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A. millefolium L. in pharmacy. What should a pharmacist know?

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Abstract

A complex aggregate of about 24 species, A. millefolium *L. agg. (Asteraceae) is one of the medicinal plants with a long tradition of use, dating back from ancient times. This paper attempts to answer to three main questions:*

What are the A. millefolium *products available in pharmacy (on the Romanian market) that a patient might be interested in?*

What are their potential uses (based on clinical evidence and officially recognized traditional use in the European Union) and the relevant posology?

What knowledge do we have about the safety of those products?

Keywords: *Achillea millefolium*

INTRODUCTION

Achillea millefolium L. agg. (yarrow), Asteraceae, is a complex aggregate of about 24 species with a diverse membership in terms of their shape and aspect, genetic, or environmental characteristics [1]. Because each species is polymorphic and difficult to differentiate from one another individually, the taxonomic issue is complex and challenging, and when reading about "*A. millefolium*" in a scientific source, one should be aware that it could refer to any of those species, to *A. millefolium sensu stricto* or to a mixture of them [2]. The country where work reported in publications was performed could provide (somewhat vaguely) clues about the species involved: studies carried out in Western European countries are likely to have been performed on *A. millefolium stricto sensu*, those performed in Eastern European countries are more likely to have used *A. millefolium stricto sensu* and *A. collina* (Becker ex Rchb.f.) Heimerl [2]. Over four decades ago, Chandler et al. pointed out that works done in North America were more likely to have used *A. lanulosa* Nutt., but today the latter is regarded as a mere synonym for *A. millefolium* L.

Its scientific name is related to the Greek legendary hero, Achilles, famous for its quasi-total invulnerability, which according to one version of the legend was connected to the use of this herb, as taught to the Greek warrior by a centaur physician named Chiron [3,4]. According to a separate etymological story, the scientific name is credited to a Greek physician by the name of Achillo, who is said to have employed the plant to heal a wounded warrior [3]. As for the specific epithet of the name, "*millefolium*", it is a Latin term meaning "thousand-leaved" (obviously a hyperbola for

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"many-leaved"), an allusion to the multitude of leaflets on both sides of the leaf rib (multipinnate leaf) [3,4].

Considering the mythical origins of its name associated with invulnerability, there is no wonder that *A. millefolium* has a long tradition of use as a medicinal plant. It has been used since ancient times as a common remedy for a variety of ailments, particularly for infectious diseases and wounds [5]. However, in 2011 Applequist and Moerman, reviewing the species were in

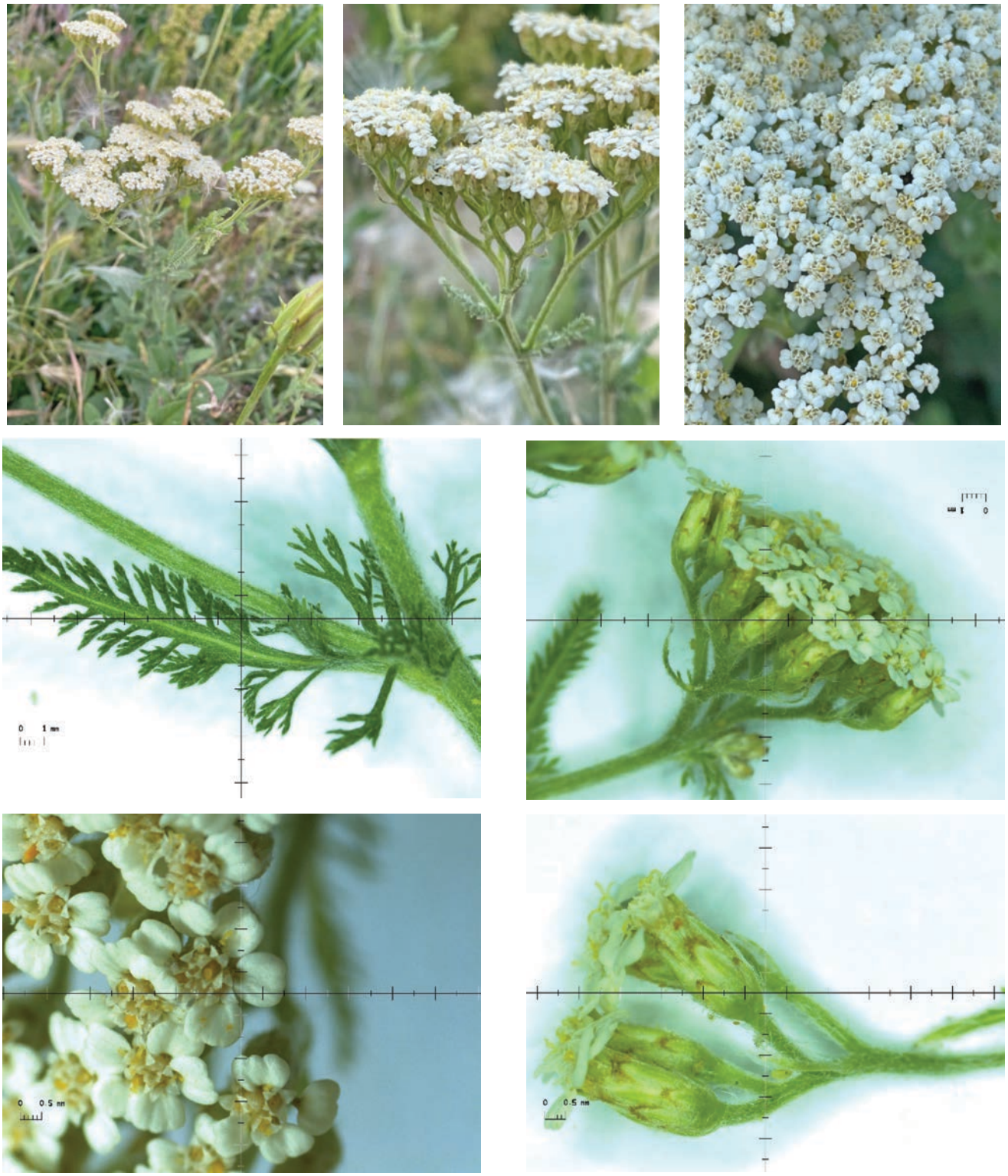

FIGURE 1. A. millefolium ***– aerial parts and inflorescences. First three images (upper row) normal photographs, and the remainders obtained with a Leica DMS1000 digital microscope***

a position to state that "Nonetheless, no human clinical trial of a single-herb yarrow product for its traditional uses has yet been conducted" [5].

This paper is not so much a comprehensive review of the species, but rather a focused review on food supplements or medicines containing extracts, essential oils or powders of parts of *A. millefolium* and what we consider essential information that a pharmacist should know about them, in order to provide counselling to his or her patients. We hereby therefore try answering the following questions:

a) What are the *A. millefolium* products available in pharmacy that a patient might be interested in?
b) What are their potential uses and the relevant posology?
c) What knowledge do we have about the safety of those products?

PRODUCTS CONTAINING *A. MILLEFOLIUM* EXTRACTS OR POWDERS AVAILABLE ON THE ROMANIAN MARKET

Using appropriate searches in the official lists of notified food supplements on the Romanian market (keywords: *Achillea millefolium*, coada-șoricelului/coada soricelului, yarrow) we identified the products derived from A. millefolium available to consumers listed in Table 1.

Using similar Google searches we identified additional herbal products (plant parts or extracts) available on the Romanian market, but we could not clarify their regulatory status, as they could not be found on the notification lists from the website of the Institute of Food Bioresources (IFB). They might have been legally notified before 2005 (the start date for IFB notifications) or could have an alternative regulatory status. Unfortunately, the website where we found them did not provide any information on the regulatory status of such products. They are listed in Table 2.

As indicated by our market analysis the highest number of food supplements containing *A. millefolium* consist of ground aerial parts marketed to be consumed as an infusion (tea) – 24 out of 38 (63.16%) products officially notified. The second most widely used dosage form was tincture – seven out of 44 total products identified (15.91%). Besides tinctures (which are a particular category of extracts), six extracts have also been identified, but for most of them little is revealed about their nature and composition, and for none the (genuine) drug:extract ratio (DER) is stated, although DER is a simple measure allowing the characterization of an extract and important (although not necessarily sufficient) in establishing phytoequivalence [6]. Glycerol, hydro-glycerol, and hydro-alcohol mixtures were the solvents used to obtain some of the extracts, whereas for others we could not identify the solvent. Five food supplements consisted of capsules containing powdered yarrow (*Millefolii flos pulvis*).

POTENTIAL USES OF *A. MILLEFOLIUM* PRODUCTS

We hereby review only the potential uses of *A. millefolium* herbal products for which there are available at least some minimal clinical data supporting that use (while also discussing the limitations of that evidence) and the traditional uses officially accepted in the European Union. At the end of the 1990s, in United States, *A. millefolium* was used (as recommended by the Physician's Desk Reference, 1998) in the treatment of anorexia and gastrointestinal issues [7]. However, clinical evidence for a variety of indications is only available from a single country (Iran). A synthetic image of the uses, dosage forms and doses is presented in Table 3.

Relief of primary dysmenorrhea and menorrhagia

In Iran yarrow has a long history of traditional use in the control of menstruation pain, which is consistent with the traditional employment of the product in inflammatory and spastic conditions (8). Similar traditional uses have been reported in other countries too, for instance in China [5]. A modest benefit of the product in this indication has been confirmed in a small clinical trial performed in that country. Jenabi and Fereidoony (2015) evaluated the efficacy of a tea made from 4 grams of *Achillea millefolium* powder infused in 300 milliliters of hot water, administered each month three times a day for three days in the treatment of primary dysmenorrhea (they evaluated the patients after the first and second months). This was a randomized, double-blind, placebo-control trial, in which the subjects were young students (19-23 years, with a mean age of 21.51 years and standard deviation (s.d.) 5.53 years). The severity of dysmenorrhea was measured with a visual analogue scale (VAS). The authors compared the change in severity score from baseline to the first month and found a statistically significant difference against placebo (1.02 vs. 0.22 and 1.59 vs. 041 in the first and second months, respectively, for both in the intention-to-treat (ITT)

TABLE 1. Food supplements containing products derived from** Achillea millefolium**, listed as oficiall notified by the Romanian Institute of Food Bioresources

No.	Product name*	Ingredient(s)	Notification date/Dossier number**	Manufacturer
1	Ulei esential de Coada soricelului MAXIMA	Essential oil	11.03.2020	Justin Pharma
2	COADA-SORICELULUI, ceai	Aerial parts	14.05.2019	Dacia Plant
3	COADA-SORICELULUI, solutie hidroalcoolica	Hydroalcoholic extract of aerial parts	25.09.2019	Dacia Plant
4	EXTRACT GLICERIC DE COADA-SORICELULUI	Glycerol extract (*herba*)	04.04.2018	Adserv
5	TINCTURA DE COADA SORICELULUI	Tincture (*herba*)	02.11.2018	Atelier Dragomirna
6	Tinctura de Coada-soricelului – *ACHILEA MILLEFOLIUM* TM	Tincture (*herba*)	07.11.2017	Plantextrakt
7	CEAI DE COADA-SORICELULUI	Aerial parts	08.01.2016	TURNU APIPLANT
8	CEAI DIN PLANTE MEDICINALE COADA-SORICELULUI	Aerial parts	17.02.2016	Plantimed Prestcomimpex
9	CEAI DE COADA-SORICELULUI	Aerial parts	18.03.2016	Farmaclass Industry
10	MONTANA PLANT TINCTURA DE COADA-SORICELULUI	Tincture (*herba*)	05.04.2016	SALA CORNELIA – MONTANA PLANT
11	COADA-SORICELULUI EXTRIN	Aerial parts	01.07.2016	IMPRINT INVENT
12	EXTRACT NATURAL DIN COADA-SORICELULUI	Aerial parts extract (solvent? DER?)	13.02.2013	ASOCIATIA SF. IOAN CEL NOU DE LA SUCEAVA
13	CEAI DIN PLANTE ECOLOGICE COADA-SORICELULUI	Aerial parts	10.05.2013	FARMACIA NATURII
14	CEAI DOREL – PLANT CEAI DE COADA-SORICELULUI	Aerial parts	06.11.2013	DOREL PLANT
15	EXTRACT NATURAL DIN COADA-SORICELULUI	Aerial parts extract (solvent? DER?)	06.02.2012	ASOCIATIA SF. IOAN CEL NOU DE LA SUCEAVA
16	CEAI DE COADA-SORICELULUI	Aerial parts	23.05.2012	GOLDPLANTNATURAL
17	CEAI COADA SORICELULUI	Aerial parts	25.08.2011	LABORATOARELE FARES BIO VITAL
18	CEAI DE COADA-SORICELULUI	Aerial parts	23.03.2010	NATURALIA COMERCIAL TRADING
19	CEAI NERA PLANT DE COADA SORICELULUI	Aerial parts	23.03.2010	BIO NERA PLANT
20	TINCTURA DE COADA SORICELULUI	Tincture (*herba*)	23.04.2010	BIO NERA PLANT
21	COADA SORICELULUI, ceai	Aerial parts	06.07.2010	PRONATURA
22	CEAI DE COADA-SORICELULUI FLORI	“Flowers”	27.07.2010	CYANI
23	TINCTURA DE COADA-CALULUI	Tincture	09.12.2010	BIO NERA PLANT
24	CEAIUL CASEI – COADA-SORICELULUI	Aerial parts	16.12.2010	TRIDENT COPRIMEX
25	EXTRACT ALCOOLIC DE COADA SORICELULUI (Achillea millefolium)	Alcohol extract	17.07.2009	NATURALIA IMPEX
26	CEAI DE COADA SORICELULUI VEDDA, 40 g	Aerial parts	17.09.2009	KALPO
27	CEAI DE FLORI DE COADA-SORICELULUI	Aerial parts	13.11.2009	CYANI
28	CEAI COADA SORICELULUI IARBA 30 g – 20 pliculete X 1,5 g	Aerial parts	25.02.2009	STEF MAR
29	COADA SORICELULUI – CEAI DE PLANTE	Aerial parts	21.01.2008	HERBARUM VERONICAE
30	CEAI DE COADA SORICELULUI	Aerial parts	07.03.2008	Alevia
31	COADA SORICELULUI – ceai de plante	Aerial parts	03.11.2008	HERBARUM VERONICAE
32	CEAI DIN PLANTE – CEAI DE COADA SORICELULUI – *Achillea millefolium*	Aerial parts	19.12.2007	CIPROD PHARMACEUTICS
33	CEAI DE COADA SORICELULUI	Aerial parts	04.2007	DIOGENE
34	CEAI COADA SORICELULUI	Aerial parts	09.2007	TRIDENT COPRIMEX
35	PROPOLIS CU COADA- SORICELULUI extract glicerohidric	Hydroglycerol extract + propolis	25.03.2019	SYNERGY PLANT PRODUCTS
36	CEAI UNITAR DIN PARTE AERIANĂ DE COADA ŞORICELULUI	Aerial parts	AC 0456	PLANTAVOREL
37	Coada şoricelului-capsule	?	AC 1097	Unicornis Trade Kft., Hungary

No.	Product name*	Ingredient(s)	Notification date/Dossier number**	Manufacturer
38	Schafgarbe Kraut Pressaft (Coada Soricelului)	Aerial parts	AB 0286	Phyto-Sapiens

* Product names are reproduced verbatim as published by the Romanian Institute of Food Bioresources on its website
** For notifications made to the Romanian regional public health centers (Cluj, Iași, Timișoara), official documents only make available the dossier number but not the notification date.

TABLE 2. Products derived from** A. millefolium **available on the Romanian market but not notified to the Institute for Food Bioresources

Commercial name	Dosage form/Ingredient(s)	Manufacturer	Web source
Coada șoricelului	Capsules (40 cps) (0.2g yarrow (*Milefolii flos*))	Laboratoarele Favisan	https://www.favisan.ro/produs/coada-soricelului/
Coada Soricelului, 60 capsule, Pro Natura	Capsules *Millefolii flos pulvis* 0.185g/cps	Medica Pro Natura	https://comenzi.farmaciatei.ro/vitamine-si-suplimente/digestie/antispastice/coada-soricelului-60-capsule-pro-natura-p347708
Tinctură de Coada Șoricelului	Tincture 50 ml (yarrow aerial parts 20 g and ethyl alcohol 70% v/v for 100 g solution)	Hofigal	https://hofigal.eu/tinctura-de-coada-soricelului-50-ml-213.html
Coada șoricelului 100 caps.	Capsules Ground yarrow (300 mg per caps). 900 mg contain 20 mg total polyphenols, of which 14 mg flavonoids and 0.01 mg resveratrol	Vita Crystal Research (Hungary)	https://vitacrystal.net/shop/gama-de-suplimente-nutritive-c-36_11/coada-%C8%99oricelului-100-caps-p-129.html
Coada șoricelului 30 capsule	Capsules *Millefolii flos pulvis* 0.185g/cps	Medica Pro Natura	https://www.farmaciarodica.ro/coada-soricelului-30-capsule-p-3842
Tinctura de Coada Soricelului	Tincture 50 ml, 38% vol. alcohol	Hypericum	https://hypericum-plant.ro/produs/tinctura-de-coada-soricelului/

TABLE 3. Potential uses of** A. millefolium **products supported by minimal clinical evidence

Indication	Dosage form	Posology
Relief of primary dysmenorrhea and menorrhagia	Infusion (4 g of herbal powder in 300 ml water)	3x/day, 3 days each month
Relief of primary dysmenorrhea and menorrhagia	Extract capsules (details not provided), 150 mg	3x/day, 3 days each month
Vulvovaginal candidiasis	A cream containing (2%) a dry extract of obtained with water at 70 °C for 1h followed by lyophilization	5g/day, 7 days
Episiotomy wound healing	An ointment (5%) containing a dry extract prepared with 90% ethanol	1 cm of ointment, 2x/day, 10 days
Nipple fissure	A yarrow tea bag applied externally after removing its excess water	At least 4x/day
Oral mucositis	Water distillated used as a mouthwash (10 kg boiled with 50 L of water)	3 minute gargling, 4x/day, 14 days
Oral mucositis	Mouthwash (3%) formulated with an extract prepared with 70% ethanol (of which ethanol was removed and sodium benzoate was added as a preservative)	10 ml, 2x/day
Recurrent idiopathic epistaxis	1% ointment obtained with a dry extract (prepared with 80% ethanol)	No specific information on application or doses was reported.
Haemorrhoids	An ointment (5%) containing an extract obtained with ethanol 50%	1g, 3x/day, 10 days
Acute gastroenteritis	Distillate (40 ppm)	0.5 mL/kg, 3x/day
Multiple sclerosis	Capsules containing a dry extract prepared by percolating 2 g of ground powder with 200 ml of water for 24h	250 mg/day or 500 mg/day

population, p<0.001). The initial VAS was 8.25±1.73 for *A. millefolii herba* and 7.91±1.47 for placebo [8]. It was preferrable for the authors to also report an effect size besides p values, but comparing the severity score changes with the initial VAS scores it seems that the benefit, although statistically significant, is relatively small.

A second clinical trial, triple-blind, randomized, and active-controlled, was also performed in Iran, and it

involved a still smaller number of young women (n = 50). The authors compared the effects of a capsule containing 150 mg of *A. millfeolium* extract (details on the extract were not provided) as an add-on to a 250 mg mefenamic acid capsule with placebo as an add-on to 250 mg mefenamic acid. The capsule and placebo were administered three times a day, whereas the mefenamic acid capsules were administered four times a day. They reported significantly less pain with the extract than with the placebo (VAS assessment), but no statistically significant difference in the pain duration was observed [9]. Another randomized controlled clinical trial with 120 women was reported by the same research team. The same design was used (placebo plus mefenamic acid vs. *A. millefolium* extract + mefenamic acid, for seven days of menstruation across 2 months). In the second month the PBAC was used to assess blood loss (BPAC, pictorial bleeding assessment chart, is a semi-quantitative instrument specifically intended for this purpose). The authors reported similar effects: statistically significant higher pain reduction for *A. millefolium*, as well as in increase in the bleeding duration (regarded by the authors as insignificant based on a "$p < 0.001$)" – for a correct assessment it was highly preferrable to report the exact p value) [10].

Radfar et al. (2018) compared a capsule containing an *A. millefolium* hydroalcoholic extract (150 mg) with a capsule containing a *Matricaria chamomilla* L. extract (250 mg), in a double-blind randomized controlled clinical trial conducted on a small sample (n=50) of female students of the Kurdistan University of Medical Sciences. For the first three days of the menstruation period, one capsule was administered every eight hours, for two menstrual cycles. At baseline, the pain score for the two groups was similar (average 6.6 vs. 6.5), but during the first cycle *A. millefolium* was associated with a significant higher reduction in pain than *M. chamomilla* (pain score 4.46±1.53 vs. 5.29±1.78). In the second menstrual cycle the pain reduction was still stronger for *A. millefolium* than *M. chamomilla*, but this time the difference was not statistically significant ($p>0.05$; again, reporting the p value would have been highly preferrable) [11].

A triple-blind clinical trial was also carried out in patients with menorrhagia. Ninety women were randomly assigned to either a treatment or a control group, respectively. The treatment consisted of *A. millefolium* capsules (it is not clear whether they contain herbal powder or an extract), which were administered as an add-on to 250 mg capsules of mefenamic acid, from the first day of menstruation for seven days. The control group used placebo as an add-on to mefenamic acid. According to the authors, both treatments resulted in a decrease in the amount of bleeding compared to the baseline. However, the effect was significantly stronger in the treatment group ($p=0.036$). A similar effect was observed in terms of the duration of bleeding, with a stronger decrease reported in the group receiving the herbal product ($p=0.042$) [12].

To conclude, four clinical trials have been conducted up to date with *A. millefolium* extracts in dysmenorrhea and all indicated that the extracts are effective in reducing menstrual pain. However, all trials have been impacted by small sample size bias (the largest study included 120 patients) and statistical reporting was imperfect. Besides, little information has been made available about the extracts used.

Vulvovaginal candidiasis

Although vulvovaginal candidiasis is not life-threatening, it can have a significant impact on the quality of life of the patients, particularly when recurrent [13]. Azole antifungals (particularly clotrimazole) are available for the treatment but there are concerns about increasing resistance. The fear of adverse effects and propensity of some consumers leads them to search for herbal alternatives to the conventional treatments [14]. *A. millefolium* has been traditionally used in the treatment of female genital disorders and its essential oil has been reported in an in vitro study to be moderately active against Candida strains [15–17]. In this context a group of Iranian researchers evaluated the effects of a vaginal cream including (2%) a dry extract of *A. millefolium* (obtained with water at 70° C for 1h followed by lyophilization) in comparison with a clotrimazole 1% vaginal cream. The extract contained 46.14 ± 4.14 mg/g polyphenols (gallic acid equivalents) and 71.21 ± 0.24 mg/g flavonoids (rutin equivalents) [14]. This was a double-blind, randomized, parallel group clinical trial carried out on a group of 80 women with vulvovaginal candidiasis and treated for seven days with one of the two creams (one application, 5 g/day). Although improvements measured through negative cultures of vaginal discharge was reported for both groups, the effect of the herbal cream was inferior to that observed with clotrimazole 1% (53% vs. 77%, $p< 0.05$). No statistically significant difference was reported with respect to improvement in valvular erythema ($p=0.1$); however, considering the relatively low p value for this

comparison, it is possible that with a higher sample size a significant difference could also be observed for this secondary endpoint. Recurrence of vaginal pruritus among cured subjects was also higher in the intervention group (42%) than in the clotrimazole group (17.85%) (p=0.001) [14]. The MIC of the extract reported in this study was considerably higher than the MIC reported for the essential oil in an vitro study (0.25 mg/ml) [16]. Combining such an extract with an essential oil obtained from the same species might have better results, but this is a hypothesis that remains to be tested.

Episiotomy wound healing

Episiotomy is a surgical incision performed during the labor (in its second stage) to enlarge the vagina and facilitate delivery [18]. Around the globe, the practice of routinely performing episiotomies tends to be replaced by a more restrictive or selective use of this surgical procedure [17], but in certain countries (like Iran) it still can be frequently used in vaginal deliveries, rates as high as 41.5% being reported [19]. Considering the traditional use of yarrow, as well as of St. John's wort (*Hypericum perforatum* L.) for wound healing, a group of Iranian researchers evaluated ointments obtained with extracts prepared from the two medicinal plants in a randomized, double-blind trial on 140 primiparous women. The dry extracts prepared with ethanol 90% were incorporated in a vaseline base in a 5% proportion. The authors used two control groups: one on which no intervention was performed and one placebo group. From a methodological point of view this is well-thought, but because the total number of subjects was 140, the ended up with 32-35 subjects in each group, i.e. a rather low sample size (still more problematic when considering that the authors used multiple time points for assessment). Subjects in the intervention and placebo groups applied and rubbed the ointment (1 cm) on the episiotomy suture daily for 10 days. Six endpoints were used (with apparently none being defined as primary). On days 7, 10 and 14 after delivery no statistically significant difference was observed in the pain (evaluated by VAS) between the two intervention groups, but they were significantly different from the two control groups ($p < 0.05$). Significantly less erythema and oedema were observed at day 7 and 10 after delivery, and significantly less ecchymosis than the control groups at 7 days. Based on these results the authors concluded that the two extracts are useful in the treatment of episiotomy [19].

Nipple fissure

Nipple fissure can occur for a number of reasons, including improper nursing technique, frequent milking, inadequate separation of the newborn from the mother's breast, and excessive cleaning of the nipples, especially with soap. Over 80% of mothers report some degree of nipple pain, and this could result in nipple fissure which, in its turn, can have a negative impact on both the mother's physical health and the bond she forms with her child [20]. Abdoli et al. (2020) evaluated the efficacy and safety of a topical application of *A. millefolium* for nipple fissure on 80 breastfeeding mothers, in a randomized clinical trial. The intervention consisted in applying for 15 minutes on the nipple and areola a yarrow tea bag after removing its excess water and let it dry. Subjects in the control group placed their own hindmilk on the same anatomical area after breastfeeding and let it dry. All subjects performed these applications at least four times day for 14 days. The authors claimed that this was a double-blind study, but considering the nature of the control group, it could hardly be so. A four-point scale was used to assess fissure intensity and the authors reported that there was a significant decrease in the fissure score in the A. millefolium group as compared with the control group at 4, 8, and 14 days "following intervention" ($p \leq 0.01$ for all three time points). Although pain decreased with time in both groups, the reduction in the intervention group was statistically significant greater than in the control group ($p < 0.001$) [20].

Oral mucositis

Oral mucositis describes damage of the oral cavity mucosa occurring following cancer chemotherapy or radiation therapy [21]. It's a common side effect of cancer treatment, affecting around 30%-50% of those getting chemotherapy, 60%-85% of people getting a hematopoietic stem cell transplant, and 90% of people getting radio- and chemotherapy for head and neck cancer [22]. Considering its long tradition of use for healing purposes, the diverse non-clinical data showing that extracts or individual components of them have antibacterial activities, as well as reports by some patients of using a distillate gargle to reduce the damage to the oral mucosa, Miranzadeh et al. (2015) assessed its effectiveness in a clinical setting. This was also performed in Iran and had a small sample size (n= 56) of adult patients with oral mucositis caused by chemotherapy. The authors used a distillate prepared from the aerial parts of *A. millefolium* (10 kg boiled with 50 L of water, resulting in a distillate with a

concentration of 12 mg/L – active ingredient not stated). The distillate was used as a mouthwash, being administered through gargling for 3 minutes (15 ml after the three meals and before bed) along 14 days. Whereas before starting the intervention about 50% of the patients had grade 3 or grade 4 oral mucositis (42.9% grade 3 and 7.1% grade 4), following the administration of distillate for seven or 14 days, only 3.6% of the patients in the verum group had grade 3 mucositis and none had grade 4 mucositis. Instead, in the control group (routine mouthwash) the percentage of patients with grade 3 or 4 mucositis increased to over 60%. Similarly, the mean severity score of oral mucositis, although "equal (2.39 ± 0.87) in both groups" (rather curious from a statistical point of view to have the same mean and standard deviation in two groups, a rather highly unlikely occurrence), decreased significantly in the intervention group but increased in the control group [21].

In a still smaller clinical trial, Hajisalem et al. (2019) evaluated the efficacy of a hydroalcoholic extract of A. millefolium in oral mucositis induced by chemotherapy in patients over 14 years of age with acute myeloid leukemia. The flowering tops of the *A. millefolium* plant were dried and ground into a powder before being macerated in a 70:30 mixture of ethanol and water. After removing the alcohol at 50° Celsius in a rotary evaporator, the resultant extract was filtered. Sodium benzoate (0.05%) was then used to preserve the resultant water extract. The authors added to the extract several additional ingredients: Brij 35 (a nonionic polyoxyethylene surfactant) in a proportion of 5%, as a co-solvent; salicylic acid (0.5%) as an antimicrobial preservative and permeation agent; menthol (0.5%, dissolved in a small amount of ethanol) as a flavouring and coolant agent; and mannitol (10%), probably as a sweetener. Of the resultant mixture a mouthwash was prepared (3%). All subjects used a chlorhexidine mouthwash twice a day (10 ml per dose), for 20 days. Besides, subjects in the intervention group also rinsed their mouth with an additional 10 ml of *A. millefolium* mouthwash, twice a day. Patients were scored for the severity of their oral mucositis at baseline and then every five days up to the 20th day. 14 patients were assigned to the treatment group, while 15 were assigned to the control group. At the 10^{th} and 20^{th} day evaluation, subjects treated with *A. millefolium* mouthwash had a significantly lower severity grade than those from the control group (at day 20, mean grades of 0.50 ± 0.52 vs. 1.67 ± 1.11, p = 0.002). Whereas in the control group about 30% of the patients had severe oral mucositis, none of the intervention group did so. The pain and need for analgesics were lower in the intervention group (but statistically significant only at day 20) [23].

In contrast to nipple fissure or oral mucositis, a small clinical trial (n=75 subjects divided in three groups) conducted on patients with radiation dermatitis resulting from radiotherapy for breast cancer treatment did not demonstrate any clinical advantage for over placebo [24].

Recurrent idiopathic epistaxis

Epistaxis (nasal bleeding) is a frequent occurrence in the general population (a 60% lifetime prevalence) and can have multiple causes: local, systemic, iatrogenic, and idiopathic [25,26]. Epistaxis can be anterior (80% to 90% of the total cases, easier to treat – with topical vasoconstrictors, direct compression, and should these fail, cautery) or posterior (10-20% of cases, only adults, more severe and difficult to treat – besides initial measures similar to anterior epistaxis, posterior nasal packing associated with systemic antibiotics is often needed) [27]. Considering the legendary use of the plant in healing and non-clinical data indicating efficacy of an extract of *A. millefolium* on stopping epistaxis (in rabbits), Hashemian et al. (2021) initiated a clinical trial to assess its efficacy in humans. This was a randomized, double-blind, placebo-controlled study in subjects with idiopathic epistaxis. As the wide majority of clinical trials performed with *A. millefolium* extracts, this was also carried out in Iran and included a small sample size. The product evaluated was a 1% ointment, where the active ingredient (extract) was prepared from *A. millefolium* leaves (sic!) by extraction with 80% ethanol. The extract was incorporated in an "Oserin-Vaseline" ointment base (it is not clear what "Oserin" is, it might be a misspelling for Eucerin) [25]. The *A. millefolium* and placebo ointments were applied as add-on to a vitamin A ointment in alternate day (i.e. one day vitamin A, the other day *A. millefolium* or placebo). No specific information was reported on the precise application and doses used. The study included 56 subjects (of which 50 finalized the trial), relatively young (mean ages of 21.1 in the intervention group and 22.9 in the control group). The bleeding severity at baseline was higher in the intervention group than in the control group (3.4 vs. 2.6, p = 0.018). After 10 days, although the intensity of bleeding evaluated through the Epistaxis Severity Score (ESS) was lower for the intervention group than the placebo group (1.54 vs. 1.99), it did not reach the

conventional threshold of statistical significance (p=0.10). Bleeding frequency and bleeding duration were also non-significantly lower in the intervention group (p= 0.24, and p=0.15, respectively). The authors claimed that for all these endpoints, measurements done at 1 month and 3 months favored the treatment in a statistically significance manner ($p \leq 0.001$ for all endpoints) [25]. However, considering the fact that the treatment was only applied during the first 10 days (only in five days of those 10) and the small sample size, such results have to be taken cautiously and confirmation in better designed and performed trials would be necessary.

Haemorrhoids

Currently, although our understanding is incomplete, it is believed that hemorrhoids (piles) develop as a result of destructive changes in the connective tissue of the anal cushions [28]. Such tissular destruction can be caused or favoured by aging, mechanical injury (driven by hard stools), and an increased expression of matrix metalloproteinases [28]. Women tend to report hemorrhoids more than men and it is estimated that the demand for hemorrhoid treatments will increase in the next two decades [29]. Because *A. millefolium* has traditionally been used in the treatment of hemorrhoids and among its chief constituents are flavonoids, some of which are venotonic agents, another group of Iranian researchers recently evaluated the efficacy of an ointment containing a hydro-alcoholic extract in a small clinical trial [30]. This was a double-blind, randomized, placebo-controlled study in carried out in adult (18 – 65 years) patients with grade 1 or 2 internal hemorrhoids. The extract was obtained by percolation at room temperature, using a 1:1 ethanol-water mixture as a solvent; the extraction was followed by concentration with a rotary evaporator. It contained 37.22 ± 1.32 mg polyphenols/100 g (expressed as gallic acid equivalents) and 17.85 ± 0.94 mg flavonoids/100 g extract (expressed as quercetin). The authors standardized the ointment based on quercetin (1.33 mg/100 mg of dry extract or 66.5 mg/100 g of ointment, respectively). The ointments were applied to the skin three times a day for 10 days, using 1 g each time. The mean age of the subjects was 41.7 ± 11.4 in the placebo group and 42.8 ± 14.1 in the intervention group. Both the pain and discomfort during defecation were assessed by VAS and decreased in both groups following treatment, but significantly more so in the herbal product group (p = 0.01). A significant improvement was also reported for the intervention with respect to the scores of bleeding intensity and frequency ($p < 0.05$), whereas in the case of pruritus the difference was not significant at the conventional significance level of 0.05, but it was close to it (suggesting that with a higher sample size it could have become significant) [30].

Acute gastroenteritis

Abdominal pain, nausea, and vomiting are typical signs or symptoms of acute gastroenteritis, a widespread infectious illness [31]. Data from Germany suggested that almost every adult has one yearly episode of diarrhea [32]. Various non-clinical data indicate that A. millefolium herbal products or extracts could be useful in gastroenteritis symptoms due to its antispasmodic (33], antiviral [34], prokinetic [35], and antidiarrheal [36] effects. Based on these facts, a small (n = 44) randomized, controlled, double-blinded (no information on blinding was provided) clinical trial was performed in patients with acute gastro-enteritis. The control group received the common standard of care, whereas the intervention group received a yarrow distillate (40 ppm, three times a day, 0.5 mL/kg). The authors claimed a faster recovery for the intervention group versus the controlled group (mean 1.31 days vs. 1.86 days, p = 0.015) [37]. Besides different sources of bias in this study, the effect size is relatively small and the clinical significance of the benefit is unclear.

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune illness that has been identified as the leading cause of non-traumatic neurological impairment in young people. In the central nervous system of these patients neurodegeneration occurs together with demyelination, gliosis (fibrous proliferation of glial cells), and inflammation [38]. It impacts more women than men and life expectancy of patients with MS tends to be shorter than for the general population [39].

The large majority of patients (about 85%) initially are diagnosed with a form of the disease known as relapsing remitting multiple sclerosis (RRMS), characterized by recovery (remission) between disease attacks. Among RRMS patients, it is expected that up to 80% will develop in time what is called secondary progressive multiple sclerosis (SPMS), characterized by worsening of the neurological disability despite the absence of relapses. There are also about 15% of patients with a third form of the disease, primary progressive multiple sclerosis (PPMS), who have no obvious relapses during their disease evolution, but

manifest increasing disability from the beginning of the disease [40]. Although the disease currently remains incurable, in recent years many new therapies have been developed (particularly monoclonal antibodies), which have been shown to reduce relapse frequencies and diminish neurological disability accumulation [41]. In the case of such diseases where no cure is available, there is often interest from both patients and healthcare practitioners for exploring complementary and alternative therapies [42].

Among the active ingredients of yarrow are apigenin and luteolin, two flavonoids shown in non-clinical studies to have neural protective effects and benefits in animal models of various neurologic diseases: cognitive deficits [43–45], Alzheimer's disease [46–50], diabetic neuropathy [51], neuroinflammation and trauma [52,53] etc. In two murine models of multiple sclerosis, apigenin showed potential for benefit through a diminished expression of α4 integrin and C-Type Lectin Domain Family 12 Member A (CLEC12A) on splenic dendritic cells, as well as an enhanced retention of immune cells in the peripheric areas of the body as compared with the control animals [54]. An *in vitro* study reported inhibition of IL-17A gene expression by apigenin, but at an unrealistic concentration (80 μM, unlike methyl prednisolone acetate for which the same effect was reported at 2.5 μM) [55]. On the other hand, luteolin has inhibitory effects on mast cells, suppressing the production of histamine, leukotrienes, prostaglandin D2, and GM-CSF (granulocyte–macrophage colony-stimulating factor) from human mast cells cultivated and simulated with Ig-E. It also prevents rat peritoneal mast cells and murine mast cells grown from bone marrow from releasing histamine, IL-6, and TNF-α [56,57]. Mast cells are known to play multiple roles in the pathogenesis of multiple sclerosis, and thus inhibiting mast cell release of various mediators is expected to help in controlling the disease [57].

The benefits of an aqueous extract of *A. millefolium* on RR-MS patients were assessed by Ayoobi et al. (2018) over a one-year period [58]. The study, triple-blind, randomized placebo-controlled, had five time points and involved patients, researchers, radiologists, and analyzers who were all blind to the treatment allocations. 75 subjects were divided into three equal groups and randomly received either 250 mg/day or 500 mg/day of the extract or a placebo (starch), all in capsule form. Of the 75 subjects, 65 completed the trial. The extract was prepared percolating 2 g of ground powder with 200 ml of water for 24h, followed by filtration, evaporation and incorporation into capsules. Apigenin and luteolin were present in the extract at the 0.28 mg/g and 1.58 mg/g concentrations, respectively. In this study, the annualized relapse rate (number of confirmed relapses in a year) was used as the primary endpoint and several secondary efficacy endpoints were also used. The extract was found to be superior to placebo in in reducing the mean annualized relapse rate: 11 for the placebo group (50% of subjects), 5 for the 250 mg extract group (22.7% of subjects), and 7 for the 500 mg extract group (33.0% of subjects) [58].

The proportion of patients who were relapse-free at the conclusion of the study was higher in the treatment groups than in the control group, and the duration to the first relapse was longer in the treatment group ($p = 0.013$ and $p = 0.039$ for the two dosages, respectively). More patients experienced fewer relapses over the course of the research, which decreased their risk of relapse. The expanded disability status score (EDSS) rose in the control group while falling in the extract groups (with the greater dose having a stronger impact in this endpoint's instance). The Multiple Sclerosis Functional Composite (MSFC) z-score for the 500 mg dose was likewise considerably greater than placebo. For the extract treatment compared to the placebo, there was a substantially more pronounced mean change in the volume of lesions on T2-weighted MR images (larger decreases were observed in the treatment groups). The pace at which information is processed as measured by the Paced Auditory Serial Addition Task (PASAT) was faster in the treatment groups than in the placebo group [58]. The study suffers from a small sample bias (only 65 subjects for 3 study arms, means an average number of 22 subjects per treatment arm).

Failed trials

In a small clinical trial (n=31) carried out in patients with chronic kidney disease, 500 mg capsules containing powdered flowers did not cause statistically significant changes in plasma nitrite and nitrate concentrations as compared with placebo. Small decreases in the intervention group and small increases in the placebo group were found, but they were not significant, and the authors speculated that higher doses or longer treatment durations might result in significant changes (59). A higher sample size might also change the significance of the results, but currently there is no evidence to support the use of *A. millefolium* in chronic kidney disease.

A topical gel of 5% *A. millefolium* (containing 5% polyphenols) was evaluated in a small randomized, double-blind clinical trial as an add-on to intralesional glucantime (an antimony salt of meglumine) in patients with acute cutaneous leishmaniasis but it failed to demonstrate a significant benefit against placebo [60].

Ghadjar et al. (2021) evaluated clinically the benefits of applying yarrow compresses prepared with yarrow infusion on the skin (on the right abdomen and near the lower ribcage) to reduce fatigue in patients with metastatic cancer undergoing radiation therapy. The control group consisted of no such application of compresses. No statistically significant effect was reported but the authors claimed a trend towards reduced fatigue [61]. Even if statistically significant, it seems highly unlikely that a potential benefit would specifically be related to the yarrow preparation (to claim such a benefit it a placebo group receiving similar compressions would be necessary, but even then, in the absence of a pharmacological mechanism to explain it, such an effect is hardly credible).

As already stated above, unlike nipple fissure or oral mucositis, a vanishing cream containing a yarrow extract failed to provide any benefit in patients with radiation dermatitis resulting from radiotherapy for breast cancer as compared with placebo [24].

Traditional uses accepted in the European Union

According to the Community herbal monograph on *Achillea millefolium* L., flos, adopted by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency, there is no indication supported by clinical evidence to allow a well-established use authorization, but there is a long-standing use in the following indications (reproduced verbatim here, as approved in the monograph):

1. Temporary loss of appetite (infusion obtained from 1.5 – 2.0 g of herbal product in 250 ml of water, 2x/day, to be taken half an hour before meals).
2. Symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating and flatulence ("Liquid extract: 10-20 drops 2-3 times daily").
3. Treatment of small superficial wounds (infusion as per the first indication, 2-3x/day)
4. Symptomatic treatment of minor spasm associated with menstrual periods (infusion as per the first indication, 2-3x/day) [62].

For the first two indications, if the symptoms persist for more than two weeks, a qualified healthcare professional should be consulted, whereas for the latter two indications such a consultation should be made if the symptoms persist for more than one week. The European herbal monograph dates from 2011 and precedes the wide majority of the clinical trials published with A. millefolium reviewed above.

SAFETY

As for many herbal products, in acute toxicity tests, extracts of *A. millefolium* were shown to have low toxicity. The administration of an aqueous extract in doses as high as 10 g/kg by oral route or 3 g/kg by intraperitoneal route did not result in mortality among Wistar rats [63]. In a 90-day repeated dose toxicity study conducted on rats, oral administration of an aqueous extract did not result in any toxicological or histopathological abnormalities [63]. The median lethal dose (LD50) in female rats, of a mixture comprising an aqueous extract of *A. millefolium* was reported to be higher than 2 g/kg [64]. FDA has classified *A. millefolium* as a non-poisonous plant and has approved it for utilization in alcoholic drink [65].

An extract prepared with 45% ethanol (with a content of 500 mg/ml) exhibited no toxicity when administered to pregnant female rats at a dosage of 2.8 g/kg [7]. There was no evidence that *A. millefolium* is causally linked with an increase in the number of resorptions or of fetal deaths, but it did cause a decrease in the weight of the fetus and a rise in placental size, but the authors speculated that at least partly this could be related to the effects of the alcohol contained by the extract [7].

A study performed in mice (using either 200 mg/kg/day of an ethanol extract administered intraperitoneally (i.p.) for 20 days or 300 mg/kg/day of a hydroalcoholic extract administered orally for 30 days) reported certain alterations in germ cells and seminiferous tubules, indicative of antispermatogenic action [66]. Previous studies showed that adding *A. millefolium in* a high proportion to the diet of rodents (25%- 50% of the diet) resulted in estrus suppression, whereas oral administration of a leaf extract in rats did not impact mating, fertility or litter size [66]. A 90-day study in male rats treated with three different doses (0.3, 0.6 and 1.2 g/kg/day) of a dried extract prepared with water at 70° from *A. millefolium l*eaves, found no clinical signs of toxicity or differences in body weight gain, but did report a significant increase in abnormal sperm with the

highest dose of extract [67]. An ethanol extract was administered for 22 days either i.p. or orally at doses of 200, 400, and 800 mg/kg/day, with a frequency of every other day and found that at 400 and 800 mg/kg/day, antispermatogenic effects were observed; the findings observed with the dose of 400 mg/kg/day seem to be reversible after day 62, whereas they seemed not reversible at the same time point with the 800 mg/kg/day [68]. Of course, man is neither a big mouse nor a big rat, but the precautionary principle justifies prudence in the light of such findings, particularly with respect to high doses and longer periods of treatment.

The essential oil was shown to have some genotoxic effects manifested by an increase in the number of diploid segregants in *Aspergillus nidulans*, probably through mitotic non-disjunction and crossing-over processes [69]. It is not clear whether this effect is also manifest in mammalian cells, but up to date the essential oil has not been clinically evaluated for therapeutic benefits. Anyway, this suggests the need of caution in the use of the essential oil.

Aqueous extracts of *A. millefolium* did not manifest mutagenic effects in three different in vitro tests, based on *Salmonella typhimurium* (TA98, TA100,TA102, TA1535,TA1537) (Ames test), two micronucleus tests on the V79 cell line, and a gene mutation assay on a mouse lymphoma L5178Y TK+/- [64]. *Allium cepa* root-tip cells were not significantly inhibited by an *A. millefolium* infusion, nor were rat bone marrow cells or human lymphocytes significantly affected by chromosome changes or cell division inhibition under treatment with the infusion [70].

Although *in vitro* mutagenicity tests are useful, they do have limitations and *in vivo* data supporting the conclusions of the *in vitro* data are needed (although in vivo data have themselves their own limitations) [71], but the fact that all data up to date are coherent in supporting lack of mutagenicity is encouraging.

Limited non-clinical and clinical data indicate that *A. millefolium* extracts have a low sensitization potential [64], but the exposure in the human studies was less than 250 subjects (quite low). To these studies, the clinical trials performed with *A. millefolium* extracts applied topically as ointments, creams, or even as an imbibed tea bag could be added, as in these no sensitization was reported [14,19,20,30]. *A. millefolium* is considered "a well-known cause of contact dermatitis" [72]. The first case of yarrow dermatitis dates back to 1899. Since then and up to 1990 at least 77 such cases have been published in the medical literature, many of the patients being sensitive to other Asteraceae species. Hausen et al. (1990) reported that in their department about 50% of the patients sensitive to Asteraceae reacted to *A. millefolium* in a routine epicutaneous test carried out after 5 years. Unsaturated guaianolides (of the group of sesquiterpene lactones), and particularly α-peroxyachifolid, seem to be responsible for this effect. The concentration of these compounds seem to increase by drying [73,74]. Although older books and journal claimed that *A. millefolium* possesses phototoxic activity and in the 1960s it was claimed that three polyine molecules are responsible of this activity, other authors demonstrated that alcohol extracts of *A. millefolium* are not phototoxic, whereas in tests based on *Candida albicans* only its roots were shown to be minimally photoactive [73]. These cases are particularly relevant for the topical application of *A. millefolium* extracts.

A case of occupational asthma induced by *Carthamus tinctorius* L. and *A. millefolium*, where skin prick tests were positive for aqueous extracts obtained from flowers derived from both species, and an inhalation bronchia challenge resulted in asthma, provides evidence that *A. millefolium* is also capable of inducing IgE-mediated sensitization [72].

CONCLUSIONS

Multiple products containing *A. millefolium* are potentially available on the Romanian market as food supplements. The wide majority of products consist of herbal teas marketed as dry herbal products. Limited evidence for clinical benefits of yarrow infusion (the most likely use of herbal teas) are only available for the relief of primary dysmenorrhea and menorrhagia and for nipple fissure (the tea bag being applied externally after removing its excess water). Limited clinical evidence for other indications has been generated with extract capsules, topical products (ointments/creams), distillates or a mouthwash obtained with a 70% ethanol extract (Table 3).

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