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Discussion Kernel

Ayurveda formulations: A roadmap to address the safety concerns

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ABSTRACT

It is a matter of serious concern that the number of case reports pointing at a possible association between the clinical toxicity and the use of Ayurveda formulations is increasing significantly over the years in scientific medical literature. Though most of these cases are connected with the presence of heavy metals such as lead, mercury and arsenic in these formulations, there are also reports suggesting toxicity due to the presence of toxic chemicals of herbal origin. In the year 2008, the Government of India took an initiative of establishing the National Pharmacovigilance Programme for Ayurveda, Siddha and Unani drugs in a structured way. However, due to lack of sustained support, this program has now become defunct. This issue is of vital importance and needs to be addressed effectively on a priority basis. In this communication, we propose the following crucial policy interventions to be introduced at different levels: a. Amendments to Drug and Cosmetic Act, b. Issuing consumer guidelines, c. Issuing prescription guidelines, d. Issuing clinical monitoring guidelines, e. Implementation of good manufacturing guidelines, f. Promoting documentation of clinical safety, g. Identifying the sources of contamination, and, h. Provision for stringent punishment. If these policy interventions are taken up and implemented, a significant positive change in the scenario can be expected in the near future.

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This communication is in response to a recent news report published in the Times of India, titled “Poison in Ayurvedic drugs” where a case of lead toxicity associated with an anti-diabetic Ayurveda formulation was recounted [1]. A few days later, another similar report citing the presence of high levels of lead in several samples of Ayurveda formulations appeared [2]. It is a matter of concern that as Ayurveda interventions are gaining popularity and global acceptability, the number of such case reports pointing at an association between the toxicity and use of Ayurveda formulations is also growing significantly over the years. For instance, a PubMed search on the topic gives more than 50 such results as of now; however, the number of individual cases recorded are much more than this number [3]. While most of these reports deal with drug toxicity due to the constituent heavy metals (such as lead and arsenic), a few of them also deal with toxicity due to herbal ingredients (aconite, for instance).

Ayurveda academicians, clinicians and even regulators have always positioned themselves in a mode of denial whenever such a

report surfaces: they usually argue that either the ‘manufacturing process’ must have been faulty, or the patient must have consumed the drug in a ‘higher-than the recommended’ dose. They often point at the inefficient ‘monitoring mechanism’ that allows the sub-standard medicines to be marketed. Another argument these stakeholders put forth is the alternative possibility of environmental and other contaminated food items being the sources of poisoning. In a nutshell, the core argument they put forth is that Ayurvedic drugs, when prepared and processed according to the recommendations of the classical textbooks of Ayurveda (especially the textbooks of *Rasashastra*) and prescribed according to the principles of Ayurveda, cannot be toxic [4–7]. Although most of these arguments may be true in many of the cases, what is often ignored is the fact that ‘theoretically safe’ formulations too can produce adverse drug reactions due to various known and unknown reasons. Therefore, the responsibility of creating this awareness among the consumers and practitioners lies on the shoulders of these stakeholders. In fact it is high time that academia, clinicians and policy-makers should confront this problem head-on, instead of refuting the possibility of such events.

It may be noted that, in the year 2008, the Government of India took an initiative in establishing the National Pharmacovigilance

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Programme for Ayurveda, Siddha and Unani drugs in a structured way. Eight regional centres, 30 peripheral centres and 55 centres in various Ayurveda colleges along with a National Resource Centre at Jamnagar were established in between 2008 and 2011. Many awareness programmes were conducted by the centre itself and also in collaboration with WHO country office, New Delhi where more than 2000 teachers and medical officers were oriented towards the concept of pharmacovigilance. The centre received more than 300 suspected reports of adverse drug reactions and out of them 200 were scrutinized and analyzed by the National Pharmacovigilance Technical Advisory Committee. However, due to lack of continued support, this initiative has not been able to further its activities [8–12].

In the following paragraphs we suggest a few concrete steps that the Government of India (Ministry of AYUSH) must consider taking while regulating the affairs related to the drug production, marketing, prescription, and monitoring.

1. Amendments to Drug and Cosmetic Act

A list of potentially toxic ingredients (heavy metals and others) has already been prepared and has been classified under Schedule-E1 of the drugs and cosmetic rules as a special category [13]. However, it includes only 21 drugs from Ayurveda and has not seen any amendment since 2010. In 2010 too, certain entries such as red oxide of lead have been removed from the list, which had 25 entries prior to this. Relevant amendments are required to be introduced in the Drugs and Cosmetic Act with the addition of potentially toxic drugs in schedule E1. This can be done with the help of an expert committee which may be asked to go through the available recent literature and to suggest the list of such ingredients to be appended to the list.

Moreover, a separate record for the appropriate procedure of *Shodhana* (detoxification/processing techniques) of poisonous drugs in recommended media is also required to be maintained [14]. The description of *Shodhana* in Ayurveda is not only as a process for purification, but also as a process to enhance the potency and efficacy of the drugs. Certain medicinal plants not categorized under poisonous drugs, such as *Vacha* [*Acorus calamus* Linn.], *Haridra* [*Curcuma longa* (Linn)], *Hingu* [*Ferula foetida* Bioss.], *Kampillaka* [*Mallotus philippensis* (Lamk.) Muell-Arg.], *Guggulu* [*Commiphora mukul* (Hook. Ex Stocks) Engl.], and others too have been recommended to pass through specific *Shodhana* process before administration. A complete understanding about *Visha*, its classifications, *Shodhana* methods, media used for detoxification procedures and research literature on the impact of *Shodhana* are the tools to make poisonous plants medically useful. There are many studies that show the utility of different *Shodhana* procedures in either reducing the concentration of toxic ingredients or in converting the toxic ingredient into a non-toxic one. In another recent experimental study, it has been shown that as *Nagabhasma* enters into different sequential stages of recommended pharmaceutical processing, its potential neurotoxicity goes on reducing [15–18].

2. Consumer guidelines

In 2016, a public notice was issued by the Department of AYUSH (now the Ministry of AYUSH). This notice advised the public to purchase and consume Ayurveda, Unani & Siddha drugs only on the prescription of the institutionally qualified and registered practitioner of the respective system. The notice also warned the public to avoid purchasing these drugs online, over the counter (OTC) and to avoid their use without medical consultation [19]. Apart from

this, not much has happened since then in creating consumer awareness in the country. There is a need for publishing detailed 'Consumer guidelines' and propagating them over newspapers, websites and other mass media to educate patients regarding the issue of probable adverse drug reactions associated with Ayurveda formulations. In 2011, a report was submitted to WHO (India) that contains the draft consumer guidelines [20]. These guidelines may be refined suitably and published as the first step in this direction. Further, information brochures and other similar documents are required to be made available to all consumers which must contain the classification of potentially toxic Ayurvedic drugs, according to their degree of possible adverse effects.

3. Prescription guidelines

There is need for developing and disseminating some 'prescription guidelines' or 'Good Prescription Practices' among all Ayurveda practitioners. This is essential keeping in view the poor standards of Ayurveda education in general [21]. These guidelines are required to be circulated among all the practicing physicians of Ayurveda stream and must include the details such as: a) maximum duration for which a specific formulation can be prescribed continuously, b) information as to whether it is safe to use a formulation in specific groups of patients such as pediatric age, pregnant women, lactating women, geriatric population etc., c) specific clinical findings and investigations that reflect toxicity, if any, d) management procedure of acute/chronic toxicity of the specific formulations, antidotes, their mode of administration, dosage etc., and, e) procedure of reporting these toxicity cases to the pharmacovigilance cell. Further, it is to be made mandatory for any prescription to include the details such as posology, daily dosage, time of intake, adjuvant, and duration of medication. It may be further noted that all Ayurveda hospitals willing to be accredited by NABH are already required to ensure the implementation of certain standards. These standards require that there has to be a policy to report and analyze the near-misses, medication errors and adverse drug events. However, a specific requirement for an independent pharmacovigilance cell at every AYUSH college and hospital must be included in these requirements.

4. Clinical monitoring guidelines

Along with prescription guidelines, mandatory 'monitoring guidelines' are required to be issued to the clinicians ensuring that repeated hematological, renal, hepatic and other relevant clinical investigations are carried out whenever a preparation with toxic ingredient(s) is prescribed for more than a reasonable period. This will help in generating safety data of these formulations. Such data on safety profile, that is likely to accumulate over the years, especially in the settings such as Ayurveda hospitals associated with Ayurveda colleges, must be published from time to time. Any food–drug interaction, drug–drug interaction, herb–drug interaction, if noticed, is required to be recorded and published. Ensuring that a working pharmacovigilance cell exists in every Ayurveda college and hospital will help in generating the data required for future updating and revising these guidelines. One of the available reports that deals with the adverse events observed in one teaching hospital gives an idea about the importance of such an activity [22]. There could be a few drugs that have a narrow therapeutic range where, the difference between toxic and therapeutic doses could be very small. Such drugs need their dosage to be adjusted according to measurements of the actual blood levels achieved, lithium being one such example. This monitoring is often possible through therapeutic drug monitoring (TDM) protocols.

There is a need for developing such protocols for potentially toxic but clinically effective drugs of Ayurveda [23].

5. Manufacturing guidelines for pharmaceutical industry

There are already sufficient rules to ensure good manufacturing practices for formulations containing potentially toxic ingredients, however, their implementation is a major problem. Since it is the State Governments that are expected to implement these standards, there needs to be a rigorous action plan in this direction. A study has reported that labeling guidelines are poorly followed in India [24]. Labeling guidelines are required to be strictly implemented making it mandatory to supply sufficient information regarding ingredients and to keep information leaflets as inserts inside the packages. Packaging of multiple doses of potentially toxic formulations in powder and other forms that are difficult to measure must be completely prohibited. Regulation of irrational combinations and dosage of proprietary products having *Rasaushadhi* is another area of concern that needs to be strictly regulated. Advertising the Ayurveda medicines has recently emerged as another problem area, which needs to be regulated [25]. Last, but not the least, it must be ensured that the formulations with potential adverse effects must not be made available over the counter.

6. Documentation of clinical safety

This should be done at various levels. The National Pharmacovigilance Programme for Ayurveda, Siddha and Unani drugs, which is in dormant state since last few years, needs to be made functional. The pharmacovigilance centres and cells are required to become proactive in reporting adverse events and publishing data in appropriate form. Reputed academic and research organizations such as Central Council for Research in Ayurvedic Sciences, All India Institute of Ayurveda, Institute of Postgraduate Teaching and Research in Ayurveda, Banaras Hindu University, National Institute of Ayurveda, etc. should undertake toxicity studies with an aim to develop technology for early detection of adverse effects and measures to overcome them through suitable modifications in the manufacturing process. AYUSH pharmaceutical industry should also be encouraged to participate in such studies. Even the accreditation standards for AYUSH colleges are required to include compulsory setting of pharmacovigilance cells with regular and timely reporting of adverse drug reactions. Long-term research plan, at least for 10 years, based on good documentation of the adverse events in the Ayurveda hospitals attached to Ayurveda colleges needs to be implemented. Steps are also required to be taken to emphasize on documentation of pharmacovigilance concerns, if any, during concomitant use of Ayurveda and modern drugs in various programmes such as National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke (NPCDCS).

7. Research to identify the sources of contamination

CCRAS and even other academic institutions of repute are required to plan detailed research on what exactly are the sources of toxicity, starting from the collection of herbs and other raw materials to their processing. One major concern that remains to be addressed is that, at present, no passport data for raw materials is available and the value chain is mostly non-transparent. It is to be ensured that the production system is completely transparent and such a step will help the policy makers in understanding and addressing the specific problem areas.

8. Provision for stringent punishment

Finally, there must be provisions for stringent punishment for violating the norms of manufacturing, prescribing and monitoring.

9. Envisioned impact of these steps over the next ten years:

a. Improved consumer awareness: The common notion that 'All Ayurvedic drugs are safe and non-toxic' is expected to stand corrected among the consumers. Consumers would weigh the benefits and risks before irrationally starting with Ayurveda interventions, and will consult qualified physicians before starting any therapy on their own.

b. Accountability of pharmaceutical manufacturers: Manufacturing practices are likely to improve with respect to the quality of the products. It is expected that complete and correct information will be available to the consumers regarding the products they use.

c. Rational prescription and monitoring practices: Rational prescription of Ayurveda formulations among the physicians is expected to become a norm. They are expected to rightly prescribe, monitor and notify adverse reactions in a timely manner. At least a few drug monitoring protocols may become available wherever the therapeutic range is very narrow.

d. Data on safety information: Academic and research institutions are expected to gather required data to identify the nature of adverse drug reactions. An inventory of possible food–drug, drug–drug and herb–drug interactions is expected to become available. This will help in framing the right kind of policies for future.

e. Availability of newer and easier ways of early detection of toxicity: At least a few methods of early detection of toxicity, and possibly, ways of management of drug-associated clinical toxicity will be available.

10. Conclusion

Every object on this planet warrants a judicious use, and, as stakeholders we can never take our duties for granted. In *Caraka Samhita* it is documented as to how rational use can make a drug a drug, and irrational one a poison. So, it is high time we develop this insight in the context of toxicity issues associated with Ayurveda formulations.

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