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Letter to the Editors

Anything to declare? Possible risks for patients' health resulting from undeclared plants in herbal supplements

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Problems due to poor quality of herbal products continue to be a major international problem. Of particular concern is the deliberate or accidental addition of other plant species or synthetic drugs leading to adverse reactions (AR). As a result, labelling of herbal products may sometimes not accurately reflect their contents, leading to adverse events or interactions attributed to specific herbs, when in fact they are actually due to misidentified plants, mislabelling and/or adulteration. Since producers may include or omit safety information on product labels at their own discretion, labels themselves may lack clinically pertinent information. In this frame, the interpretation of specific ARs to herbal products might also be difficult [1].

During the last 3 years, Florence University Pharmacovigilance system received several reports from patients referring to the unexpected effectiveness of 'Olivis', a dietary supplement marketed in Italy by the company SerVis as an adjunct to hypertension therapy. The declared components of this liquid preparation were extracts of leaves and buds of olive (*Olea europea* L.), leaves, flowers, fruits of hawthorn (*Crataegus oxyacantha* L.), flowers of fumitory (*Fumaria officinalis L.*) and shepherd's purse (*Capsella bursa pastoris* L.). Furthermore an AR report was present in the National Institute of Health phytovigilance database concerning a female patient affected by hypertension, admitted to the hospital after an episode of hypotension and bradycardia. The patient had spontaneously replaced her antihypertensive therapy with 25 Olivis drops day^{-1}. After an episode of hypotension, the dose was reduced to 8 drops day^{-1}, maintaining good blood pressure control. One month later, she suspended the treatment and soon after faced a hypertensive crisis. The patient re-assumed 15 Olivis drops day^{-1}, resulting in good blood pressure control and eventually in the reported AR.

The reported AR raised suspicion as the available data on the ingredients of Olivis did not indicate significant hypotensive effects for olive and hawthorn and several studies on shepherd's purse have shown both lowering and elevation of blood pressure [2]. Therefore the product was analyzed at Florence University Mass Spectrometry Centre and Department of Pharmaceutical Sciences Laboratory, by means of HPLC-ESI-ITMS and NMR, to assess the possible presence of synthetic drugs (ACE inhibitors, β-adrenoceptor blockers, angiotensin II receptor antagonists, calcium channel antagonists, α-adrenoceptor antagonists), as well as undeclared natural compounds with hypotensive activity.

No synthetic drugs were found in the preparation, but analyses showed the presence of indole alkaloids, principally ajmaline and reserpine. The concentration of reserpine in the sample was 1.57 μg ml^{-1}, corresponding to a suggested dose of 3.5–12.0 μg day^{-1}, while the concentration of ajmaline was 861.8 μg ml^{-1}, corresponding to a suggested dose of 1.8–6.5 mg day^{-1}. Since both compounds are absent in label-declared herbal ingredients, addition of an extract from an undeclared Rauwolfia species was suspected [3].

In this case the significant effect observed on blood pressure raised suspicions of possible adulteration of Olivis with synthetic antihypertensive drugs. However, further laboratory investigation revealed that a reserpine/ajmaline containing plant species had been used in the product. Neither of these alkaloids is permitted in food supplements according to Italian regulations. Whilst both of them are effective in lowering blood pressure, only reserpine

was present at an active concentration. Ajmaline is a well-known cardioactive drug with an anti-arrhythmic profile and the potential of induction of bradycardia and hypotension, but its side effects have been reported only after rapid intravenous injection of doses significantly higher than in the present case [4]. Reserpine, while being an authorized drug, is rarely prescribed nowadays due to its poor tolerability and unfavourable safety profile. We concluded therefore that the reported side effects were mainly due to reserpine present in the undeclared plant species.

Information was transmitted to the Italian Ministry of Health, and it arranged for the withdrawal of the product from the market. After some months a new product with a similar composition was marketed by the same producer. A subsequent analysis conducted by us showed no undeclared Rauwolfia species in the new product.

This case highlights the potentially serious health risks posed by the lack of effective controls on the quality of herbal products [5]. Clinicians should be aware of the potential for such cases to arise and the need to take a detailed history of herbal products used by patients. Where ARs to herbal products report significant pharmacological effects which are not expected with the declared herbal ingredients, then undeclared active ingredients are possible and should be fully investigated.

Competing Interests

There are no competing interests to declare.

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