Adverse events with ayurvedic medicines- possible adulteration and some inherent toxicities [version 2; peer review: 2 approved, 1 approved with reservations]

Previously titled: Adverse events with ayurvedic medicines- Adulteration and inherent toxicities

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Abstract
Ayurvedic medicine, a traditional system of medicine practiced in the Indian subcontinent is considered to be devoid of adverse effects. We report three cases which highlight the possibility of adverse events related with the use of ayurvedic products. A 35 years old woman with hepatitis took ayurvedic powder medicine and with swarnabhasma (gold salt) had her liver injury worsened, possibly due to alkaloids, and developed nephrotic syndrome, possibly due to gold salt. A 57 years old hypertensive man was taking ayurvedic medicine containing reserpine which had long been withdrawn from the allopathic system of medicine due to wide range of side effects. A 47 years old woman with rheumatoid arthritis was taking an unknown tablet containing a steroid as an adulterant for 2 years and developed side effects typical of steroid excess. We like to highlight the fact that ayurvedic medicines do have propensity to cause adverse effects due to adulterations or inherent constituents like alkaloids, and hence are may not always be completely safe.

Keywords
Ayurvedic medicine, heavy metals, alkaloids, adulteration

Open Peer Review

Reviewer Status
Invited Reviewers
1 2 3

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Kshirod Kumar Ratha, National Research Institute of Ayurvedic Drug Development, Kolkata, India
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Any reports and responses or comments on the article can be found at the end of the article.
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Author roles: Paudyal B: Conceptualization, Data Curation, Supervision, Writing – Review & Editing; Thapa A: Data Curation, Writing – Original Draft Preparation; Sigdel KR: Data Curation, Supervision, Writing – Review & Editing; Adhikari S: Formal Analysis, Supervision, Writing – Review & Editing; Basnyat B: Conceptualization, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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Background

Ayurveda is one of the most renowned traditional systems of medicine, and has been widely practiced in the Indian subcontinent, including Nepal, since the 2nd century BC. People have faith with ayurveda as it is based on the use of natural products, and is considered to be devoid of adverse effects. Allopathic medicines on the other hand are known to have adverse effects, and are generally prescribed based on risk versus benefit for a particular disease and patient. Alternative forms of medicine like ayurveda are usually thought by patients and ayurvedic doctors alike to be harmless, and are also advertised similarly. But it has been proven that certain constituents of ayurvedic products, like heavy metals and alkaloids, can have adverse effects, and the possibility of these adverse events needs to be highlighted so that both the practitioners and consumers will become cautious in their use, as with allopathic medicines.

Sometimes, patients receive unknown powders adulterated with drugs such as steroids in the name of ayurvedic medicine, prescribed by traditional healers. People’s faith in ayurvedic medicines has been exploited by many healers who prescribe such unnamed powders to patients, especially with chronic diseases like arthritis and asthma, leading to adverse events.

Case 1

A 35 years old Newar woman from suburban Kathmandu who was a housewife, developed jaundice, vomiting and low grade fever. Family members took her to a local healer who claimed to be an ayurvedic practitioner. He prescribed a combination preparation called “puriyas” in paper packets containing several powder medicines and gold salt (swarnabhasma). Despite the treatment, she became sicker with deepening of jaundice and significant weight loss (almost half of her previous body weight) in about one week. She was then rushed to the emergency department (ED) of Patan Hospital, Lalitpur, Nepal (April, 2018). On presentation to ED, her laboratory parameters, with normal range in parantheses, were as following:

Complete blood count (CBC): white cell count 10.9 (4–10) × 10⁹/L; neutrophils 70%; lymphocytes 22%; monocytes 8%; red blood cells 4.8 (4.2–5.4) × 10⁹/L; haemoglobin 12.1 (12–15) g/dL; platelets 136 (150–400) × 10⁹/L.

Biochemistry: random blood sugar 123 (79–160) mg/dL, urea 59 (17–45) mg/dL; creatinine 1.3 (0.8–1.3) mg/dL; sodium 138 (135–145) mmol/L and potassium 4.3 (3.5–5) mmol/L.

Hepatic panel: bilirubin total 65.73 (0.1–1.2) mg/dL and direct 43.9 (0–0.4) mg/dL; alanine transaminase (ALT) 566 (5–30) units/L; aspartate transaminase (AST) 494 (5–30) units/L; alkaline phosphatase (ALP) 155 (50–100) IU/L; albumin 3.0 (3.5–5) g/dL, International normalized ratio (INR) 2.0 (0.9–1.2)

Urine examination: albumin 3+, sugar- nil, white cell count 1–2/ high power field, red blood cells- nil, 24 hour urine protein- 3.5 gm/ day

Viral hepatitis panel: Hepatitis A virus (HAV) IgM, Hepatitis E virus (HEV) IgM, HBsAg, Hepatitis C virus (HCV) IgM- all negative

She was admitted and diagnosed as fulminant hepatic failure with possible infective hepatitis and nephrotic range proteinuria. The powder was stopped, and she was managed with supportive treatment (intravenous fluids, intravenous ceftriaxone 1 gm and oral doxycycline 100 mg twice daily for 7 days, daily blood glucose and alternate day hematology, electrolytes, renal and hepatic biochemistry monitoring). She was discharged from hospital in two weeks after she started improving. She recovered, with bilirubin and transaminases falling gradually to normal after three weeks (bilirubin-total 1.0 mg/dL and direct 0.6 mg/dL, ALT 30 units/L and AST 23 units/L). Her proteinuria also decreased gradually (24 hour urine protein- 0.8 gm/day), and urine dipstick for protein was negative at one month.

Case 2

A 57 years old gentleman from Kathmandu, a teacher by occupation had come for a blood pressure check-up at the medical outpatient department (OPD) of Patan Hospital, Lalitpur,
Nepal in June, 2018. He told the doctor that he had been taking an ayurvedic medicine called “Tensarin” for high blood pressure for the past 3 years. The composition leaflet revealed that this drug contained several herbal preparations, one of which was “Rauwolfia serpentina” from which the active substance “Reserpine” is derived. His blood pressure during this visit was 140/80 mm Hg. Reserpine is not a recommended agent for treating hypertension due to its adverse effects such as decreased cardiac output, bradycardia, sedation, depression, diarrhea, and increased gastric acid. Fortunately, our patient had no adverse effects of reserpine. We explained to him the risks of the drug he was receiving, then switched him to amlodipine 5 mg once daily. He has been in regular follow up now and his blood pressure continues to be well controlled.

Case 3
A 47 years old Aryan woman from suburban Lalitpur who was a housewife, came to the OPD of Patan Hospital in April, 2018 with a complaint of excessive weight gain. She claimed that she was gaining excessive amount of weight despite maintaining her normal diet and physical activity. She also had sore muscles and bruises on her body. On further inquiry, she said that she had been experiencing pain over multiple joints for past 2 years. She was taking some unlabeled tablet (Figure 2) prescribed to her by a local practitioner whom she believed to be an ayurvedic doctor. The tablet controlled her pain, and it also made her feel “strong” as she could perform her chores that she was unable to, prior to that medication. On further questioning as to why she chose this form of medication, she said that she believed the ayurvedic medicine were potentially harmless. The drug was sent for chemical analysis, and it revealed that the tablet consisted of prednisolone, an exogenous steroid. Soon after we stopped the unlabeled medicine, she started to have more pain and swelling in the small joints of both hands and symptoms suggestive of steroid withdrawal were noted. She was subsequently diagnosed as rheumatoid arthritis based on clinical features and laboratory parameters: C- reactive protein- 25 mg/L (normal < 5 mg/L), Rheumatoid factor- 30 IU/mL (normal < 25 IU/mL). She was then managed with disease modifying anti-rheumatic drugs (DMARDs); oral methotrexate 7.5 mg per week for 2 weeks followed by 15 mg per week thereafter and oral hydroxychloroquine 400 mg once daily. Low dose steroid (oral prednisolone 20 mg daily) was continued with gradual taper and stopped over 3 months. When last seen 3 months ago (October, 2018), her arthritis was well-controlled with DMARDs without steroid preparations or unlabeled medicines.

Discussion
In the first case, the patient with jaundice due to infective hepatitis was taken directly to an alternative medicine practitioner. Jaundice is a problem which most of the Nepalese people in general, regardless of the status of their education, consider as a disease requiring alternative medicine such as ayurvedic medicines. Even if they consult allopathic clinicians first, many take ayurvedic medicines after a period of time as it usually takes many days to weeks for jaundice to resolve; and their faith in ayurvedic medicines gets strengthened. But unfortunately, many plant products contain alkaloids such as pyrrolizidine which are toxic to the liver, and may precipitate or worsen liver injury. In our patient, it was not clear whether the medicine she received initially contained harmful alkaloids as the analysis was not done. It was also not clear whether the worsening of her liver disease was caused by the disease process itself or the use of the powder medicine, but we can at least say that these products were not helpful in dealing with her liver problem as is generally believed. We see many patients coming to our clinic with worsened jaundice after the intake of ayurvedic products.

Our first patient also received gold in the form of swornabhasma that has been linked with kidney injury and nephrotic syndrome. Ayurvedic products contain certain amounts of different heavy metals like gold, lead, mercury, copper, iron, arsenic, zinc, and cadmium that are believed to have therapeutic benefits. Studies have shown that most of the ayurvedic products contain these metals in amounts exceeding WHO permissible limits, and can potentially cause harmful consequences to human health. The possibility of the potentially toxic amount of these heavy metals should also be considered and precautions taken. So it is imperative that the amount of such constituents in each of the ayurvedic products be mentioned on the label so that patients have some idea of the substance and the quantity being taken.

Our second patient had been taking reserpine in the form of ayurvedic product, as an antihypertensive agent. Though there are studies demonstrating the safety and efficacy of reserpine use as an antihypertensive agent, the present allopathic guidelines do not support the use of such adrenergic inhibitor as a first line treatment for hypertension, nor is it included among any of the indications for treating hypertension. Reserpine causes depletion of norepinephrine, thereby producing adverse effects such as decreased cardiac output, bradycardia, sedation, depression, diarrhea, and increased gastric acid. Its wide range of side effects led to the limitation of its use in allopathic system of medicine several decades ago, but it is still used in the ayurvedic system. Moreover, the product Tensarin did

![Figure 2. Unlabeled tablet taken by case 3.](image-url)
not have the exact amount of reserpine and other constituents mentioned in its label. So it was risky to continue the drug without knowing the exact amount the patient was receiving.

Adulteration of ayurvedic products has been another alarming issue. We see many patients with arthritis and asthma like our third patient, coming to our clinic with classic Cushingoid character and many of the other adverse events of chronic steroid usage: hypertension, weight gain, hyperglycemia, osteoporosis, bone fracture, muscle weakness, ocular effects, gastrointestinal effects, and electrolyte imbalance, following years of taking adulterated ayurvedic products. Adrenal crisis when stopping these drugs is a potential problem.

Most people in South Asia believe that ayurvedic products are safer and more effective for chronic diseases. Patients with chronic disease are more vulnerable to mishaps related to ayurvedic products because they want to get rid of their chronic disabling condition, and tend to try alternative medicine products in the hope of safety and cure. Many of these chronic diseases (diabetes, hypertension, arthritis, cancer) may have no cure in either allopathic or alternative medicine practices, and patients should be counselled regarding this fact so that expectations are realistic.

### Conclusion

Ayurvedic medicines may be beneficial to health, but are not devoid of adverse effects. Adverse events may be due to adulteration or some inherent constituents like alkaloids. Each chemical compound in any ayurvedic preparation should be listed in the manufacturer’s label along with the amount which may lead to proper dosing, and may reduce adverse events. Proper counselling by health professionals, especially regarding adverse events, will play an important role in minimizing harm.

### Consent

Written informed consent for publication of clinical details and clinical images were obtained from the patients.

### Data availability

All data underlying the results are available as part of the article and no additional source data are required.

### Grant information

This work was supported by the Wellcome Trust [106680].

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### References

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Phaik Yeong Cheah
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Thank you for asking me to review this interesting paper. My review is brief as most of the issues have been addressed by the other reviewers. In addition, although I have training in pharmacy and pharmaceutics, I do not have expertise in ayurvedic medicine.

My main comment is regarding terminology.

The term “adverse effects” is used by many but it is not an official FDA/ICH GCP term. If the authors would like to use this term, please provide definition and reference.

“Adverse events”, “adverse drug reaction (ADR)” - please see definition provided by ICH GCP and FDA guidelines. The term side effect is often used instead of “adverse drug reactions”. ADR implies that there is a causality whereas adverse events does not.

Eg. see Conclusion.

Ayurvedic medicines may be beneficial to health, but are not devoid of adverse effects. Adverse events may be due to adulteration or some inherent constituents like alkaloids.

Adverse effects and adverse events are not the same thing.

Please check for typos and grammatical errors – eg. in the abstract
Typo “35 years old woman” should be “35 year old woman” etc
We like to highlight – we would like to highlight

Finally, for the Discussion section, do the authors have any recommendations or research agenda?

Thank you
Is the background of the cases' history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
No

Is the conclusion balanced and justified on the basis of the findings?
Partly

**Competing Interests**: No competing interests were disclosed.

**Reviewer Expertise**: ethics, engagement

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 30 Oct 2019

**Sudeep Adhikari**, Patan Academy of Health Sciences, Lalitpur, Nepal

Thank you for the review.

Corrections of typos and grammatical mistakes have been done in the revised version, especially in the abstract section.
The term "adverse events" has been used instead of "adverse effects".

**Competing Interests**: none
Kshirod Kumar Ratha  
National Research Institute of Ayurvedic Drug Development, Kolkata, West Bengal, India

1. Coming to the contents and case reports mentioned in this article, review on this article would be lengthier than the article itself.

2. The first sentence / paragraph of the abstract / introduction need refinement. Ayurveda never considered to be devoid of adverse effects. The classics have vividly explained possibilities of adverse effects and their management systematically.

3. Further, many statements need to be re-written. Ayurveda never used alkaloids exclusively in their formulations. Alkaloids are not sole but, a part of the formulation. The concept of Ayurveda drug formulation is entirely different than as understood by the authors in the manuscript.

4. The first case have taken puriyas (possibly a packaging system that dispensed medicines in a paper wrapping) from a self-claimed Ayurvedic healer, which contained Swarna bhasma.
   1. The medicine was only given in a paper wrapping. In such case, how it was ascertained that the puriya contain Swarna bhasma. The medicine was not subjected to any analysis in order to claim they had Swarna bhasma in toxic levels.
   2. Previous disease history or reports are not considered to check the condition of patient prior to medications. When she visited the so called Ayurveda physician; already she was presenting with some liver pathology. In such case, how to confirm that the manifestation is because of puriyas. Further, how many days the puriyas were consumed, what were the doses, how they were administered is unclear.
   3. One doesn't or should not become a Ayurvedic healer just by claiming.
   4. Gold is claimed to be toxic by the authors by citing a reference. It is fine for that specific instance. Processed Gold (Swarna bhasma) is entirely different than the Gold that is being highlighted by the authors. Please refer: Paul and Sharma (2011)\(^1\) and Jamadagni et al. (2015)\(^2\) for further needful information.

5. The 2\(^{nd}\) case: No clear mentioning regarding whether the "TENSARIN" was taken by patient under prescription or by OTC. Withdrawing the drug was a good decision, but patient was put on allopathic medicine again though his Blood Pressure was near normal to his age. (Lin et al. (2016)\(^3\)) . Claiming to have achieved normo-tension when patient was already normal with previous medications need attention. Reserpine as an extract is the culprit in unregulated dose, but blame has been put on Sarpagandha and formulations containing Sarpagandha. It is unclear (from the discussion) whether the patient is taking reserpine or Sarpagandha? What is being used in the formulation? Again, the drug regulating mechanisms existing in the country need a serious retrospective analysis here.

6. The 3rd case again talks about some unidentified traditional healer whom the patient believed as an Ayurveda physician.

7. The conclusion given by the article is unrealistic as they opine to mention all the CHEMICAL COMPOUNDS present in a formulation. Even the authors mention of probability of adverse events by the prior medications, but in my opinion until the causation is not fully established,
reporting and blaming a medicine / medical system is unethical.

8. These cases are treated and reported in Nepal? If, so how the practices are regulated there. It is a matter of series concern. In India, the system is regulated at different levels. The administration at Nepal should take a serious note on such practices and develop a stringent mechanism.

9. The discussion highlighted upon alkaloids like - pyrrolizidine and possibility of hepatic impairment. Which medicine from the three cases being reported in the manuscript contain pyrrolizidine? Hypothetical predictions harm systems.

10. Authors themselves are expressing that the patients/sufferers are wasting time by running here and there for satisfactory relief. In such cases, it is better generating awareness and implement stringent drug regulating and implementing practicing policies. Blaming a system will not yield anything.

Ayurveda concepts of drug administration are quite different than the conventional approaches. Besides other basic requirements; understanding digestive ability, metabolic capability, tolerability of the patient to a specific dose of the drug, psycho-somatic constitution etc. of the patient is essential before starting treatment. The observations made in the article appears to be illogical and based on inadequate data. They need a further thorough review.

A drug can be panacea or poison. Drugs fulfilling the criterion of a standard drug will always become panacea provided, if it is used properly. On the other hand, a poorly prepared or manufactured drug however used skillfully, will always prove to be a poison. Classics of Ayurveda do mention the hazards of drugs, which are not properly manufactured. Seers have prescribed specific processing techniques that remove harmful properties from these drugs. There is no sufficient evidence in the article to confirm the harmful nature of the formulation.

Overall, it becomes clear from the manuscript that there is a serious need of looking into the drug regulating mechanisms in the country instead of blaming a system as such.

References

Is the background of the cases' history and progression described in sufficient detail?
Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly
Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the conclusion balanced and justified on the basis of the findings?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ayurveda Medicine, Medicinal Plant Ethnobotany, Clinical trial with Ayurvedic drug, QC herbal drug

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
Ayurveda classics and only Rauwolfia is rarely prescribed in Ayurveda.

References

PubMed Abstract

Is the background of the cases' history and progression described in sufficient detail?
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Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
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Is the conclusion balanced and justified on the basis of the findings?
No

**Competing Interests:** No competing interests were disclosed.

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Author Response 29 Jul 2019

**Sudeep Adhikari**, Patan Academy of Health Sciences, Lalitpur, Nepal

Thank you for your constructive comments.

The cases reported/discussed by the author are very serious. The authors tried to malign the Ayurveda system which is evident from the title of the manuscript itself which need to be rectified.

**Answer-** The title of the manuscript has been revised as- 'Adverse events with ayurvedic medicines- possible adulteration and some inherent toxicities'. The revised title does not intend to malign the Ayurveda system, but tries to raise the issues of adulteration and some inherent
toxicities of medicines that have given bad name to the system of Ayurveda.

All natural drugs are not always safe. The medicines mentioned in the manuscript in puriya (packet form or unlabelled without a valid prescription) are usually unethical and unlawful. Without a valid prescription and certificate of analysis of the drug it is very difficult to say they were Ayurvedic drugs. Also, without a valid prescription by a registered medical officer they can not be confirmed as Ayurvedic doctors rather the authors could labelled them as Quacks without any medical degree.

Answer- The traditional healers who claimed themselves to be ayurvedic practitioners prescribed the unlabeled puriyas and tablets to our patients. Analysis of the puriya drug taken by case 1 was not done. However the tablet taken by case 3 was analysed and steroid was found to be present. Hence we have raised the issue of adulteration in the name of ayurvedic medicines, giving bad name to the Ayurveda.

In case 1, as the base line data of patient who had jaundice before the administration of drug was also not available, which makes it difficult to speculate liver injury caused by Ayurvedic drugs without any histopathology and drug analysis report. Hence, the link between the drug and liver failure can not be linked convincingly.

Answer- The base line data of the first patient is not available. We have not performed histopathology and drug analysis report. So we are not sure if the drug contained harmful alkaloids, and if the worsening of the liver disease was due to disease process itself or the unlabeled drug that was given. We have mentioned this in our revised manuscript. Here we wanted to focus that at least the alternative drug our patient tried did not help in her liver problem as is generally believed by Nepalese population.

Properly manufactured and prescribed in a therapeutic dose is always safe even in pediatric age group. Genuine Ayurvedic Metallic preparations also can be prescribed as they contains permissible metallic traces. Proper control on manufactuing and Quality control of any drug is the out look of the regulatory bodies of the state.

Answer- The case 1 also received swarnabhasma (gold salt) for jaundice, and developed kidney injury. Heavy metals can be beneficial if used in permissible amount, but there are reports of presence of different heavy metals exceeding the maximum permissible amount in different ayurvedic preparations. This raises the issue of possible toxicities of these inherent constituents of ayurvedic medicines.

Rauwolfia also in a small dose is very good for treating hypertension. The amount of Rauwolfia present and the reserpine amount required to cause the adverse effect needs to be highlighted. Because Rauwolfia contains so many alkaloids apart from Reserpine, which cause less possibility of adv. effect than Reserpine. The combination of Rauwolfia with other drugs is usually mentioned in Ayurveda classics and only Rauwolfia is rarely prescribed in Ayurveda.

Answer- Although reserpine has safely been used in treating patients with hypertension in some studies in the form of Rauwolfia, the routine use of reserpine as antihypertensive agent has not been recommended by any of the current guidelines of allopathic medicine. Moreover, the ayurvedic preparation our patient was taking for hypertension did not have label regarding amount of reserpine in each tablet. So we have raised the issue about mentioning the exact amount of each chemical constituent in any ayurvedic product so that the patients have some idea about the substance and the quantity being taken.
Sanjib Kumar Sharma  
Department of Internal Medicine, B.P. Koirala Institute of Health Sciences, Dharan, Nepal

The Authors tried to explain a common scenario of the use of alternate medicine observed by the many clinicians (albeit not documented much) in Nepal. The case reported is of importance to clinical practice and written well.

Ayurvedic medicines have been used in Nepal since the time immemorial. Ayurvedic and herbal medicines are known to cause varying degrees of drug-induced liver injury. Severe liver injury related to Ayurvedic and herbal medicines is studied to certain extent from the Indian subcontinent. Below are my comments for the note of the authors.

Case 1: The lady developed features of acute liver failure. Ingestion of gold formulation is known to cause hepatic injury by when the storage capacity of lysosomes exceeds. The parenteral preparation can, however, cause acute fulminating hepatic failure. Hepatotoxicity by pyrrolizidine alkaloids, often a composition in Ayurvedic medicine has been long recognized.

Although the authors presume that the gold or other content of the consumed Ayurvedic medicine is likely to be the factor causing liver failure, the etiology of the liver injury is not clear in this case report. Histopathological study of the liver biopsy would have shed more light to understand the nature of the liver injury. Moreover, analysis of the available sample should have allowed knowing if proposed alkaloids were actually present in the Ayurvedic medicine consumed.

Case 2 – Reserpine is no more produced by pharmaceutical companies. It is implicated multiple side effects including postural hypotension, has not been tested as monotherapy in a clinical trial. However, reserpine had been used in large renal disease prevention program in India and was reported to have good blood pressure control without much adverse effect. A Chinese study of polypill contained low dose reserpine and had not shown more adverse effects. Similarly, reserpine was found to be safe in the treatment of cocaine dependence. In this clinical trial the safety results suggest that reserpine was safe and well tolerated by the participants.

Case 3: The case exampled the common problem faced by clinical. Adulterated Ayurvedic medicine is a common issue in the Indian subcontinent. In 2011, Ayurvedic research center of KEM hospital Mumbai, India, reported out of the 244 Ayurvedic samples that were analyzed for steroid 96 samples were tested positive. About 18 samples had more than one steroid. This case report may help to create awareness among practicing clinician not aware of the problem or habit of looking into it.
References
3. Mani M: What we should do for chronic renal failure in India. *Journal of Mahatma Gandhi Institute of Medical Sciences*. 2017; 22 (2). Publisher Full Text

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Competing Interests: No competing interests were disclosed.

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Author Response 29 Jul 2019

Sudeep Adhikari, Patan Academy of Health Sciences, Lalitpur, Nepal

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**Competing Interests:** none