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Quality assessment of *Andrographis paniculata* products reveals significant labelling inaccuracies and contaminations

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Summary

BACKGROUND: *Andrographis paniculata* products have gained in popularity for the management of respiratory infections since the COVID-19 pandemic. None of these products holds marketing authorisation and all are sold as herbal food supplements. Current herbal food supplement regulations generally do not impose quality assessments prior to commercialisation, such that the quality of herbal food supplements available to consumers is largely unknown.

STUDY AIM: To assess the quality, purity and labelling accuracy of *A. paniculata*-containing products, focusing on andrographolide content (the pharmaceutically active component) and the presence of contaminants and residues.

METHODS: Forty *A. paniculata*-containing products were purchased from 13 countries: 13 from pharmacies and 27 from online retailers readily accessible to consumers in Switzerland. Samples were analysed using ultra-high-performance liquid chromatography–ultraviolet (UHPLC-UV) and ultra-high-performance liquid chromatography–mass spectrometry (UHPLC-MS) based on the European Pharmacopoeia method. Contaminants and residues were assessed using inductively coupled plasma mass spectrometry and gas chromatography–mass spectrometry, respectively.

RESULTS: All samples except one contained *A. paniculata*. The measured daily dose of andrographolide was compared to the labelled dose. Andrographolide content ranged from 29% to 174% of the labelled dose, with only 2 products accurately labelled, while 20 were underdosed and 1 overdosed. Two products contained quercetin, which interfered with UHPLC-UV analysis. Additionally, three online-purchased products contained toxic contaminants, including a heavy metal (mercury) or pesticides (strychnine, butralin).

CONCLUSION: This study reveals widespread mislabelling and underdosing in *A. paniculata*-containing food supplements marketed internationally, along with the presence of impurities that pose risks to consumers in products bought online. Regulatory authorities must implement stringent quality controls to ensure consumer safety and product transparency.

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Introduction

One in four people in Switzerland take food supplements, including herbal products [1]. Herbal products are consumed for a variety of purposes, often driven by the perception that they are 'natural', so less harmful than conventional pharmaceutical medicines. Herbal products are considered herbal medicinal products or herbal food supplements depending on whether they are marketed with a health or with a nutritional claim, respectively, as well as the dosage of the pharmacologically active substance [2]. This in turn determines whether they are subject to drug or food regulations [3, 4]. In Europe, several governments, including Switzerland, hold a list of botanicals that can only be commercialised as a herbal medicinal product and not a herbal food supplement, mainly because of safety concerns [5].

Despite their widespread use, herbal food supplements are generally not subject to safety or quality assessment before commercialisation, so their quality depends on the manufacturer [3]. Also, the regulatory framework for herbal food supplements differs from country to country and is generally less rigorous than that of herbal medicinal products [3]. Concerns have been raised about the safety of various herbal products, including unsanitary manufacturing conditions, adulteration, plant misidentification, contamination with heavy metals or pesticides, and inaccurate labelling [6, 7]. Despite this, few high-quality studies have assessed the quality and safety of herbal food supplements.

ABBREVIATIONS

A. paniculata	*Andrographis paniculata*
HPLC	high-performance liquid chromatography
MS	mass spectrometry
UHPLC	ultra-high-performance liquid chromatography

Andrographis paniculata is an Asian medicinal plant primarily used in traditional medicine to treat respiratory infections [8, 9]. *A. paniculata* is currently available worldwide, but only as a herbal food supplement [10]. Andrographolide, the main component and the pharmaceutically active substance, is thought to have anti-inflammatory, antiviral and immunity-stimulating properties [11]. A systematic review and meta-analysis of randomised controlled trials suggested that *A. paniculata* extract (an andrographolide dose of 60 mg/day) may reduce the severity and frequency of cough symptoms of upper respiratory tract infections [12, 13], but robust clinical evidence is still lacking [9]. More recently, the Thai government recommended *A. paniculata* as a remedy for mild cases of SARS-CoV-2 infections [14], leading to a surge in consumption, including in Western countries where it was already used for the symptomatic treatment of the common cold [15], sometimes outpacing regulatory oversight.

We investigated the quality and purity of herbal products marketed as containing *A. paniculata*, obtained from pharmacies or purchased online internationally – including from Switzerland – focusing on contaminants (heavy metals) and residues (pesticides). We developed an analytical approach based on ultra-high-performance liquid chromatography (UHPLC) combined with two independent detection methods – mass spectrometry (MS) and ultraviolet (UV) – to analyse 40 commercially available *A. paniculata*-containing products.

Materials and methods

The sample of herbal products containing *Andrographis paniculata*

Between 3 February and 18 August 2023, 40 products containing *A. paniculata* were purchased by the investigators and analysed before their expiry date. Of these, 13 were purchased opportunistically directly from pharmacies (Ph) in seven countries, including Switzerland, and 27 were ordered from online sources (On) accessible from Switzerland (table 1). To be included in the study, the product had to mention *A. paniculata* on its labelling and had to be intended for oral use. One pack of each product was purchased, and the brand name, place of purchase, formulation, indications, labelled dose of *A. paniculata* and andrographolide per serving, recommended dosages, Good Manufacturing Practice certification from the manufacturer, and cost per pack were recorded.

Pharmacy-purchased products

Pharmacies selling products containing *A. paniculata* were identified opportunistically in seven countries in Europe, Asia and North America. Countries, and consequently pharmacies, were selected based on their proximity to the authors' places of residence or locations visited for professional or personal reasons. Researchers, acting as lay customers, purchased *A. paniculata* over the counter for health reasons. Pharmacy staff were unaware that these samples would be analysed for research purposes. Products were purchased based on the pharmacist's recommendation; the investigators did not request a specific brand. In Switzerland, some formulations of *A. paniculata* require a medical prescription, so these products were obtained directly by traditional Chinese medicine physicians or therapists.

Online-purchased products

A. paniculata-containing products were also ordered online for delivery to Switzerland. The online search was conducted using three different search engines: Google, Ecosia and Bing. Search terms used were: "Andrographis", "Andrographis paniculata", "Kalmegh" (the Thai name of *A. paniculata*), "Buy Andrographis" and "Andrographis dietary supplements". The first author clicked on the hyperlinks from the first results page of each search engine, which led directly to company websites selling *A. paniculata*-containing products. All such products available on these websites were purchased, without setting a maximum number of products per site. Product labels were not considered during the selection process.

Chemicals and extracts

In this study, the reference extract of *A. paniculata* was sourced from the United States Pharmacopeia (USP; Rockville, MD, United States). Standard reference compounds, including andrographolide, neoandrographolide and andrographiside, were purchased from Merck Sigma Aldrich (Saint Louis, MO, United States). Quercetin was procured from Fluka (Buchs, Switzerland). All references are reported in supplementary file 1 in the appendix, available for download as separate file at https://doi.org/10.57187/s.4728.

Laboratory analyses

For each *A. paniculata* product, analyses were performed in triplicate.

Qualitative assessment of Andrographis paniculata

The qualitative evaluation of *A. paniculata* was carried out in all 40 products (solids and liquids) using ultra-high-performance liquid chromatography (UHPLC)–high-resolution mass spectrometry (HRMS), which identifies compounds based on their retention time (RT) and exact mass *(m/z)* (method detailed in supplementary file 2 in the appendix (available for download as a separate file at https://doi.org/10.57187/s.4728). Sample preparation is described in the appendix, supplementary file 3. A reference extract of *A. paniculata* was used to authenticate products by providing a characteristic chemical signature (supplementary file 1 in the appendix). The identity of the three most intense peaks was confirmed using exact mass and pure standards of andrographolide, neoandrographolide and andrographiside.

Quantification of andrographolide

The quantity of andrographolide was measured in 33 solid products, while liquid samples were excluded due to insufficient content information. Analysis was performed using ultraviolet and mass spectrometry detection, as detailed in the appendix (supplementary file 4 in the appendix). HPLC-UV, the European Pharmacopoeia reference method, is widely used by manufacturers for quantifying

bioactive compounds in plant-based supplements due to its accessibility [16]. Mass spectrometry detection was employed to resolve co-eluting signals inherent to complex matrices, ensuring greater selectivity.

Analysis of contaminants and residues

All 40 samples were analysed for the presence of contaminants and residues. Measurements for heavy metals and pesticides were performed at an accredited laboratory (ISO 17025). For the identification and quantification of heavy metals, the samples were prepared using a method involving high-pressure microwave-assisted acid digestion. Arsenic, lead, cadmium, mercury and nickel were analysed using inductively coupled plasma mass spectrometry (single-quadrupole inductively coupled plasma–mass spectrometry [ICP-MS]). The assay detection range for arsenic was 0.01–0.4 mg/kg dry matter; for lead, it was 0.003–0.4 mg/kg (dry matter); for cadmium, 0.002–0.4 mg/kg mg/kg (dry matter); for mercury, 0.005–0.4 mg/kg (dry matter); and for nickel, 0.1–0.4 mg/kg (dry matter). More-concentrated samples were diluted in accordance with these detection ranges. Pesticides were extracted using the QuEChERS method and subsequently analysed by liquid chromatography-mass spectrometry/mass spectrometry [17].

Labelled and measured daily doses of andrographolide

For each solid *A. paniculata* product with complete labelling, we calculated the labelled daily dose by multiplying the single serving dose by the maximum daily servings (dosage) given on the labelling. We calculated the

Table 1:
Characteristics of *Andrographis paniculata*-containing products obtained from labelling and estimated daily dose of *Andrographis paniculata* and andrographolide.

Product code	Country of purchase/ dispatch	Formulation	Manufacturer claims GMP compliance?	Number of other ingredients	Maximum daily dosage	Daily dose of, mg/ day *	Daily dose of andrographolide, mg/day *
Ph1	Switzerland	Powder	No	0	NA	NA	NA
Ph2	Switzerland	Capsule	No	0	6	720	NA
Ph3	Switzerland	Tablet	No	4	2	200	20
Ph4	France	Capsule	No	11	4	200	10
Ph5	USA	Capsule	Yes	0	1	400	80
Ph6	USA	Capsule	No	0	2	1600	48
Ph7	Germany	Capsule	No	0	2	700	35
Ph8	USA	Capsule	No	0	2	800	60
Ph9	Luxembourg	Capsule	No	0	2	1000	100
Ph10	USA	Capsule	Yes	0	3	1200	120
Ph11	Thailand	Capsule	No	0	3	600	180
Ph12	Canada	Capsule	Yes	0	3	1200	120
Ph13	Switzerland	Liquid	No	0	NA	NA	NA
On1	USA	Capsule	Yes	0	6	3000	NA
On2	Belgium	Capsule	Yes	0	6	NA	NA
On3	Germany	Capsule	No	0	2	800	NA
On4	Netherlands	Capsule	No	0	2	800	NA
On5	UK	Capsule	No	0	4	1880	NA
On6	Germany	Capsule	No	0	10	2700	NA
On7	Germany	Capsule	No	0	2	700	35
On8	Poland	Capsule	No	0	4	2000	NA
On9	Austria	Capsule	No	0	2	700	35
On10	Germany	Capsule	Yes	0	1	400	40
On11	USA	Capsule	Yes	0	1	400	80
On12	Lithuania	Capsule	Yes	0	2	800	NA
On13	USA	Capsule	Yes	0	1	400	40
On14	France	Capsule	No	1	6	2250	132
On15	USA	Capsule	Yes	0	2	900	150
On16	France	Capsule	No	0	2	1000	100
On17	Belgium	Capsule	No	0	2	1000	100
On18	USA	Capsule	Yes	0	4	1600	40
On19	Austria	Capsule	No	0	3	900	90
On20	USA	Capsule	Yes	0	3	1200	120
On21	France	Capsule	No	0	6	1800	180
On22	USA	Liquid	No	0	2.8 ml	700	NA
On23	Austria	Liquid	No	0	60 drops	NA	NA
On24	Poland	Liquid	No	0	3 ml	NA	NA
On25	USA	Liquid	No	0	360 drops	NA	NA
On26	USA	Liquid	No	0	80 drops	2857	NA
On27	USA	Liquid	No	0	30 drops	NA	NA

Product codes: Ph = purchased from pharmacies; On = ordered from online sources

GMP: Good Manufacturing Practice; NA: information not available on labelling.

* Calculated as the labelled dose of *Andrographis paniculata* or andrographolide per serving multiplied by the maximum daily number of recommended servings per day.

labelled andrographolide daily dose based on its proportion in the extract. For instance, product *Ph10*'s labelling indicated 400 mg of *A. paniculata* per capsule with 10% andrographolide; with three capsules daily, the labelled doses were 1200 mg and 120 mg, respectively. Similarly, we calculated the measured daily dose of andrographolide for each sample using the average of the triplicate values for both ultraviolet and mass spectrometry methods. For comparison of measured versus labelled daily dose of andrographolide, and versus the daily therapeutic dose, we considered results obtained using UHPLC-UV. However, mass spectrometry results were prioritised when there were substantial differences between these two methods. HPLC-UV is insufficient when it comes to analysing complex matrices such as those based on several plant extracts.

Statistical analyses

We first compared andrographolide quantification results from UHPLC-UV and UHPLC-MS methods by analysing the measured daily dose of andrographolide using a two-tailed student's t-test, Pearson correlation and Bland–Altman analysis, considering p-values <0.05 as statistically significant. We then compared the measured and labelled daily doses, considering any deviations beyond the ±10% pharmacopoeial tolerance as inaccurately labelled [18]. Finally, we assessed whether the measured daily dose in each product met the recommended therapeutic dose (60 mg/day) for upper respiratory tract infections [8].

Ethics

Ethics approval was not required for this study as it did not involve human participants, animal subjects or any other ethical concerns.

Results

Andrographis paniculata-containing products

In this quality control study of 40 herbal products containing *A. paniculata,* 13 were purchased from pharmacies (Ph) and 27 online (On), as detailed in table 1; 24 came from European countries, 15 from the USA or Canada and 1 from Thailand. The cost of a 7-day supply ranged from CHF 10.30 to 67.15 with an average of CHF 27.40.

The majority of products (33/40) were sold in a solid form (mainly capsules), while the remaining 7 were in a liquid form. According to labelling, 37 products had been prepared exclusively with an extract of *A. paniculata*, 1 with a mixture of *A. paniculata* and *Eleutherococcus senticosus* (On14) and 2 with a mixture of plants and vitamins (Ph3 and Ph4). Seventeen products lacked labelling information about the quantity of andrographolide; 14 of these had been purchased online and 3 from pharmacies.

One product (identical brand, packaging and labelling) was unintentionally purchased three times from three different sources (On20, Ph12 and Ph10), and three other products were purchased twice (On7 and Ph7; On11 and Ph5; On17 and Ph9). Despite this, each sample was analysed as an individual product. One product (On1) was received unlabelled, and another product (solid) was excluded from the analysis as it had expired by the time the quality control analyses were performed.

Quality assessment of *Andrographis paniculata* extract

Before analysing products containing *A. paniculata*, we characterised a standardised reference methanolic extract of this plant using UHPLC-HRMS. This analysis revealed the presence of signals attributable to characteristic compounds already described from this plant, belonging to the diterpene lactone chemical family [19] (figure S1 in the appendix, available for download as a separate file at https://doi.org/10.57187/s.4728). The chromatogram showed andrographolide as the most intense peak (RT = 2.06 min, *m/z* 395.2070 $[M+HCOO]^-$, Δ: 0.25 ppm), followed by neoandrographolide (RT = 2.48 min, *m/z* 525.2706 $[M+HCOO]^-$, Δ: 1.20 ppm) and andrographiside (RT = 1.73 min, *m/z* 557.2601 $[M+HCOO]^-$, Δ: 0.54 ppm). These identities were confirmed by comparisons with pure reference standards. Additionally, ultraviolet detection at 220 nm highlighted andrographolide as the compound with significant absorption. Given its status as the literature-established bioactive constituent and its chromatographic predominance, andrographolide was selected as the primary chemical marker for quality control of *A. paniculata*-based products [15].

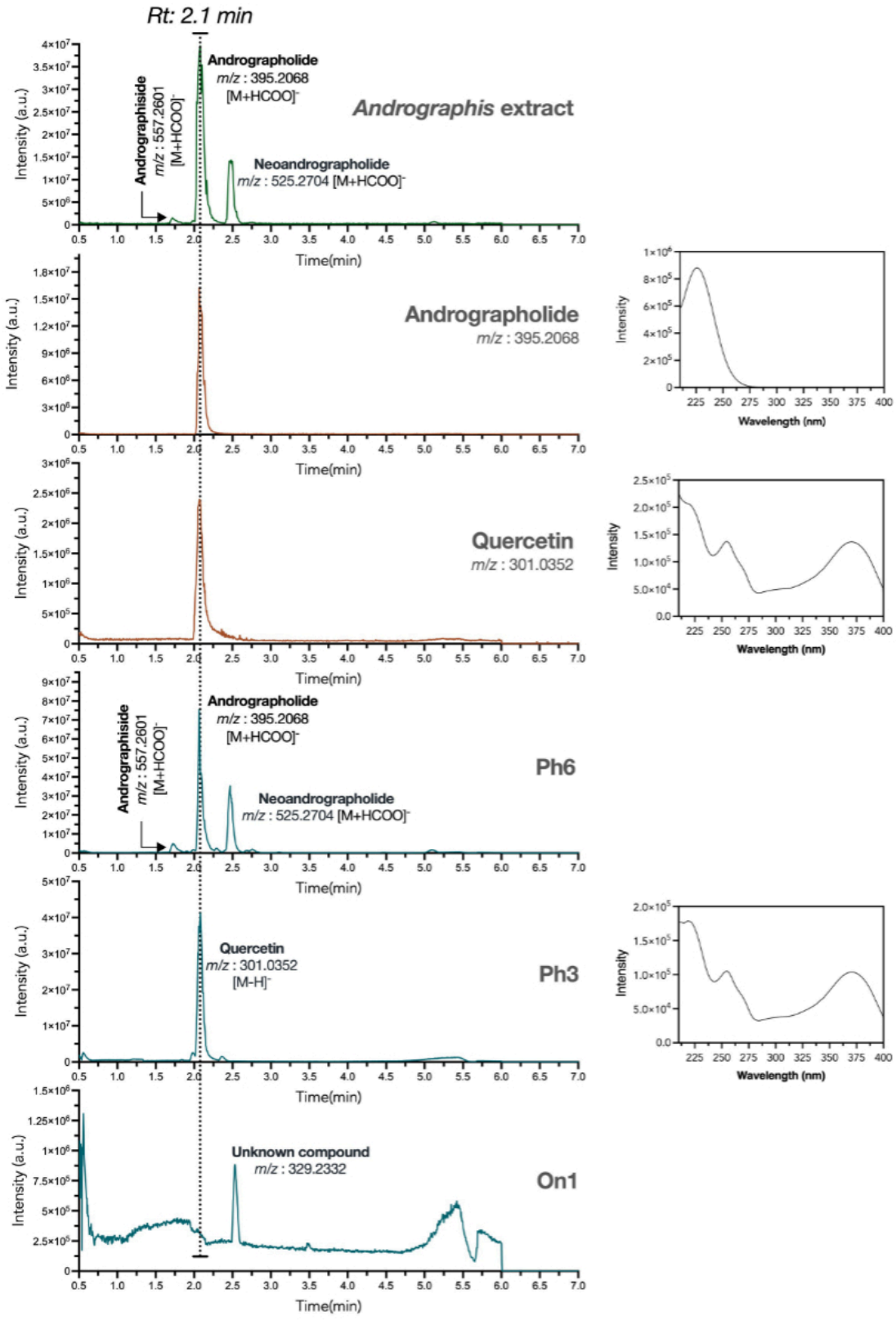
Among the 40 products analysed, only one (On1) lacked the 3 characteristic peaks presented in the appendix (supplementary file 5, figure S1). Most products had a smaller andrographolide peak and a larger neoandrographolide peak than the reference standard. In five products (Ph1, Ph2, On2, On12, On25), neoandrographolide was the most intense analyte.

In addition to the *A. paniculata* extract, Ph3 and Ph4 contained an abundant flavonoid, quercetin. Using high-resolution mass spectrometry, an intense signal of *m/z*: 301.0351 ($[M-H]^-$) was recorded at the very same retention time of andrographolide and unexpectedly corresponded to the exact mass of quercetin. This was corroborated by the ultraviolet detection, which revealed a typical flavonoid ultraviolet spectrum for this peak (figure 1). Finally, the injection of a pure standard of quercetin confirmed co-elution of this compound and andrographolide (detailed further in the appendix, supplementary file 5). To prevent bias in measurement, a mass spectrometry detection method was developed in addition to the standard ultraviolet method.

Quantification of andrographolide

A Bland-Altman plot comparing the measured daily dose of andrographolide using the UHPLC-UV and UHPLC-MS methods is presented in figure 2. These results are comparable ($t(62) = 0.83$, $p = 0.39$) using the two methods, except for two products, Ph3 and Ph4. The Pearson correlation coefficient (r) between the results obtained using the UHPLC-UV and UHPLC-MS methods was 0.44 overall ($p \leq 0.01$) and 0.97 after removing these two outliers ($p < 0.01$). The ultraviolet and mass spectrometry methods produced similar results for most products, independently confirming andrographolide levels (supplementary file 6 in the appendix, figure S2). The UHPLC-UV method was deemed reliable for the quantification of andrographolide, except for samples Ph3 and Ph4, where quercetin interference skewed the results. In such cases, the UHPLC-MS method proved more accurate.

Figure 1: UHPLC-PDA-HRMS chromatograms, comparing standardised extract of *Andrographis paniculata* (green trace) vs marketed herbal products (blue traces) and pure standards (orange traces). Andrographolide and quercetin were found to elute at the same retention time (rt: 2.1 min) but were unequivocally discriminated after their exact mass. Various herbal products differed in chemical content: Ph6 resembled *A. paniculata* extract, Ph3 contained andrographolide with a dominant quercetin signal and On1 lacked characteristic *A. paniculata* signals. HRMS: high-resolution mass spectrometry; On: online; PDA: photo diode array; Ph: pharmacy; UHPLC: ultra-high-performance liquid chromatography.



For 20 of 23 products with complete labelling, the measured daily dose of andrographolide was lower than that claimed on the labelling (figure 3). Products purchased online had a higher median labelled daily dose of andrographolide (90 mg/day; range: 35–180 mg) than those from pharmacies (70 mg/day; range: 10–180 mg). The measured dose of andrographolide ranged from 29% to 174% of the labelled dose. Only two products (Ph4 and On13) were accurately labelled, while 91% of products were inaccurately labelled. In one case (On18), the measured dose exceeded the labelled amount; this discrepancy was not explained by a high-dosage regimen.

Of the 33 products in solid form, the labelled daily dose of andrographolide ranged from 10 mg to 180 mg per day. As displayed in figure 3, the measured daily dose of nine products (27%) reached at least 60 mg of andrographolide, which is the recommended therapeutic dose for upper respiratory tract infections [8]. Even though Ph4 and On13were labelled correctly, they did not reach the therapeutic dose. The daily dose of andrographolide varied from batch to batch within products of the same brand, as shown with products On7 and Ph7(20.3 mg vs 29.4 mg); On11 and Ph5 (27.2 mg vs 23.1 mg); On17 and Ph9(67.8 mg vs 56.5 mg). Twelve of the 33 solid products claimed to have been manufactured in accordance with Good Manufacturing Practice in their labelling. Of these, only On18 and On20 reached the therapeutic dose of andrographolide, and On13 was accurately labelled. There was no pattern observed between labelling accuracy and country of origin.

Analysis of contaminants and residues

Of the 40 *A. paniculata*-containing products analysed, we identified levels of mercury that exceeded the maximum

Figure 2: Bland-Altman plot of measured andrographolide using UHPLC-MS versus UHPLC-UV expressed in daily dose for each product purchased in a pharmacy or online. The solid line represents the mean difference and the dashed lines represent the limits of agreement (mean difference ± 1.96 standard deviations). MS: mass spectrometry; UHPLC: ultra-high-performance liquid chromatography; UV: ultraviolet.

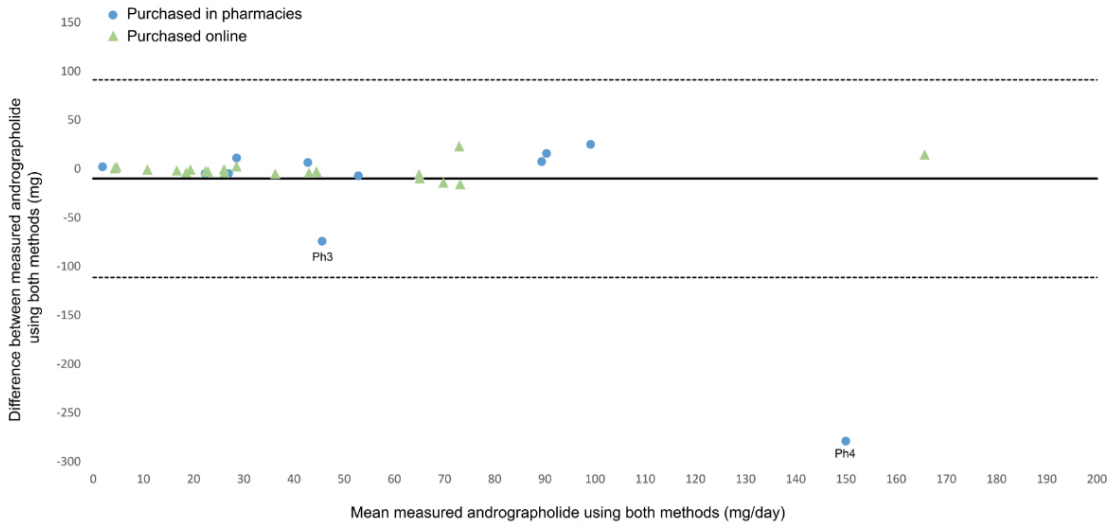
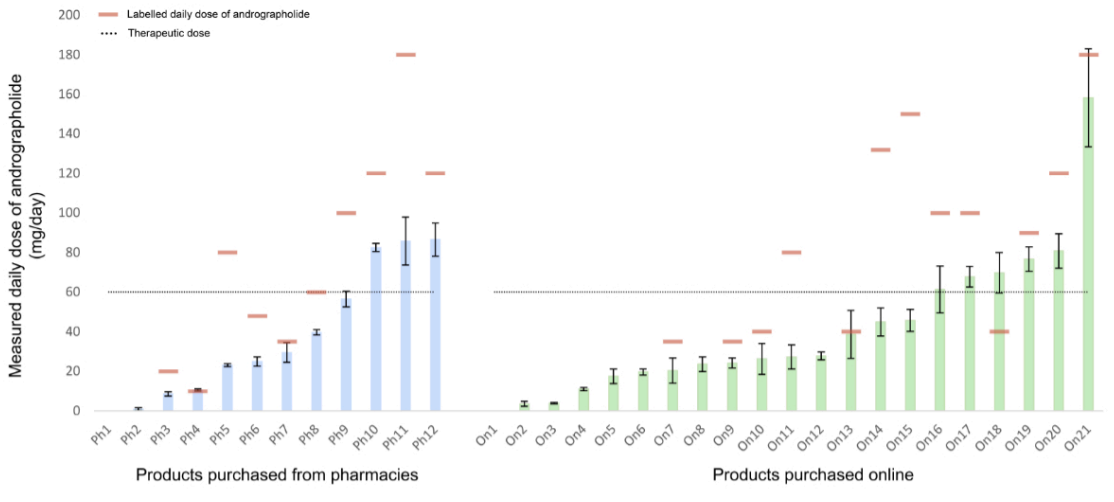


Figure 3: Daily dose of andrographolide measured with UHPLC-UV in pharmacy products (light blue bars) and online products (light green bars) compared with those on the label (red dash) and with the therapeutic dose (dotted line). The data are from three product replicates ± standard deviation (SD). UHPLC: ultra-high-performance liquid chromatography; UV: ultraviolet. * no information about daily serving; ** no andrographolide detected.



authorised levels in one product and another two products contained contaminants (pesticides) (table 2). These three products had all been purchased online. Product On5 contained 0.153 mg/kg of mercury (maximum tolerated according to the European legislation: 0.100 mg/kg), product On19 contained 0.023 mg/kg of butralin and On8 contained 0.058 mg/kg of strychnine. Butralin and strychnine are both pesticides banned throughout Europe [20, 21].

Discussion

In this quality control study of 40 *A. paniculata* herbal products sourced from pharmacies worldwide and online retailers available to Swiss consumers, the majority were found to be of poor quality, including products claiming to have been made according to Good Manufacturing Practice guidelines. All products except one, which was delivered without a label, contained *A. paniculata*. For most products, the quantity of andrographolide was substantially lower than that indicated on the product's labelling and only one third met the recommended daily therapeutic dose of andrographolide for upper respiratory tract infection. The presence of quercetin in two products further complicated accurate andrographolide quantification. Quercetin, which was listed as an ingredient on the label of these two products, is commonly used as a food supplement for its potential antioxidant and anti-inflammatory properties and is regarded as safe at moderate doses (≤1000 mg/day) [22]. However, it may have been used as an adulterant to

Table 2:
Levels of heavy metals and pesticide residues detected in products containing *Andrographis paniculata*.

Product code	Heavy metal (mg/kg) (ICP-MS)					Pesticides (mg/kg) (LC-MS/MS)	
	Arsenic (As) (max: NA)	Lead (Pb) (max: 3.0)	Cadmium (Cd) (max: 1.0)	Mercury (Hg) (max: 0.1)	Nickel (Ni) (max: NA)	Strychnine	Butralin
Ph1	0.16	0.113	0.085	0.006	2.1	ND	ND
Ph2	0.17	0.116	0.086	ND	2.2	ND	ND
Ph3	0.02	0.017	ND	ND	0.6	ND	ND
Ph4	0.06	0.044	0.015	0.010	0.3	ND	ND
Ph5	0.03	0.098	0.005	ND	1.3	ND	ND
Ph6	0.22	0.183	0.132	ND	2.2	ND	ND
Ph7	0.02	0.008	ND	ND	1.0	ND	ND
Ph8	0.04	0.091	0.012	ND	1.3	ND	ND
Ph9	0.07	0.015	0.004	ND	2.8	ND	ND
Ph10	0.03	0.062	0.003	ND	0.3	ND	ND
Ph11	0.01	0.038	0.003	ND	1.0	ND	ND
Ph12	0.18	0.177	0.018	ND	1.3	ND	ND
Ph13	0.02	0.017	0.010	ND	0.3	ND	ND
On1	0.91	1.46	0.181	0.015	2.5	ND	ND
On2	0.33	0.209	0.087	ND	2.6	ND	ND
On3	0.03	0.006	0.005	ND	1.0	ND	ND
On4	0.71	1.50	0.040	0.020	10.3	ND	ND
On5	0.14	0.766	0.051	**0.153**	2.3	ND	ND
On6	0.08	0.266	0.038	0.009	1.8	ND	ND
On7	0.02	0.010	0.004	ND	1.0	ND	ND
On8	1.36	0.953	0.428	0.023	1.4	**0.058**	ND
On9	0.02	0.007	0.003	ND	1.0	ND	ND
On10	0.03	0.115	0.008	ND	1.2	ND	ND
On11	0.03	0.134	0.006	ND	1.7	ND	ND
On12	0.04	0.027	ND	ND	0.2	ND	ND
On13	0.08	0.023	0.010	ND	0.8	ND	ND
On14	0.11	0.054	0.096	ND	3.2	ND	ND
On15	0.17	0.052	0.107	ND	5.0	ND	ND
On16	0.03	0.056	0.005	ND	0.2	ND	ND
On17	0.07	0.017	0.005	ND	3.0	ND	ND
On18	0.03	0.065	0.004	0.007	0.4	ND	ND
On19	0.06	0.030	0.002	ND	0.9	ND	**0.023**
On20	0.03	0.060	0.005	0.006	0.4	ND	ND
On21	0.03	0.056	0.004	ND	1.0	Below LOQ	ND
On22	0.01	0.010	0.013	ND	0.9	ND	ND
On23	ND	ND	ND	ND	ND	ND	ND
On24	ND	0.003	ND	ND	ND	ND	ND
On25	ND	ND	ND	ND	0.9	ND	ND
On26	ND	0.015	0.004	ND	0.4	ND	ND
On27	ND	ND	ND	ND	0.2	ND	ND

Product codes: Ph = purchased from pharmacies; On = ordered from online sources

ICP-MS: inductively coupled plasma–mass spectrometry; LC-MS: liquid chromatography–mass spectrometry; LOQ: limit of quantification; MS: mass spectrometry; NA: non-available; ND: non-detectable.

falsely enhance the peak of andrographolide, as both compounds share the same retention time when analysed with the pharmacopoeial reference method. Alarmingly, three products purchased online contained toxic contaminants: one exceeded European safety limits for mercury and two others contained pesticide residues of strychnine and butralin, substances banned or heavily regulated in the European Union, Switzerland and the US [21]. Even though the measured doses of each contaminant were well below the lethal dose, this finding represents a serious breach of safety standards [20]. As no safe threshold has been established for butralin or strychnine, it cannot be excluded that the two products in which these pesticides were detected may pose health risks, even at low exposure levels.

The levels of the characteristic compounds – namely andrographolide, andrographiside and neoandrographolide – varied among the products analysed. This finding is consistent with previous studies, and is likely attributable to differences in extraction methods and plant parts used [23, 24]. Standardising the extraction process would help ensure consistent composition and quality of plant-based products. Our findings of inaccurate labelling of *A. paniculata*-containing products are consistent with previous studies on other food supplement products purchased online or from a single country. In these studies, 25% to 88% of herbal products, including *Curcuma longa* (turmeric)and *Lavandula angustifolia* (lavender), were inaccurately labelled due to suspected adulteration and/or a quantity of the active substance that was not within ±10% of the labelled dose [25–27]. Other studies of products containing *Hypericum perforatum* and *Rhodiola rosea* showed inaccurate labelling and the presence of contaminants in products sold as herbal food supplements, but not in products containing the same herb but sold as herbal medicinal products [28, 29]. Regarding contaminants, a case of strychnine contamination has previously been reported in *Panax ginseng* (ginseng)-containing herbal products [30]. In our study, although the mercury level exceeded the maximum authorised limit in one herbal product, the overall proportion of affected samples remained lower than that reported in a large-scale study assessing the quality of herbal products purchased in China, where nearly one third of products contained at least one heavy metal above safety thresholds [31]. A similar difference was previously reported, with herbal food supplements manufactured in China showing higher heavy metal levels than those from North America [32]. While our findings only apply to products containing *A. paniculata*, similar issues are likely to affect other herbal food supplements.

In most countries, herbal food supplements can be purchased over the counter in pharmacies, health food stores or on the internet, like other food supplements. Unlike herbal medicinal products, which are regulated by the same drug regulators as any other medical drug, herbal food supplements do not require proof of safety or efficacy before being marketed in Switzerland, Europe or the US [3]. In addition, once marketed, the quality of herbal food supplements is not controlled, in contrast to herbal products marketed as herbal medicinal products. Manufacturers in certain countries such as the US are expected to comply with Good Manufacturing Practice guidelines and to display this on their labelling. However, our findings showed that even *A. paniculata*-containing products with Good Manufacturing Practice labels can be inaccurate. The distinction between regulations applied to herbal food supplements and herbal medicinal products may not be clear to the general public, making it difficult for consumers to assess the quality of herbal food supplements they buy. Physicians and pharmacists should be informed of this and educate patients about the risks of buying herbal food supplements or other products online, particularly due to the risk of ingesting contaminants and residues that they would not otherwise encounter. Clinicians should also actively enquire about herbal food supplement consumption by their patients, particularly in situations of unexplained symptoms or suspected intoxication. Moreover, it is possible that a prescribed herbal product fails to have the expected effect on the clinical course of a disease because it is underdosed and the prescriber and the patient have no way of knowing that this is the reason for lack of efficacy.

To improve consumer safety, stronger regulation of locally marketed herbal food supplements is needed. Since *A. paniculata* is only available as a herbal food supplement, introducing a herbal medicinal product version would ensure higher product quality. However, applying the same strict standards as herbal medicinal products could disadvantage small manufacturers, reducing product availability and pushing consumers towards lower-quality alternatives. A balanced solution would be third-party certification to verify product quality, helping consumers make informed choices. In the US, voluntary certification programmes such as ConsumerLab.com, NSF International and US Pharmacopeia already help ensure the quality of herbal food supplements. Expanding similar initiatives globally could enhance consumer protection while maintaining accessibility to herbal products.

We acknowledge several limitations of our study. First, these 40 products are not meant to be representative of all herbal products sold online or in pharmacies in Switzerland or abroad. The overall sample size was modest, with most brands of *A. paniculata*-containing products represented by only one batch sample, which may not capture overall variability. Second, the pharmacies and websites where these samples were obtained were selected opportunistically rather than randomly. While it is not feasible to analyse all such products on the market at such a high standard, our results indicate a pattern that we believe would hold with a larger sample size. Additionally, our analyses were conducted with on an international sample using two robust analytical methods, ensuring the accuracy and validity of our results. Finally, since we only quantified andrographolide in solid forms, our findings may not apply to products in other forms.

Our study highlights the poor quality of most *A. paniculata*-containing herbal products sold as herbal food supplements, even when compliance with Good Manufacturing Practice is claimed. The frequent mislabelling of *A. paniculata*-containing products should alert clinicians, pharmacists and regulatory authorities. The general public should be aware of the risks associated with ordering products online, including ingesting potential contaminants and residues. We emphasise the need for stricter yet pragmatic regulation of the global herbal food supplements market and, amid varying regulatory frameworks worldwide, we

propose that a standardised labelling system be used to identify products whose quality has been independently verified.

Data sharing statement

Deidentified data derived from analysed samples will be made available upon reasonable request from qualified researchers whose proposed use of the data has been approved by the investigators and participating institutions. Data will be shared after publication, under a formal data sharing agreement, and only for samples collected and processed in accordance with applicable ethical and regulatory approvals.

Declaration of use of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors – who are not native English speakers – used ChatGPT for proofreading. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

The appendix is available for download as a separate file at https://doi.org/10.57187/s.4728.