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Adverse events related to herbal dietary supplements and over-the-counter medications containing laxatives: a 10-year update from the Italian Phytovigilance and Pharmacovigilance systems

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Abstract

Introduction. Products containing anthraquinones (AQ) are associated with an increased risk of serious adverse events (AEs). We performed an update of the available evidence retrieved by the spontaneous reports of AE associated with herbal dietary supplement (DS) and over-the-counter medications (OTC-M) used as laxatives.

Methods. Analysis and evaluation of AE reports retrieved from the Italian Phytovigilance and Pharmacovigilance systems was performed from February 2011 to December 2020.

Results. Totally 110 AE reports, 24 related to herbal DS and 86 to OTC-M, were analyzed. Most subjects were females. Herbal products analyzed mostly contained AQ derivatives. Most AEs were gastrointestinal (41.6%), central nervous system (18.2%), and dermatological disorders (12.6%).

Conclusions. The number of AE reports recorded in the last 10 years is still relatively low. However, given the seriousness of some AEs, that does not represent a guarantee of safety. This study may contribute to enhance public awareness on the risks associated with misuse or abuse of laxatives.

Key words

- dietary supplement
- herbal medicinal product
- adverse event
- phytovigilance
- pharmacovigilance

INTRODUCTION

Chronic constipation is a common functional bowel disorder among adults, it is characterized by persistently difficult, infrequent, or incomplete intestinal evacuation, and can originate from several causes [1]. Self-reported constipation and the consequent use of laxatives increase with age [2] and are more common among women [3]. Lifestyle and dietary modifications are considered the first steps in the treatment of chronic constipation. Laxatives, which work by influencing bowel movements and facilitating intestinal evacuation through different mechanisms and often of plant origin,

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are reserved for patients who do not respond to non-pharmacological approaches [1].

Herbal products derived from medicinal plants commonly promoted to treat constipation include aloe (*Aloe* spp.) juice, leaves and fruits of senna (*Cassia angustifolia*, *C. acutifolia*), cortex of *Cascara sagrada*, hypogeal parts of rhubarb (*Rheum* spp.), psyllium husk (*Plantago psyllium*), and radix of liquorice (*Glycirrhiza glabra*) [4]. In Italy, these herbal products are usually marketed as dietary supplements (DS), notified to the Ministry of Health and/or as medications (M), mainly over-the-counter (OTC), registered by the Italian Medicines Agency (AIFA, Rome, Italy).

Herbal DS and OTC-M are generally bought as self-prescription, therefore often without advice from healthcare professionals (i.e., general practitioner, community pharmacist) [5]. In general, DS are marketed with claims of nutritional and physiological effects, whereas OTC-M are authorized for treating or preventing disease, or for restoring, correcting or modifying physiological functions [5].

In Italy, suspected adverse events (AEs) associated with DS are reported to the Italian National Institute of Health (ISS, Rome, Italy) [6], while those associated with OTC-M are notified to the AIFA. The number of AE reports associated with DS has increased in the recent years [7], raising concern among healthcare professionals [8]. Products containing anthraquinones (AQ) derivatives are known to be used primarily worldwide as oral laxatives and have various biological effects, also associated with an increased risk of serious AEs [9, 10].

In 2021, the European Commission has confirmed the adoption of the regulation prohibiting the use of all preparations based on *Aloe* spp., as well as those containing emodin and aloe-emodin, through specific amendment relating to botanical species containing AQ derivatives [11]. Furthermore, as there is the possibility of harmful effects on health associated with the use of *Rheum* spp., *Cassia* spp. and *Rhamnus* and their preparations in DS, such substances were placed under Union safety evaluation [12].

In this context, we performed an update of the available evidence retrieved by the spontaneous reports of AE associated with herbal DS or OTC-M used as laxatives through an analysis of the Italian Phytovigilance and Pharmacovigilance systems.

METHODS

Following our previous publication [4] and considering the new Union legislation [12], this updated analysis of spontaneous AE reports retrieved from the Italian Phytovigilance [6, 7, 13, 14] and Pharmacovigilance [15-20] systems was performed by evaluating all suspected AEs associated with herbal DS or OTC-M used as laxatives recorded from February 2011 to December 2020.

The Italian Phytovigilance system, under the coordination of the ISS, collects spontaneous reports of suspected AEs related to DS, while the Italian Pharmacovigilance system, coordinated by AIFA, collects spontaneous reports of suspected AEs related to OTC-M, allowing also online reporting through two dedicated web sites (www.vigierbe.it and www.vigifarmaco.it).

The following demographic, clinical and pharmacological characteristics were collected and analyzed: (1) patient data (age, sex, and clinical history); (2) suspected DS or OTC-M information (product type, dosages, and duration of treatment); (3) AEs description (criteria of seriousness, dechallenge, rechallenge and outcome); (4) and concomitant treatments if present.

The seriousness of each AE was evaluated according to the World Health Organization (WHO) criteria. The classification by Edward and Aronson was also considered [21]. A comparison between serious and non-serious AEs was performed both for reports submitted to the ISS and AIFA. Moreover, AEs were codified through the Medical Dictionary for Regulatory Activities (MedDRA), described and organized in terms of System Organ Class (SOC) and Preferred Term (PT) [22]. In the phytovigilance and pharmacovigilance fields, "dechallenge" refers to the stopping of the suspected product, usually after an AE [19]. A positive dechallenge refers to the AE disappearing after the stopping of the suspected product. On the contrary, a negative dechallenge refers to the persistence of the AE after the withdrawal of the suspected product. Moreover, "rechallenge" refers to the restarting of the same suspected product. A positive rechallenge refers to the AE recurring after restarting the suspected product. Conversely, if the AE does not recur after the restarting of the suspected product the rechallenge is defined as negative.

A multidisciplinary group, composed of clinical pharmacologists, toxicologists, pharmacists, epidemiologists, and experts in phytotherapy and phytovigilance, evaluated each AE report calculating the causality assessment according to the WHO criteria [23]. When more than one active compound was present in the suspected product (both in the case of DS or OTC-M), the attribution of causality concerned the whole commercial product. The composition of products was reported, excluding excipients, as on the label of the package.

Continuous data were expressed as mean ± standard deviation (SD) and categorical variables were expressed as count or percentages.

RESULTS

Italian National Institute of Health

Up to December 2020, the ISS received a total of 2,365 reports of AE, of which 42 (1.8%) concerned AEs related to herbal DS used to treat constipation. From February 2011 to December 2020, 24 new AE reports were recorded in the Italian Phytovigilance system *(Table 1)*. The mean age of patients was 52±17.3 years, and 62.5% were females. Overall, 66.7% of AE reports were defined as "serious" and required hospitalization, but in one report seriousness was unknown. Healthcare professionals reporting the suspected AEs were mainly physicians (66.7%) and pharmacists (25.0%). Most subjects (54.2%) reported to use herbal DS for constipation. The information on the dosage taken by the patients was compatible with what was reported on the label of the suspected products in 6 AE reports (25.0%), while the dosage was higher in 9 cases

Table 1
Characteristics of patients reporting suspected adverse events to dietary supplements and medicinal products used as laxatives

Characteristics	Italian Phytovigilance System (ISS)			Italian Pharmacovigilance System (AIFA)		
	Overall	Serious[a]	Non-serious[a]	Overall	Serious[b]	Non-serious[b]
	n=24 (%)[c]	n=16 (%)[c]	n=7 (%)[c]	n=86 (%)[c]	n=31 (%)[c]	n=53 (%)[c]
Age (mean ± SD)[d]	52±17.3	51.3±15.9	57.1±19.7	64.9±21.5	60.5±25.4	68.1±18.2
Sex						
Male	9 (37.5)	7 (43.7)	2 (28.6)	36 (41.9)	10 (32.3)	25 (47.2)
Female	15 (62.5)	9 (56.3)	5 (71.4)	50 (58.1)	21 (67.7)	28 (52.8)
Comorbidities						
≥1 comorbidities	11 (45.8)	8 (50.0)	3 (42.9)	35 (40.7)	18 (58.1)	16 (30.2)
No comorbidities	-	-	-	-	-	-
Not reported	13 (54.2)	8 (50.0)	4 (57.1)	51 (59.3)	13 (41.9)	37 (69.8)
Comedications						
≥5 drugs	1 (4.2)	-	1 (14.3)	12 (14.0)	2 (6.5)	10 (18.9)
1-4 drugs	15 (62.4)	9 (56.3)	5 (71.4)	16 (18.6)	9 (29.0)	6 (11.3)
No drugs	1 (4.2)	1 (6.2)	-	-	-	-
Not reported	7 (29.2)	6 (37.5)	1 (14.3)	58 (67.4)	20 (64.5)	37 (69.8)
Reason of use						
Constipation	13 (54.2)	8 (50.0)	5 (71.4)	51 (59.3)	13 (41.9)	38 (71.7)
Abuse	-	-	-	7 (8.0)	7 (22.6)	-
Weight loss	3 (12.5)	3 (18.8)	-	1 (1.2)	-	1 (1.9)
Meteorism	2 (8.3)	2 (12.5)	-	-	-	-
Others	3 (12.5)	2 (12.5)	1 (14.3)	7 (8.0)	4 (12.9)	3 (5.7)
Not reported	3 (12.5)	1 (6.2)	1 (14.3)	20 (23.3)	7 (22.6)	11 (20.7)
Causality assessment						
Definite	-	-	-	-	-	-
Probable	9 (37.5)	7 (43.7)	2 (28.6)	11 (12.8)	10 (32.3)	1 (1.9)
Possible	15 (62.5)	9 (56.3)	5 (71.4)	18 (20.9)	11 (35.4)	6 (11.3)
Unlikely	-	-	-	-	-	-
Not reported	-	-	-	57 (66.3)	10 (32.3)	46 (86.8)
Reporter qualification						
Physician	16 (66.7)	13 (81.3)	3 (42.7)	49 (57.0)	22 (71.0)	27 (51.0)
Pharmacist	6 (25.0)	2 (12.5)	3 (42.7)	22 (25.6)	6 (19.3)	16 (30.2)
Other professional	1 (4.2)	1 (6.2)	-	5 (5.8)	2 (6.5)	2 (3.7)
Patient	1 (4.1)	-	1 (14.2)	8 (9.3)	1 (3.2)	6 (11.3)
Drug company	-	-	-	2 (2.3)	-	2 (3.8)
Outcomes						
Recovered	12 (50.0)	6 (37.5)	6 (85.7)	38 (44.2)	12 (38.7)	26 (49.0)
Improvement	3 (12.5)	1 (6.3)	1 (14.3)	27 (31.4)	12 (38.7)	15 (28.3)
Sequelae	2 (8.3)	2 (12.5)	-	1 (1.1)	1 (3.2)	-
Persistent	1 (4.2)	1 (6.2)	-	3 (3.5)	-	3 (5.7)
Not reported	6 (25.0)	6 (37.5)	-	17 (19.8)	6 (19.4)	9 (17.0)
Latency*						
≤7 days	8 (33.3)	7 (43.7)	-	56 (65.1)	21 (67.7)	34 (64.3)
8-30 days	4 (16.7)	2 (12.5)	2 (28.6)	7 (8.1)	2 (6.5)	5 (9.4)
>30 days	4 (16.7)	1 (6.3)	3 (42.8)	3 (3.5)	1 (3.2)	2 (3.7)

Continues

Table 1
Continued

Characteristics	Italian Phytovigilance System (ISS)			Italian Pharmacovigilance System (AIFA)		
	Overall	Serious[a]	Non-serious[a]	Overall	Serious[b]	Non-serious[b]
	n=24 (%)[c]	n=16 (%)[c]	n=7 (%)[c]	n=86 (%)[c]	n=31 (%)[c]	n=53 (%)[c]
Not reported	8 (33.3)	6 (37.5)	2 (28.6)	20 (23.3)	7 (22.6)	12 (22.6)
Duration of treatment						
≤7 days	9 (37.5)	7 (43.7)	-	57 (66.3)	23 (74.2)	33 (62.3)
8-30 days	4 (16.7)	2 (12.5)	2 (28.6)	4 (4.6)	1 (3.2)	3 (5.6)
>30 days	3 (12.5)	1 (6.3)	3 (42.8)	3 (3.5)	1 (3.2)	2 (3.8)
Not reported	8 (33.3)	6 (37.5)	2 (28.6)	22 (25.6)	6 (19.4)	15 (28.3)
Dechallenge						
Positive	14 (58.3)	8 (50.0)	6 (85.7)	42 (48.8)	18 (58.0)	24 (45.3)
Negative	-	-	-	1 (1.2)	-	1 (1.9)
Not reported	10 (41.7)	8 (50.0)	1 (14.3)	43 (50.0)	13 (42.0)	28 (52.8)
Rechallenge						
Positive	2 (8.3)	-	2 (28.6)	2 (2.3)	-	2 (3.8)
Negative	22 (91.7)	16 (100)	5 (71.4)	-	-	-
Not reported	-	-	-	84 (97.7)	31 (100)	51 (96.2)
Laboratory test						
Yes	13 (54.2)	9 (56.3)	3 (42.8)	30 (35.0)	13 (42.0)	17 (32.1)
No	-	-	-	-	-	-
Not reported	11 (45.8)	7 (43.7)	4 (57.2)	56 (65.0)	18 (58.0)	36 (67.9)
Specific treatment						
Yes	16 (66.7)	14 (87.4)	1 (14.3)	34 (39.5)	17 (54.8)	17 (32.1)
No	3 (12.5)	1 (6.3)	2 (28.6)	27 (31.4)	7 (22.6)	20 (37.7)
Not reported	5 (20.8)	1 (6.3)	4 (57.2)	25 (29.1)	7 (22.6)	16 (30.2)

AE: adverse event; AIFA: Agenzia Italiana del Farmaco, Italian Medicines Agency; ISS: Istituto Superiore di Sanità, Italian National Institute of Health; SD: standard deviation.
*Days between starting of treatment and AEs onset.
[a]In one case seriousness was *Not reported*.
[b]In two cases seriousness was *Not reported*.
[c]% refers to the total of each column.
[d]In the Italian Pharmacovigilance System, in 6 cases "age" was not reported.

(37.5%). In all other cases, the dosage was not reported. The treatment duration varied from 1 day to 10 years. In more than half of the AE reports (66.6%), users were also taking other pharmacological and/or non-pharmacological treatments. The presence of concomitant conditions was described in 45.8% of the suspected AE reports. Information on dechallenge was reported in 14 (58.3%) cases and it was always "positive". Information on rechallenge was reported in 24 (100%) cases and it was "positive" in two. According to the WHO criteria, 9 (37.5%) AE reports were judged as "probably" and 15 (62.5%) "possibly" related to the suspected herbal DS. Following the MedDRA classification system, the majority of AEs were related to the SOC "Gastrointestinal disorders" (n=17, 32.1% out of 53), followed by "skin and subcutaneous tissue disorders" (n=14, 26.4% out of 53), and "central nervous system disorders" (n=5, 9.4% out of 53) *(Table 2)*. Considering both the total number of AEs belonging to different SOCs and the total number of subjects reporting at least one AE, there are no differences in the order of the most reported SOCs. In particular, "gastrointestinal disorders" were reported by 80.91% of subjects, "central nervous system disorders" by 35.45%, and "skin and subcutaneous tissue disorders" by 24.55%. Herbal DS associated with suspected AEs mostly involved AQ derivatives (79.2%), and only one case of *melanosis coli* was found. Details of each AE report retrieved from ISS are described in the *Supplementary Table available online*.

Italian Medicines Agency

Up to December 2020, the AIFA collected about 581,219 reports of suspected AE, of which 94 (0.02%) were associated with the use of OTC-M to treat constipation. From February 2011 to December 2020, 86 new AEs were recorded in the Italian Pharmacovigilance system *(Table 1)*. The mean age of patients was 64.9±21.5 years, and 58.1% were females. Overall, 36.1% of AE reports were defined as "serious" and required hospitalization, while in two cases seriousness was not reported. Healthcare professionals reporting the suspected AEs were mainly physicians (57%), fol-

Table 2
Adverse events (AE) grouped by System Organ Class (SOC)

SOC	N. AEs (ISS)	N. AEs (AIFA)	Total (%)	% on total number of AEs (a)	% on total number of subjects (b)
Gastrointestinal	17	72	89 (41.59)	41.59	80.91
Central nervous system	5	34	39 (18.22)	18.22	35.45
Skin	14	13	27 (12.62)	12.62	24.55
Investigations	2	13	15 (7.01)	7.01	13.64
Other	1	8	9 (4.21)	4.21	8.18
Electrolyte imbalances	1	7	8 (3.74)	3.74	7.27
Cardiovascular system	3	3	6 (2.80)	2.80	5.45
Metabolism	1	4	5 (2.34)	2.34	4.55
Immune system	4	1	5 (2.34)	2.34	4.55
Renal system	1	2	3 (1.40)	1.40	2.73
Musculoskeletal	1	2	3 (1.40)	1.40	2.73
Hepatic system	2	1	3 (1.40)	1.40	2.73
Respiratory system	1	1	2 (0.93)	0.93	1.82

(a) Total number of AEs belonging to the different SOCs: 53 from ISS + 161 from AIFA = 214.
(b) Total number of subjects reporting at least one AE: 24 from ISS + 86 from AIFA = 110.
AIFA: Agenzia Italiana del Farmaco, Italian Medicines Agency.

lowed by pharmacists (25.6%). The information on the dosage taken by the patients was compatible with the therapeutic indications reported in the summary of product characteristics of the suspected OTC-M in 46 AE reports (53.4%), while the dosage was higher in 18 cases (20.9%). In all other cases, the dosage was not reported, or it was described as overdose, abuse or out of therapeutic indications (off-label). The treatment duration varied from 1 day to 7 years. In 32.6% of the AE reports, users were also taking other pharmacological and/or non-pharmacological treatments. The presence of concomitant conditions was described in 40.7% of cases. Information on dechallenge was reported in 43 cases (50%) and was "positive" in 42 of them. Information on rechallenge was reported in 2 cases (2.3%) and was always "positive". According to the WHO criteria 11 (12.8%) AE reports were judged as "probably" and 18 (20.9%) "possibly" related to OTC-M. Fifty-seven reactions were unclassified because of insufficient information. Most AEs were "gastrointestinal disorders" (n=72, 44.7% out of 161), followed by "nervous system disorders" (n=34, 21.1% out of 161) and "skin and subcutaneous tissue disorders" (n=13, 8.1% out of 161) *(Table 2)*. As mentioned above, "gastrointestinal disorders" were reported by 80.91% of subjects, "central nervous system disorders" by 35.45%, and "skin and subcutaneous tissue disorders" by 24.55%. OTC-M associated with the suspected AEs mostly involved AQ derivatives (91.9%). Details of each AE report retrieved from AIFA are described in the *Supplementary Table available online*.

DISCUSSION

The evaluation of the Italian Phytovigilance and Pharmacovigilance spontaneous reporting systems allowed us to characterize a total of 110 new AE reports. Of these, 24 were associated with herbal DS and 86 were related to OTC-M. Among the latter, only one report was related to a synthetic drug containing bisacodyl. It is worth highlighting the high increase in the number of AE reports between the analysis period discussed in the previous publication (N=26, period 2002-2011) [4] and the second period analyzed in this paper (N=110, period 2011-2020), especially in the Pharmacovigilance system. Nevertheless, the underreporting effect has to be taken in account. Of notice, given the seriousness of some AEs, the relatively low number of reports collected in the last decade does not represent a guarantee of safety.

Concerning demographic characteristics, most AE reports involved females, and the mean age was lower for subjects experiencing AEs associated with herbal DS containing laxatives. In general, in most countries laxative use in females is higher than males [24]. However, evidence published in the literature describing the use of laxatives in the community is controversial. In fact, some studies reported a higher laxative use in women, in particular in the United States, United Kingdom, Germany, France, Italy, Brazil and South Korea [25]. Laxative use generally increases with age, although with relevant differences between countries [24]. Moreover, it is well known that women experience several constipation symptoms and abnormal bowel habits more frequently than men [26], thus explaining a relatively higher prevalence of laxative use and the potentially associated AEs in this subgroup. Considering our evidence, it is difficult to draw any conclusions in terms of patients' characteristics due to the relatively small sample size, composed by subjects who experienced a laxative-related AE, and the lack of information on the total number of laxative users. However, to improve constipation management in community and primary healthcare settings, knowledge of the true prevalence and utilization of laxative use and consumers' characteristics is still required [24].

Products associated with suspected AEs in our analysis mostly involved AQ derivatives. Considering the reports collected by the phytovigilance system, we evaluated the characteristics of herbal DS available on the market in terms of their composition and formulation. This relevant aspect should always be taken into consideration by both healthcare professionals and consumers. In fact, most of the reports concerned products containing more than one active compound and, sometimes, more than one AQ-containing plant. In particular, the majority of serious AEs were related to products with two or more plants containing AQs. This is an extremely important safety issue because there is no scientific evidence that demonstrates a favorable benefit risk profile in the case of combination of multiple active substances [27].

Considering data for both herbal DS and OTC-M, in our sample gastrointestinal disorders were the most frequently reported AEs, both by analyzing the total number of AEs belonging to different SOCs and the total number of subjects reporting at least one AE. In particular, abdominal pain and cramps, which are associated with the well-known pharmacological properties of AQ derivatives [9]. Laxatives containing AQ derivatives should be used following their specific indications (acute constipation and/or as purgatives prior to diagnostic endoscopy) and only for a short-term period (not to be used for more than 1 week) [28]. AQ derivatives increase the release of prostaglandin and other inflammatory mediators, and the concentrations of fluids and electrolytes in the colon, resulting in a stimulation of peristalsis that could be responsible for gastrointestinal symptoms [29]. Regarding the case of *melanosis coli*, the use of AQ-containing laxatives has been already associated to its occurrence [30]. In particular, *melanosis coli* is a dark-brown discoloration of colon mucosa, and it is induced by AQ derivatives in 9-12 months, disappearing over weeks to months after the end of treatment [31]. However, even though AQ laxatives can be associated with *melanosis coli*, it is noteworthy that, in the case observed in our analysis, the causality assessment was judged as "probable" due to the concomitant assumption of other pharmacological treatments. This does not exclude the possibility that there are several cases of *melanosis coli* or other similar disorders caused by prolonged use of AQs, difficult to detect due to their long-term onset. The occurrence of gastrointestinal AEs observed following the use of this kind of laxatives could also be associated with their duration of treatment. We cannot exclude the inappropriate use of these products in our sample, considering that a relatively high number of subjects reported intake of these laxatives for more than 1 week.

In general, the cause of constipation should always be ascertained and, if a laxative is needed, soft laxatives (*i.e.*, osmotic laxatives, poo-softener laxatives, etc.) should be the treatment of choice because they are generally safe and well-tolerated [32], particularly in specific subgroups of patients (*i.e.*, pregnancy, lactation, elderly, etc.) [33-36]. In this context, it is mandatory to clarify the possible association between an inappropriate AQ laxative use and the onset of serious diseases. Recently, our research units conducted a systematic review and meta-analysis reporting a higher risk of colorectal cancer (CRC) in subjects using AQ laxatives compared to "other" or "no laxative" use [10]. Although not at a statistically significant level, and considering all limitations affecting these analyses, our study provides the best risk estimate available for subjects undergoing AQ laxatives use. Of notice, no eligible studies included in the meta-analysis reported information on dosage and length of treatment with AQ laxatives, highlighting the need of further high-quality population-based safety studies.

The second most frequently reported AEs were included in the "skin and subcutaneous tissue disorders" SOC, mainly related to suspected products containing senna (*Cassia angustifolia*) compounds and experienced by subjects within 6 days of use. In the literature little evidence, regarding dermatological reactions to sennosides, is present. A review by Vilanova-Sanchez and colleagues [37], evaluating the safety of senna-based laxatives as long-term treatment for constipation in children, reported that senna-induced dermatitis is a rare event, but may occur when patients need a higher dosage. No evidence on the safety of AQ laxatives use in adults regarding dermatological reactions was found. In many cases, dandelion (*Taraxacum officinale*) and senna were involved together in the same products, often in association with fennel (*Foeniculum vulgare*) or cascara (*Rhamnus purshianus*). Despite dermatological reactions associated with AQ derivatives being generally infrequent, considering the high prevalence of use of these products in the community [24], healthcare professionals should consider this clinical occurrence. Moreover, these medicinal plants should be used with caution by patients with known hypersensitivity.

Another clinically relevant condition associated with inappropriate use of laxatives, in particular those containing AQ derivatives, is electrolyte imbalance [38]. Long-term and high dose treatment with laxatives can lead to dehydration and electrolyte imbalances like hyponatremia, hypokalemia, hyperuricemia, and hyperaldosteronism. If electrolyte imbalance is not properly corrected, it can lead to alterations of heart function (such as arrhythmias), muscle weakness, and other clinically relevant medical occurrences [4]. For instance, dehydration and hypokalemia together can cause renal insufficiency [39].

As previously mentioned, due to the lack of standardization in the production process of herbal DS, the number of active compounds can vary, further complicating the assessment of potential drug-DS interactions [27]. In this context, we observed a relatively high number of subjects who experienced an AE associated with laxative use during an oral anticoagulant therapy. AQ compounds (i.e., sennosides), increasing bowel motility, potentially decrease vitamin K absorption causing elevated INR (international normalized ratio) values [40]. Therefore, in subjects treated with warfarin, such as those observed in our analysis, AQ laxatives may play a role in the exaggerated anticoagulation and subsequent bleeding complications. Healthcare professionals and consumers should consider that AQ-containing plants and soluble fibers can decrease drug absorption by decreasing gastrointestinal transit time [41].

Our study has several strengths. First, the phytovigilance and pharmacovigilance spontaneous reporting system play a key role in exploring the safety profile of DS and OTC-M both from a local and international perspective, thus increasing generalizability of our findings. In addition, the causality assessment was performed for all AE reports, thus providing valuable insights concerning the clinical relevance of serious AEs associated with herbal DS and OTC-M used as laxatives. Furthermore, considering that data concerning the use of these products is not always available, neither in term of packages sold nor in terms of population exposed, and that population-based studies for risk estimation are difficult to conduct, national spontaneous reporting systems are

the first valuable approaches to monitor safety signals from DS and OTC-M for regulatory actions.

This update analysis conducted on AE reports retrieved by national spontaneous reporting systems has also several limitations. The first one is represented by the underreporting, which is likely to affect herbal DS and OTC-M to a higher extent as compared to prescription drugs, due to their perceived better safety profile by both consumers and healthcare professionals, who may not always take into consideration these products as suspected causative agents in the onset of an AE. Additionally, post-marketing surveillance is not mandatory for DS, thus spontaneous/voluntary reporting may further underestimate the real prevalence of DS-related AEs. Finally, spontaneous AE reports may lack or report incomplete clinical data (i.e., concomitant products, concomitant medications, comorbidities, etc.), thus making the application of the causality assessment challenging.

CONCLUSIONS

Despite the wide use of herbal DS and OTC-M containing laxatives, the total number of AE reports recorded in the last 10 years is still relatively low. However, the extent of underreporting may be significant since they are bought by consumers mainly as self-prescription products. In particular, based on the "natural origin" of herbal DS, they are usually perceived by the community as being safe and free of side effects. Furthermore, given the seriousness of some AEs, especially related to DS, the low number of reports does not represent a guarantee of safety.

This study may contribute to increase public awareness and alert healthcare professionals on the health risks associated with the use of DS and OTC-M containing laxatives, especially those containing AQ derivatives. Finally, this study may enhance consumers' attention regarding the risks associated with the misuse or abuse of laxatives containing AQ derivatives.

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