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Original Article

Safety of complementary and alternative medicine in children: A 16-years retrospective analysis of the Italian Phytovigilance system database

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ABSTRACT

Background: Dietary supplements and homeopathic medicines are largely used in children as complementary and alternative medicine (CAM) to treat different health conditions. Safety of CAM is unknown when they are marketed. This study analysed suspected CAM-related adverse reaction (AR) in pediatric population.

Methods: The Italian Phytovigilance system was searched for reports of suspected AR related to CAM use in children (0–18 years) from 2002 to 2018. AR reports were evaluated and information about patient's demographic characteristics, suspected CAM, conventional medications, and ARs were collected. In particular, we evaluated whether patient's and CAM characteristics, and concomitant drugs could be potential predictors of ARs seriousness.

Results: We evaluated 206 pediatric CAM-related AR reports, of which 69 were serious. Patients were mostly treated with only one CAM (n = 193), and 39% of AR reports were related to products containing 2–5 components. Most reported ARs were related to dietary supplements (57.18%), and skin and subcutaneous tissue disorders (40.29%) were the most involved System Organ Class. CAM-related AR reported as serious were higher in subjects exposed to homeopathic medicines (ROR 3.13 [1.88–5.22]), to CAM in presence of concomitant medications (ROR 1.77 [1.01–3.10]), to CAM containing 2–4 components (ROR 2.18 [1.13–4.22]), and to more than three concomitant CAM (ROR 7.81 [1.97–32.69]).

Conclusion: We provide new insights on factors that might increase the risk of serious AR associated with CAM use in children: products containing more than two components and simultaneously administered with conventional medications can represent a potential risk in children.

Background

Complementary and alternative medicine (CAM) include dietary supplements, homeopathic medicines, herbal preparations, homemade preparations, and galenic preparations including herbals (Dalla Libera et al., 2014). These products are often use to complement or in alternative to conventional medicines to prevent or treat diseases in the paediatric population (Pitetti et al., 2001; Zollman and Vickers, 1999).

In the last decade the use of CAM has increased in the population, representing a significant part of healthcare regimes also in children (Posadzki et al., 2013). The estimates of CAM use in adults range yearly from 20% to 28% in United Kingdom and from 34% to 38% in United States (Lorenc et al., 2009). A systematic review finds a worldwide prevalence of CAM use in the general population between 23% and 62% (Harris and Rees, 2000). Also in children the estimates of CAM use are quite high, ranging from 11% (Spigelblatt et al., 1994) to 51% (Lim et al., 2005). The variability of the estimates depends on the definition of CAM and the study design (http://www.cdc.gov/nchs/data/

Abbreviations: AR, Adverse Reaction; ATC, Anatomical Therapeutic Chemical; CAM, Complementary and Alternative Medicine; CI, Confidence Interval; MedDRA, Medical Dictionary for Regulatory Activities; ROR, Reporting Odds Ratio; SOC, System Organ Class; WHO, World Health Organization

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nhsr/nhsr012.pdf; (Barnes et al., 2008; Harris et al., 2012; Robinson et al., 2008; Simpson and Roman, 2001).

In children and adolescents, CAM are generally used to treat back or neck pain, head or chest colds, anxiety or stress, attention-deficit hyperactivity disorder, and sleep disorders (https://nccih.nih.gov/health/children). Of note, pediatric patients who turns to CAM could also be affected by chronic, recurrent or incurable conditions, infections, allergy and general disorders (Tomassoni and Simone, 2001).

In this context, the efficacy and safety of CAMs use remains relatively underestimated, and the potential of interactions (*i.e.*, CAM-drug interaction, CAM-disease interaction), acute or chronic toxicity, or withdrawal that may be experienced by children who are administered CAM concomitantly with, or in lieu of, their prescribed drugs, is easily imaginable (Kemper, 2001). In fact, in the scientific literature the number of reports of suspected adverse reaction (AR) associated with CAM use has significantly increased in the last years (Menniti-Ippolito et al., 2008).

In Italy, as in other high-income countries, the range of CAM used to treat children can be various and can include self-care techniques, treatments requiring consultations with qualified healthcare professionals and/or the use of herbal products or homeopathic medicines. Only few investigations have estimated the prevalence of CAM users in Italy (from 13% to 15%), reporting that homeopathy is the most frequently used CAM, followed by hand treatments, phytotherapy and acupuncture (Dolceamore et al., 2012). These treatments are more common in Northern Italy. In Tuscany, the region where CAM are widely used and where they are partially reimbursed also within the Regional Health Service, the prevalence of CAM users is 15–20%, and 45% of the surveyed population considers useful at least one type of CAM (Dolceamore et al., 2012).

In Italy, as in many other Countries, CAM, in particular dietary supplements, are notified and not registered as conventional drugs (http://www.epicentro.iss.it/farmaci/pdf/FEP2015/Gargiulo.pdf) and, thus their safety profile is not known before they are on the market. Since 2002 in Italy, spontaneous reports of suspected ARs potentially related to CAM are collected within the Phytovigilance system coordinated by the Italian National Institute of Health (Crescioli et al., 2018; Mazzanti et al., 2017).

The aim of the present study was to analyse (in terms of frequency and seriousness) suspected ARs associated with the use of CAM in the pediatric population (0–18 years). We also attempted to identify the presence of potential predictors associated with CAM-related AR seriousness in this population.

Materials and methods

All reports of suspected CAM-related AR from patients aged less than 18 years were included in the present analysis and individually evaluated by a multidisciplinary group of experts in the fields of pharmacology, clinical toxicology, phytovigilance, pharmacovigilance and pharmacoepidemiology. We considered all reports collected between January 1st, 2002 and January 29th, 2018.

From the *ad hoc* reporting form (www.epicentro.iss.it), it was possible to retrieve all information about: (1) patient's demographic characteristics (*i.e.*, age, gender, ethnic group) and (2) clinical status; (3) ongoing therapy (*i.e.*, number of CAM components, administration route, therapy duration, and dosages): suspected CAM were codified according to the CAM definitions present in the European Pharmacopoeia (categorized as dietary supplements; herbal preparations and galenic formulations; other herbal preparations not included in the former paragraphs and other preparations of natural origin but non-plant; homeopathic medicines; and nutrition/diet products) (http://www.europarl.europa.eu/cmsdata/135562/ENVI%202017-10%20WS%20CAM%20%20PE%20614.180%20(Publication).pdf), and concomitant medications were classified by the Anatomical Therapeutic Chemical (ATC) classification system; (4) a description of AR, codified using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and organized by System Organ Class (SOC) (Lombardi et al., 2018); (5) AR degree of seriousness, classified according to the World Health Organization (WHO) criteria as fatal, life-threatening, or requiring hospitalization of the patient, or causing serious/permanent disability, or causing congenital abnormalities, or other clinically relevant conditions (https://apps.who.int/iris/bitstream/handle/10665/67378/WHO_EDM_QSM_2002.2.pdf;jsessionid=EF4F54EFF6FBD634E21D2C075ADCA3C0?sequence=1). Although in the same report two or more AR of different clinical seriousness could be present, following WHO guidelines, we performed the seriousness assessment taking into account each report as a whole. Consequently, even if serious and non-serious ARs could be present in the same report, we applied the result of the assessment to each AR within the same report.

For each AR report, causality (categorized as certain, probable/likely, possible, unlikely, or unclassifiable) was assessed according to the WHO system for standardized case causality assessment (https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf). If a CAM contained more than one component (*i.e.*, minerals, vitamins, probiotics, herbs, etc.), as on the label of the package, the attribution of causality concerned the whole commercial product, excluding excipients. We also evaluated potential predictors associated with the reporting of ARs seriousness, such as age classes, gender, number of components simultaneously administered, and presence of concomitant medications.

Descriptive statistics are shown as frequencies and percentages for categorical data and as means with standard errors for continuous data. Considering that one AR report could comprehend more than one AR and more than one CAM, all analysis regarding CAM products were performed by CAM-AR pair rather by report. Univariate and multivariate logistic regression were used to estimate the reporting odds ratios (RORs) with 95% confidence intervals (CIs) of potential predictors of AR seriousness. ROR values for each variable were reported both as crude values and adjusted for age, gender and presence of concomitant allopathic medications. All results were considered to be statistically significant at $p < 0.05$. Data management and statistical analysis were carried out using STATA 14.

Results

During the study period, the total amount of AR reports collected within the Italian Phytovigilance system was 1506, of which 206 (13.7%) were referred to pediatric patients, and herein evaluated (Table 1). Sixty-nine AR reports were defined as serious (33.5%) and, of them, 59 led to hospitalization. No AR report was associated with patient's death. Most of AR reports referred to Caucasians and to children, with a mean patients' age of 36 months (range 12–72). The male/female rate of AR reports was 1.25. A total of 105 AR reports (50.97%) presented a complete resolution and 27 (13.11%) an improvement. For 59 AR reports (28.64%) data on the outcome were not available. Overall, patients used only one CAM when AR occurred ($n = 193$, 93.69%), and the majority of them did not use any other concomitant medications ($n = 154$, 74.76%). Eighty AR reports (38.83%) were related to products containing 2–5 components. This frequency was higher for AR reports defined as serious ($n = 31$, 41.89%). Considering the causality assessment, 24 AR reports were defined as certain, 49 probable, 40 possible and 7 unlikely. Unfortunately, 86 AR reports (41.75%) were unclassifiable due to lack of needed information. Hospital physicians and pharmacists were the most frequently involved healthcare professionals in CAM-related ARs reporting.

The total number of CAM-AR pairs was 369 (Table 2). Of them, 198 (53.65%) were defined as non-serious. The most frequently reported ARs were those related to dietary supplements ($n = 132$, 66.67%) and homeopathic medicines ($n = 32$, 16.16%), both for serious and non-serious CAM-AR pairs.

Table 1
Patients' clinical and demographic characteristics.

	AR reports overall 206 *N* (%) out of 206	Non-serious/ Not-defined AR reports 132 *N* (%) out of 132	Serious AR reports 74 *N* (%) out of 74	*p-value*[#]
Median (IQR) CAM-AR pairs for each patient	1 (1–2)	1 (1–2)	2 (1–3)	0,005*
***N* ARs/patient**				
1	116 (56.31)	81 (61.36)	35 (47.30)	0.043*
2	52 (25.24)	33 (25.00)	19 (25.68)	
3+	38 (18.45)	18 (13.64)	20 (27.03)	
Age				
Median (range) months	36 (12–72)	36 (12–72)	24 (5–84)	0.191
Age classes (WHO)				
Neonates (<1 month)	13 (6.31)	5 (3.79)	8 (10.81)	0.029*
Infants (1–23 months)	65 (31.55)	40 (30.30)	25 (33.78)	
Children (24–143 months)	114 (55.34)	81 (61.36)	33 (45.59)	
Adolescents (144–192 months)	14 (6.80)	6 (4.55)	8 (10.81)	
Gender				
Male	111 (53.88)	62 (46.97)	49 (66.22)	0.027*
Female	89 (43.20)	66 (50.00)	23 (31.08)	
Not reported	6 (2.91)	4 (3.03)	2 (2.70)	
Ethnicity				
Caucasian	159 (77.18)	100 (75.76)	59 (79.73)	0.028*
Mediterranean	5 (2.43)	4 (3.03)	1 (1.35)	
African	3 (1.46)	1 (0.76)	2 (2.70)	
Asian	6 (2.91)	1 (0.76)	5 (6.76)	
Not reported	33 (16.02)	26 (19.70)	7 (9.46)	
***N* of administered products**				
1	193 (93.69)	127 (96.21)	66 (89.19)	0.076
2	8 (3.88)	4 (3.03)	4 (5.41)	
3+	5 (2.43)	1 (0.76)	4 (5.41)	
***N* of CAM components simultaneously administered**				
1	62 (30.10)	45 (34.09)	17 (22.97)	0.070
2–5	80 (38.83)	49 (37.12)	31 (41.89)	
6–10	34 (16.50)	20 (15.15)	14 (18.92)	
11–15	22 (10.68)	16 (12.12)	6 (8.11)	
16+	8 (3.88)	2 (1.52)	6 (8.11)	
Seriousness				
Non-serious	88 (42.72)	88 (66.67)	–	
Serious - Hospitalisation or prolonged hospitalisation	59 (28.64)	–	59 (79.73)	
Serious - Congenital abnormalities	–	–	–	
Serious - Severe or permanent disability	–	–	–	
Serious - Life threatening	6 (2.91)	–	6 (8.11)	
Serious - Other clinically relevant conditions	4 (1.94)	–	4 (5.41)	
Not defined	44 (21.36)	44 (33.33)	–	
Outcome				
Complete resolution	105 (50.97)	62 (46.97)	43 (58.11)	0.180
Improvement	27 (13.11)	20 (15.15)	7 (9.46)	
Invariant/worsening	8 (3.88)	5 (3.79)	3 (4.05)	
Not available	59 (28.64)	38 (28.79)	21 (28.38)	
Still unresolved	–	–	–	
Resolution with sequelae	7 (3.40)	7 (5.30)	–	
Concomitant drugs				
Yes	52 (25.24)	27 (20.45)	25 (33.78)	0.035*
No	154 (74.76)	105 (79.55)	49 (66.22)	
Causality Assessment				
Certain	24 (11.65)	15 (11.36)	9 (12.16)	0.394
Probable	49 (23.79)	32 (24.24)	17 (22.97)	
Possible	40 (19.42)	26 (19.70)	14 (18.92)	
Unlikely	7 (3.40)	2 (1.52)	5 (6.76)	
Unclassifiable	86 (41.75)	57 (43.18)	29 (39.19)	
Reporter qualification				
Hospital physician	111 (53.88)	59 (44.70)	52 (70.27)	0.007*
Paediatrician	24 (11.65)	18 (13.64)	6 (8.11)	
General practitioner	16 (7.77)	15 (11.36)	1 (1.35)	
Pharmacist	49 (23.79)	36 (27.27)	13 (17.57)	
Other healthcare professional	4 (1.94)	3 (2.27)	1 (1.35)	
Patient/citizen	1 (0.49)	1 (0.76)	–	
Not reported	1 (0.49)	–	1 (1.35)	

* *p-value* <0.05.
\# *p-value* of the comparison between serious and non-serious AR reports.

Table 2
Serious and non-serious CAM-AR pairs according to European Pharmacopeia classification.

CAMs	Overall 369 *N* (%) out of 369	Non-serious CAM-AR pairs 198 *N* (%) out of 198	Serious CAM-AR pairs 171 *N* (%) out of 171
Dietary supplements	211 (57.18)	132 (66.67)	79 (46.20)
Homeopathic medicines	92 (24.93)	32 (16.16)	60 (35.09)
Herbal preparations	25 (6.78)	14 (7.07)	11 (6.43)
Nutrition/diet products	24 (6.50)	16 (8.08)	8 (4.68)
Homemade preparations	9 (2.44)	4 (2.02)	5 (2.92)
Galenic preparations	8 (2.17)	–	8 (4.68)

On the 206 spontaneous reports, a total of 350 ARs were indicated. Table 3 reported the distribution of ARs according to SOC classification. Overall, the most frequently reported SOCs were: skin and subcutaneous tissue disorders (40.29%), followed by gastrointestinal disorders (14.29%) and central nervous system disorders (8.29%). Of notice, the majority of ARs for each SOC were serious, except for skin and subcutaneous tissue disorders, gastrointestinal disorders, psychiatric conditions, pregnancy, puerperium and perinatal conditions, eye disorders, and endocrine disorders.

Table 4 reports the distribution of CAM-AR reports and the potential associations between their seriousness and gender, age classes, CAM classification, presence of concomitant medications, number of components and total number of CAM simultaneously administered. Risk of having a CAM-related AR reported as serious was significantly lower in female (adjusted ROR of 0.35 [95% CI: 0.22–0.56]), and in children compared to neonates (adjusted ROR of 0.24 [95% CI: 0.09–0.66]). Conversely, risk of serious CAM-related AR was significantly increased in subjects exposed to homeopathic medicines (crude ROR of 3.13 [1.88–5.22]), to CAM in presence of concomitant medications (adjusted ROR of 2.59 [95% CI: 1.58–4.25]), to 5–8 and more than 9 components simultaneously administered (adjusted ROR of 2.22 [95% CI:

Table 3
Distribution of ARs according to SOC classification.

SOC	ARs overall 350 *N* (%) out of 350	Non-serious ARs 207 *N* (%) out of 207	Serious ARs 143 *N* (%) out of 143
Skin and subcutaneous tissue disorders	141 (40.29)	109 (52.66)	32 (22.38)
Gastrointestinal disorders	50 (14.29)	33 (15.94)	17 (11.89)
Central nervous system disorders	29 (8.29)	12 (5.80)	17 (11.89)
Respiratory. thoracic and mediastinal disorders	20 (5.71)	11 (5.31)	9 (6.29)
Vascular disorders	18 (5.14)	5 (2.42)	13 (9.09)
Psychiatric disorders	16 (4.57)	12 (5.80)	4 (2.80)
Immune system disorders	11 (3.14)	4 (1.93)	7 (4.90)
Diagnostic examinations	11 (3.14)	1 (0.48)	10 (6.99)
General and administration site conditions	10 (2.86)	3 (1.45)	7 (4.90)
Traumatism. intoxication and procedural complications	8 (2.29)	4 (1.93)	4 (2.80)
Cardiac disorders	8 (2.29)	2 (0.97)	6 (4.20)
Hepatobiliary disorders	7 (2.00)	1 (0.48)	6 (4.20)
Metabolism and nutrition disorders	6 (1.71)	1 (0.48)	5 (3.50)
Eye disorders	5 (1.43)	4 (1.93)	1 (0.70)
Pregnancy. puerperium and perinatal conditions	5 (1.43)	3 (1.45)	2 (1.40)
Renal and urinary disorders	2 (0.57)	–	2 (1.40)
Musculoskeletal and connective tissue disorders	1 (0.29)	1 (0.48)	–
Blood and lymphatic system disorders	1 (0.29)	–	1 (1.70)
Endocrine disorders	1 (0.29)	1 (0.48)	–

1.17–4.22] and 1.99 [95% CI:1.03–3.85], respectively), and to 2 and more than 3 CAM simultaneously administered (adjusted ROR of 3.78 [95% CI: 1.65–8.65] and 7.71 [95% CI: 2.39–24.94], respectively).

Regarding concomitant medications, the most frequently co-prescribed drugs in our sample were antibacterials for systemic use (ATC class J01*: amoxicillin, amoxicillin/clavulanate, azithromycin, and clarithromycin), drugs for obstructive airway diseases (ATC class R03*: betamethasone, salbutamol), cough and cold preparations (ATC class R05*: ambroxol), other analgesics and antipyretics (ATC class N02*: paracetamol), and nonsteroidal anti-inflammatory drugs (ATC class M01*: ibuprofen) (Data not shown).

Discussion

Our study aims to explore and to characterize ARs associated with the use of CAM in children and adolescents reported from January 2002 to January 2018 in Italy through an analysis of the Italian Phytovigilance database. To our knowledge, this is the first study

Table 4
Predictors of CAM-related ARs seriousness.

	Crude ROR of serious AR ROR (95% confidence interval)	*p*-value	Adjusted[#] ROR of serious AR ROR (95% confidence interval)	*p*-value
Gender				
Male	Ref		Ref	
Female	0.37 (0.24–0.56)	<0.001*	0.35 (0.22–0.56)	<0.001*
Age classes (WHO)				
Neonates (<1 month)	Ref		Ref	
Infants (1–23 months)	0.43 (0.16–1.17)	0.098	0.48 (0.17–1.34)	0.163
Children (24–143 months)	0.18 (0.07–0.47)	0.001*	0.24 (0.09–0.66)	0.005*
Adolescents (144–192 months)	0.53 (0.15–1.80)	0.310	1.13 (0.31–4.14)	0.853
CAM products				
Dietary supplements	Ref		Ref	
Homeopathic medicines	3.13 (1.88–5.22)	<0.001*	1.86 (0.98–3.52)	0.056
Nutrition/diet products	0.83 (0.34–2.04)	0.693	0.51 (0.18–1.44)	0.204
Galenicals	–	–	–	–
Homemade preparations	2.09 (0.54–8.00)	0.283	1.44 (0.34–6.11)	0.617
Herbal preparations	1.31 (0.57–3.03)	0.524	0.80 (0.32–2.02)	0.639
Concomitant drugs				
No	Ref		Ref	
Yes	2.84 (1.80–4.47)	<0.001*	2.59 (1.58–4.25)	<0.001*
***N* of CAM components simultaneously administered**				
1	Ref		Ref	
2–4	1.92 (1.10–3.33)	0.021*	1.66 (0.91–3.01)	0.097
5–8	2.38 (1.31–4.32)	0.004*	2.22 (1.17–4.22)	0.014*
9+	2.94 (1.65–5.24)	<0.001*	1.99 (1.03–3.85)	0.040*
***N* of CAM administered products**				
1	Ref		Ref	
2	3.19 (1.45–7.04)	0.004*	3.78 (1.65–8.65)	0.002*
3+	12.36 (4.26–35.86)	<0.001*	7.71 (2.39–24.94)	0.001*

* *p-value* <0.05.
[#] ROR values adjusted for age, gender and presence of concomitant allopathic medications.

conducted over a such long period that addresses potential factors associated with the reporting of serious CAM-related ARs in pediatrics.

Within the Italian Phytovigilance database, 13.7% of all reports is related to pediatric patients. This proportion is similar to that observed for conventional medicines in the National Pharmacovigilance System (data not shown, 17%) within the same period. This result suggests a good quality of the Phytovigilance database, while highlighting the importance of monitoring the safety of CAM, also considering the absence of clinical trials both in the adult and pediatric population.

In terms of CAM-related ARs, our estimates showed a higher frequency of non-serious AR reports (64%), particularly in males, children (2–12 years), and Caucasians. Of notice, no ARs caused patient's death, and, although 59 AR reports have been correlated with hospitalization, an improvement or a complete resolution was registered in most cases. We also observed a higher frequency rate for skin and subcutaneous tissue disorders, gastrointestinal disorders, and central nervous system disorders respect to other SOCs. These demographic and clinical results are in line with those already reported for conventional drugs in children (Lombardi et al., 2018).

In general, the principal reason for CAM use in children includes fear of ARs from conventional medications. In fact, CAM users frequently consider unconventional therapies to be safe, as they are "natural" (Committee on Children with, 2001). In contrast, several analysis have showed that the use of CAM may be associated with clinically significant ARs, especially in paediatric population (Meyer et al., 2013).

Lim and colleagues, in order to describe types of ARs associated with CAM use as seen by Australian pediatricians during three years of observation, collected and analyzed a total of 39 cases, including four reported deaths (Lim et al., 2011). Their results highlighted several areas of concern, including the risks associated with the failure to use conventional medicine, the medication changes made by CAM practitioners and risk associated with dietary restriction. The reported deaths have been associated with a failure to use conventional medicine in favor of homeopathic treatment. Fortunately, our results are quite different from those mentioned above, where most cases were considered to be serious, life-threatening or fatal, providing reasons for concern and further monitoring of the safety of CAM therapies and their associated use in children.

Other cases of ARs and toxicities potentially related to herbs and other CAM have been reported, including seizures, hepatitis, cardiac arrhythmias and allergic reactions (Constable et al., 2007; Kim et al., 2013). Some studies have also documented the contamination of several CAM with heavy metals (*e.g.*, lead, arsenic) and resultant toxicity (Genuis et al., 2012; Ting et al., 2013; Yu et al., 2017). As documented in other analysis (Adams et al., 2013; Barnes et al., 2008; Kruskal, 2009), indirect ARs of CAM use include the dangers of withholding conventional therapies in favor of CAM treatments.

In our sample, most patients were taking only one CAM product at the time of AR, with a total amount of 1–5 components simultaneously administered within the same product, demonstrating a quite good management of these treatments in children.

Scientific literature shows that children with recurrent conditions appear to use CAM more frequently, and most of these children do not receive CAM alone, as they are concomitantly using conventional prescribed therapies (Vohra et al., 2012). Of particular interest, we observed that the risk of CAM-related AR seriousness is modified by the simultaneous administration of concomitant medications. In fact, it is well known that safety aspects of concomitant administration of CAM and conventional drugs in children are still poorly investigated (Du et al., 2014). In our sample we observed that the most co-administered medications were antibacterials for systemic use, drugs for obstructive airway diseases, cough and cold preparations, analgesics and antipyretics, and nonsteroidal anti-inflammatory drugs. This evidence is comparable to those already reported regarding medication most used in children in Italy (Lombardi et al., 2018). Considering the large variability in the composition of CAM products, it is very difficult to assess which factor between CAM components and conventional drug caused the adverse reactions. This scenario becomes even more complex if we consider that several CAM products contain more than one component. In fact, according to our results, exposure to more than 4 natural components influence CAM-related ARs seriousness. The majority of CAM contain several components, which are still poorly characterized both in terms of pharmacokinetics and pharmacodynamics (Yang et al., 2014), especially in children where pharmacokinetic and pharmacodynamic parameters differ from those in adults (Allegaert and van den Anker, 2014; van den Anker et al., 2011). Thus, in the context of pediatrics, CAM components may exert multiple physiological activities, modifying CAM safety profile and CAM-related ARs seriousness, respectively.

Moreover, many CAM are self-administered without any recommendation from healthcare professionals and therefore without any acknowledgement of their efficacy and safety. Risky behaviors associated with self-prescription of CAM include the substitution of allopathic medications (George and Topaz, 2013). These behaviors may conduct to delays in the appropriate medical intervention or decrease the adherence to conventional treatments of proven efficacy, thus contributing to unnecessary morbidity. This is particularly evident for homeopathic medicines, as we observed in our populations, where this kind of treatments has been associated to a higher risk of serious CAM-related AR. This could be explained by their ineffectiveness in treating acute and chronic diseases, resulting in their worsening, rather than to their direct toxicity (Posadzki et al., 2012).

It is also important to note that several studies have documented that most caregivers do not disclose the use of CAM for their children (Ben-Arye et al., 2011; McClafferty et al., 2017). One study of CAM and over-the-counter medication use in children with asthma in primary care practices, has found that 54% of caregivers do not disclose the usage to providers (Sidora-Arcoleo et al., 2008). Other studies have reported rates of non-disclosure as high as 66% (Chao et al., 2008).

We also observed that most of AR reports in our population are related to dietary supplements, highlighting the importance of a deep knowledge of these products in terms of their composition and related safety. In this framework, considering that every year in the United States 23,000 emergency department visits are attributed to ARs related to dietary supplements (Geller et al., 2015), it is not difficult to understand the clinical impact that dietary supplements and other CAM can have in the general population, particularly in children. Moreover, difficulties in evaluating the safety of CAM include differences in regulation and standardization of available products (as compared with conventionally used medications). In fact, CAM are classified as dietary supplements or as foods depending on the country they are marketed in, and they only have to be notified to health authorities before entering the market without any efficacy and safety evaluations. As consequence, CAM with similar labeled ingredients may differ significantly in herb content and potency, leading to different safety profiles (Ekor, 2014).

Although CAM has received increased attention and evaluation by Western medicine in recent years, few data from controlled clinical trials in children exist in published scientific literature (Kemper et al., 2008). A synthesis of the Cochrane reviews assessed the efficacy, clinical implications and limitations of CAM use in children, evaluating whether a CAM intervention should or should not be performed on the base of the evidence published in literature. Authors report that only a minority of systematic reviews provide a definitive recommendation to the CAM use in children, underlining also that the methodological quality of included studies is commonly low and the need for more research (Meyer et al., 2013).

Our study has several points of limitation and strength. First, its retrospective nature may have led to an underestimation of CAM-related ARs, since not all children presenting an AR, even if serious, report the adverse event to the Phytovigilance system. Second, our

analysis is based on spontaneous reports of CAM-AR that are affected by limits that include inaccurate and incomplete information, mainly related to lack of clinical data (Scavone et al., 2018). Given that, we cannot always exclude the absence of information not listed in the reports that might have influenced the clinical evaluation of each case (*i.e.*, previous/current patient medical conditions which could affect the evaluation of causality assessment). Thus, considering our evidence, only few AR reports (around 25%) were rated as certain or probable with regard to causality, highlighting the importance of further improving the quality of clinical information reported in AR reports. Third, CAM may contain a large quantity of components and the attribution of an AR to a specific herbal component could be very difficult. In fact, the high variability of CAM products reported, particularly in terms of product composition, did not allow us to perform a disproportional analysis to detect a risk signal. Lastly, administrative monitoring systems are not available for dietary supplements, so no database of users exists. Thus, it is very difficult to quantify risks trough observational pharmacoepidemiological studies (as for example case-control or cohort studies). Given all these considerations, spontaneous reports are the only tools available to monitor safety of CAM. Their collection, evaluation and analysis is important to provide regulatory authorities with safety signals to stimulate regulatory actions.

Despite these limitations, this is the first analysis performed in Italy evaluating potential predictors of CAM-related AR seriousness in the pediatric population. Moreover, considering that we have extracted and analyzed all reports collected in the Italian Phytovigilance database, our safety considerations on CAM used in children can be considered quite representative. The Italian Phytovigilance system is a valid safety data source and we believe that phytovigilance studies are a valid scientific tool, simple and inexpensive, that allows healthcare professionals to detect and better characterize CAM-related AR in clinical practice.

Conclusion

CAM-related ARs, in particular serious ones occurring in children, could represent a challenge for healthcare professionals. The present study provides new insights on the factors that might increase the risk of serious ARs and, to the best of our knowledge, represents the largest phytovigilance analysis performed in Italy.

We believe that the Italian Phytovigilance system might represent the best strategy to estimate and characterize the clinical burden of ARs related to CAM in outpatients, with the final goal of improving their appropriateness of use in the population, especially in children.

In this context, we are able to confirm that CAM, especially those containing more than two components and when simultaneously administered with concomitant conventional medications, can represent a potentially inappropriate therapeutic approach in pediatrics.

Further studies are needed in this population to investigate the effectiveness and safety of CAM, potential effects of long term use as well as possible interactions of CAM components with concomitantly used conventional medicines.

Conflict of interest

None.

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