



Editorial

Ayurvedic drugs in case: Claims, evidence, regulations and ethics



Just before the Independence Day, on August 13, 2016, the Governor of Maharashtra Shri C. Vidyasagar Rao expressed deep concerns over the misleading advertisements of Ayurveda, Siddha, Unani and Homoeopathy (ASU&H) drugs. The Governor was addressing senior professors, scientists and students at Savitribai Phule Pune University during a function to release two volumes of book on 'AYUSH in Public Health' written by eminent social scientist Professor R K Mutatkar. In the speech, the Governor expressed deep concern over the fact that many Ayurvedic and traditional medicines being sold in the market through commercial advertisements in media claiming to cure diseases like diabetes without scientific evidence or clinical trials to support these claims. The Governor further appealed that the Government must take strict action against such advertisers to protect public interests.

This entire issue has scientific, socio economic, legal, moral and ethical dimensions. Misleading advertisements, tele-marketing, multi-level marketing, direct selling and e-tailing pose new challenges. Several eminent public personalities or celebrities as Brand Ambassadors are promoting various products by making unrealistic claims. Many television channels are broadcasting misleading advertisements with tall claims luring desperate patients. It is hoped that the new Consumer Protection Act 2015 Bill is cleared soon and the law will take strict course to put stop to blatant cheating through misleading commercial advertisements claiming cure for many incurable diseases.

1. Drugs and Magic Remedies Act

In July 2016, just about a month before the Governor's appeal, Maharashtra State Food and Drug Administration (FDA) had issued notices to two manufacturers of Ayurvedic products because their advertisements were objectionable. The Drugs and Magic Remedies Act (Objectionable Advertisement) 1954 (DMR 1954) prohibits claims related to diagnosis, cure, mitigation, treatment or prevention of any disease, disorder or condition specified in the Schedule, which currently include 56 diseases such as diabetes, cancer, AIDS, asthma, obesity. The state FDA has reportedly served 1434 notices under the DMR Act to various print and electronic media across in the year 2013–14. Of course, this is just a tip of the iceberg.

The Minister of State for AYUSH Shri Shripad Yesso Naik during question hour in Parliament has stated that "the government is in the process of bringing the amended Drugs and Magic Remedy Act. The Law department has already approved it. Medicines sold

through such advertisements while misguiding the public should be stopped". This is indeed an affirmative step. The Minister has admitted that several advertisements of medicines in print and electronic media are making tall claims and the complaints are true to an extent. J-AIM applauds the Governor of Maharashtra and the AYUSH Minister for taking clear stand in the public interest.

2. Ayurvedic, Siddha, Unani drugs

The current Drug and Cosmetic Act and Rules (DCA&R) contain regulatory provisions for and Ayurvedic, Siddha, Unani (ASU) drugs. Understandably, the nature of allopathic drugs and ASU drugs are distinctly different from each other. However, many issues related to safety, quality and efficacy remain common to any drug - be it modern or ASU. The National Policy 2002 of Indian Systems of Medicine clearly states the need for substantial evidence for Ayurveda patent and proprietary (P&P) products, however this recommendation still awaits implementation. Currently P&P ASU drugs can be put in the market without any scientific or clinical data as evidence. Increasing number of reports and publications are questioning safety of ASU drugs. Current scientometrics suggests increase in case reports showing adverse events with ASU products. The manufacturers need to be more responsible and proactive to ensure safety, quality and efficacy of ASU drugs especially when people have more expectations from Ayurveda products.

The traditional knowledge and years of experience generated from Ayurveda practices is certainly valuable for discovering new drugs for diabetes. There can be two approaches to develop evidence based Ayurvedic medicines. First, to undertake robust documentation of prevailing practices to show tangible benefits of Ayurvedic drugs in clinical management of diabetes. This approach should bring clinical experiences, case records, and textual information from classical traditional practice as evidence of benefits [1]. The second approach can be of reverse pharmacology where systematic discovery of new drugs and formulations based on knowledge of Ayurveda can be undertaken. Scientific data generated from such studies should be presented as evidence for safety, quality and efficacy. Earlier, a team of Indian scientists including Drs Rama Ashok Vaidya, Urmila Thatte, V Mohan, under the New Millennium Indian Technology Leadership Initiative (NMITLI) of the Council for Scientific and Industrial Research (CSIR) have reported promising leads for management of diabetes and highlighted value of traditional knowledge inspired drug discovery following the reverse pharmacology approach.

Currently, most of the ASU drugs are sold for treatment of difficult-to-treat and Non-Communicable Diseases (NCDs).

Peer review under responsibility of Transdisciplinary University, Bangalore.

<http://dx.doi.org/10.1016/j.jaim.2016.08.005>

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Obviously because the market of drugs for NSDs is very large. As per the World Health Organization data NCDs account for about 60% (5.87 million) of all deaths in India. The four major contributors - cardiovascular diseases, cancer, chronic respiratory diseases and diabetes make the largest contribution to morbidity and mortality in India. There is no definitive cure available to either of these conditions, while surgical advances and powerful new drugs are known to be responsible to reduce mortality and morbidity. Most of the NCDs including the four major contributors are listed in the Schedule of DMR Act. This means, no claims regarding their diagnosis, cure, mitigation, treatment or prevention are allowed by existing provisions of the Law. In any case, the Government must discourage and castigate efforts to flout the current laws causing risk to patients who are suffering from a serious medical condition. Since this subject is very complex, let's take diabetes as a representative case for the purpose of this editorial.

3. Ayurvedic drugs and diabetes

The diabetes drug market is rapidly growing as India is moving to become world diabetes capital. The major market share is from sale of prescription drugs, however, because of their limitations and side effects, increased number of people are trying various alternatives. This has opened new lucrative opportunities in India for herbal medicines and ASU drugs. People generally believe that herbal drugs are safe and so they are inclined to use them even at higher cost. This opportunity was sensed by marketing wizards during last decade when number of misleading advertisements started appearing in print, electronic and social media.

The first red flag about this issue was raised by United States FDA (US FDA) when they reported that certain products sold as ayurvedics, herbal drugs or dietary supplements, actually contained active pharmaceutical ingredients. The US FDA had issued warning letters to number of companies selling products claiming to treat, cure, prevent, or mitigate diabetes and related complications to consumers in the US. In 2013, the US FDA detected presence of synthetic metformin in Ayurvedic tablets manufactured by a Gujarat based Indian company. Incidentally, metformin, which is most preferred drug for type 2 diabetes was discovered from traditionally used medicinal plant. Today, one tablet of 500 mg metformin costs about Rs 1.25 when average cost of so called anti diabetes herbal tablet is about five times or more. The present socio economic scenario seems to be conducive to market for spurious herbal drugs and so more strict regulation and constant surveillance is required.

One of the basic principles of pharmacovigilance demands that every product should be subjected to continuous studies and vigilance throughout its lifecycle. The frame of evidence also changes in the reference with changing disease dynamics and advancing biology. For example, the incidence of diabetes is shifting to lower age groups. The outcome assessment in diabetes has shifted from mere measurement of blood glucose levels to glycated hemoglobin. Scientific evidence cannot be founded on scattered information and a few old studies. The current approach expects proper outcome assessment based on state of art research and experiments that explore fundamental questions.

4. Ayurvedic drugs from CSIR and CCRAS

In the year 2010 with lot of fanfare CSIR had launched two herbal products one named Memory Plus through Central Drug Research Institute (CDRI) and another product named Asmon through Indian Institute of Chemical Biology (IICB). Today, we do not know their commercial fate, however their scientific credential still remain obscure. Earlier, sometime in 1995, CCRAS had

launched antimalarial drug named Ayush 64, with lot of hype, however even after over two decades of existence it has hardly any impact even in national programs.

In contrast, systematic rigorous scientific research on traditional Chinese medicine - qinghaosu resulted in discovery of new drug - artemisinin, which has become a drug of choice as standard treatment of Malaria [2]. Ironically, when Dr Youyou Tu was receiving a Nobel Prize in 2015 in recognition of her work on artemisinin; around the same time CSIR announced another 'breakthrough' of a scientifically validated anti-diabetes herbal drug, named 'BGR-34' based on Ayurveda for management of type-II diabetes mellitus. This drug is claimed to be jointly developed by two CSIR laboratories, National Botanical Research Institute (NBRI) and Central Institute for Medicinal and Aromatic Plant (CIMAP). However, as this editorial is being written, no information about this product was available from CSIR or NBRI or CIMAP official websites. The reputed scientific database like PubMed, Scopus did not show any research article related scientific studies on BGR 34. The Clinical Trial Registry - India (CTRI) did not have any record of diabetes clinical trials registered from CSIR, NBRI or CIMAP.

In March 2016 Press Information Bureau, Government of India announced that the National Research Development Corporation (NRDC) of the Department of Scientific & Industrial Research, Ministry of Science & Technology have signed a License Agreement for commercialization of Ayush-82, an ayurvedic formulation for prevention and management of Diabetes developed by Central Council for Research in Ayurvedic Sciences (CCRAS) New Delhi, an apex organization for research in Ayurveda under the Ministry of AYUSH. According to present Chairman, NRDC, patients prefer Ayurvedic drugs as it can be seen that in the recent past NRDC licensed 12 Ayurvedic drugs developed by CCRAS to 32 companies in India. It is remarkable to take Ayush products to industries, however, in the interest of public health, it is crucial to critically look at the validity of scientific evidence in support of various claims.

In a documentary available on YouTube and being shown on electronic media, CCRAS scientists have stated: "when you take this (Ayush 82), dose of insulin is reduced gradually. After six months, insulin can be stopped. It does not cause any side effect, on the other hand, patient's quality of life gets improved We have completed a trial in 806 patients in Punjabi Baug, New Delhi." These claims are expected to be supported by scientific evidence. However, no published scientific papers are available in PubMed/Scopus nor CTRI registration details are available. Without these details, it will be very difficult to justify the serious claims made by CCRAS.

Strangely, when a new and more appropriate route of phyto-pharmaceuticals [3] is available, these products are registered as Ayurvedic P&P medicines, rather than a robust regulatory approval path through the Drug Control General of India. Sadly, instead of publishing in credible scientific journals, the research councils preferred to create headlines in popular print and electronic media. This is certainly worrying and calls for serious introspection.

5. Serious concerns

Eminent experts are already asking questions about scientific validity of both these products. A pioneer of Reverse Pharmacology Dr Ashok Vaidya, Research Director of Kasturba Health Society, who was also the chairman of the Steering Committee CSIR NMITLI programmer for antidiabetic herbal drug research feels "The ingredients have diverse activities. But are the concentrations in the formulation adequate for efficacy? How was the clinical tolerability? Where is the statistical analysis of the trial data? Were there any interactions with other concomitant antidiabetic modern drugs? What animal models of diabetes were used for testing the

formulation? Was glycohemoglobin reduced more than 0.5% in three months? If all such work has been carried out, as done earlier, then the discovery has to be hailed and advanced for its global use. If not, then we have to go back to the laboratory and clinic to generate such data.” According to Dr Zankhana Buch, an Ayurveda physician at AyurVAID Hospitals, Bangalore “Complex, progressive metabolic disorder such as diabetes a single formulation may not work across patients at different stages of disease evolution. Further, the absence of indications-contraindications for administration of the BGR-34 medicine is a serious omission and has implications for patient safety. Without classical Ayurveda holistic approach, health outcomes shall be marginal, may not be sustained and can pose potential safety hazards as I have seen in the case of BGR-34.”

A veteran pharmaceutical scientist Dr M D Nair expresses that “I feel very concerned about the lack of transparency in the approval and marketing of BGR 34 in the Indian market exposing our population to a drug not fully validated by any standards. Validation or invalidation for an indication such as Diabetes with outcomes being easily measurable to reach objective decision making on efficacy should be immediately carried out by some responsible agency. It has nothing to do with Modern versus Ayurvedic approaches. What is needed is generation of adequate statistically and clinically significant empirical evidence for efficacy and safety of the product, regardless of what system we promote”.

According to well-known pharmacologist Prof Y K Gupta from All India Institute of Medical Sciences, New Delhi “It seems marketing strategy has taken predominance over the hard core science. Having CSIR lab logo on attractive packaging of the product may generate confidence in the public, therefore it is the responsibility of CSIR to ensure that the trust on CSIR retains its credibility. CSIR lab should have clear stand if they endorse the claims!! If all is correct, we much appreciate the development of a good and effective poly herbal formulation for diabetes by a CSIR lab. If they do not fully endorse all claims of the product, it must go for more studies or alter the label claim as per the validated study results.”

Ms Shailaja Chandra, former Secretary, Department of AYUSH says “In a video clip on the internet several senior members of a Government funded research council can be viewed providing information and promoting the use of an Ayurvedic drug which is being sold commercially. The use of the product is being advised for treating a serious condition - diabetes. Such advocacy can be perilous and lead to self-treatment which is fraught with needless risks. It invites a conflict of interest charge and brings the entire science of Ayurveda and the research work done for long into disrepute”.

Many senior scientists from CSIR are extremely skeptical of such populistic and market driven propaganda, which actually tarnishes credibility of India's largest scientific network. Many concerned experts are requesting CSIR and CCRAS to enlighten them regarding these critical questions. A quick analysis of data currently available in public domain indicate that it is not rigorous enough to support various tall claims made by these products. Strictly speaking, both the above mentioned ASU products cannot be exception to scrutiny in the light of current DMR Act and proposed Consumer Protection Bill 2015. These products being promoted by governmental agencies, doctors, scientists, which is

purely a commercial activity, is questionable. The moral, ethical and public health responsibility on CSIR and CCRAS in this case is unavoidable.

6. Way ahead

Ayurveda has huge potential for natural product drug discovery of new the phytoactives as novel chemical scaffolds [4]. Admittedly, scientifically robust path of discovery and development of evidence based ASU drugs is not an easy task. Discovery of artemisinin from traditional Chinese medicine required over three decades of rigorous scientific work. India needs to follow the robust path of discoveries like reserpine, which require high level of commitment from socially responsible scientific and industrial community. The Government regulations, oversight and surveillance is required to ensure that gullible patients are not exploited. What is being sporadically done under the pretext of herbal drug development is certainly not in line with the basic principles, ethos and practice of Indian traditions. The AYUSH community has responsibility to preserve legacy and ensure that its credibility is not compromised for cheap publicity or short term economic gains. In a long run such inept efforts can erode credibility and likely to bring disrepute to Indian traditions and knowledge heritage. The great traditional knowledge systems like Ayurveda, Siddha and Unani are deeply rooted in Indian culture. Indian people need quality assured, safe, affordable and effective ASU drugs. Globally, there is increasing consensus among scientific community that mere pharmacological interventions with drugs are not sufficient for management of NCDs. The physiological interventions through lifestyle and behavioral modifications are gaining much more recognition. Health protection, disease prevention and simple yet effective medicines are the real strengths of AYUSH systems. ASU community has unique leadership opportunity to offer novel healthcare models through yoga, meditation, *panchakarma* and principles of *swasthavritta* for safer and affordable public health to the Indian and global community.

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Available online 16 September 2016