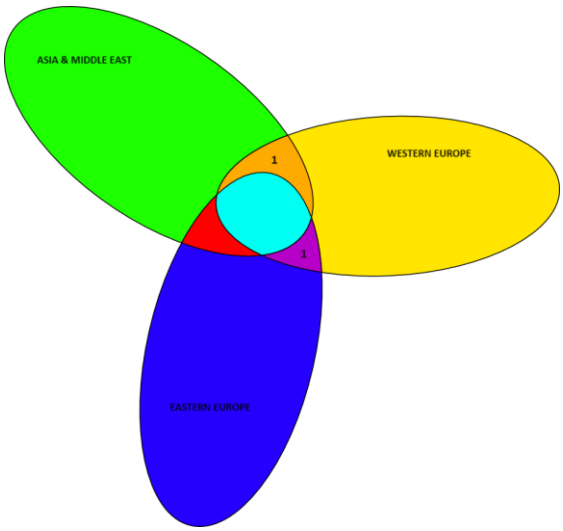

Figure 1: Venn Diagram regarding the number of common species used for Herbal Treatments between the studied regions.

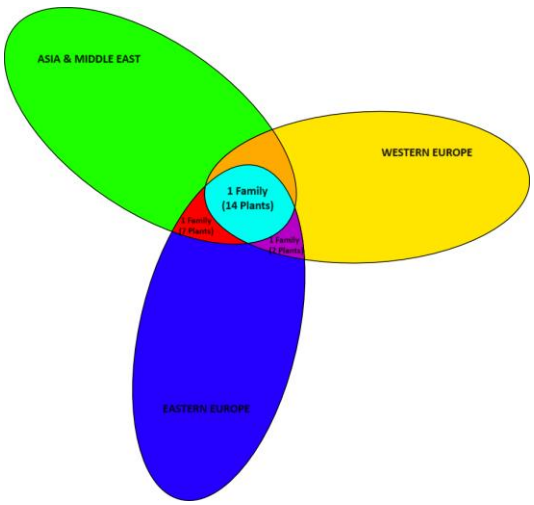

Figure 2: Venn Diagram regarding the number of common families and species used for Herbal Treatments between the studied regions.

Table I: Medicinal plants and their use according to geographic areas (see Figure 1&2).

Family	Species	Area of use		
		South Asia & Middle-East	Western Europe	Eastern Europe
Magnoliaceae;	*Magnolia denudata* (BYS)	Yes	No	No
Asteraceae	*Xanthium strumarium* (BYS)	Yes	No	No
Apiaceae	*Angelica dahurica* (BYS)	Yes	No	No
Leguminosae	*Glycyrrhiza uralensis* (BYS, GGT))	Yes	No	No
Lamiaceae	*Scutellaria baicalensis* (BYS)	Yes	No	No
Apiaceae	*Ligusticum chuanxiong* (BYS)	Yes	No	No
Lamiaceae	*Mentha arvensis* (BYS)	Yes	No	No
Polyporaceae	*Poria cocos* (BYS)	Yes	No	No
Leguminosae	*Astragalus membranaceus* (BYS)	Yes	No	No
Ephedraceae	*Ephedra sinica* (BYS, GGT, Ma- huang)	Yes	No	No
Campanulaceae	*Platycodon grandiflorum* (BYS)	Yes	No	No
Asteraceae	*Atractylodes macrocephala* (BYS)	Yes	No	No
Saururaceae	*Saururus chinensis* (BYS)	Yes	No	No
Fabaceae	*Pueraria lobata* (GGT)	Yes	No	No
Lauraceae	*Cinnamomum cassia* (GGT)	Yes	No	No
Paeoniaceae	*Paeonia lactiflora* (GGT)	Yes	No	No
Rhamnaceae	*Ziziphus jujuba* (GGT)	Yes	No	No
Rannunculaceae	*Nigella sativa*	Yes	No	No
Chrysantemum	*Ageratum conyzoides*	Yes	No	No
Boraginaceae	*Heliotropium indicum*	Yes	No	No
Urticaceae	*Urtica dioica*	Yes	No	No
Asteraceae	*Artemisia afra*	Yes	No	No
Papaveraceae	*Chelidonium majus*	Yes	No	No
Zingiberaceae	*Zingiber officinale*	Yes	No	No
Asteraceae	***Echinacea angustifolia* (*Esberitox*)**	**Yes**	**Yes**	**No**
Sapotaceae	*Butyrospermum parkii*	Yes	No	No
Caprifoliaceae	***Sambucus nigra* (*Sinupret*)**	**No**	**Yes**	**Yes**
Primulaceae	*Primula veris*	No	Yes	No
Polygonaceae	*Rumex acetosa*	No	Yes	No
Verbenaceae	*Verbena officinalis*	No	Yes	No
Gentianaceae	*Gentiana lutea*	No	Yes	No
Primulaceae	*Cyclamen europaeum*	No	Yes	No
Myrtaceae	*Eucalyptus globulus* (Myrtol, Cineole)	No	Yes	No
Bromeliaceae	*Ananas comosus*	No	Yes	No
Acanthaceae	*Andrographis paniculata* (Kan Jang)	Yes	No	No
Araliaceae	*Eleutherococcus senticosus* (Kan Jang)	Yes	No	No
Tropaeolaceae	*Tropaeolum majus (Angocin® Anti-Infekt N)*	No	Yes	No
Brassicaceae	*Armoracia rusticana (Angocin® Anti-Infekt N)*	No	Yes	No
Cupressaceae	*Thuja occidentalis* (*Esberitox*)	No	Yes	No
Fabaceae	*Baptisia tinctoria* (*Esberitox*)	No	Yes	No
Pinaceae	*Pinus spp* (Myrtol)	No	Yes	No
Rutacese	*Citrus aurantifolia* Myrtol	No	Yes	No
Solanaceae	*Capsaicin*	No	Yes	No
Rutaceae	*Dictamnus albus*	No	Yes	No
Rutaceae	*Dictamnus hispanicus*	No	Yes	No
Asteraceae	*Petasites hybridus*	No	Yes	No
Asteraceae	*Inula helenium*	No	No	Yes
Asteraceae	*Helianthus annuus*	No	No	Yes
Asteraceae	*Achillea ptarmica*	No	No	Yes
Asteraceae	*Anacyclus pyrethrum*	No	No	Yes
Asteraceae	*Grindelia squarrosa*	No	No	Yes
Lamiaceae	*Mentha x pipperita*	No	No	Yes
Berberidaceae	*Berberis vulgaris*	No	No	Yes
Geraniaceae	*Geranium robertianum*	No	No	Yes
Alliaceae	*Allium cepa*	No	No	Yes

Alliaceae	*Allium sativum*	No	No	Yes
Cupressaceae	*Juniperus communis*	No	No	Yes
Lamiaceae	*Salvia officinalis*	No	No	Yes
Scrophulariaceae	*Verbascum phlomoides*	No	No	Yes
Lamiaceae	*Origanum majorana*	No	No	Yes
Lamiaceae	*Sideritis scardica*	No	No	Yes
Asteraceae	*Artemisia vulgaris*	No	No	Yes
Asteraceae	*Artemisia abrotanum*	No	No	Yes
Crassulaceae	*Bryophyllum pinnatum*	No	No	Yes
Lamiaceae	*Leonurus cardiaca*	No	No	Yes
Asteraceae	*Bidens tripartita*	No	No	Yes
Asteraceae	*Tussilago farfara*	No	No	Yes

Plants common to several geographic areas written in Bold letters.

Table II: Medicinal plants from around the world and their specific effects in CRS.

Plant	**Part**	**Traditional use**	**Main Active Compounds / Mechanism**
Magnolia denudata (BYS)	Flower (Flos)	Granules, Decoction, Oral liquid, **BYS**	Analgesic, Anti-inflammatory, Antibacterial.
Xanthium strumarium (BYS)	Fruits (Fructus)		
Angelica dahurica (BYS)	Root (Radix)		
Glycyrrhiza uralensis (BYS, GGT)	Root (Radix)		
Scutellaria baicalensis (BYS)	Root (Radix)		
Ligusticum chuanxiong (BYS)	Rootstalks (Rhizoma)		
Mentha arvensis (BYS)	Plant (Herba)		
Poria cocos (BYS)	Fungi		
Astragalus membranaceus (BYS)	Root (Radix)		
Ephedra sinica (BYS, GGT, Ma- huang)	Plant (Herba)		
Platycodon grandiflorum (BYS)	Root (Radix)		
Atractylodes macrocephala (BYS)	Rootstalks (Rhizoma)		
Saururus chinensis (BYS)	Plant (Herba)		
Pueraria lobata (GGT)	Root (Radix)	**GGT** pills	Anti-inflammatory, Antiviral.
Cinnamomum cassia (GGT)	Stems (Ramulus)		
Paeonia lactiflora (GGT)	Root (Radix)		
Ziziphus jujuba (GGT)	Fruits (Fructus)		
Nigella sativa	Seeds (Seminibus)	Capsules, Essential oil	Analgesic, Anti-inflammatory, Antiseptic, Antioxidant.
Ageratum conyzoides	Plant (Herba)	Fresh plant juice	Anti-inflammatory, Antibacterial, Detoxifying, Hemostatic.
Heliotropium indicum	Plant (Herba)	Plant juice instillation	Analgesic, Anti-inflammatory.
Urtica dioica	Plant (Herba), Roots (Radix)	Extract	Anti-inflammatory, Antioxidant, Antiallergic, Nasal decongestant
Artemisia afra	Flower (Flos), Leaves (Folia), Stems (Ramulus), Roots (Radix).	Tea, Inhalations, Essential oils	Anti-inflammatory, Analgesic, Antiallergic,
Chelidonium majus	Aerial parts (Aeria), Rootstalks (Rhizoma), Roots (Radix).	Alcoholic extracts, Fresh rhizome.	Anti-inflammatory, Immunomodulatory.
Zingiber officinale	Rootstalks (Rhizoma)	Root extracts	Antiallergic, Antimicrobial,

			Antioxidant.
***Echinacea angustifolia* (*Esberitox*)**	Aerial parts (Aeria), Roots (Radix)	Fresh herb, Freeze-dried herb, Alcoholic extract, ***Esberitox***, Tea.	Anti-inflammatory, Antiviral, Immunomodulatory.
Butyrospermum parkii	Fruits (Fructus)	Shea butter	Nasal decongestant
***Sambucus nigra* (*Sinupret*)**	Flowers (Flos)	Extract, Capsules, ***Sinupret***	Nasal decongestant, Mucolytic, Anti-inflammatory, Antiviral, Antibacterial.
Primula veris	Flowers with Calyx (Flos & Calyx)		
Rumex acetosa	Aerial parts (Aeria)		
Verbena officinalis	Aerial parts (Aeria)		
Gentiana lutea	Roots (Radix)		
Cyclamen europaeum	Roots and Tuber (Radix et Tuber)	Tincture	Nasal and sinus drainage
Eucalyptus globulus (Myrtol, Cineole)	Leaves (Folia)	Volatile oils, **Myrtol, Cineole.**	Nasal decongestant, Expectorant, Anti-inflammatory, Antiseptic, Febrifuge.
Ananas comosus	Stems (Ramulus), Fruits (Fructus).	Bromelain extract	Anti-inflammatory, Immunomodulatory, Mucolytic.
Andrographis paniculata (Kan Jang)	Plant (Herba)	Extract (**Kan Jang**)	Anti-inflammatory, Immunomodulatory, Febrifuge.
Eleutherococcus senticosus (Kan Jang)	Roots (Radix)		
Tropaeolum majus (Angocin® Anti-Infekt N)	Plant (Herba)	Extract (***Angocin*® Anti-Infekt N)**	Anti-inflammatory, Immunomodulatory, Antiviral, Antibacterial.
Armoracia rusticana (Angocin® Anti-Infekt N)	Roots (Radix)		
Thuja occidentalis (*Esberitox*)	Aerial parts (Aeria)	Extract, ***Esberitox*** pills	Antiviral, Immunomodulatory.
Baptisia tinctoria (*Esberitox*)	Roots (Radix)		
Pinus spp (Myrtol)	Leaves (foliatus), Shoots (Surculus), Stems (Ramulus).	Essential oils, **Myrtol** capsules	Antioxidative, Anti-inflammatory, Antibacterial, Mucolytic.
Citrus aurantifolia Myrtol	Fruits (Fructus), Flowers (Flos), Seeds (Seminibus), Stems (Ramulus), Leaves (foliatus).		
Capsaicin	Fruits (Fructus), Seeds (Seminibus),	Extract	Antioxidative, Anti-inflammatory, Antibacterial, Mucolytic, Nasal decongestant.
Dictamnus albus	Roots (Radix), Stems (Ramulus).	Infusion	Anti-inflammatory, Mucolytic, Expectorant, Febrifuge.
Dictamnus hispanicus	Roots (Radix), Stems (Ramulus).	Infusion	Anti-inflammatory, Mucolytic, Expectorant, Febrifuge.
Petasites hybridus	Rootstalks (Rhizoma), Leaves (foliatus).	Essential oils	Antiallergic, Nasal decongestant.
Inula helenium	Roots (Radix)	Extract	Anti-inflammatory
Helianthus annuus	Flowers (Flos)	Extract	Anti-inflammatory
Achillea ptarmica	Flowers (Flos)	Extract	Anti-inflammatory
Anacyclus pyrethrum	Roots (Radix)	Extract	Anti-inflammatory
Grindelia squarrosa	Aerial parts (Aeria)	Extract	Anti-inflammatory

Mentha x pipperita	Aerial parts (Aeria), Leaves (Foliatus).	Essential oils, Extract.	Anti-inflammatory, Nasal decongestant.
Berberis vulgaris	Roots (Radix), Fruits (Fructus), Stems (Ramulus), Bark (Cortex).	Tincture	Anti-inflammatory, Antibacterial, Nasal decongestant.
Geranium robertianum	Aerial parts	Herbal tea	
Allium cepa	Aerial parts (Aeria)	Oral (decoction /infusion)	Anti-inflammatory, Antibacterial, Nasal decongestant.
Allium sativum	Bulb (Bulbus)	Bulb extract	Antibacterial, Antioxidant.
Juniperus communis	Bulb (Bulbus)	Essential oils	Anti-inflammatory, Antibacterial,
Salvia officinalis	Shoots (Surculus), Berries (Bacca)	Oral (decoction /infusion), Extract	Anti-inflammatory, Antioxidant.
Verbascum phlomoides	Leaves (Foliatus)	Oral (decoction /infusion)	Anti-inflammatory, Antioxidant, Expectorant.
Origanum majorana	Flowers (Flos)	Oral (decoction /infusion), Aqueous extract	Anti-inflammatory, Antibacterial, Immunomodulatory.
Sideritis scardica	Flowers (Flos)	Oral (decoction /infusion), Aqueous extract.	Anti-inflammatory, Antibacterial, Immunomodulatory.
Artemisia vulgaris	Flowers (Flos), Leaves (Foliatus), Stems (Ramulus), Roots (Radix).	Tincture, Extract, Tonics, Tea, Powder, Essential oils.	Antifungal, Antiviral, Antiallergic, Im-munomodulatory.
Artemisia abrotanum	Flowers (Flos), Leaves (Foliatus), Stems (Ramulus), Roots (Radix).	Tincture, Extract, Tonics, Tea, Powder, Essential oils.	Antifungal, Antiviral, Antiallergic, Im-munomodulatory.
Bryophyllum pinnatum	Leaves (Foliatus)	Sap drink	Anti-inflammatory
Leonurus cardiaca	Aerial parts (Aeria)	Tea	Anti-inflammatory
Bidens tripartita	Plant (Herba)	Oral (decoction /infusion),	Anti-inflammatory, Antioxidant.
Tussilago farfara	Leaves (Foliatus), Flowers (Flos).	Tea, Syrup	Anti-inflammatory, Antioxidant.

4. DISCUSSIONS

The use of Complementary and Alternative Medicine (CAM), including Herbal Medicine (HM), can be documented in a rather large percentage of patient population, usually at opposite ends of the disease spectrum: either for chronic, minor illnesses (e.g., back pain or arthritis) or for devastating, life-threatening conditions (e.g., cancer or AIDS). This is due to the perception of ineffectiveness or toxicity.[18,165] In severely ill patients, this might be a marker for distress. Other reasons for trying CAM may include lack of further therapeutic option or boredom of conventional healthcare pro-viders with the management of chronic problems. Some patients are also frustrated by the lack of results obtained with conventional medicine or desperate to treat severe illnesses. Other believe it to be risk-free and therefore prefer it to conventional treatments.[18,166] Regardless of the reasons, we consider that great attention should be given to this type of treatment, as it has been present for millennia, in different cultures and geographical regions and it still yields surprising therapeutical results.

What is particularly interesting, especially in Western cultures, is the reluctance of patients to admit using CAM.[27] Ernst et al. reported the percentage to vary from 9 to 65%.[18] In Germany and the United States, there is

evidence to suggest that the use of CAM has become increasingly prevalent.[18]

In otolaryngology, perhaps the condition most often treated with CAM therapies is chronic rhinosinusitis (CRS). Rotenberg and Bertens, report 15.6% of CRS patients admitted to using alternative therapies to treat their CRS.[27,167] Krouse and Krouse report 29% have used herbal therapy.[27, 168] CAM is promoted through social media and its popularity may also be explained by increasing healthcare costs and poor access to healthcare systems.[27,169] The decrease of costs varies from 0 to 30% according to a 2012 Dutch study by Kooreman and Baars, when CAM is used.[27,170] In the state of South Australia, a survey found that 52.2% were CAM users.[27,171]

Ethnobotany is a multidisciplinary science that deals with the traditional knowledge of plants and their relation with people. Its practice is based on the collaboration of several researchers, such as biologists, pharmacists, physicians, anthropologists, and linguists. A 2016 report estimated 374,000 plant species globally[143,172], of which 7.5% are used as medicinal plants.[143,173] Some studies claim that 70–95% of the world's population uses plants as a primary form of medicine[143,173], and in Germany, up to 90% of the population uses herbal medicines.[143,174] It is worth mentioning that some species are used both in Europe and Asia, sometimes even in Latin America.[143,175,176]

Ethnobotanical knowledge can be considered as part of local ecological knowledge (LEK) and it is, most of the times, regarded as traditional.[163] This is obviously also dependent on the geographical area, customs and traditions. That is why our study is attempting a comparison of regional use of HM. Asian and Middle-East knowledge is most of the time documented and represents the bases for millennia of use.

Western Europe has oriented the knowledge towards scientific research and rationally proven effects which automatically led to developing industrial products (extracts and mixtures of extract) that are safe to use and currently present in CRS management protocols.

Eastern Europe remains the unknown quantity of the equation, as the herbal use, although ancient, hasn't been properly documented and organized. The plants are not widely spread and their use remains somewhat traditional, even mystical and confided to regions.[149] The rural regions of southeastern Europe represent a unique social and environmental context for ethnobotanical studies, owing to the occurrence of a large mountainous area that is recognized as a hotspot for both biodiversity and cultural/ethnic/religious diversities. Phytotherapy still maintains an important role in the treatment of many diseases in the Balkans and a number of ethnobotanical studies were carried out in the last decade.[149,154,177-180]

Ethnopharmacological knowledge is by no means new to European medical practice and has its roots in the Greek and Roman cultures, being essentially influenced by works of Dioscorides, Pliny the Elder, Galen, Theophrastus, and Hippocrates.[146, 181–184] In Western and Central Europe, herbalism played an important role in drug discovery beginning with the nineteenth century, as it led to industrial development of most medicine starting from ancient phytotherapy knowledge. Comparatively, in Easter Europe phytotherapy remained somewhat in the stages of traditional and folkloric use. This is in part due to the influence of the former communist regime and in part to inaccessibility or illegibility of ancient texts (e.g., monasteries, archives not open for the public), use of old languages and idioms not yet translated (old Slavonic language), use of obscure or extinct terminology (e.g., only vernacular names or obsolete Latin names), difficulties in obtaining information from old individual who still possess it (sometimes transmitted only within the families).[146, 181, 185–190]

Romania has a rich ethnomedical and ethnobotanical heritage unfortunately undocumented and studied as compared to other Eastern European countries, such as Poland[146,181,191–194], Estonia[146,181, 195-197], Bosnia and Herzegovina[146,177,181,198], and Russia[146,164,181,199] where the existing ethnobotanical resources are already thoroughly studied or actualized in several ethnobotanical surveys.

A geographical and biological comparison of results will give us a most surprising conclusion that no single plant is commonly use as HM in all three documented regions and only two plants can be considered as overlapping results: *Echinacea angustifolia* for Asia and Western Europe and Sambucus nigra for Eastern and Western Europe (Figure 1 & Table I). The Asteraceae family is the most encountered in all three regions with 4 plants in Asia, 1 in Western Europe and 9 in Eastern Europe. The Lamiaceae family is also used in Asia and Eastern Europe with a total of seven plants whilst the Cupressaceae family is represented in Western and Eastern Europe by two different plants (Figure 2 & Table I). These conclusions are naturally defined by geographical and biological conditions and also by folkloric and spiritual traditions that should be further researched and discussed.

Most herbal supplements are marketed in the form of an extract from one or more botanical sources. They can be taken orally in capsule form or as an additive to tea. The most commonly used HM comes from Chinese medicine as a multitude of Chinese herbal extracts and herbs.[26,27] *Glycyrrhiza uralensis* Fisch. [Leguminosae; Glycyrrhizae Radix] and *Ephedra sinica* Stapf Bull. Misc. Inform. Kew are both used in mixtures such as BYS and GGT whilst *Zingiber officinale* Roscoe, Trans. Linn. Soc. London is used in GGT but also as a solitary plant (Table II).

In Western medicine, substances such echinacea, bromelain, capsaicin, *Urtica dioica* and also scientifically developed mixtures (*Sinupret*) are widely spread.

Chinese traditional medicine employes a number of mixtures that usually include *Magnolia denudata* Desr. [Magnoliaceae; Magnoliae Flos], *Xanthium strumarium* L. [Asteraceae; Xanthii Fructus], and *Angelica dahurica* Benth. et Hooker f. [Apiaceae; Angelicae Dahuricae Radix]. The theory behind their use is that three herbs eliminate the 'wind evil,' and in the pathological context, the wind, especially the external wind, is associated with colds, flu, and viruses.[4,200] This plant combination is believed and sometimes proven to treat sinus congestion and headaches as well as to cure viscous runny nose and headaches in CRS.[4,15]

Magnolia denudata Desr. [Magnoliaceae; Magnoliae Flos] has a long history of clinical use for managing rhinitis, CRS, and headache. Its anti-allergic, an-ti-inflammatory, and antibacterial activity have been reported.[4,201]

Xanthium strumarium L. [Asteraceae; Xanthii Fructus] has also been described as active in allergic rhinitis with its anti-inflammatory, analgesic, and antioxidant ef-fects.[4,202]

Angelica dahurica Benth. et Hooker f. [Apiaceae; Angelicae Dahuricae Radix] is commonly used in allergic rhinitis.[4,203]

Other herbs such as *Glycyrrhiza uralensis* Fisch. [Leguminosae; Glycyrrhizae Ra-dix], *Poria cocos* (Schw.) Wolf [Polyporaceae; Poria (Hoelen)], *Astragalus membranaceus* Bunge [Leguminosae; Astragali Radix], *Platycodon grandiflorum* (Jacq.) A. DC. [Campanulaceae; Platycodi Radix], and *Atractylodes macrocephala* Koidz [Asteraceae; Atractylodis Rhizoma Alba] are believed to promote immune system development, improve mucosal immune function, and have anti-inflammatory ef-fects.[4,204-206] Combining herbs that resist external pathogens with herbs that have immunomodulatory effects is an essential principle of HM composition, which has the advantage of managing CRS from a complex and multifactorial perspective.[4,15] Some included studies reported effects on immunity and inflammation, affecting the levels of interleukins, tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). We must also note that CRS can accompany more serious conditions such as benign and malign tumors of the nose and sinuses and specific chronic inflammations, which brings into perspective the fact that TNF-α and CRP values in particular are significantly lower after treatment with HM.[4,207-217] Immunomodulation effects are of particular interest to scientists studying CRS[4,218] and that herbs with immunomodulatory effects are already frequently used in HM studies (e.g., *Astragalus membranaceus* Bunge [Leguminosae; Astragali Radix]).

Pertinent observations have been made regarding the potential effect of HM on the recurrence of CRS. Several studies reported that the recurrence rate of CRS was significantly lower after use of HM[4,219], suggesting a potential relationship with inflammation and immunomodulation.[4,220]

The limitations of our study are represented by the fact that we did not exclude therapies that have received recommendations (including negative recommendations) for use in CRS by a professional body as outlined in the European Position Paper on Rhinosinusitis and Nasal Polyps 2012.[2] We also did not exclude HM use in allergic or acute sinusitis as we considered these as linked to the evolution of CRS. The fact that this was not a systematic but rather a narrative review could also be considered as a drawback.

4. CONCLUSIONS

Complementary and alternative medicine can be defined as diagnosis, treatment, and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine.

Chronic rhinosinusitis (CRS) is a commonly spread affliction with complex bearing on the patient's QoL and severe economic effects for healthcare systems around the world. The limitations of current classical treatment have brought to attention complementary and integrative treatments, including HM, although large scale surveys are still required. It has been reported that one-third of U.S: population uses some form of CAM which amounts to an estimated $23 billion annually. Yet it is still unclear why most of the patients are reluctant to report this use to their physicians. This information is mandatory in order to avoid possible adverse side effects and interactions from poorly-studied plant extracts.

Patients in Western countries seek a holistic and integrated treatment and are sometimes disappointed in the results of classical medicine. Some of them resort to herbal treatments as a desperate solution to incurable and terminal disease. The use of HM may sometimes be considered as a reversion to irrational approaches to medical practice.

Eastern cultures on the other hand have been using HM for centuries as main therapies and have documented it accordingly. Most studies regarding plant extracts or mixtures come from China and South-East Asia and are usually scientifically performed.

The rural regions of Eastern Europe represent a unique social and environmental context where ancient traditions are still kept and numerous cultures and nationalities come together. Despite the strong history behind this topic in the Balkans and East European countries, documentation of plant use is scares. This is due in part to communist influence regarding spirituality and tradition and also to inaccessibility or il-legibility of ancient texts (e.g., monasteries, archives not open for the public), use of old languages and idioms not yet translated (old Slavonic

language), use of obscure or extinct terminology (e.g., only vernacular names or obsolete Latin names) or difficulties in obtaining information from old individual who still possess it (sometimes transmit-ted only within the families). Detailed research within remote rural areas of the Balkans may bring surprisingly new knowledge on herbal treatments.

Although certain plant families seem to be common in use for all continents and regions, the actual common plants are few. This is explainable by geographical and biological differences. The influence of folklore and spirituality in this regard remains to be studied further.

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