

# Achillea moschata Wulfen

Subjects: Plant Sciences

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*Achillea moschata* Wulfen (Asteraceae) is a suffruticose chamaephyte. It is endemic to the Alpine region and grows between 1400 m and over 3000 m a.s.l. on cliffs, stony ground, and moraines, exclusively on silica. It is known by various common and vernacular names, including *erba iva*, *taneda*, *daneda*, and *aneda*. The decoction of its flower heads, which represents the drug, is traditionally used to treat digestive tract disorders. The balsamic time coincides with anthesis (July–August).

Keywords: primary data ; traditional decoction ; flower heads ; aqueous and methanolic extracts ; mass spectrometry

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## 1. Introduction

*Achillea moschata* Wulfen (Asteraceae) is a suffruticose chamaephyte. It is endemic to the Alpine region and grows between 1400 m and over 3000 m a.s.l. on cliffs, stony ground, and moraines, exclusively on silica. It is known by various common and vernacular names, including *erba iva*, *taneda*, *daneda*, and *aneda*. The decoction of its flower heads, which represents the drug, is traditionally used to treat digestive tract disorders <sup>[1]</sup>. The balsamic time coincides with anthesis (July–August) <sup>[1]</sup>.

This entry is derived from an ethnobotanical survey related to the European Interreg Italy–Switzerland *B-ICE* project. The main purpose of this project is to create a management model useful in dealing with emerging issues in Valmalenco (Sondrio, Lombardy, Northern Italy) due to climate change. Glacial retreat and diminished snowfall are adversely affecting tourism in the area. Therefore, the *B-ICE* management model includes strategies aimed at looking for new tourism avenues, such as the revitalization of traditional practices linked to medicinal and food wild plants <sup>[1]</sup>. Specifically, the work focuses on Chiesa in Valmalenco, which is the main village of the Valley. It has about 2400 inhabitants, is located at approximately 1000 m a.s.l., and is enclosed by the Bernina Alps.

Previous ethnobotanical works that mentioned *A. moschata* referred to the Alpine and Pre-alpine regions, with special focus on the Italian territory <sup>[1][2][3][4][5][6]</sup>. Common aspects regarding the traditions of use emerged: from the employed plant parts (flower heads, flowered aerial parts, and flowered epigeal organs) to the most popular preparations (decoctions/infusions and digestive liqueurs). Folk uses in the Alpine and Pre-alpine regions mainly referred to a digestive, antispasmodic, and carminative action. They also mentioned antiseptic, emollient, anti-inflammatory, and painkiller properties, as well as hypotensive characteristics <sup>[1][2][3][4][5][6]</sup>.

Concerning previous phytochemical studies, the literature proposed various works on the essential oil composition <sup>[7][8][9]</sup> and the polar extracts <sup>[9][10][11][12]</sup>, as well as the non-polar and aqueous profiles <sup>[9][13]</sup>, obtained from the dried flowered aerial parts. The acetonetic extracts were also analyzed for the identification of the epicuticular components <sup>[14]</sup>. Finally, Apel et al. (2021) evaluated and compared the hydroalcoholic extracts (methanol/water) of three congeneric species: *A. millefolium*, *A. moschata*, and *A. atrata* <sup>[15]</sup>.

The characterization of the aqueous extract proposed in the literature deserves further investigation, with morphological studies on the target species aimed at investigating the secreting structures responsible for productivity in secondary metabolites lacking. Indeed, previous micromorphological contributions focused on European and Western Asian congeneric species <sup>[16][17][18][19][20][21]</sup>. Regarding the biological activity, *A. moschata* extracts were generally screened for their radical scavenger properties with spectrophotometric assays such as the DPPH test <sup>[11][12]</sup>. Moreover, studies never reported the aqueous extract, which is significant, being the traditional decoction used in folk medicine in the Alpine and Pre-alpine regions. Only recently, Vitalini et al. <sup>[9]</sup> tested several extracts, including the aqueous one, for their anti-inflammatory activity, evaluating the modulation of interleukins 8 and 1 $\beta$  on CaCo-2 cells. Concerning congeneric species, the antioxidant potential of different extracts was evaluated as radical scavenger activity, but no in vitro studies were reported to date in the literature <sup>[10][22][23][24]</sup>.

## 2. Phytochemical Investigation

Regarding the phytochemical investigation, the qualitative profile of the aqueous and methanolic extract of the dried flowered aerial parts of *A. moschata* was evaluated. One of the elements of novelty offered was the faithful reproduction of the traditional aqueous preparation, which was directly documented in the form of decoction through the ethnobotanical survey conducted in the study area. Another original aspect concerned the characterization of the polyphenolic content of the traditional preparation, with the aim to better understand its potential in terms of bioactive compounds. Furthermore, this analysis was enriched with the characterization of the methanolic extract obtained by extraction with solvents of increasing polarity. This, in turn, facilitated a comparison with the literature data currently available about the target species, which mainly refer to this type of extract <sup>[10][11][12][15]</sup>.

The LC-MS/MS analyses allowed for the identification of all the main compounds, detecting a qualitative overlap between aqueous and methanolic extracts. A total of 31 compounds were identified, 28 of which were detected in both extracts. To this end, luteolin C-glucoside (4), desmethoxycentaureidin (27), and isorhamnetin (28) were found only in the methanolic extract, even if only in trace amounts. Among the 31 total compounds (31 in negative ion mode, 27 in positive ion mode), 5 were phenolic acids, 13 were flavonols, and 13 were flavones. In detail, the phenolic acids were represented by caffeoylquinic acids or dicaffeoylquinic acids isomers (1, 2, 11, 13, 19), with all present in both extracts. Flavonols were detected as glucosides and aglycones, and they were quercetin (6, 29), kaempferol (7, 30), isorhamnetin (12, 14, 16, 28), mearnsetin (9, 10), syringetin (17), eupatolin (21), and chrysosplenol-D (or jaceidin) (31) derivatives. These were also detected in both extracts, except for isorhamnetin aglycone (28), which was found only in the methanolic extract. Analogously, flavones were detected as glucosides and aglycones of apigenin (3, 15, 25), apparently the most abundant component, luteolin (4, 8, 23), isoorientin (18), axillarin (24), chrysoeriol (or hispidulin) (26), and desmethoxycentaureidin (27). Finally, malonyl derivatives of luteolin (luteolin 7-malonyl-glucoside, 20) and apigenin (apigenin 7-malonyl-glucoside, 22) were identified in the two extracts. Special attention was paid to apigenin 7-malonyl-glucoside (22), whose peak has a higher relative abundance in respect to the other as opposed to the methanolic one, thus revealing an important feature of the traditional preparation, considering that the decoction extraction process adopted for the analysis was derived from the folk medicine.

Regarding the phytochemical profiling of the phenolic content of *A. moschata*, the literature proposed only five works. Two of these highlighted the quali-quantitative characterization of the methanolic extract <sup>[11][12]</sup>; one proposed the quali-quantitative analysis of the acetone/water extract, later solubilized in methanol/water <sup>[15]</sup>; one focused on the quantification of the total polyphenolic content of the methanolic fraction <sup>[10]</sup>; and, finally, a more recent work, proposed a quantitative comparison between the methanolic extract and the aqueous preparation, without presenting any chromatogram and fragmentation pattern of the listed compounds <sup>[9]</sup>.

From a comparison with these papers <sup>[9][11][12][15]</sup>, the phytochemical characterization identified the highest total number of compounds. The phenolic classes were found to be the same, including simple phenols (phenolic acids) and flavonoids (flavones and flavonols). Moreover, the identification exhibited 14 exclusive compounds, not detected in the other profiles: vicerin-2 (3), schaftoside (5), eupatolin (21), axillarin (24), chrysoeriol/hispidulin (26), isorhamnetin (28), quercetin-3,3'-dimethylether (29), 6-hydroxykaempferol-3,6-dimethylether (30), and chrysosplenol/jaceidin (31), as well as glycosides of syringetin (17), luteolin (4), and isoorientin 7-methyl ether (18). In addition, the detection of two malonic acid derivatives, luteolin 7-malonyl-glucoside (20) and apigenin 7-malonyl-glucoside (22), highlighted another unique feature of the profiles, both in the methanolic extract and the decoction. Specifically, the latter compound seems to be highly concentrated in the aqueous extract and, both molecules were previously identified only in congeneric species such as *A. millefolium*, *A. alpestris*, and *A. ceretanum* <sup>[25]</sup>.

These phytochemical data deepened the field work conducted by the research group on the traditional uses of *A. moschata* in the very distribution area of the species. This aspect further distinguishes the survey from previous works, which based their phytochemical investigation on ethnobotanical data obtained in the scientific literature <sup>[9][11][12][15]</sup>, or sometimes analyzing commercial forms of the herbal drug, instead of spontaneous ones <sup>[15]</sup>.

## 3. Morphological Investigation

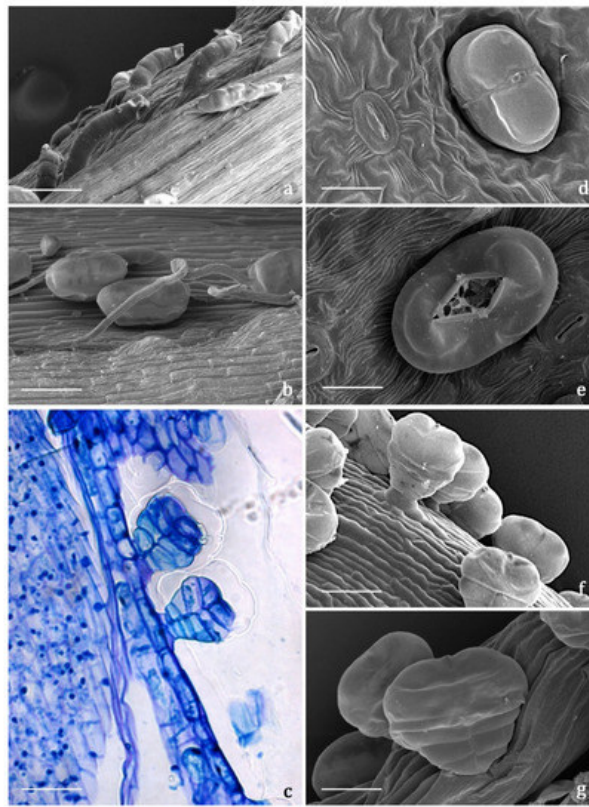
### 3.1. Botanical Description

*Achillea moschata* presents creeping woody stems from which ascending sterile shoots and erect flowering branches start. The latter are sub-glabrous or with short hairs. The leaves are alternate, deeply pinnate with a lanceolate–spatulate outline and 7–10 segments on each side. The basal leaves are pedicellate, while the cauline ones are sessile, toothed,

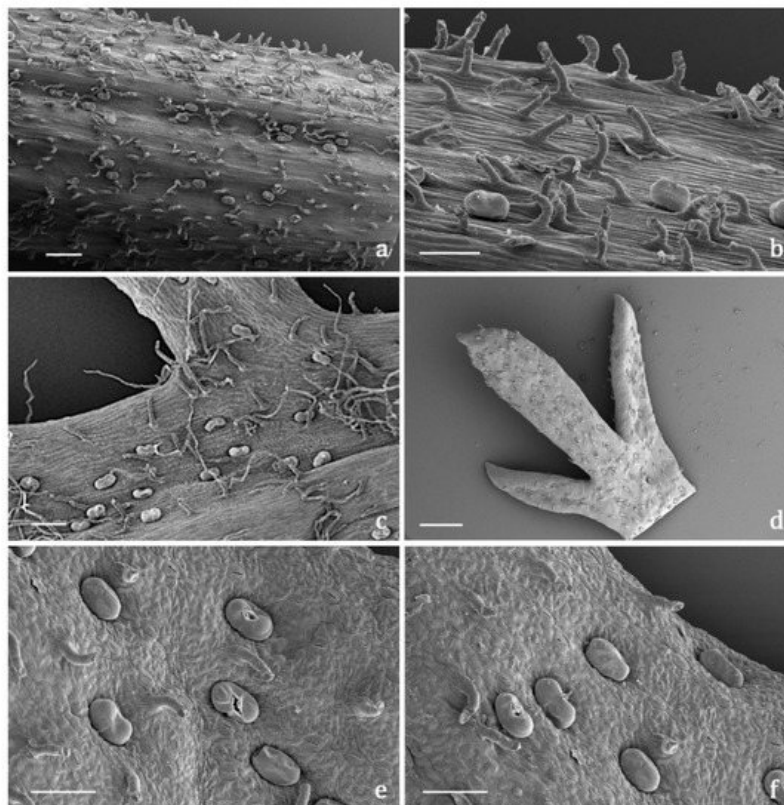
and progressively linear. The leaves are strongly aromatic, hairless, or with scattered hairs [26]. The flowers are grouped in small flower heads (*capitula*) with a diameter of 2–6 mm, in turn gathered in loose corymbs, with each composed of about 10 flower heads. The peduncles of the flower heads are cylindrical, striated, sub-glabrous, or with scattered hairs [27]. The *capitula* are composed of both ray (6–9) and disk (10–15) florets. The receptacle is conic or convex, enclosed by various layers of imbricate involucre bracts. The bracts are obovate-oblong, sub-glabrous [27], with narrow transparent membranous margin, yellowish-to-brownish, and whole or notched only towards the apex with shallow denticles. The disk florets vary in number, from 10 up to 15 per head and are hermaphrodite. Each floret is subtended by an interfloral scale called “palea”. The corolla tube is yellow with the top split in 5 apical laciniae overhanging the tube. The stamens are 5 with free filaments and connate anthers, welded in a sleeve surrounding the stylus with deeply bifid stigma; the carpels are 2 forming a unilocular inferior ovary. The ray florets are 6–9 per head, pistillate, fertile, 3–4 mm long. The corollas are white, with a tubular lower portion surmounted by a ribbon-like extension, the ligule, ending with sub-round denticles, with scattered golden glands on the lower side [26]. The stigma is 2-lobed, with a papillose surface.

### 3.2. Indumentum

The *indumentum* of the examined organs in all the replicates showed a general consistency both in terms of trichome morphotypes and distribution pattern. Both covering and glandular hairs were observed (**Figure 1**). The formers were simple, multicellular, uniseriate, and distinguished in two subtypes: short and 5–7 celled with isodiametric cells of uniform diameter from the base to the apex, so as to appear digitiform (**Figure 1a**); long and filamentous with a pointed apex which may be straight or slightly twisted (**Figure 1b**). Although the cell number could not be defined based on LM and SEM analyses, the literature data indicated the occurrence of 5-celled filamentous hairs in some congeneric species [15] [17]. The basal cells of both subtypes were usually protruding from the epidermal surface of the organs bearing them, and sporadically appeared swollen. The short digitiform hairs were distributed on flowering stems and on both leaf sides (**Figure 2a–f**), while the long filamentous ones were on the leaf abaxial sides, on the abaxial side of the involucre bracts, and on peduncles of the *capitulum* (**Figure 2c** and **Figure 3a–d**). The glandular trichomes belonged to a single morphotype (**Figure 1b–g**) that was a 10-celled biseriate, composed of two rows of five cells each (**Figure 1c,f,g**). There are two basal cells, two stalk cells, and six secretory cells, as already described in some congeneric species [19][20]. At full growth, the mature glands presented a peculiar bilobed, heart-like shape, resulting from the expansion of the cuticle covering the apical cells. In fact, during development, the subcuticular space at the apex grew into a sac-like structure, although it was unclear whether the sac embraced four or six apical cells (**Figure 1f,g**). These hairs may be sunken or may protrude to varying degrees from the epidermal surface because of the different elongation of the basal cells (**Figure 1d–g**). They appeared sunken on the flowering stems, leaves, involucre bracts, and interfloral scale of the disk florets (**Figure 2a–f** and **Figure 3a–d,g–j**), but protruded from the epidermis of the corolla of both disk and ray florets and on their ovaries (**Figure 3k–m** and **Figure 4a–f**). On the abaxial surfaces of involucre bracts, trichomes presented a peculiar distribution pattern: filamentous glands and trichomes were arranged in two rows in troughs along either side of the leaf midrib (**Figure 3b–d**). Most of the secretion was discharged externally following the rupture of the cuticle, along a predetermined line of weakness, visible on the apical cuticular layer (**Figure 1e** and **Figure 2e–f**). The cuticular envelope appeared broken to several degrees in many of the mature glands. Fractured cuticles also revealed the flocculent appearance of the secreted materials within the subcuticular chamber (**Figure 1e**).

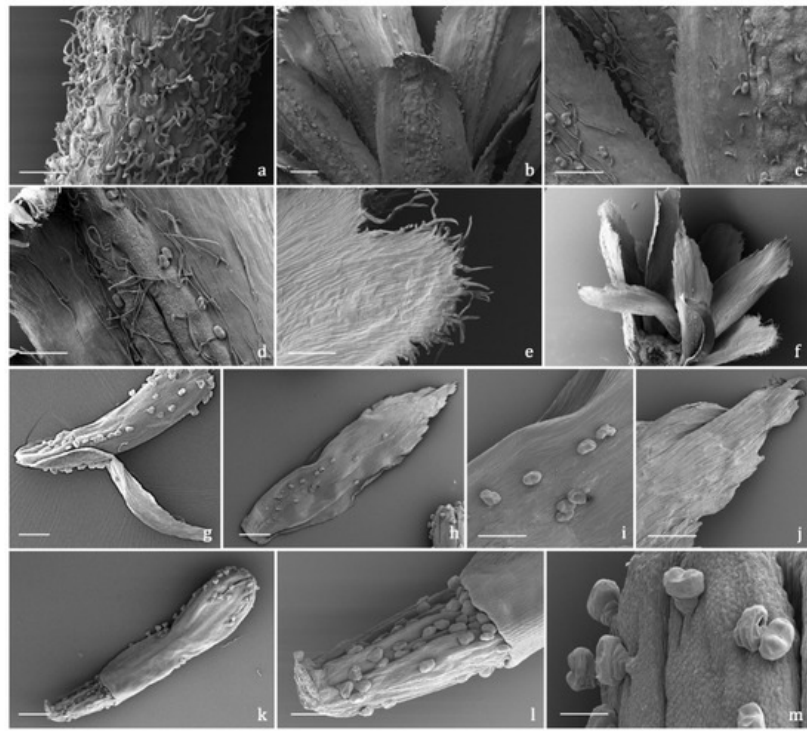


**Figure 1.** SEM and LM micrographs showing the covering and glandular trichomes observed on the vegetative and reproductive organs of *Achillea moschata*. (a) Short digitiform trichomes. (b) Long filamentous trichome and biseriate glandular trichomes. (c) Longitudinal section of biseriate 10-celled glandular trichomes stained with Toluidine Blue. (d) Sunken biseriate glandular trichome with intact cuticle. (e) Sunken glandular trichome showing the rupture of the cuticle along a line of weakness. (f,g) Protruding biseriate 10-celled glandular trichomes. Scale bars: 50  $\mu\text{m}$  (a–c,f); 20  $\mu\text{m}$  (d,e,g).

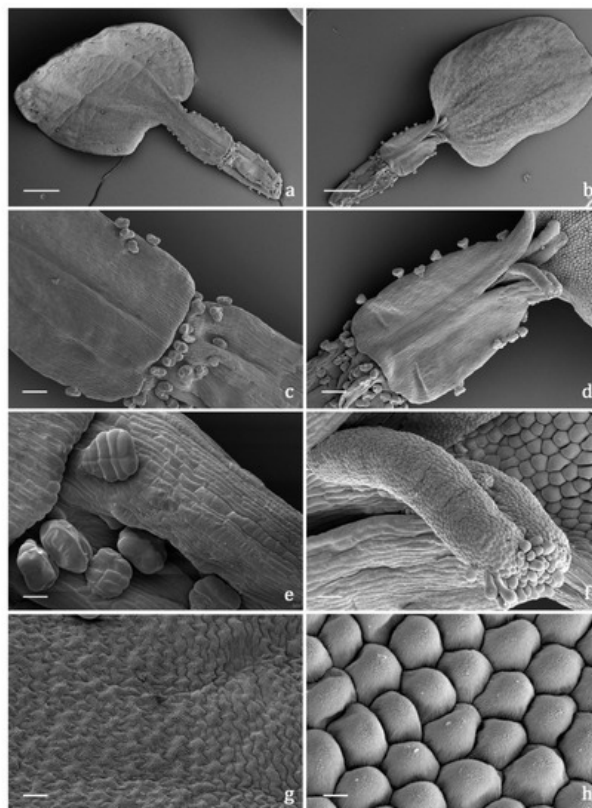


**Figure 2.** SEM micrographs showing the flowering stem and leaf morphology of *Achillea moschata*. (a,b) General view (a) and detail (b) of a flowering stem with biseriate glandular trichomes and digitiform covering trichomes. (c) Leaf abaxial surface with the two types of covering trichomes (short digitiform and long filamentous) and the biseriate glandular hairs. (d) General view of the apical portion of a deeply pinnate leaf (adaxial side). (e,f) Details of the leaf adaxial side with sunken biseriate glandular trichomes and digitiform hairs; notice the broken cuticle of several glandular trichomes for the release of the secreted materials. Scale bars: 500  $\mu\text{m}$  (a,d); 100  $\mu\text{m}$  (b,c,e,f).





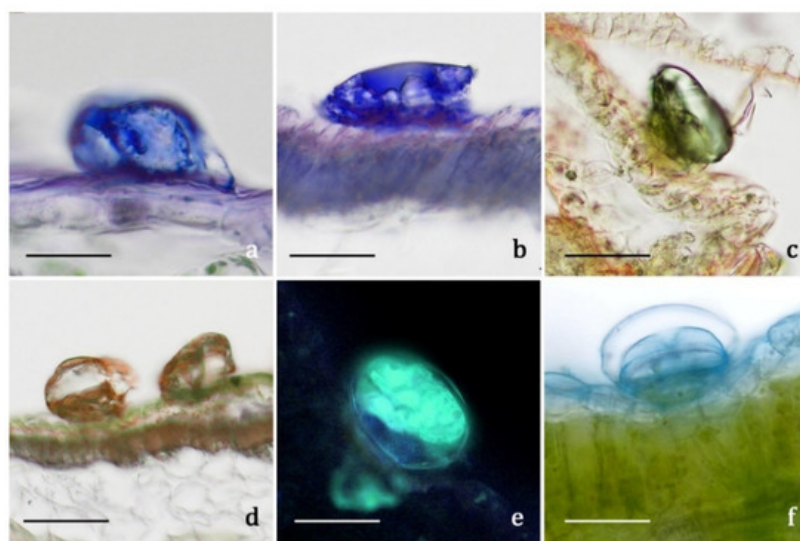
**Figure 3.** SEM micrographs showing the peduncle of the *capitulum* and the involucre bracts (**a–f**) and the disk florets (**g–m**) of *Achillea moschata*. (**a**) Peduncle of the *capitulum*. (**b**) General view of the involucre bracts (abaxial sides). (**c,d**) Details of the abaxial side of the involucre bracts with biserial glandular trichomes and long filamentous hairs. (**e**) General view of the involucre bracts (adaxial sides). (**f**) Details of the apical portion of the abaxial side of an involucre bract. (**g**) General view of a disk floret subtended by an interfloral scale. (**h–j**) Interfloral scale: general view (**h**), details of the median portion (**i**), and of the apical portion (**j**) of the abaxial side. (**k–m**) Disk floret: general view (**k**), details of the ovary (**l**), and of the apical portion (**m**) of the corolla. Scale bars: 200  $\mu\text{m}$  (**a–f,g,h,k**); 100  $\mu\text{m}$  (**i,j,l**); 50  $\mu\text{m}$  (**m**).



**Figure 4.** SEM micrographs showing the pistillate ray florets of the *capitulum* of *Achillea moschata*. (**a,b**) General view of a ray floret: abaxial (**a**) and adaxial (**b**) sides. (**c,d**) Details of the proximal portion of the corolla tube and of the distal portion of the ovary: abaxial (**c**) and adaxial (**d**) sides. (**e**) Biserial, 10-celled glandular trichomes on the distal portion of the ovary. (**f**) Details of the 2-lobed stigma with a papillose surface. (**g**) Epidermis of the ligule adaxial side with elongated puzzle-like striated cells. (**h**) Epidermis of the ligule adaxial side with isodiametric conical striated cells. Scale bars: 500  $\mu\text{m}$  (**a,b**); 100  $\mu\text{m}$  (**c,d**); 20  $\mu\text{m}$  (**e,f**); 10  $\mu\text{m}$  (**g,h**).

### 3.3. Histochemistry

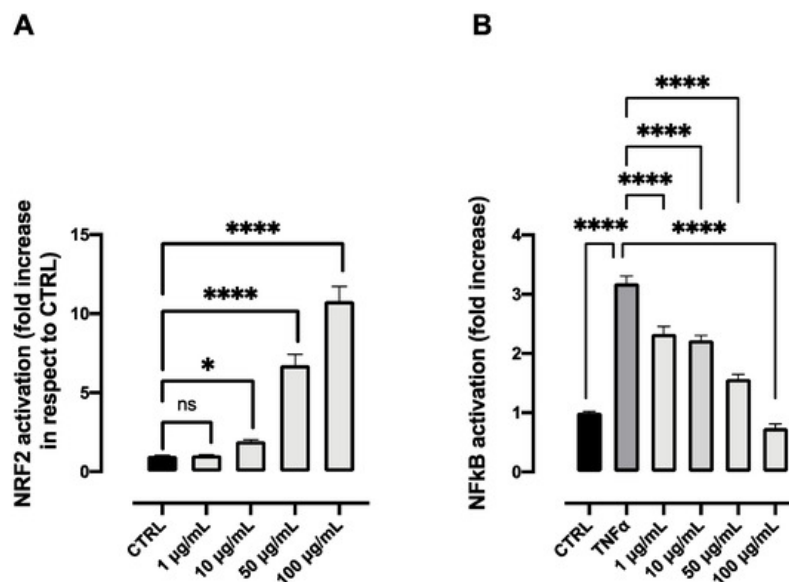
The secretion products of the biserial glandular trichomes exhibited positive responses both to lipophilic tests, such as Fluoral Yellow-088 and Nadi reagent (**Figure 5a,b**), and to the  $\text{FeCl}_3$  test (**Figure 5c,d**), specific to polyphenols, and to the  $\text{AlCl}_3$  test (**Figure 5e**) and Naturstoff reagent A specific to flavonoids. They showed weak coloration or negative responses to the hydrophilic dyes Alcian Blue (**Figure 5f**) and Ruthenium Red. Concerning internal tissues, the histochemical observations turned out to be uneven, since the results were generally negative for all the employed dyes, with sporadic weak positive responses only for polyphenols. Only one previous histochemical investigation was performed on a congeneric species, *A. millefolium*, and the production of monoterpenes was ascertained [17]. The secretory products are released externally after cuticle rupture: the volatile terpenoids emitted in the air are responsible for the typical aroma of *A. moschata*, while the polyphenolic/flavonoidic components presumably cover the epidermis constituting epicuticular exudates. Considering the overall micromorphological results, researchers exclude the presence of internal secretory structures, as well as the massive accumulation at tissue level of the polyphenols and flavonoids detected in the aqueous and methanolic extracts. The main sites of synthesis, accumulation, and release of such substances, along with volatile terpenoids, were represented by the biserial glandular trichomes, distributed on the whole plant epidermal surfaces, being particularly abundant on the inflorescences (involucral bracts, interfloral scales, corollas, and ovaries of both disk and ray florets).



**Figure 5.** LM and FM micrographs showing the histochemical results on the secretory materials of the biserial glandular trichomes of *Achillea moschata*. (**a,b**) Nadi reagent. (**c,d**) Ferric Trichloride test. (**e**) Aluminum Trichloride test. (**f**) Alcian Blue test. Scale bars: 30  $\mu\text{m}$  (**a,b,e,f**); 50  $\mu\text{m}$  (**c,d**).

## 4. Biological Activity

The aqueous extract was evaluated for its antioxidant and anti-inflammatory potential in two different cell lines. Regarding the antioxidant activity, researchers tested the ability of the extract to activate the response of NRF2, a transcription factor associated with antioxidant enzymes, and which plays a master role in redox homeostasis in the cells. Data reported in **Figure 6A** show significant increase of NRF2 activation compared to the control. The activity is already significant at 10  $\mu\text{g/mL}$ , while at the highest tested dose, 100  $\mu\text{g/mL}$ , the increment is even higher than the one registered with BDX (Bardoxolone), a synthetic NRF2 activator used as a positive control. Concerning the anti-inflammatory activity, **Figure 6B** highlights some remarkable results. Indeed, the extract was able to significantly decrease the inflammatory response due to the stimulation of  $\text{TNF}\alpha$  already at 1  $\mu\text{g/mL}$ , while at 100  $\mu\text{g/mL}$ , the response was comparable to control values. Cell viability was assessed and found to be comparable to the control values in both cell lines for all the tested concentrations (data not shown).



**Figure 6.** NRF2 activation (A) and anti-inflammatory activity (B) of different concentrations of the aqueous extract obtained from the flower head of *Achillea moschata*. Data are reported as mean  $\pm$  SD. The statistical significance difference of each concentration in respect to the control was analyzed by one-way ANOVA followed by the Bonferroni post-test. \*  $p < 0.05$ , \*\*\*\*  $p < 0.0001$ , ns = not significant.

Notably, it was the first time that these biological activities were reported in vitro for the aqueous extract of *A. moschata*. The antioxidant activity of *A. moschata* was previously reported using the DPPH assay, demonstrating, in in vitro conditions, a direct radical scavenging activity of the polyphenolic constituents of the species [9]. However, it is now well established that in in vivo conditions, the scavenging of radicals by polyphenols, and in general by antioxidants, cannot occur due to kinetic constraints (with the exception of vitamin E as a scavenger of lipid peroxyl radicals) [28]. Hence, the in vivo antioxidant defense of small antioxidants, such as polyphenols, is not due to a direct radical scavenging mechanism but rather to the activation of the NRF2 (NF-E2-related factor 2) signaling pathway which upregulates the enzymatic removal of the precursors of radical species, such as hydroperoxides, in two-electron redox reactions. researchers demonstrated herein the ability of polyphenols from *A. moschata* to activate the NRF2 pathway, a mechanism which could result in an in vivo antioxidant defense mechanism.

For the anti-inflammatory activity, an in vitro study was conducted on the aqueous extract by Vitalini et al. [9] on CaCo-2 cells focusing on the modulation of the release of interleukins. However, the novelty of the work regarding the study of the anti-inflammatory mechanism, which once activated, led to an anti-inflammatory response of which the release of inflammatory interleukins is one of the effects. The activation of NFkB is only partially related to the transcription of interleukins; it is responsible for numerous other mediators [29]. A strict crosstalk between inflammation and oxidative stress and between the two transcriptional factors involved, NFkB and NRF2, is now well established. When inflammation occurs as a primary disorder, it induces oxidative stress as a secondary disorder, which can further enhance inflammation. On the other hand, when oxidative stress is induced, inflammation develops as a secondary disorder and further enhances oxidative stress [30][31]. Based on this mechanism, the anti-inflammatory activity of the aqueous extract could be related not only to its action on the NFkB pathway, but also to the activation of NRF2. Because of the striking importance these two pathways have in the regulation of anti-inflammatory and antioxidant processes, it is notable that the aqueous extract is able to significantly work even at low concentrations on both processes.

Regarding the previous studies on the potential biological activity of *A. moschata* extracts [9][11][12][15], the phenolic profile was generally investigated concerning antioxidant and anti-bacterial properties. Once again, the tested activities rarely considered the traditional uses, or they did not describe them properly [9][15]. Moreover, even in such cases as these, the tested extracts deviated from the traditional remedies documented in the considered ethnobotanical studies.

With reference to the composition of the hot aqueous extract, which faithfully reproduces the decoction traditionally used and which was firstly characterized, researchers proposed hereafter some considerations on the available literature data. Regarding the biological activity, researchers performed a survey with special focus on the gastrointestinal tract. The scientific literature documented an interesting in vitro anti-inflammatory ability ascribable to some of the main compounds found in the aqueous and methanolic extracts. As for the mechanisms, a few studies conducted on apigenin 7-glucoside (15) and chlorogenic acid (2) recorded important antioxidant and radical scavenging activities. The inhibition of the expression and translocation of Nuclear factor-kappa B (NF-kB) and of the production of pro-inflammatory cytokines, such

as Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and Interleukin-8 (IL-8), was also detected [32][33][34][35][36][37]. Apigenin 7-glucoside was also considered as a potential candidate against gastric cancer progression [38], due to the positive modulation of intracellular Reactive Oxygen Species (ROS) production. Moreover, some authors attributed to chlorogenic acid the healing properties of *Taraxacum* spp. on gastrointestinal disorders such as dyspepsia and gastritis [39]. The inhibition of the nuclear translocation of NF- $\kappa$ B, with the subsequent dwindling of COX-2 gene expression and of Prostaglandin E2 (PGE2) production, could be the mechanism underlying the anti-inflammatory activity of dicaffeoylquinic acids (13). In addition, another mechanism can be considered, namely, the inhibition of the expression of Inducible Nitric Oxide Synthase (iNOS) and the production of Nitric Oxide (NO) [40][41]. Karbab et al. [42] ascribed to isorhamnetin 3-O-beta-glucoside, which is one of the potential compounds for peak number 16, anti-inflammatory properties related to the inhibition of protein denaturation. Little has been reported on compound number 22, apigenin 7-malonyl-glucoside, which characterizes the aqueous extract. Han et al. [43] showed that it is one of the potential NF- $\kappa$ B inhibitor activity components of *Flos Chrysanthemi*, while Martínez-Vázquez et al. [44] described a sedative effect of the *Dracocephalum moldavica* L. aqueous extract with a high content of apigenin- and luteolin 7-malonyl-glucosides. Malonyl-glucosides can either be hydrolyzed in the gastrointestinal tract up to their relative glucosides [45], or absorbed in their intact form [46], thus exerting their activity in both conditions.

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