Expanding the scientific horizon of integrative medicine

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This paper discusses the future research direction for integrative medicine. Structure of clinical methods and objective outcomes of biomedicine should be integrated for patient examination of Ayurveda. This helps to identify exact clinical features of the disease for selection of herbal formulations. Defining such a holistic clinical presentation is a prerequisite for patient selection before conducting reverse pharmacology studies. The latter will reveal underlying mechanisms of drug action and lead to 'holistic drug development'.

Keywords: Biomedicine, complimentary and alternative medicine, integrative medicine, physician scientist, reverse pharmacology.

Introduction

INTEGRATIVE medicine (IM), as defined by the *British Medical Journal* (*BMJ*), is the use of interventions from traditional medical practice alongside biomedical treatments and principles[1]. In this special section on Integrative Medicine we discuss the simultaneous use of interventions from biomedicine as well as complementary and alternative medicine (CAM) for a range of diseases, especially Ayurveda herbals and Yoga, in a framework of biomedical diagnosis with or without its therapies. The special section consolidates pilot studies in IM which have a potential to impact on patient care. Millennia of experience on traditional medicines (TM) and several hundred years of clinical knowledge of biomedicine existing within the healthcare paradigm provide a unique opportunity in India for IM research. Contributions in this special section use IM arising out of Indian systems of medicine for improved continuum of chronic rather than acute care and identify candidate diseases for future IM studies, using clinical biomedical science as the best evidence. Another indication of better care of patients is a comparison with their previous treatments (study method to compare outcomes at the end of treatment to baseline parameters in the same patient is known as before and after design)[2]. Evidence-based medicine ratings as formulated by the US Preventive Services Task Force are used to judge the quality of submissions[3]. Outcomes in these studies showed the potential of IM to provide long-term chronic care under WHO's ICC model in identified diseases[4]. Biomedical human resources are limited and especially in rural areas. Traditional health practitioners are first on call and should, where possible, be exposed to cross-fertilization by other disciplines.

Ayurveda is prominent among Indian TM and has a large pharmacopeia. Modern science practitioners often dispute the holistic approach of TM and disagree with the studies on its therapeutics for lacking statistical power and point out methodological errors. Consequently, the clinical studies at this stage of renaissance of Ayurveda are at the best qualitative. Several studies exploring Ayurveda using the 'biases' of quantitative methods led to poor outcomes[5]. Ayurveda as practised now should be judged with tolerance as it might have been done by Osler, who frequently pointed out that the scientific approach lacked the understanding of the emotional and social aspects of patient care in alternative medicine[6]. Garrod, Osler's contemporary and successor, would have 'inspired intense clinical work' and a biochemical determination of the structure of this old clinical treasure in an exploration for newer drugs[7]. What in Ayurveda are the traditional indications for the therapeutics used? How do the clinical features of such diseases and outcomes as described in Ayurveda compare to contemporary biomedical terms? Oslerian wisdom guides us to explore current clinical relevance of Ayurveda therapeutics. Reasoning behind selecting these drugs in Ayurveda should be understood through comparable biomedical diagnosis as pathogenesis, immunological surveillance, cell killing or gene expressions are increasingly known for many diseases. The literature on phytochemicals is rich in laboratory-based studies that can be applied to herbal remedies. A thorough literature review, not necessarily systematic[8], of CAM and its comparable biomedical literature, especially relating to pathogenesis and therapeutics is an essential pre-clinical reading for IM physicians.

Better patient care

Qualitative studies in IM often underlie patient care protocols. But in the future quantitative studies should be planned for wider use to ensure successful therapeutic

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regimens. A few Indian qualitative, observational and patient-based rather than laboratory IM studies, based on biomedical methods, have already gained international attention[9]. They incorporated best practice and biomedical insights to develop IM, such as mutual dialogue between different medical systems, adoption of currently available best evidence for both individual and population medicine, and internationally accepted patient safety guidelines[10]. IM is appropriate for financially stretched regions because it is low-tech and low cost; both for research and patient care. IM utilizes locally available resources, high-quality clinical skills supported by healthcare knowledge to address the unmet needs of chronic diseases in resource-poor settings, both in hospital practice and primary care. Two-way communication between biomedicine and CAM is a pre-requisite for developing IM. This encourages CAM, e.g. Ayurveda to understand biomedical-based theories of mechanisms underlying disease, evidence-based medicine, infection and sepsis, critical care needs of chronic patients, differential diagnosis, classification and staging of diseases, systematic patient follow-up, stratified medicine and public health. In the process biomedicine learns what is often termed holistic (from *Aadi* – routed in mind to *Vyadhi* – disease) body constitutions[10] such as *Prakruthi*, structured approaches for drug selection in CAM for *Vikruthi* (diseased state)[10], synergism and safe use of herbals and patient-centric approaches in management, as well as detailed history-taking and face-to-face enquiry – practices which some critics believe have been lost in recent times. Two-way communication also enhances patient participation in IM care protocols. Patients collaborate with treatment teams to share their experiences on previous treatments. Successful IM is interpreted according to its outcomes, documentation and robustness of data.

New drug development

The outcomes from IM studies could identify clinical potential of Ayurveda medicines for chronic diseases and might lead to new drug development. Such studies can expand the scientific horizon of patient care in IM. The indications for selection of drugs in Ayurveda are clearly outlined and take several years to learn in Ayurvedic universities. They are locally distinctive *doshas* (three energy principles involved in the balance or imbalance of the physiology)[10], meaning complex patterns of differing symptoms and signs, producing typical 'constellations' of clinical signs and symptoms, summarized as *vikruthi*. Qualitative studies as described using IM methods would define a subset of patients who respond to the selected drug[10,11]. Presenting clinical features of patients belonging to this subset of disease becomes the inclusion criteria for the same CAM drug in the next phase of the study. Other clinical features of the disease described in biomedical or traditional literature should be listed as exclusion criteria. Outcome measures for this phase should be those in biomedicine. Secondly, at this phase of IM clinical study using CAM drugs on the narrower group (subset) of patients, 'reverse pharmacology' could be applied[12]. This process will hopefully quickly identify a traditional formulation that has the potential for worldwide use, albeit not a molecular drug.

IM studies in lymphoedema, a common problem in India, have now produced clinical evidence sufficient to justify promotion as a candidate disease for the reverse pharmacology process. Lymphatic filariasis is a common cause of lymphoedema. This presents commonly as lower extremity lymphoedema and genital swellings. Lymphoedema is a highly disabling disease transmitted by mosquitoes and endemic in 78 countries. IM studies on lymphoedema began in 2003, and after a decade of clinical experience IM subsets of patients who respond to Ayurvedic formulations are defined. The Department of AYUSH, Government of India, funded a community-level morbidity control study using self-care and IM in two lymphatic filariasis endemic districts of South India. A total of 730 patients (851 limbs) completed the three and a half month follow-up. There was a statistically significant (1%) reduction up to mid thigh-level volume measurement for both small (0.7–1.1 liters) and large (1.8–5.0 liters) limbs (statistical p value at 0.000). The study proved that self-care and IM are possible in resource-poor Indian village settings. Figure 1 shows the response observed in lymphoedema for IM.

Better funding should ensure that a subset of patients undergo skin biopsy (example; incisional biopsy from left lower leg at base line in Figure 1). Histopathological (epidermal, collagen and elastin changes) and immunohistochemical (to study lymphatics) analysis of tissue

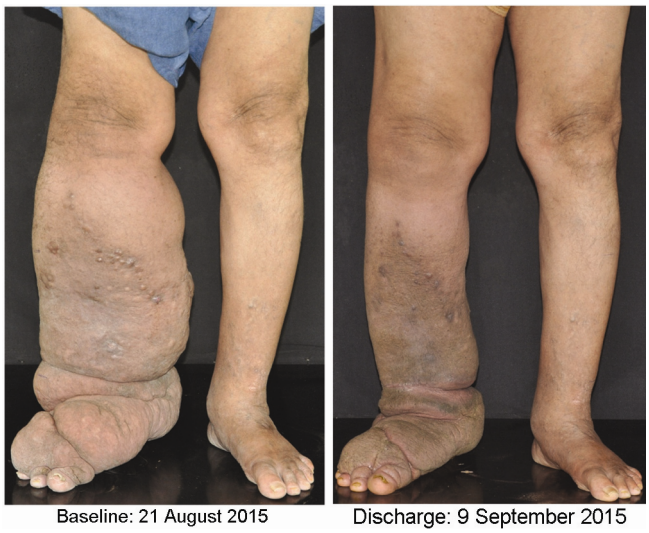

Figure 1. Changes in lymphoedematous limb after 14 days of integrative medicine treatment.

samples (blood, tissue fluid and biopsied tissue) should be done by a pathologist. Another set of samples obtained at the same biopsy procedure should be analysed at a molecular biology laboratory. Parameters for analysis should be determined by known mechanisms. These must include estimation of pro-inflammatory Th2 cytokines (IL-4, IL-6 and IL-10) and pro-fibrotic cytokines (IL-5, IL-13 and TGF-beta), ratio of MMP1/TIMP4 and MMP8/TIMP4, angiogenesis and collagen regulation. Subsequently, the patients should be treated with manufactured drugs available in, for example, Kerala Government owned 'Oushadhi' that uses Government prescribed 'Good Manufacturing Practices'. At the end of the study the same methods should be repeated. A positive outcome of such an intersectoral and multi-institutional joint research quickly defines the indications and mechanism of action for traditional Ayurvedic drugs as described previously[13] was selected through clinical studies. This is a short-cut method to explore hundreds of Ayurvedic formulations available in the marketplace. It is also a low-cost drug development from IM. Improving the efficacy of such defined Ayurvedic formulations should be the third step to secure the wealth of natural resources of medicinal plants[14]. The above study continuum would simulate a 'physician–scientist' approach[7], but could only be designed by IM clinicians' led collaborative research teams involving pathologists, molecular biologists, genetic engineers and Ayurveda drug manufacturers.

However, CAM alone continues to lose the battle for superior level of evidence as measured by science and medical statistics. Experts and supporters such as Prince Charles' Foundation for IM are divided on its utility to meet the global challenge of providing affordable and quality healthcare. The editor of the *British Medical Journal* Fiona Godlee[15], wrote 'Integrated care is what we want', while Colquhoun[16] commented 'it is science degrees without science'. Internationally, long debates continue on the level of evidence that should be used during IM treatments that involve CAM. Dominance of quantitative studies led to lack of funding to genuine research teams working on developing patient care protocols of IM. This is an opportunity lost for clinician-led intersectoral reverse pharmacology research groups. Would such studies lead to a molecular drug? Safety of such new chemical entities and other questions could be answered by more in-depth research. However, the immediate priority is to treat millions of suffering chronic patients.

In pursuit of best practices, the IM objective outcomes and structured clinical methods of biomedicine should be adopted for bedside clinics of Ayurveda and other traditional medicines. This unique methodology aims at transforming tacit knowledge of traditional medicines into explicit reproducible and protocol-based cocktail IM treatments. Such enquiries would prove to be economical, eco-friendly, especially to save biodiversity, and would develop sustainable patient-centric, empathetic chronic care. The outcomes of the studies would be applicable to resource-poor locations and any medical centre. They will give respite for the decline in popularity of Ayurveda among Indians as their first choice for consultation[17,18].

1. Rees, L., Integrated medicine: imbues orthodox medicine with the values of complementary medicine. *BMJ*, 2001, **322**, 119–120.
2. Greenhalgh, T., *How to Read a Paper: the Basics of Evidence based Medicine*, Blackwell Publishing, London, 2007.
3. Harris, R. P. *et al.*, Current methods of the US preventive services task force. A review of the process. *Am. J. Prev. Med.*, 2001, **3**, 21–35.
4. WHO, Chronic diseases and health promotion [internet]. World Health Organization, Geneva, 2016; http://www.who.int/chp/knowledge/publications/icccreport/en/ (accessed on 27 June 2016).
5. Park, J. and Ernst, E., Ayurveda medicine for rheumatoid arthrits. A systematic review. *Semin. Arthritis. Rheum.*, 2005, **34**, 705–713.
6. Ryan, T. J., Does India need a William Osler for the millennium. *Curr. Sci.*, 2013, **104**, 169–170.
7. Goldstein, J. L. and Brown, M. S., The clinical investigator bewitched, bothered and bewildered, but still beloved. *J. Clin. Invest.*, 1997, **99**, 2803–2812.
8. *Cochrane Library*, John Wiley, London, 1999; http://www.cochranelibrary.com/ (accessed on 27 June 2016).
9. Witte, W. H. and Bernas, M., Silver bullets and shotguns in lymphedema therapy. *Lymphology*, 2007, **40**, 1–2.
10. Narahari, S. R., Ryan, T. J., Bose, K. S., Prasanna, K. S. and Aggithaya, G. M., Integrating modern dermatology and Ayurveda in the treatment of vitiligo and lymphedema in India. *Int. J. Dermatol.*, 2011, **50**, 310–334.
11. Narahari, S. R., Ryan, T. J., Aggithaya, M. G., Bose, K. S. and Prasanna, K. S., Evidence based approaches for Ayurvedic traditional herbal formulations. Toward an ayurvedic CONSORT model. *J. Altern. Complement. Med.*, 2008, **14**, 769–776.
12. Mashelkar, A. R., India's R&D. Reaching for the top. *Science*, 2005, **307**, 1415–1417.
13. Narahari, S. R. *et al.*, Community level morbidity control of lymphoedema using self care and integrative treatment in two lymphatic filariasis endemic districts of South India. A nonrandomized interventional study. *Trans. R. Soc. Trop. Med. Hyg.*, 2013, **10**, 1093/trstmh/trt054.
14. Narahari, S. R., Collaboration culture in medicine. *Indian J. Dermatol.*, 2013, **58**, 124–126.
15. Godlee, F., Inetgrated care is what we want. Editors choice. *BMJ*, 2012, **344**, e3959.
16. Colquhoun, D., Science degrees without science. *Nature*, 2007, **446**, 373–374.
17. Sing, R. H., Declining popularity of AYUSH, the recent report of National Sample Survey Organization. *Anals Ayur. Med.*, 2015, **4**, 1–2.
18. Oyinlola Oyebode, O., Kandala, N., Chilton, P. J. and Lilford, R. J., Use of traditional medicine in middle-income countries: a WHO–SAGE study. *Health Policy Plann.*, 2016, 1–8; doi: 10.1093/heapol/czw022.

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