Education

Integrating modern dermatology and Ayurveda in the treatment of vitiligo and lymphedema in India

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Absract

Background Globally, governments have recognized the growing popularity of Complementary and Alternative Medicines and the possibility of their combined use with biomedicine. Decisions within the Government of India have led to a conducive environment for conducting clinical studies, to achieve integration of more than one system of medicine, so that their combined benefits can be brought to bear on chronic, difficult-to-treat conditions.

Aim To develop integrative dermatology treatment protocols for patients with long-standing skin diseases who have received treatment from many centers.

Materials and Methods A team of doctors from modern dermatology, Ayurveda, yoga therapy, and homeopathy studied recruited patients to develop mutual orientation on each therapeutic system and a working knowledge of approach to their clinical diagnosis. Six-hundred thirty-eight patients affected by lower limb lymphedema requiring skin care as a major part of treatment were treated integrating modern dermatology and Ayurveda. Three-hundred eighty-one vitiligo patients were examined and treated to understand the clinical presentations and treatment options in Ayurveda.

Results A two-step cluster analysis performed by SPSS Version 16 showed average volume reductions of 13.3% and 23% on day 14, 19.7% and 31.1% on day 45, and 23.4% and 39.7% on day 90 of treatment in small and large lymphedematous limbs. Inflammatory episodes before the onset on this treatment was reported by 79.5% of our lymphedema patients, and 9.4% reported this at the end of three months after our treatment. Among vitiligo patients, we found that 39.6% of patients had *kapha*, 39.8% *pitta*, 10.8% had *vatha* and 0.52% has *tridoshaja* presentation. There are over 100 treatment options available in Ayurveda to treat vitiligo.

Discussion Each system of medicine recognizes the same disease albeit with minor difference in description. Skin care procedures like washing and emollients restore the barrier function and skin health. We have converged Ayurvedic skin care with that of dermatology with an aim of achieving patient management that is better than that achievable by a single system alone. Overload of the lymphatic system due to loss of epidermal barrier function and consequent inflammation from bacteria and soil irritants is responsive to selected Ayurvedic herbal preparations.

Conclusion It is evident that integration at the therapeutic level is possible, although the pathological basis is interpreted differently. Irrespective of background understanding of the given disease, a mutually oriented multisystem therapeutic team was able to effectively use medicines from more than one system of medicine and to develop guidelines for their prescription and a patient care algorithm.

Introduction

The global scenario

The practice of integrating biomedicine with other systems of healthcare is growing in popularity and is supported in the USA, the UK, and other countries. Having set its seal of approval on the term "alternative medicine" with the establishment of its Office of Alternative Medicine in 1991, the National Institutes of Health proceeded to initiate a National Center for Complementary and Alternative Medicine in 1998, thereby emphasizing the suggestion that many systems of alternative medicine can

be seen to complement biomedicine.[1] From this, it follows that doctors who use both systems in a carefully integrated way ought to be able to derive benefits from both systems without losing anything in the process.[2] To explore this possibility, programs in integrative medicine were started at the University of Maryland and the University of Arizona, Tucson, followed shortly thereafter by the founding of Osher Institutes of Integrative Medicine at the University of California, San Francisco, Harvard University Medical School and, more recently, at the Karolinska Institute in Stockholm.[3] In addition, Johns Hopkins Medical School has been committed for several years to running integrative medicine programs with traditional Chinese medicine (TCM) and runs foreign outreach programs such as that conducted with the National University of Singapore, in Singapore.[4] Over half of the top 50 medical schools in North America have now publicly declared their interest in integrative medicine. Most, like Harvard's Osher Centre[5] and Johns Hopkins, have their primary focus on TCM.

In the early 1990s, the Department of Dermatology at Oxford University became host to a policy making and awareness organization called Global Initiatives for Traditional Systems (GIFTS) of Health (http://www.giftsofhealth.org), which had been established in 1993 at the US National Museum of Health and Medicine, chaired by Gerard Bodeker and co-directed by Terence J Ryan (author TJR). Amongst its many achievements, GIFTS was responsible for the two-volume *World Health Organization Global Atlas of Traditional Medicine*. Oxford provides all its clinical students with an introduction to complementary and alternative medicine (CAM).

Currently, there is much to criticize with regard to the actual practice of CAM, and evidence to support the efficacy of alternative systems of medicine is lacking. However, if the choice of therapy can be skillfully matched to, for example, skin problems in patients who may respond well to alternative methods of treatment, this may demonstrate that CAM can be used to the benefit of billions of persons. Hence, it is important to prove its efficacy.

The Indian scenario

Health care in India is compartmentalized into Western biomedicine (termed ''allopathy''), homeopathy, and the Indian System of Medicines (ISM). The ISM includes Ayurveda, yoga and naturopathy, Unani, Siddha, and homeopathy, which are collectively referred to by the acronym ''AYUSH''. Yoga therapy (also part of the Ayurvedic system) is included as the traditional family practice of treating common illnesses by experience gained through generations (traditional healers). The ISM represents the well-established systems of medicine used by the rural masses in India. It is ancient and has developed on the basis of sound logic and centuries of observation of nature.[6]

Although the Indian Government lists 106 traditional systems of medicines,[7] only Ayurveda, yoga, Unani, Siddha, and homeopathy (AYUSH) are taught in universities. Ayurveda is the most widely used system among the ISM. Its training is rigorous and requires 5.5 years of undergraduate education and three years of postgraduate training, although this is not widely acknowledged by biomedically trained dermatologists. There are two Ayurveda universities, 240 colleges, and 26 pharmacy colleges across India, which together admit over 7,500 undergraduate students annually. More than 30 national laboratories are involved in Ayurveda-related research and development. The *Ayurvedic Pharmacopoeia of India*, published by the Indian Government in two parts, comprises a total of seven volumes.[8] In addition, the country hosts as many as 8,405 industrial units producing ISM drugs,[9] including an Indian subsidiary of Unilever, Inc., England.[10] Ayurveda is also practiced and taught in other Asian countries, such as Nepal, Sri Lanka, and Malaysia.

Many urban doctors in India have university degrees in both biomedicine (MBBS) and Ayurveda (BAMS). The great majority of medical practitioners in rural India hold degrees in either Ayurveda or other ISM disciplines. The Ayurveda curriculum includes many components drawn from biomedicine, mostly with the aim of training practitioners to manage emergencies, reduce maternal mortality, etc. (Government of India; order no. B-8/96AyCMM; October 30, 1996). Several Ayurveda medical colleges and symposia offer training in equivalent biomedical terminology. Fifty years ago, the Indian Government offered biomedical degrees (MBBS) to Ayurveda doctors (GCIM [Graduate of College of Indigenous Medicine] degree holders) who underwent short courses in biomedical hospitals. In many provincial states of India, Ayurveda interns undergo short training courses in modern biomedical hospitals. As a result, numerous English translations of ISM terminologies and accounts of ISM practices are published in India as continuing medical education (CME) articles, historical translations,[11] or medical textbooks, albeit that this material is not supported by clinical studies. Many patients take Ayurvedic treatments along with biomedical therapy, on their own, with or without the knowledge of their treating doctor. Most of the evidence for these treatments is derived from an Indian oral tradition of integrative treatment. We have been unable to find reports of any carefully conducted studies.

Legal and ethical issues underlying trials in India

We were aware that guidelines for ISM trials have been published recently, but we were informed by the highest available authority on clinical trial issues in the country, the Drugs Controller General of India (DCGI), that there

are no rules governing trials of integrative treatments in India. However, in the process of conducting the integrative studies reported herein, we adhered to all guidelines on Ayurveda, Siddha, and Unani (ASU) drugs.

Clinical studies in India are regulated by the Drugs and Cosmetics Act and its Amendments (DCA).[12] According to the revised Schedule ''Y'' of the DCA, ''a clinical trial is a systematic study of a new drug(s) in human subjects to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining the safety and/or efficacy of the new drugs''. Clinical trials of drugs are designed to evaluate prospectively the safety and effectiveness of new drugs and/or new formulations. The DCA defines a ''new'' drug as a ''new chemical entity'' (NCE) or a drug which has been approved for a certain indication, by a certain route, in a certain dosage regimen, but which is now proposed for use for another indication, by another route, or under another dosage regimen. The Indian Council for Medical Research (ICMR), the highest policy-making body on health research in India, issued ethical guidelines in 2000, updated in 2006,[13] but relaxed these rules for trials of Ayurvedic traditional formulations (ATFs). The ICMR has difficulty in subjecting traditional remedies to the rigorous procedures synthetic drugs are required to undergo to establish their safety and efficacy.

Clinical evaluations of herbal remedies and medicinal plants that are to be used in the biomedical system and which may later be used in biomedical hospitals must follow the procedures laid down by the DCGI for trials of biomedical drugs. When clinical trials of herbal drugs used in recognized ISM and homeopathy systems are to be undertaken in biomedical hospitals, ISM or homeopathy physicians must be invited to participate as co-investigators/collaborators/members of the expert group in designing and evaluating the study. It would be neither ethically acceptable nor morally justifiable for a biomedical physician without any concept of or training in a traditional system of medicine to carry out the clinical evaluation of a plant or substance to be used according to references in the ancient literature of such a traditional system.

When a substance is to be clinically evaluated for a therapeutic effect not originally described in the texts of the traditional system, or when the method of preparation differs from that described in the text, it must be treated as an NCE, and the same type of acute, subacute, and chronic toxicity data should be elicited. Any extract or compound isolated from a plant and any compound formulation including among its ingredients plant, metal, mineral, or animal products that have not been used before and are not mentioned in the ancient literature should be treated as an NCE and, therefore, should undergo all the processes of evaluation required for biomedical drugs before being evaluated clinically.

By contrast, ASU drugs or formulations that are subjected to clinical evaluation by experts in those systems of medicine, and which may later be used in ASU hospitals and clinics, are subject to considerably reduced ICMR requirements regarding testing for toxicity in animals if they are already in use in the ISM or have been described in ISM texts. Neither would any toxicity study be required for a Phase II trial. This is the unique *reverse pharmacology* approach applied in the evaluation of traditional formulations for traditional indications.[14] If reports suggest toxicity, if the herbal preparation is to be used for more than three months, or if a larger, multicentre Phase III trial is planned based on the results of a Phase II study, a 4–6 week toxicity study in two species of animal is required. Good manufacturing practice (GMP) standards for the formulations are not required for Phase I and II trials.

The Indian Government's Golden Triangle Partnership

In July 2004, the Indian Ministry of Health and Family Welfare established the Golden Triangle Partnership (GTP). The GTP is a research scheme mandated to promote collaborative research into ISM in a manner that allows for the scientific and biomedical validation of findings and to develop new drugs. Major Indian research groups participating in the GTP include the institutes of the ICMR, the Central Council for Research in Ayurveda and Siddha (CCRAS), and the Council for Scientific and Industrial Research (CSIR). Skin diseases and lymphatic filariasis (LF) are among the priority areas targeted by the GTP.[15] An important feature of this policy decision is that it enables trials to skip pre-trial toxicity and laboratory tests on drugs that are mentioned in the 100 classical Ayurveda texts currently used in clinical practice in India. Therefore, under this scheme, studies of standardization, molecular characterization, and clinical trials can be undertaken simultaneously. The GTP scheme came into existence through the wisdom of the then-health minister of India, Dr. C. P. Thakur, professor of internal medicine at Lucknow Medical College, and was supported by, amongst others, the then-director general of the CSIR, Professor R. A. Mashelkar, the then-deputy director general (DDG) of the ICMR, Dr. Nandini K.K, and the director general of the CCRAS, Professor G. S. Lavekar.

The need for a properly designed study

The present situation in India is therefore conducive to the performance of clinical studies in order to achieve the integration of the country's various systems of medicine so that their combined benefits can be brought to bear on chronic, difficult-to-treat conditions, such as the all-too-often neglected skin diseases suffered by the Indian rural population.

As Verma[6] has written, despite the existence of various regulatory bodies and the educational establishments described above, there is little control over the practice of ISM, and many cases in which it has failed are seen by dermatologists. Naturally, it is failure rather than success that takes a patient in search of further advice. The ISM needs to prove its safety and efficacy if it is to survive in the long term. This paper narrates the conception and implementation of a clinical study instigated by the Institute of Applied Dermatology (IAD), Kasaragod, Kerala, and describes the challenges that arose during the study and how they were negotiated. Although it is very important for a small non-government organization (NGO) such as ours to create advocacy among funding agencies and biomedical doctors in India, our performance so far in this respect has been dismally poor. However, opportunities are still open as the ICMR and the Prime Minister's Office have formed separate committees to study our methods of treatment. Their recommendations to support our integrative treatment program are pending. We have had national media support, which has provided news coverage.[16] Patients often travel for over 1 day to reach our centre, and we admit patients from more than 10 provinces of India.

As far as we are aware, there is neither a protocol for nor a publication providing a thorough description of clinical practice and rigorous assessment of patient outcomes in integrative dermatology.

This paper presents the treatment programs and assessment methods used in a unique approach to integrative dermatology, developed in response to particular needs in the Indian subcontinent, by a local, integrated team of practitioners. These methods are periodically reviewed by members of our international advisory board, which includes participants from leading medical institutions in North America and Europe.

The origin of the study

During 1993, Terence J Ryan (TJR), Professor of Dermatology at Oxford University, began to investigate alternative systems of medicine and voiced his support of the Global Initiative for Traditional Systems (GIFTS) of Health (http://www.giftsofhealth.org), chaired by Dr. Gerard Bodeker, who was advising on CAM in a forum of policymakers from around the world. The aim of GIFTS was to build partnerships at a global level between traditional health practitioners, scientists, educators, and decision-makers in order to improve the services provided to patients. TJR's primary objective was to explore low-cost and locally available, effective but safe alternative medicines for skin care in the developing world. TJR served as president of the International Society of Dermatology, and as secretary and later chairman of the International Foundation of Dermatology.[17] In 1999, the IAD, based in Kerala's northernmost town of Kasaragod, began to explore Ayurvedic treatments for skin care and the administration of these Ayurvedic practices in chronic skin disorders. A multisystem doctor (MSD) team of investigators began to observe and collect data on the patients who attended the IAD. Prior to 1999, the first author (SRN) commonly noticed that patients with chronic skin disease would try biomedical treatment to control acute exacerbations while managing chronic stages using alternative or Ayurveda systems of medicine. Some patients were referred to his clinic by peripheral doctors (including the third author, KSB) from remote villages. Many of these patients had lymphatic filariasis or vitiligo, both of which are highly prevalent in the region.

In 2002, Vaqas and Ryan discussed a low-cost integrative treatment paradigm for lymphedema, using traditional Indian medicines and yoga, suitable for administration in rural communities.[18] At that time, the IAD had already been engaged in such a program for a number of years and was looking for collaborators. This led to an exchange and the incorporation of TJR's recommendations into our work. Subsequently, TJR closely mentored the whole program, thereby helping to popularize CAM among policymakers around the world.

A patient-centered approach

In retrospect, it is easy to recognize which aspects of the program were most appreciated by patients because they were usually those that are seldom available in biomedical clinics. These aspects included: (i) hearsay and often personal experience of efficacy accompanied by few side-effects; (ii) careful and holistic questioning based on history-taking procedures in homeopathy (but without prescribing according to that system); and (iii) individualized prescribing that could be altered according to need, even on a day-to-day basis. Moreover, although the program bore the costs associated with a research program, these were, nevertheless, taken over a period of six months, lower than those associated with a biomedical approach to therapy.

However, obtaining evidence in support of these views was challenging.

Addressing theoretical challenges before embarking on clinical studies

In the absence of published guidelines, the development of patient treatment protocols for integrative dermatology presented a considerable challenge, especially in terms of building consensus in the diverse team, agreeing how to establish evidence of efficacy, and obtaining peer review.

Establishing mutual orientation in multiple systems of medicine and cross-medical system dialogues

Long discussions were required to develop the necessary trust and mutual understanding of one another's approaches

and disciplines[19] (i.e. biomedicine, Ayurveda, yoga medicine, homeopathy, and patient counseling) in order for the MSD team to function optimally under the many circumstances presented by different patients. During the trial, consensus reached in bedside discussions was e-mailed to the UK mentor (TJR) to seek his opinion and approval. In the event of his disagreement, the topics were once again discussed within the team and the cycle repeated. TJR has also visited the IAD every year since 2005 in order to see patients, teach, and review medical records on a case-by-case basis.

Our objective was to integrate treatment options available in Ayurveda into biomedical dermatology prescriptions, basing the latter on the textbook *Dermatology in General Medicine*, by Fitzpatrick *et al.*[20] The interview protocol used in homeopathic practice was used to elicit a most detailed history; this protocol was chosen because homeopathy prescribes on the basis of a ''totality of symptoms'', knowledge of which is achieved only after lengthy questioning and listening to the patient's story.[21] Counseling of patients was included to address their overall needs and to explain the new therapeutic approaches used in integrative dermatology. The orientation process involved descriptions of Ayurvedic and biomedical approaches to patient care, such as the pathophysiological concepts briefly summarized below and in-depth history taking (eliciting symptoms).

Original descriptions in Ayurveda are written in Sanskrit. The English translations used in this paper are biomedical terms identified in the course of parallel examinations of patients conducted by Ayurvedic physicians and dermatologists. They need not reflect the exact meaning of the Ayurvedic or Sanskrit terminology.

In biomedicine, the dermatologist examines, recognizes, and names physical signs, such as the hypopigmented insensitive patch manifested in tuberculoid leprosy. Although it is known that this patch is caused by a particular immunosurveillance failure for *Mycobacterium leprae*, the dermatologist will not explore the reasons for this host failure but will prescribe drugs against the bacteria. The treating of such a patient in Ayurveda will entail a long exploration of the background or constitution (*prakruthi*) of the patient. Treatment will aim to return to normal the disturbed host factors and establish homeostasis. In modern physiological terms, and under the contemporary medical focus, this may be described as, in part, restoring immunosurveillance. Asian systems of medicine give greater attention to a concept of free flow of energy. In Ayurveda, which is concerned with energy, the goal of treatment is to establish equilibrium in the three *doshas*, which, in the diseased states, are described in Ayurvedic terminology as *vikruthi* or *dosha vaishamya* or *roga*, and represent the energy components that underlie a presenting physiology.[22] Thus, the white patch and sensory loss in leprosy may not be given much weight yet nonetheless may respond quickly to therapy that restores the constitution.

There are three types of energy principle (*doshas*) involved in the balance or imbalance in the physiology, according to Ayurvedic theory: motion (*vata* [''wind''] in Sanskrit); metabolism[6] (*pitta* [''combustion, heat production''] in Sanskrit), and structure (*kapha* [''water''] in Sanskrit, which indicates the slow, cooling, binding, stable aspects of physiology). Recent research suggests a genetic basis to this diagnostic typology.[23] Derangements of these *doshas* can occur either in any combination (63 are possible)[24] or independently, although the latter is rare. Determination of the physical constitution (*prakruthi*) of the individual is a mandatory clinical exercise prior to diagnosing the disease and deciding on the ATF, dosage and treatment regimen to be offered to the patient.[24] In Ayurveda, viewing a clinical presentation as it relates to its pathological description (*vikruthi*) is more important than naming a physical sign (as in dermatology).[24] However, in modern dermatology, the act of recognizing the interaction of the genetic code with the environment and the pathology underlying a physical sign represents the beginning of an approach more similar to those of Asian systems of medicine. The ATF is selected on 11 parameters elicited during the clinical examination,[25] including: *prakruthi*; tissue functions altered by energy principles (*dooshyam*); habitat (*desha*); age (*vayas*); the duration of the illness and the season of the year in which it began (*kala*); the patient's digestive power (*agni*); genetically determined behavior patterns (*satwa*); the patient's capacity for food intake (*ahara shakthi*); the immunity of the patient (*bala*); and ''dietary ecosystems'' (*sathmyam*). The method of diagnosing a disease in Ayurveda comprises five diagnostic steps (*nidana panchaka*),[26] which involve establishing: (i) cause (*nidana*); (ii) prodrome (*purva roopa*); (iii) systemic signs and symptoms (*roopa*); (iv) trial and error response to therapies (*upashaya*); and (v) derivation of the etiopathogenesis of the disease (*samprapthi*).

Regulating and adjusting the constituents of the patient's food is a prerequisite before the onset of oral or topical medication in Ayurveda. Whenever the pathogenesis of disease is not clear and no provisional diagnosis can be made, exploratory therapy is trialed using an ATF, which is most likely to result in the amelioration of illness.[7] In such cases, the ATF and/or its dosage may change during the course of treatment, and leeway is allowed for retrospective diagnosis consequent on the therapeutic trial if the response is positive. The provisional diagnosis is made in the absence of laboratory investigations.

Ayurveda holds that the *prakruthi* is determined at conception[22] and that no known medicine is able to change it. Baseline *prakruthi* and *sthaneeya vikruthi* analysis is therefore essential when applying an ATF because neither the medicine nor any food administered should aggravate the Ayurvedic indicators of health (*swasthya*).[27] The treatment design of any *dosha vaishamya* (disease) is influenced by the *prakruthi* and *sthaneeya vikruthi* of the patient.[25] These are the bases of the much-emphasized individualized treatment of Ayurveda, which takes into account all types of body constitutions and their responses to therapy. Failure to analyze the *prakruthi* and *sthaneeya vikruthi* and the nine other parameters, and failure to include the clinical features or presentations of contraindicated *prakruthi* into exclusion criteria, would be similar to conducting a trial of a drug known to be toxic to the liver without first assessing liver function in the trial participants.

With only a few exceptions, different medicines are used for each type of disease. A few ATFs can be used in all individuals regardless of the disease. However, the efficacy of such drugs by and large is less than that of ATFs specific to particular diseases. In the same way, *agryaoushadha* are formulations that can be administered in any disease within a defined group,[28] such as *Acacia catechu* (*khadira*) in skin diseases (*kushta*) and *Curcuma longa* (*nisha*) in diabetes (*madhu meha*). However, these practices cannot be equated to the ''indications of prescribing'' applied in biomedicine.

Unfortunately, the experience – and, hence, the knowledge – of numerous Ayurvedic doctors in the use of the same therapies in individualized treatment regimes, amassed over the course of centuries, was not recorded. Thus, there is no consensus on the ''list of indications'' for an ATF.

Differential diagnosis as a clinical methodology was probably not developed beyond *upasaya* in Ayurvedic texts. However, the present teaching curriculum (Government of India; order no. B-8/96AyCMM; October 30, 1996) describes ''differential diagnosis'' (*vyavachedaka nidana*) and delivers it in Ayurveda medical colleges. Differential diagnosis is considered during the different steps of clinical diagnosis, such as *nidana* (cause), *purvaroopa* (prodrome), *roopa* (systemic signs and symptoms), *upasaya* (trial and error response to therapies), and *samprapthi* (derivation of the etiopathogenesis of the disease).

We will briefly narrate a structure we used as a foundation to develop the integrative treatment protocol. This may be helpful to anyone wishing to undertake studies to evolve new algorithms for the integrative management of any disease using our approach. The following list enumerates the steps that led to a patient treatment protocol.

1 The first step adopted by the MSD team focused on choosing the disease for which the protocol was to be developed. The MSD team decided to select a chronic disease, in which a patient might visit one doctor after another and investigate one system of treatment after another in search of relief. We chose to focus on the highly prevalent condition of lymphedema. Clinical pictures of a sample of patients with lymphedema were then viewed by each member of the MSD.
2 A case history was taken for each patient, after which clinical examinations were conducted separately by the members of the MSD team in order to allow team members to arrive at their own conclusions about the disease. The process of reaching these conclusions followed the guidelines standard in the respective therapeutic disciplines (i.e. provisional diagnosis in allopathy, *nidana panchaka* in Ayurveda, totality of symptoms in homeopathy). Detailed medical records for each case were maintained by each doctor and collated in one file per patient. The MSD team members then simply read the case records written by one another. This identified the commonalities in clinical findings.
3 These inferences on the illness of a given patient were then disseminated within the MSD team. The language used for presentation was English. However, the terminologies used to describe the disease or treatment and the pathophysiological basis of each treatment were presented using the descriptions native to the respective disciplines (e.g. ''the *dosha vaishamya* in this patient is *vata-kaphaja*''; ''*prakruthi* is *kapha*'', etc.); thus the dermatologist in the team presented using biomedical terms.
4 At the end of each member's presentation, team members jotted down any terms or words they did not understand.
5 In the following sessions, each team member delivered theory classes in their respective disciplines, quoting references from standard books. Discussions and learning processes continued for several sessions until each member of the team had a working knowledge of all the terms applied and of how they related to the clinical presentation in question.
6 The mutual orientation gained in this way was strengthened by seeing more patients and repeating the discussion process.
7 We then began to search for available descriptive English translations of Ayurveda,[11] with or without comparative biomedical terms. This gave us information on whether others thought differently about the interpretation of pathophysiology and clinical presentations. We were unable to find a description of lymphedema in the translated literature we searched. However, such literature was available for vitiligo and for a few other diseases, such as psoriasis and eczema.

8 At this stage, the MSD team visited a few nearby medical colleges (Ayurveda, homeopathy, and biomedical colleges) to obtain the model case sheets used by their students and hospitals.

9 We then began to document clinical features. Having examined the various methods of recording case histories and clinical findings, we developed an integrative case sheet derived from the general case-taking models followed in the teaching institutions. This included the complete case history, facts that help the practitioner to arrive at *nidana panchaka*, and the totality of symptoms or clinical diagnosis. The detailed case history also included information on the substances used during the *upashaya* stage of *nidana panchaka*, intake of drugs, and diet as an aggravating or precipitating factor. The case sheet contained options to allow each member of the MSD team to discuss the case separately, after which their notes were amalgamated.

10 We then spent some time with legal experts in order to discover how a combined case sheet might be interpreted legally.

11 We subsequently decided to follow the most objective parameters for diagnosis and prognosis by using whichever system described them best. Objective indicators were best described by biomedical dermatology. Hence, the MSD team decided to adopt biomedical diagnosis and indicators of improvement. Decisions on diagnostic tests to be employed and if and when they were to be repeated to determine how the patient responded to integrative treatment were to be made by the biomedical dermatologist. Patients in whom diagnosis was not clinically difficult were rarely subjected to confirmatory investigations, but diagnosis was supported by baseline and follow-up photographs. However, in patients whose clinical presentation was insufficient to determine the disease, skin biopsy and other investigations necessary to confirm the final diagnosis were carried out wherever indicated.

12 The most important clinical step before the selection of a drug is the *vikruthi* table. At this stage we developed such a table for the disease under study by detailing the clinical presentation in Ayurveda and finding comparable biomedical descriptions. The *vikruthi* table could be developed only after a series of patients had been examined. Baseline photographs and the clinical notes for each patient examined were pooled to develop the *vikruthi* table.

13 At this stage, a second level of dialogue was instigated with the aim of establishing mutual orientation to allow all members of the MSD team to understand the therapeutics available in each system of medicine for the same disease. Using the *vikruthi* table, the MSD team identified the most common presentation of the disease. Then the MSD team decided which clinical subtype should be selected for integrative treatment. On this basis, drugs for trial can easily be short-listed. In lymphedema (known as *shleepada* in Ayurveda), our initial study included the *kapha–vatha* variety of local pathology (*sthaneeya vikruthi*) on the basis of the lymphedema *vikruthi* table. *Nalpamaradi* oil was the drug selected for this clinical subtype. We developed the *vikruthi* table for vitiligo (Table 1) after examining 381 patients. In future studies we will be

Table 1 *Vikruthi* table for vitiligo

Ayurvedic term in *Vatha*	Comparable biomedical term	Ayurvedic term in *Pitta*	Comparable biomedical term	Ayurvedic term in *Kapha*	Comparable biomedical term
Ruksha	Xerosis on inspection	*Daha*	Burning sensation	*Shwetha*	White in color
Aruna	Dusky red color	*Roma vidhwamsa*	Absence of hair on the lesional skin in hairy areas	*Ghana*	Thickened skin
Mandala	Annular	*Padmapathra prateekasha*	Color of lotus petal	*Guru*	Feeling of heaviness of affected body part (*anga*)
Parusha	Xerosis on palpation	*Raktha*	Bright red color	*Kandu*	Itching
Paridhwamsi	Galloping lesions with repigmentation in the opposite side or middle of the lesions. Lesions appear broken or exploded			*Snigdha*	Oily appearance of skin
Krishna	Areas of dark repigmentation within the lesional skin when examined for the first time			*Bahala*	Involvement of large body area presenting with multiple lesions

able to select drugs on the basis of the clinical subtype that can be identified using the vitiligo *vikruthi* table (e.g. *avalguja beejadi kashaya* for predominantly *kapha* subtype). One of the clinical features of the *kapha* subtype is the presence of pruritus before the lesion appears (Table 1). We will describe the drug selection process in more detail below. (See also[25]).

14 The MSD team continued to engage in frequent sessions of mutual orientation as described above on the diseases observed in the patients presenting at the integrated clinic. As and when necessary, the team held discussions with other biomedical specialists (e.g. urologists, physicians, oral pathologists), Ayurvedic specialist doctors in disciplines such as internal medicine (*kaya chikithsa*), surgery (*shalya tantra*), toxicology (*agada tantra*), obstetrics and gynecology (*prasuti tantra*), and botanists, taxonomists, and Sanskrit scholars, etc. These sessions helped to resolve any problems that required more expert opinion.

15 We developed a system of process documentation whereby each step in patient and drug selection was recorded in an algorithmic fashion. This required the provision of a detailed case sheet identifying the patient's *prakruthi* and case history, a table to identify clinical points by which to determine the *dosha viashamya* (disease) (as described in[25]) and the finer details of drug administration as described in traditional Ayurvedic texts. Monitoring for response to treatment (outcome measures) and adverse events was objective and was narrated as in biomedical practice for the given disease. Patients were given detailed information sheets about the disease and treatment. The telephone numbers of MSD team members were given to patients so that they could reach them immediately in cases of emergency.

16 During the follow-up, the MSD team reviewed the response to treatment. At this stage, any decisions to change or modify treatments or dosages were made in response to the outcome measures of individual examinations. Thus, if the disease presented in *kapha* form and the response to treatment of vitiligo was poor, the Ayurvedic doctor in the MSD team would decide if additional *kapha*-reducing (*hara*) drugs should be added, the dosage of medicine increased, the patient's dietary ecosystem reassessed, or the patient's digestive capacity *(kosta*) re-determined, etc. We followed a general rule whereby we decided to change the treatment course (thereby adding confounding factors) only on the basis of clinical features elicited by Ayurvedic assessment and not according to objective prognostic indicators in the biomedical assessment. Similarly, any aggravation of disease caused by Ayurvedic medications was regarded as an adverse event or error in patient or drug selection. For ethical reasons, the treatment approach was subject to immediate review in this event. This means that the selection and continuation of Ayurvedic drugs were decided by the Ayurvedic doctor on the basis of Ayurvedic principles, whereas biomedical drugs were prescribed by the biomedical dermatologist.

Establishing evidence of efficacy

Traditional systems of medicine often involve highly complex treatment models and patterns of intervention. Personalized treatments are based on individual strengths and weaknesses. Therefore, to assess the effectiveness of ISM interventions integrated with mainstream biomedicine, it is crucial that the traditional medicine used be brought into alignment with evidence-based medicine, in this case evidence-based dermatology.[29] Systematic reviews have found that many clinical trials of aspects of CAM have insufficient statistical power, poor controls, and demonstrate inconsistency of treatment or products and lack of comparison with other treatments.[30] This necessitated our search for the most appropriate study design for a proposed integrative dermatology treatment protocol. The World Health Organization (WHO) has recommended adopting a ''black-box design'' when conducting studies for the clinical evaluation of traditional medicines.[31] This means that, during clinical trials, treatments and their components are to be delivered precisely as they would be in routine existing practice, based on descriptions in their respective, often ancient, literature, of which not every copy of the text is similar.

The Indian Council for Medical Research (ICMR) recommended designing pilot observational studies to explore the feasibility of conducting larger trials for validation if the outcomes of the pilot trials were encouraging. This is mainly because the available ''guidelines'' on research methodology for double-blind control studies to evaluate procedure-based therapies in traditional medicine lack clarity. On this issue, the WHO's expert committee concluded that ''as far as possible it is preferable to conduct the studies using double-blind techniques but it may be difficult [to do this] in procedure-based therapies of traditional medicines, as it is impractical or impossible for the practitioner to be kept ignorant of what treatment patients are receiving''. Therefore, when we began to develop an integrative treatment model, we did not set out to achieve the level of evidence of a well-conducted randomized control trial (RCT) design but instead embarked on a large case series using objective outcome measures.

Obtaining peer review and guidance

We decided to share our findings and hoped to incorporate any suggestions that emerged in the course of peer

discussions and debates. Therefore, results from our first case report up to a large case series were presented periodically on the international platform, including at meetings of the International Society of Dermatology, the European Academy of Dermatology and Venereology, and the Indian Association of Dermatologists, Venereologists, and Leprologists. At this stage, the British Epidermoepidemiological Society (BEES) supported our group by awarding it a bursary to cover the costs of attending a three-week training course on evidence-based dermatology delivered by Professor Hywel Williams at the International Cochrane Skin Centre, Nottingham, UK. Shortly before his death, Sir Richard Doll, Regius Professor of Medicine at Oxford University, in discussion with TJR, carefully reviewed our approach. Additional training was received from the ICMR, New Delhi. Publications, including editorials, on our integrated approach to the treatment of lymphedema appeared in lymphology journals.[32,33] The *Journal of Lymphedema* brought out a special supplement on our integrated approach, which included reference to patient participation.[34] Three national-level seminars with the participation of international experts in the subject from India, the UK, the Netherlands, and Germany were conducted at Kasaragod, Kerala. These were supported by the Kerala State Council for Science, Technology, and Environment, Thiruvananthapuram (KSCSTE), the ICMR, and the Department of Science and Technology, New Delhi (DST).[35] Patients who received integrated treatment participated in these meetings and demonstrated the self-care skin treatments they practice. James Nordland, Clinical Professor, Wright State University Boonshoft School of Medicine, Dayton, Ohio, provided an expert opinion on vitiligo.

Structuring a well-formulated research question

It is our opinion that the ability to structure a well-formulated clinical question derives from experience in research, teaching and, most importantly, evidence-based clinical practice because medical practice and medical research are mutually dependent.[36] We began by constructing this research question:

"In children and adults suffering from chronic and difficult-to-treat dermatological diseases, are therapies from Ayurveda and/or yoga therapy, administered serially or simultaneously with biomedicine, useful for improving quality of life and other clinical outcome measures in the disease under study?"

Although we did not use homeopathy as therapy, we acknowledged its clear advantages in terms of eliciting history. We used protocols derived from homeopathic practice mainly for the purposes of history taking and to treat mental stress in vitiligo.

Materials and methods

On the basis of the issues discussed above, the integrative dermatology patient care program focused at first on only two highly prevalent diseases:

1 Lymphedema affecting the lower limbs that required skin care as a major component of treatment, and
2 Vitiligo.

Our principal purposes in focusing on vitiligo were to increase understanding of its clinical presentation and treatment options.

Searches for sources of best evidence

When we began integrative dermatology work 13 years ago, potential sources of Ayurvedic data were restricted to personal experience, the experience and knowledge of colleagues or experts, classical textbooks, and commentaries. Web-based databases and searches were only just evolving in India. However, numerous English translations of ISM descriptions were published in India as either CME articles or as medical books, albeit not supported by clinical studies.[11] The major publishing houses covering this type of material include the Chowkhamba Sanskrit Series Office, Varanasi. Most published works include the authors' observations on treatment regimens set up at a personal level.[37] Current scientific publications arising from clinical work are rarely found in mainstream biomedical databases, primarily because most Ayurvedic journals are not indexed by such databases. Biomedical journals in India that are available on the World Wide Web in general do not publish on Ayurveda or integrative studies. Hence the DST in New Delhi funded us to map databases containing Ayurvedic journal publications and to develop a search strategy to locate articles within them.[38] Several open-access databases across the world host Ayurvedic literature.[39] The most important of these are the Annotated Bibliography of Indian Medicine[40] and the National Science Library (NSL), National Institute of Science Communication and Information Resources (NISCAIR).[41] Furthermore, there are large numbers of postgraduate dissertations and PhD theses, about 800 of which are documented every year.[42] Most systematic reviews on Ayurvedic medicine include only RCTs, whereas the majority of publications are observational studies.[43]

Ethical clearance

The IAD Institutional Ethics Committee gave clearance for the study in 2004, having consulted with national and international ethicists. In fact, this represented the first time ethical clearance for an Ayurvedic study had been granted in India by an independent ethics committee appointed by the IAD. Details of the legal process can be found in the ICMR guidelines.[13] At the time of writing this article, a bill relating to ethics is before parliament pending enactment. Hence, ethical clearance is not

Table 2 Clinical aspects of lymphedema in the terminologies of Ayurveda (in Sanskrit) and biomedicine (patients examined, $n = 638$; limbs, $n = 857$)

Description	Biomedicine	Ayurveda
Name of disease	Lymphedema	*Shleepada*
Pathophysiology	Inadequate drainage of lymph	Derangements of *rasa vaha srotus*
Prognosis	Not curable	Not curable after 1 year's duration
Inflammatory episode explained	Yes	Described as "*pitta prakopa*"
Vector-borne etiology	Recognized	Not recognized

at present a legal requirement, although funding agencies insist on ethical approval.

Reducing bias in a multidisciplinary team with different approaches to patient management

In the provision of integrative patient care, our objective was to achieve the safe, effective, combined use of Ayurvedic and biomedical medicine and additional yoga exercises in lymphedema. Only objective clinical endpoints were used. Before the actual trial began, the MSD team agreed that, irrespective of the system of medicine used and the method in which it was administered, outcomes would be measured according to objective parameters which allowed for comparison (i.e. photographs taken at baseline and at every follow-up consultation). Confounding factors were minimized by limiting the use of additional medications. Decisions to prescribe additional drugs (e.g. antibiotics) were made by the dermatologist in the group after consultation with other members.

Our objectives, approved by the KSCSTE, were:

1 To carry out an MSD team review of patient management in Ayurveda (including yoga), biomedicine, and homeopathy, and of the standard literature on the therapeutics of each of these systems of therapy;
2 To facilitate the examination of a given patient by an Ayurvedic doctor, a yoga therapist, a homeopathic doctor, and a dermatologist;
3 To compare provisional diagnoses according to biomedicine and Ayurveda for a given disease, and
4 To understand the diagnoses referred to in (3) above and the prognoses by applying biomedical investigations.

Recruitment of patients

The Ayurvedic doctor recruited the patients for the study and selected the Ayurvedic herbal medicines used for each patient as narrated in Narahari *et al.*[44] Patients came from 10 different provinces of India and were often required to travel for more than 1 day to reach Kasaragod. The study was conducted in the outpatient department (OPD) and in the outsourced inpatient hospital of the IAD. Only 26 patients defaulted on follow-up.

Over the period between October 2003 and September 2009, integrative therapy was administered to 638 patients with lymphedema of one or both lower limbs (case records referred to 857 limbs) of any duration, who were able to perform the variety of yoga exercises. Patients presenting with acute inflammatory episodes, known as dermatolymphangioadenitis, were excluded (Table 2).

In our study of vitiligo, we examined 207 male and 174 female patients, including 45 children (for a total of 381 patients).

Integrative patient care

Chronic patients with longstanding dermatological diseases who had been treated at many centers were offered integrative dermatology treatment. An acute inflammatory presentation was an exclusion criterion in lymphedema. Patients were informed that the OPD would provide palliative treatment, care, and counseling on a weekly basis. Three doctors trained in different systems of medicine (dermatology, Ayurveda, and homeopathy) and, in the case of lymphedema, a yoga therapist, separately examined patients attending the OPD. The diagnosis was made as per the standard literature in each system of therapy, namely: as a provisional diagnosis in biomedicine; as *samprapthi* in Ayurveda; and as a totality of symptoms in homeopathy. This inference on the illness of a given patient was reviewed by the MSD team. The dermatologist guided decisions on any biomedical diagnostic tests to be carried out, when indicated. A dialogue aimed at establishing mutual orientation and understanding of the therapeutics in each system of medicine for the same disease was achieved at this stage at the bedside. Findings in a given patient were analyzed against the background of a literature review on the same disease, in all systems of medicine, with particular reference to treatment, possible drug interactions, and prognosis, after which the MSD team decided on the combination or serial order of the system and modality of therapies to be administered. The guidelines formulated in the chosen system(s) of medicine represented the basis of drug therapy. Clinical presentation, investigations, follow-up, and adverse effects were documented and supported by photographs. Biomedical clinical outcome measures were used to decide the prognosis of treatment.

Dermatology counseling

Patients first underwent a detailed counseling session lasting for at least 1 hour. During this process, patients and their family members were given complete details of the treatment program using a PowerPoint presentation. Lymphedema, also referred to as lymphatic filariasis, is a prevalent disease in our locality. It is

spread by mosquitoes and is usually treated by the mass administration of drugs in order to break transmission, but this treatment has little effect in terms of controlling morbidity. Counseling of lymphedema patients emphasized the care of entry points, self care and the need for the life-long practice of treatment and the use of compression bandages.

Information during counseling for vitiligo patients included explanations of the methods of treatment in Ayurveda and biomedicine, the prognosis as explained in both systems, and the need for treatment duration of at least one year before it is clear whether or not the patient has benefited. A consultation with the homeopathic doctor for vitiligo was included as part of the counseling.

All patients were informed that the integrative regimen did not promise any cure. Usually, patients were not admitted to the treatment program on the day of baseline counseling. Instead, they were provided with informative materials on integrative treatment and asked to convey their decision later. Occasionally patients were given contact details (after obtaining permission) of other individuals in their vicinity who had taken our treatment. Thus, patients opted to take our treatment only after participating in a series of discussions and enquiries, and a consultation and counseling process. Willing patients attended a further session of admission counseling during which they were at liberty to decide against treatment. If they wished to enter treatment, they were asked to sign consent forms approved by the institutional ethics committee. Patients received counseling during every follow-up, primarily in order for us to ascertain whether treatment instructions were being followed as advised. Often the counselor telephoned patients to improve their concordance with treatment.

Patient selection

According to Ayurveda, analysis of *prakruthi* and local skin pathology (*sthaneeya vikruthi*[45]) is mandatory before prescribing ATF. This process can be conducted in two steps. The first is carried out at the time of screening, which occurs at the stage of assessment for eligibility, when patients whose biological constitutions (*prakruthi*) contraindicate the ATF under trial are excluded. The second step refers to exclusion as a consequence of local clinical features indicated by the patient's local skin pathology. The *prakruthi* of a patient is assessed by around 20 groups of characteristics. Assessing contraindications precedes any decisions on prescribing and dosage, and depends on analysis of *prakruthi*, *sthaneeya vikruthi,* and methods of clinical diagnosis (*nidana panchaka*[46]), along with the 11 other parameters. These selection criteria must be developed for each disease before embarking on any trial, in keeping with the model of the individualized treatment table.[25] At the beginning of the patient assessment, and before recruiting the patient for trial, we made detailed notes on the patient's clinical presentation, clearly defining the stage of the disease (*roga avastha*) and enumerating the properties of the specific ATF (pharmacology including posology) to be used. We then developed tables containing clinical descriptions of *vata*, *pitta,* and *kapha* presentations for each disease (*vikruthi* tables). An example of a *vikruthi* table developed by us for lymphedema (called *shleepada* in Ayurveda) is now available.[47] Over time, skin changes in lymphedema become increasingly conspicuous and troublesome (elephantiasis), and therefore the management of local features (*sthaneeya vikruthi*) is as important as management of the systemic condition. (Dermatology has ignored these gross and common skin manifestations, and we feel entirely justified as dermatologists in giving this condition the focus it deserves.) These locally distinctive *doshas*, meaning complex patterns of differing symptoms and signs, produce typical ''constellations'' of clinical signs and symptoms that are summarized in the *vikruthi* table for lymphedema. These features are caused by the different responses of tissues to the pathophysiological processes and, consequently, rational treatment should be formulated on the basis of these differing responses or *doshas*. During the selection of medicines for skin diseases (*kusta roga*), additional clinical descriptions of disease affecting the basic body tissues, which stabilize and nourish the body (*dhathu gata kusta*[48–50]), should be elicited.[25] This would give more of the information needed to establish the stage of the disease and to guide the selection of the ATF. Finally, inclusion and exclusion criteria for a trial involving an ATF were developed by referring to the structured questionnaire format to identify the *prakruthi*, the individualized treatment table, the *vikruthi* table, and *dhathu gata kusta* tables.

Study design

Because we used objective parameters as outcome measures, in line with *Cochrane Handbook for Systematic Reviews of*

Table 3 Selection of Ayurvedic skin care solution: ''*phanta*''

Name of *phanta*	Dominant clinical features of disease-affected organ (*sthaneeya vikruthi*)	Herbal contents
Manjistha	Clinical features described as *vatha*	*Rubia cordifolia*
Sariva	Clinical features described as *pitta*	*Hemidesmus indicus*
Yestimadhu	Clinical features described as *kapha*	*Glyceriza glabra*
Triphala	Physician is unable to distinguish the dominance of any one of *vatha*, *pitta,* or *kapha*	*Terminalia chebula*, *Terminalia belerica*, *Emblica officinalis*

Interventions (Version 5.0.2)[51] recommendations, we decided to use a case series design, albeit that we recognize the RCT as the reference standard methodology. The RCT is an expensive design and was not possible with the money granted for this pilot study.

Integrated treatment delivery

Lymphedema. Integrated skin care procedures for lymphedema are described.

Soap and water wash. A nurse or a multipurpose health worker, assisted by the patient's attendant, gave a meticulous soap and water wash every day. The type of soap used for skin care was selected after determining the pH using litmus paper.[52] Although they are not routinely available on the Indian market, the recommended soaps were in the acidic range. The wash removed dirt and deposits between the folds on larger limbs. A menstrual regulation syringe was used to spray boiled tepid water between the folds. The foul odor of some wounds was treated initially with ringer lactate solution.[53] Maggots, if present, were removed from the wounds by applying 5% permethrin for 4–8 hours.[44]

Phanta soaking. Following the limb wash, the affected limb was immersed in an Ayurvedic skin care "*phanta*" solution for 20 minutes, after which it was dried using a cotton towel. Special attention was given to eliminating moisture from skin folds and from between the toes. *Phanta* selection was made according to "patient selection" above. Most patients required *yasti madhu* (*Glycerrhiza glabra*) powders (Table 3).

Phanta was prepared by soaking one part (30 g) of the fine powder of the dried officinal part of *Rubia cordifolia* (common madder or Indian madder) with eight parts (2 l) of boiled water in a plastic container closed by a lid for 12 hours.[54] This solution is diluted with 16 parts (4 l) of warm water just before use.[55] The limb is dipped in the *phanta* solution and soaked by pouring the solution over it continuously for 20 minutes.

Phanta is a variety of *kashaya* preparation. *Kashaya* (herbalized liquids) are usually prepared by combining one part of medicinal herbal powder and 16 parts of water in a mud pot and boiling the solution over a low flame until one-eighth of the water remains. As it is made using fine powder, *phanta* is the easiest to absorb of the five varieties of herbalized liquid preparations (*kashaya kalpana*). *Phanta* is prepared by overnight soaking in boiled water. *Kashaya* and *phanta* are used for ulcer care as topical soaking solutions. Different methods of using these solutions are described in Ayurveda.[56] Depending on the *sthaneeya vikruthi*, the ulcer may be flushed with *kashaya*, sesame oil (*taila*), milk, ghee, or cow's urine (*gomutra*).[55] Nadkarni recommended using *phanta* in the same way as *kashaya* as it is likely to be absorbed faster than other types of *kashaya kalpana* in the given time of 20 minutes.[54]

Classical teaching in Ayurveda refers to *shleepada* as a *kapha*-dominant condition. The systematic eliciting of clinical features using the *sthaneeya vikrithi* table indicated that most of our patients had *kapha*-dominant *sthaneeya vikruthi*, although *vatha* features were also found in many. *Phanta* solutions were selected for their specific properties and actions based on the *sthaneeya vikruthi*. For example, *manjistha phanta* was used to improve the *vatha-kapha sthaneeya vikruthi* manifested in the affected limb (Table 3).

Entry point care. In cases of fungal intertrigo, colorless Castellani's paint was applied; in the absence of response, clotrimazole 1% cream was used. Eliminating intertrigo was the most difficult part of entry point care. Ayurvedic herbal dusting powders (*avachoornana*)[57] were applied between the toes and in the gaps of large folds. These come in the form of tablets (Tricawin; Dabur Pharmaceuticals Ltd, Ghaziabad, Uttar Pradesh, India). However, recently this product became unavailable, and hence we began using *rasnadi choorna* (a coarsely powdered mixture of 19 herbs, the main ingredients of which are *Pluchea lanceolata* root [*rasna*] and *Cedrus deodara* stem [*devadaru*][58]). Many patients had associated gravitational eczema. They were treated with topical betamethasone dipropionate 0.05%. Oozing manifestations were initially treated with topical steroids applied under occlusion. Ordinary plastic sheets were purchased, disinfected, and placed over the eczematous area after the application of betamethosone cream. A long-stretch compression bandage was applied in a figure of eight over the plastic and retained in place for at least 8 hours. Ulcers, if infected, were treated with appropriate antibiotics. Unhealthy granulation tissues and slough on the base of the ulcer were treated with *jatyadi thaila*, an oil-based preparation made with 19 herbs. The main ingredients of this liquid preparation are tender leaves of *Jasminum officinale* (*jathi*), stem bark of *Azadirachta indica* (*nimba*), root of *Trichosanthes dioica* (*patola*), and tender leaves of *Cassia*

Figure 1 Indian manual lymph drainage using herbal oil selected as described in Table 4

Table 4 Selection of Ayurvedic herbal oils used in Indian manual lymph drainage

Ayurvedic oil*	Dominant clinical features of disease affected organ (***sthaneeya vikruthi***)	Major herbal contents of the oil (not the complete list)
Nalpamaradi[63] *thaila**	Any combination of *vatha* and *kapha* disease	*Ficus bengalensis*, *Ficus recemosa*, *Ficus religeosa*, *Ficus lacor*, *Curcuma longa*, *Pumaria parviflora*
Pinda thaila[63]	Any combination of *vatha* and *pitta* disease	*Rubia cordifolia*, *Vateria indica*, *Hemidesmus indicus*
Chandanadi thaila[63]	Clinical features of *pitta*	*Santallum album*, *Curcuma longa*, *Glyceriza glabra*
Shuddabala thaila[63]	Clinical features of *vatha*	*Sida cordifolia*, *Tinospora cordifolia*, *Alpinia galangal*

*"*Thaila*" is sesame oil. This word cannot be translated as "any oil".

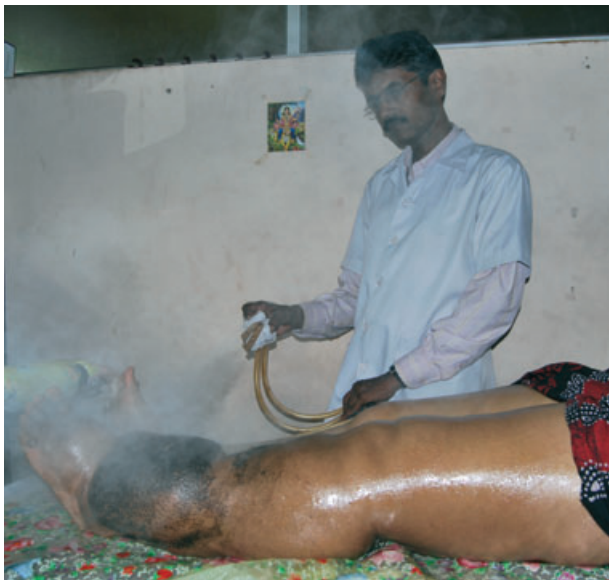

Figure 2 *Ekanga swedana*, localized heat treatment to the affected limb. This is performed after Indian manual lymph drainage and is administered only under medical supervision

Figure 3 Patient performing yoga exercises prior to undergoing Indian manual lymph drainage as part of home-based self-care in integrated treatment for lymphedema

fistula (*aragwadha*).[59] Skin care included the regular cleaning and paring of nails and hair. Patients were strictly advised to use good, well-fitting footwear, which sometimes required specific construction by a cobbler.

Indian manual lymph drainage (IMLD). This is a skin care procedure administered in Ayurveda, classified under the broad category of *abhyanga*.[60] *Abhyanga* involves massage of the affected parts of the body using both palms while the patient lies supine on a massage table or cot. Part 1 of IMLD (*unmardhana*, a type of non-oil massage[61]) requires the masseur to apply a "squeezing" pressure using both palms and fingers and moving from the tip of the toes to the upper edge of the lymphedema. Non-oil massage is performed for 10 minutes with the patient in a supine position. Part 2 of IMLD (*udhwarthana*, a massage using oil[49]) is then performed (Fig. 1). In *udhwarthana*, oil is applied to the skin, and the body is massaged in the opposite direction to hair growth,[62] with more pressure than in general massage (*abhyanga*). Oil is selected according to local skin pathology, which, in over 95.7% of our patients, was that of *kapha* + *vatha*, and hence the oil selected was *nalpamaradi thaila* (Table 4).[63] First, the selected oil is smeared over the affected limb. The limb is then gripped in both hands and massaged from the distal to proximal ends in a continuous sliding movement from the tip of the toes to the upper edge of the lymphedema. A spiral movement is made at the upper edge towards the medial side of the thigh along the direction of the great saphenous vein.[53] The cycle is repeated with the patient in supine and prone positions for 10 minutes in each position. During the distal to proximal movement in IMLD Parts 1 and 2, the patient breathes out slowly or holds the breath after exhalation. The patient takes a sudden and deep inhalation during the pause between the end and beginning of IMLD strokes. In this study, IMLD was administered by a masseur who subsequently coached the patient's home caregiver in the technique.

Ekanga swedana (inducing sweat over the affected limb). Patients with hardened limbs showing non-pitting edema

Table 5 Pre- and post-Indian manual lymph drainage (IMLD) yoga exercises and *pranayama*

Pre-IMLD yoga exercises	Post-IMLD yoga exercises
Swastikasana	*Tadasana* 1 and 2
Vajrasana	*Trikonasana*
Gomukhasana	*Padanguli namana*
Padmasana	*Gulpha namana*
Bhekasana makarasana	*Gulpha chakrasana*
Prasruta hastapadasana	*Paschimothanasana*
Viparita karani	*Bhujangasana makarasana*
Shavasana 1 and 2	*Prasruta hastapadasana*
Pranayama	*Viparitha karani*
Ujjayi	*Shavasana* 1 and 2
Anuloma-viloma	Pranayama
Recaka kumbhaka	*Ujjayi*
Surya bhedana	*Anuloma-viloma*
Bhastrika	*Recaka kumbhaka*
	Surya bhedana
	Bhastrika

("organized limbs") were given Ayurvedic heat treatment (Fig. 2) over the affected limb (*ekanga swedana*[56]) during the initial 14 days of treatment. This procedure is carried out under medical supervision. Herbalized steam, made with the roots of 10 herbs (*dasha mula*),[64] is passed through a pipe and sprayed directly over the affected area. An additional layer of the oil used for massage (*udhwarthana*) is applied over the area before the herbalized steam is sprayed. The steam is sprayed until the treated limb shows uniform "beads of moisture" over the heated part and is continued until the patient is unable to tolerate the heat any longer.[64] This takes an average of 15–20 minutes. This procedure is called *nadi sweda*,[56] and the clinical endpoints that define the ceasing of heating are described as *samyak swinna lakshana*.[56] The patient then rests outside the procedure room in an environment that is not fan-cooled, with the foot elevated, until the heat in the limb settles to a level comparable with the temperature elsewhere in the body and the sweat or moisture on the limb dries naturally (30–45 min). The Ayurvedic doctor on our team (author GMA) performed this procedure after IMLD Part 2.

Yoga exercises. Lymph drainage is effected by a combination of yoga exercises (Fig. 3) and IMLD. Eight yoga exercises (*asanas*) and five special breathing techniques (*pranayamas*) are practiced before IMLD, and 10 *asanas* and five *pranayamas* are performed afterwards. (Table 5).

Compression bandaging. After IMLD, boiled or steam-sterilized cotton cloth is wrapped around the limb in order to prevent the soiling of the compression bandages. Long-stretch compression bandages 15 cm in width were used. Depending on the length and swelling of the limb, the number of compression bandages used ranged from two to eight per limb. The compression bandage was applied in a figure of eight, as described by Foldi *et al.*[53] During the supervised part of the treatment, foam padding and microcellular rubber moulds were used underneath the compression bandage.

Diet. In Ayurveda, patients are asked to observe dietary restrictions while on medication.[44] Restricted dietary items include 17 varieties of incompatible food (*virudha ahara*) that are labeled as *virudha*[65] (with respect to the patient's habitat, the season, incompatible combinations, etc.), are slow to digest (*guru*), are sour (*amla*), are non-vegetarian, or contain milk or milk products.

Overall improvement in the condition of the skin was the only objective considered during the integrative treatment protocol. *Nalpamaradi* oil was selected for huge limbs with xerosis,

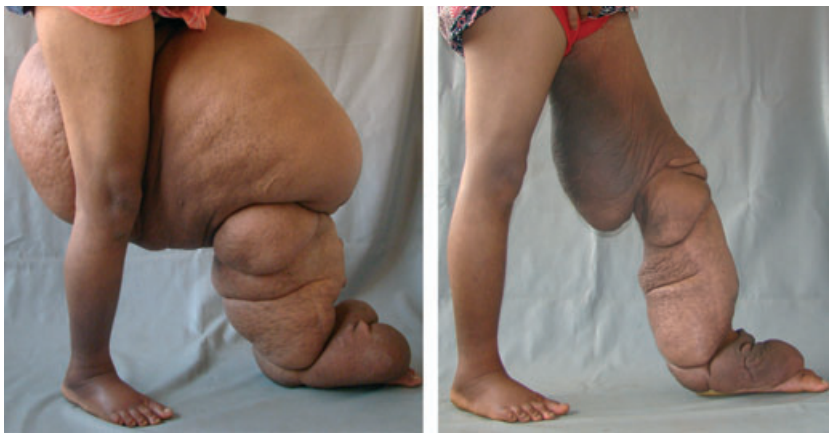

Figure 4 The affected limb in a compliant patient with lymphedema at (a) baseline and (b) after 55 d of integrated treatment

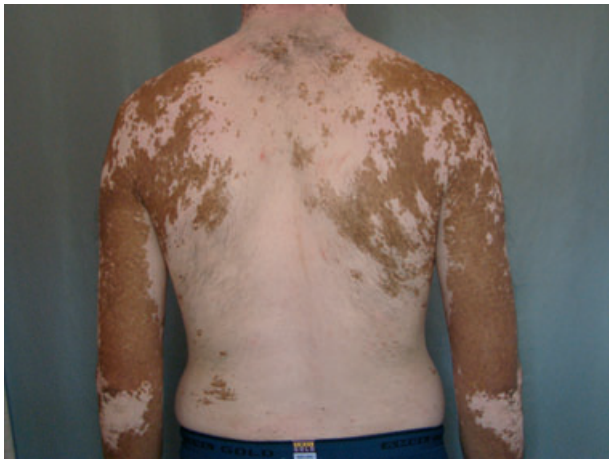

Figure 5 A patient with vitiligo (*switra*) showing the clinical subtype defined in Ayurveda as *kaphaja*, typified by bright white and large/multiple lesions (*bahala*)

dependent edema of the foot, "black" pigmentation, nodules, and warty growth. We observed that the absorption of oil by the skin increases in line with the level of severity of xerosis. About 50–80 ml of oil is needed for 20 minutes of *udhwarthana* for one limb. Similar observations have been made in biomedicine, which requires an emollient to be applied in such cases. Although this Ayurvedic oil is selected for its *kapha hara* properties, the addition of IMLD results in objective changes that are generally not observed when biomedicine is used alone. In Fig. 4, the baseline photograph shows a limb after several years of treatment with biomedicine alone (mostly consisting of topical steroids or emollient oils); the second photograph shows the same limb after 55 days of integrative treatment. (See pretest–post-test design.[66]) It should be noted that the drug or Ayurvedic oil is selected on the pathophysiological basis described above. Before we finalized our integrative skin care protocol, drugs were selected in accordance with the guidelines given in the respective literatures, whereas their combined application to a patient was guided by the collective clinical wisdom of the group. We made this selection using the *vikrithi* table. *Vikrithi* tables were developed on the basis of individualized treatment tables.[25]

Vitiligo

Vitiligo is clearly and fully described in Ayurveda. By contrast with biomedicine, Ayurveda categorizes several sub-varieties of disease, even within the same patient, and attributes them to imbalances and dominance of *kapha*, *vatha,* or *pitta*.[48,67,68] Large or multiple lesions appear in the *kapha* variety. Xerotic lesions indicate the *vatha* variety. Red or bright red lesions mark the *pitta* variety. There are also subtypes (Fig. 5). Thus itchy lesions are a subtype of *kapha*. A discussion group (acad_iadvl@yahoogroups.com) within the Indian Association of Dermatologists, Venerologists and Leprologists (IADVL) regards itchy lesions in vitiligo as a common presentation with a poor prognosis. At our institute, *kapha* varieties accounted for 39.6% of the 381 patients presenting with vitiligo. Biomedical textbooks do not discuss this presentation.

The clinical terminology used in vitiligo is listed in Table 6. Based on skin pathology (*sthaneeya vikruthi*), vitiligo is subclassified as in Table 1.

In Ayurveda, the constitutional imbalances and repigmentation of vitiligo are believed to reflect a response to therapies focused on the gastrointestinal tract, especially on purgation (*sadhyosnehana*[69] and *virechana*[70] [monthly pulses of controllable and induced purgation, MPCIP]), which is believed to be most effective in the *pitta* variety of vitiligo. Where it is

Table 6 Clinical aspects of vitiligo in the terminologies of Ayurveda (in Sanskrit) and biomedicine

Descriptor	Biomedicine	Ayurveda
Name of disease	Vitiligo or leucoderma	*Switra* or *kilasa* or *swetha kusta*
Pathophysiology	Multifactorial pigment disorder	Derangement in the dietary ecosystem (*sathmya*), sudden and frequent extreme variations in food and induced environment temperatures (e.g. drinking refrigerated water immediately after hot tea). Movement of deranged *dosha* into deeper tissues
Treatment ingredient	Molecule derived from *Psoralia corylifolia/Ammi majos*	Herbal medicine containing *Psoralia corylifolia* and others
Prognosis as per the literature	Recurs despite medical or surgical treatment	Better prognosis when lesions are of recent origin or short duration (*nava*), thin (*thanu*), with pigmented hairs (*asukla roma*). Poor prognosis if: duration is > 1 year; hairs are depigmented (*shukla roma*); lesions cover the external genitalia, lips, and fingertips (*antejatam*); lesions appear following burns (*agnidagdhaja*); coalescing lesions coalesce (*samslista*), or lesions cover large areas of skin (*bahala*)
Signs of activity	As described in Fitzpatrick *et al.*[20]	Lesions show Köbner's phenomenon associated with reduced digestive ability subjectively determined by the time taken to digest food as reported by the patient (*medo dhathu* involvement [see [25]]); lesions coalesce

contraindicated, the frequency of the stools is increased by prescribing *triphala choorna* daily (*anulomana*[71]).

All patients were asked to carry out MPCIP (*sadhyosnehana* and *virechana* in Ayurveda) on a monthly basis. This procedure is performed as follows.

1 Early on Saturday morning, after washing the face, the patient drinks one cup of hot water on an empty stomach to confirm the complete digestion of food consumed the previous day. While drinking the hot water, the patient should expect to experience eructation. If the eructation does not feature the odor or taste of the food consumed the previous evening, it is assumed that this food has been digested overnight. The patient is ready to begin treatment.

2 After confirming that food taken on the previous evening has been digested, 50 ml of cow's ghee in liquid form with hot water is consumed. To liquefy ghee, immerse the bottle of ghee partially in a vessel containing hot water. The patient should then continue to sip half a cup of hot water (in the same way as we drink coffee or tea) once every 30 minutes. Each time eructation occurs, it should be expected to carry the odor of ghee, indicating that the ghee consumed is still in the stomach. The patient should continue to sip hot water once every 30 minutes until the eructation containing the smell of ghee stops (*shudda udgara*). *Shudda udgara* (Sanskrit for ''clear eructation'') indicates that the ghee is no longer in the stomach. ''Clear eructation'' is, therefore, a clinical test to confirm that the ghee taken by the patient has been digested or has passed into the duodenum and that the stomach is once again empty. This may take 1–12 hours to occur. The patient is advised to consume only easily digestible food such as gruel after achieving clear eructation.

3 The following day, the patient performs the MPCIP procedure. The patient takes three tablets of *ichhabhedi rasa*[72] early in the morning on Sunday, again on an empty stomach. The patient is permitted to drink boiled and cooled water before taking the tablets. Purgation is expected to start within 60–90 min. According to Ayurveda, a minimum of 10 stools must be passed to obtain the therapeutic benefit from these tablets, although 25–30 stools is considered optimum. The patient is advised to drink cooled, boiled water frequently to maintain hydration until purging is affected (i.e. an average of 10–20 times). The purging process stops immediately when any hot food or liquids are consumed orally. Thus purgation can be stopped at will. The word *icha* means ''at will'' and *bhedi* means ''purgation''.

4 Outcome measures of MPCIP fall into three subcategories of signs and symptoms that may occur at the time of purgation: (i) lightness of the body (*laingiki* in Ayurveda); (ii) the passing of 10–11 stools (*vegiki*); and (iii) the passing of stools that are foamy and sticky. The last subcategory is considered to represent the endpoint (*anthiki* or *kaphantha*).[73] Purgation should be stopped by taking hot food at this stage.

5 The patient should drink cold water frequently to prevent dehydration. If the subject becomes exhausted during the procedure of induced purgation, there is no requirement to wait for the numbers of peristalses given above to occur. The patient should stop purgation by taking hot food and should not consume any more cold food or drink that day. If hot water is taken, purging will stop. Hence hot water is to be taken only when the patient wants to stop purging.

6 Once the purging stops, the patient should consume *conjee* (gruel) or hot food items that are easily digested. During this procedure, the patient may also experience one or two bouts of vomiting.

7 This procedure of purging should be practiced once per month only.

After purgation, Ayurvedic oral preparations are taken daily for one month until the next cycle of MPCIP.

Over 100 Ayurvedic formulations for vitiligo are described in the literature. However, these tend to be prescribed more for their role in the management of skin disease in general (on the basis of *dosha vaishamya* [disease]) and its constitutional background factors, rather than specifically for vitiligo, just as biomedical dermatologists will prescribe washing and emollient techniques for skin care in general and sometimes a ''tonic'' for general health. Ayurveda recognizes only a few disorders for specific therapies in a manner that matches that of biomedicine. These include psoriasis (*eka kusta*), eczema (*vicharchika*), and lymphedema (*shleepada*) but few other skin disease entities.

Both biomedicine and, even more so, Ayurveda recognize the staging of disease and may require additional staging and changes of therapy. We have some way to go before we can identify which drug is more efficacious at which stage, and which topical therapy is more suitable for which lesion, even in the same patient.

Over the past two years, a team from the IAD has explored very fully how best to undertake systematic reviews of Ayurvedic texts and any other literature focusing on vitiligo. A description of the method of this exploration has been presented for publication. The review has proven to be a resource for improving our understanding of the disease and its management, but it has also encouraged us to focus on only a few therapies.

A *kapha* state of the skin is treated with *avalguja beejadi kashaya* (*kashaya* is herbalized liquid), with or without *prakshepa dravya*.[74] A *vatha* variety is prescribed *thikthaka ghrutha*.[75] A *pitta* variety is prescribed *kakodumbarikadi kashaya*.[76] For the latter, the *kashaya* is prepared by adding 20 g of rough herbal powder to 800 ml of water and boiling the solution over a low flame until 100 ml of water remains. A portion of 50 ml of this *kashaya* should be consumed twice daily after food. *Kashaya* should be prepared every day. In *kapha* patients, finely powdered *Psoralia corylifolia* seed

(called *prakshepa dravya*) is sprinkled over the condensed decoction of herbalized liquid *avalguja beejadi* before consumption. If the patient also shows significant *pitta* features associated with *kapha*, this *prakshepa dravya* should not be used.

All patients are instructed to expose themselves to the midday sun for at least 10–15 minutes per day, although achieving whole-body exposure is difficult for many of them.

Disease activity. Active disease is characterized by new lesions, the Köbner phenomenon (depigmentation at sites of trauma such as scratches), expansion of the convex edges of lesions, and the whitening of hairs in the lesion (leucotrichia). Any improvement that becomes apparent in some lesions while others are active is considered to indicate that the therapy is sufficiently effective to warrant continuation.

Patient satisfaction. Some patients wish for total repigmentation, whereas others are satisfied by achieving near total repigmentation of sites exposed to public view.

Consensus. Each patient was examined by the team, and consensus on details such as whether there was expansion or repigmentation was recorded as a majority view. Thus the degree of disease activity was judged subjectively, and both the doctors' and the patient's opinions were taken into account. Objective systems of photography have been introduced but are not yet fully developed.

Discontinuation of drugs. The exacerbation of vitiligo was noticed following *shwitra nashaka vati*. On investigation of this widely available preparation, we found that its ingredients and methods of preparation did not match those outlined in the classical Sanskrit texts.

Iccha bhedi rasa caused vomiting and gastritis in most of the patients who were given it. On further investigation, we realized that patient selection was at fault.

Results

Outcome measures used for assessing the efficacy of treatment in lymphedema are described here.

1 Limb volume changes measured by water volume displacement (the reference standard in lymphology). This was supplemented by circumference measurements taken at eight points along the limb: metatarsal; mid-foot; ankle; end of calf; maximum calf bulk; patellar region; mid-thigh; and maximum bulk on standing.
2 Frequency of inflammatory episodes. Many patients suffered periodic acute dermatolymphangioadenitis before the treatment. This might range from monthly episodes to once-yearly episodes or, rarely, a first attack only. After treatment, the frequency of inflammatory episodes was expected to decrease. Patients in current inflammatory episodes with fever were excluded from the trial.
3 Reduction in entry points (intertrigo, folliculitis, eczema, or any other focus of infection) following treatment.

Data on treatment outcomes in lymphatic filariasis are maintained in a Microsoft Access database (Version 12). Figure 6 shows how its basic links appear on the computer screen. This database can instantly retrieve data using SPSS analysis.[77] Results obtained following two-step cluster analysis are shown in Fig. 7. This is an automatic

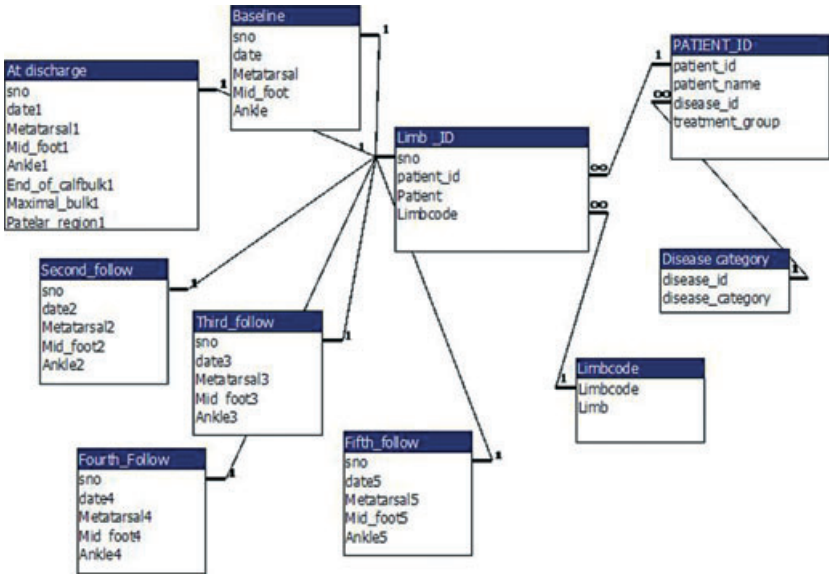

Figure 6 Basic links used in the Microsoft Access (Version 12) database of lymphatic filariasis patients

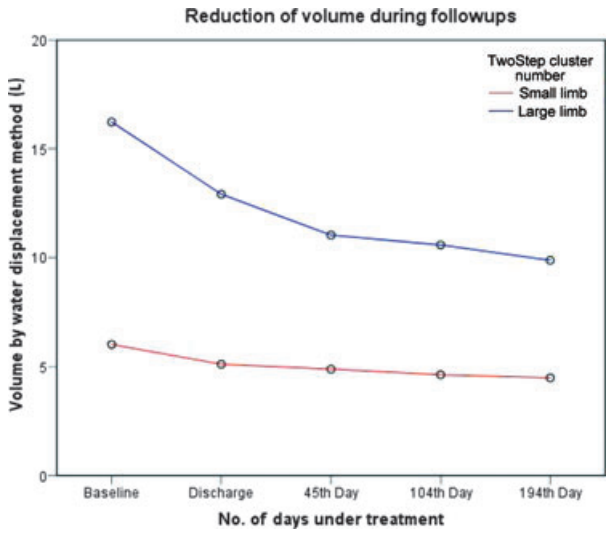

Figure 7 Volume reduction in lower limb lymphedema (857 limbs) following two-step cluster analysis using SPSS Version 16

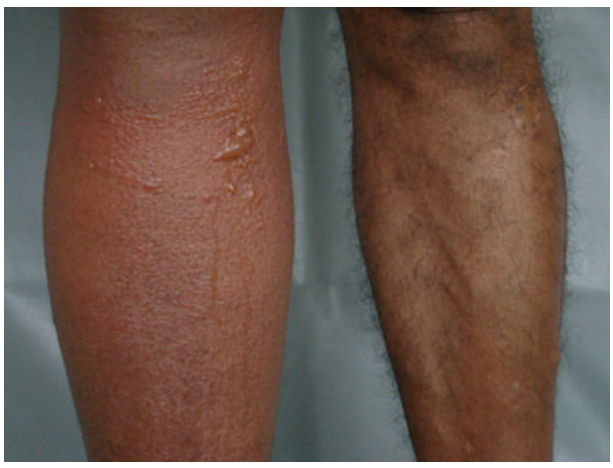

Figure 8 Dermatitis medicamentosa in response to *nalpamaradi taila* used in Indian manual lymph drainage

Table 7 Percentage reduction in volume from baseline in lymphedema

Classification by SPSS 16	Discharge	Day 45	Day 90	Day 180
Small limb	13.3	19.7	23.4	25.6
Large limb	23.0	31.1	39.7	44.2

analysis performed by SPSS Version 16 (SPSS, Inc., Chicago, IL, USA) when it considers that the data available are sufficiently large. The two-step cluster analysis procedure is an exploratory tool designed to reveal natural groupings (or clusters) within a dataset that would otherwise not be apparent. The algorithm employed by this procedure has several desirable features that differentiate it from traditional clustering techniques: classification of data by SPSS 16 revealed 643 limbs as small, 168 limbs as large, and 46 limbs as belonging to an "outlying cluster" (medical records were maintained for each limb). We have not yet identified a treatment failure among these 857 lymphedematous limbs in patients who are concordant with the treatment program. The adverse events observed included irritant and allergic contact dermatitis in response to *nalpamaradi* oil used for IMLD in five limbs (Fig. 8). About 10.7% of patients developed scattered sterile pustules over the massaged limbs. Analysis of variance (ANOVA) (also called Chi-squared or paired-sample *t*-test) showed average volume reductions of 13.3% and 23.0% on day 14, 19.7% and 31.1% on day 45, and 23.4% and 39.7% on day 90 of treatment in small and large limbs, respectively (Table 7). All patients improved, but previous surgery was found to compromise treatment outcome. Improvement depends on compliance, but as patient concordance was a prerequisite for acceptance on this program, compliance tended to be good.

Among vitiligo patients, we found that 39.6% of patients had *kapha*, 39.8% had *pitta*, 10.8% had *vatha,* and 0.52% had *tridoshaja* presentations. In the *tridoshaja* variety of vitiligo, it is not possible to differentiate which energy principles (*doshas*) are involved in the balance or imbalance in the physiology that supposedly caused the vitiligo lesions.

Discussion

Globally, governments have taken cognizance of the growing popularity of CAM and the potential for its combined use with biomedicine. Some governments are quite restrictive: in a number of European countries, legislation to promote safe use requires that CAM is practiced in collaboration with a biomedical doctor. Skin and wound treatments are estimated to account for a third of all traditional medicine use in the "traditional health care" sector. By contrast, they account for only 1–3% of all biomedical pharmaceuticals used.[78] A systematic review of surveys of CAM utilization among dermatological patients in industrialized countries showed that 35–69% of them used CAM,[79] which possibly reflects the success and failure rates of biomedical treatments of skin disorders. Therefore, in acknowledgement of the trend towards the practice of integrative medicine among leading Western medical institutions, most governments now recognize the need to facilitate "pluralistic systems of health care" to look after the health needs of their populations. No

single medical system can satisfy the needs of a whole population. If a CAM system has advantages over biomedicine for a given pathology, applying the two together within a system of integrative medicine may produce results superior to those of biomedicine alone. Ayurveda is unique because Ayurveda-specific accounts of particular pathologies can now be translated into Western medical terminology, making integrative practice easier to formulate.[25]

Developing countries generally possess their own traditional systems of health care, which may have been practiced for centuries, even millennia. The WHO now recommends that historical practice and theory over such time durations be accepted as evidence in their own right. Quoting Dr. Christian Kessler, of Hanover Medical School, Hanover, Dr. M. S. Bhagel, the director of India's premier Ayurveda Institute at Jamangar and former vice-chancellor of Gujarat Ayurveda University, writes that many publications are retrievable only via hand searches of references and interviews of experts. Common Western databases and CAM databases list only a small number of Ayurvedic studies. Various studies are published in regional languages, many of them only as abstracts, and a large number of these are postgraduate dissertations and PhD theses. The majority of studies refer to evidence of Cochrane levels[29] 2–4 and very few cite level 1a or 1b evidence. Group sizes are small in these studies. This makes the studies vulnerable to methodological error. Rationales for selected study designs are not always properly described.

However, we are not aware of any scientifically conducted study on the integration of more than one system of medicine prior to our own experience. Neither do any regulatory authorities issue guidelines in this regard. In 2008, the ''University of Michigan Experience''[80] in integrative medicine was published, but this did not include Ayurveda. Moreover, this paper gives no details of which medicines were administered and how.[80] In the same year, we submitted a letter to this journal, which was rejected with the advice that we write a detailed narrative article explaining the step-by-step methodology of the actual practices used in our OPD.

It took over seven years for the IAD to form a multisystem team of doctors and to evolve the mutual orientation required to develop the trust in and understanding of one another's disciplines – Ayurveda, homeopathy, and biomedicine – that were necessary to enable the team to function optimally under the many circumstances presented by different patients. During the period of this mutual orientation, the WHO published its general guideline emphasizing that, during any clinical trial of traditional medicine, treatment and all of its components should be delivered as they would be in routine existing practice, based on descriptions in the classical literature. The WHO recommended that each traditional system develop a black-box design applicable to the nature of that system of medicine.[31] In 2004, our local state government supported our proposal to establish a weekly OPD. At the same time, the Global Program for the Elimination of Lymphatic Filariasis recommended exploring local health traditions of skin care in the management of the disease.[81] In particular, Vaqas and Ryan discussed a low-cost treatment paradigm using traditional Indian medicines and yoga, suitable for rural communities.[18] At that time, the IAD had already been engaged in such a program for a number of years and was looking for collaborators.

The availability of numerous descriptive English-language translations of Ayurvedic texts marked the starting point for theoretical integration. Using these as reference points, we studied each clinical sign and symptom in given patients. This helped us to develop *vikrithi* tables (of comparable medical terms) for the diseases under study. The follow-up examination of patients over a reasonably long time is essential before a *vikrithi* table can be constructed. Gaya Dasa considered the atrophy of lesional skin (called *thanu* in Sanskrit) and a coppery red color (*thamra*) of the lesion to represent the *vata* subtype in vitiligo.[67] However, we did not observe these features in any of our 381 vitiligo patients. Neither do the two classical compendiums of Vagbhata[68] and Susrutha[48] mention these clinical features under vitiligo. Vagbhata[68] mentions red color and the absence of hairs in lesional skin in hairy areas under the *pitta* subtype of vitiligo. In India the most common presentation with these two clinical features is leprosy. Early vitiligo is often considered as a differential diagnosis for leprosy.[82] In Ayurveda, the loss of sensation is described under skin diseases (*kusta*). Some clinical descriptions in *dhatugata kusta*[25,48–50] are similar to those of leprosy, albeit that a separately named disease is found in the literature. The absence of coarse hairs over a few lesions was observed in some of our patients, but no coppery red or atrophied lesions were seen. Leprosy patients were not included in our study. In general we see lesions of a bright red color (*raktha*) during *pitta* presentation. Hence, when drawing up the *vikrithi* table for vitiligo, we excluded certain clinical features described in particular classical Ayurvedic texts.

Treatments in ISM are said to be individualized. However, in the process of drawing up *vikrithi* tables in an integrative approach to clinical examination and diagnosis, our MSD team observed patterns of clinical subtypes which guide drug selection in Ayurveda. This means that a given drug may be administered to a set of patients presenting with defined clinical features. For example, *pitta kapha hara* drugs that include *Ficus hispida*

Table 8 Frequency of inflammatory episodes following integrated treatment

	Baseline	Day 104 from baseline
Limbs without frequent inflammatory episodes	112 limbs (20.5%)	290 limbs (90.6%)
Limbs with frequent inflammatory episodes	434 limbs (79.5%)	30 limbs (9.4%)

(*kakodumbarika*) could be administered in *pitta* (Table 1) presentations in vitiligo.[76] An analogy can be drawn between the use of these drugs and the use of groups of drugs in internal medicine, particularly the use of hypertensive drugs belonging to different drug groups. In much the same way as a practitioner may change a prescription for beta-blockers to one for alpha-blockers without changing the patient's diagnosis or recognizing a need for more investigations, ATFs within a group of drugs for different subtypes may be changed in order to achieve a better response on the basis of the initial clinical examination and the construction of a *vikrithi* table.

The benefits of skin care are mentioned in Ayurveda and in biomedicine. Ayurveda describes how lymphatic channels (*srothomukha*) become dilated and how metabolic activity in the skin (*bhrajaka pitta*) increases to improve the color of the skin.[83] Part 2 of IMLD facilitates lymph drainage by correcting the pathophysiology of lymphedema.[84] According to biomedicine,[18] skin care procedures such as washing and the application of emollients restore the barrier function and health of the skin. The biomedical skin care regimen, found typically in texts by Foldi *et al.*,[53] includes the coordination of breathing and medial spiral movement during manual lymphatic drainage, neither of which are mentioned in Ayurvedic texts. As yoga does include such procedures, we integrated these into our protocol in order to facilitate lymph movement through the lymphatics.

The progression of disease in lymphedema is directly linked to the frequency of inflammatory episodes.[85] Entry points are portals for the entry of bacteria that eventually precipitate a fever episode. This highlights the significance of adequate entry point management. We managed entry points through a combination of biomedical drugs and Ayurvedic treatment procedures. Eczema, folliculitis, and other entry points were treated using appropriate biomedical drugs. We used Ayurvedic skin-soaking (*phanta*) solutions to treat entry points, including tiny breaks on the skin.[86] It is common for filarial lymphedema patients to suffer from large, difficult-to-heal ulcers (we are increasingly identifying these as reflecting a venous component of the pathogenesis) and micro/macro entry points. A total of 79.5% of our patients reported experiencing inflammatory episodes before the onset of this treatment, and 9.4% reported such episodes at three months after our treatment (Table 8). The treatment compliance of those with recurring inflammatory episodes was poor.

In lymphedema, elastin fibers disappear, and the increase in collagen probably reflects failure to clear cytokines like transforming growth factor (TGF). The increase mainly occurs in collagen type III, which has a long fiber and does not knit into a pliable endogenous stocking. Lymph that collects in this mesh of collagen can be pushed out by indentation massage or by squeezing the skin as in grade 1 (normal) skin. As the pathology shifts to grades 2 or 3 (thickened skin to trophic changes), the tissue becomes increasingly fibrotic, and the proportion of lymph held decreases. Affected limbs are called "organized limbs" at this stage. Much of the hardness in organized limbs develops because the pressure caused by tissue fluid results in a resistant fibrotic network. At all stages, therapy can shift some fluid and reduce the pressure. Collagen is deposited as a skeletal fiber to resist mechanical forces especially in bone but also in skin.[87] Agents such as steroids, weightlessness, or immobility in paraplegic subjects contribute to a slowing down of deposition. The other controlling factor is the removal of collagen by collagenases. The latter are inhibited when mechanical forces and tension build up. Importantly, collagenases increase in activity and effectiveness when the mechanical tension stretching fibers is reduced. Our integrated treatment reduces tissue fluid and thus probably reduces the pressure exerted on the fibroblast. Therefore, it is likely that collagenase gradually becomes more effective and, in the long term, fibrosis can be reduced. This also happens to tissues such as the uterus after parturition. Collagenases are more effective at body temperature than at skin temperature, and heating is known to reduce fibrosis.[88] We incorporated *ekanga swedana*, heating the limb using medicated steam (after IMLD Part 2), into our protocol for treatment of lymphedema. All 137 limbs showed significant differences as a result of the integrated treatment protocol, particularly in the metatarsal, mid-foot, ankle, and mid-thigh measurements. Girth around the metatarsal region is particularly resistant to therapy in grade 2 lymphedema. Some patients with grade 3 lymphedema gain additional benefits from *swedana* that is incorporated routinely into the integrated treatment protocol as described in Ayurveda classics.[89] Finally, there may be active components in herbs that stimulate collagenases and other proteases. This does not completely explain the observation of decreasing skin fold thickness in our patients, but it contributes towards an explanation of some of the variables determining response.

The Ayurvedic skin care measures used in our protocol are known to improve the health of the skin. The

consensus statement of the International Society of Lymphology[90,91] stresses the importance of skin care. Skin care procedures such as washing and the application of emollients restore the barrier function and skin health.[18] Therefore, by integrating these procedures, along with the rationale for their use, we have converged Ayurvedic skin care with that of dermatology with the aim of achieving patient management that is better than that achievable by a single system alone.

Respiration is known to facilitate venous and lymph drainage. The lymphatic drainage of the thoracic, abdominal, and pelvic organs and extremities is influenced by intra-abdominal and intrathoracic pressure. Diaphragmatic breathing exercises increase the lymphatic output of the thoracic duct and large lymph trunks, and, hence, the output from the peripheral lymphatic system.[53] Effective breathing for lymphedema patients involves taking a deep breath through the nose, holding the breath, and then making a long, slow exhalation through the mouth.[18] In our protocol, *anuloma-viloma* of *pranayama* refers to the same technique.[92] This technique is also cited in cardiology texts to stimulate the parasympathetic nervous system versus the sympathetic nervous system, but there is insufficient knowledge to indicate whether this would affect lymphatic contractility. The sequence of *yoga asanas* performed was arranged in such a way that lymph would be drained first centrally and then from the periphery. This can be presumed by the movement of muscles first in the shoulder girdle and laterally towards the lower limbs. Experiments using radioisotope scans showed that even small-amplitude ankle movements increase the clearance of lymphatic fluid from the lower limbs.[93] Thus: (i) the lymphatic system drains into the large veins in the thorax and is affected by breathing; (ii) lymphatic and venous drainage are affected by body posture, which supports the roles of both yoga breathing and exercises; (iii) regulated body movements and massage promote lymph flow; (iv) overload of the lymphatic system from the venous system is reduced by regulated body movements, massage, and limb elevation; and (v) overload of the lymphatic system caused by the loss of the epidermal barrier function and consequent inflammation from bacteria and soil irritants is probably responsive to selected Ayurvedic herbal preparations.

Systematic reviews of Ayurvedic journal publications eliminated all research except that carried out using an RCT design.[94] The rationale for this approach is that RCTs provide the strongest support for causality because the randomization of subjects to treatment conditions eliminates the possibility that some unknown factor other than the treatment may cause the outcome.[43] Although several publications on Ayurvedic medicines are available in electronic databases for non-dermatological diseases, most studies of these medicines have adopted biomedical study designs with little regard to Ayurvedic principles of treatment. Sir Michael Rawlins, chairman of the National Institute for Clinical Excellence (NICE), the UK advisory body on the efficacy of therapy, delivering the Harveian Oration before fellows of the Royal College of Physicians in October 2008, discussed the pros and cons of levels of evidence and the RCT.[95] Where the effects of treatment are large and dramatic, RCTs may be inappropriate.[30] The RCT also limits the ability to generalize outcomes to patients of different ethnic backgrounds, with different severities of disease, and when disease is associated with comorbidities. However, if the pathogenesis of disease is the same in all subgroups, the outcomes of the RCT can be generalized.

As we have discussed, Ayurveda recognizes three clinical subtypes of vitiligo. This recognition supports our case series design for the study of the efficacy of integrative dermatology treatment. Results in lymphedema are summarized in Fig. 7; although observational studies tend to provide larger treatment effects than RCTs, bias is un-likely to give rise to a 10-fold artificial difference in disease outcome. No RCTs were conducted to establish treatments for myxodema (1891) or pernicious anemia (1926) or the effectiveness of penicillin during World War II, but confidence in the benefits of these treatments is sustained, even now![95] According to the *Cochrane Handbook for Systematic Reviews of Interventions*,[51] it may sometimes be appropriate to conduct a systematic review of non-randomized studies of the effects of health care. If the course of a disease is uniform or the effects of an intervention are dramatic, then it is unnecessary and unethical to conduct an RCT.[51] We also found that systematic reviews of evaluations of surgical treatments and the efficacy of therapeutic devices and procedures in biomedicine include non-randomized studies.[96] Non-randomized studies include experimental studies (such as quasi-randomized trials) and observational studies with controls (such as controlled before–after studies, concurrent cohort studies, and case–control studies) or without concurrent controls (such as before–after studies, cross-sectional studies, and case series).[97] Most published articles (68–87% of feature articles and brief communications in *Annals of Internal Medicine*, the *British Medical Journal,* and *The New England Journal of Medicine*) describe non-randomized studies.[96] Further proponents of WHO recommendations have argued that the RCT was designed and continues to be used for single-intervention drug studies. Insistence on the unmodified use of RCTs to establish an evidence base in Ayurveda fails to comprehend the complexity of Ayurvedic treatment methods.[31] R. L. Nahin, director of the National Institute of Complementary and Alternative Medicine (NICAM), advocates the full spectrum of studies without

identifying the underlying mechanism of action for each intervention, provided there is a clear, clinically relevant endpoint.[30] As there was no prior experience of integrating Ayurvedic approaches into biomedicine in dermatology, we had to develop, refine, and standardize the treatment components through mutual orientation. Therefore, it was not appropriate to evaluate the protocol in a randomized trial, as collective clinical ''equipoise'' was not present.[96] Our results in integrated skin care may be considered in this context.

As the science of integration is just evolving in dermatology, it is likely that new approaches will be developed. Any consideration of Indian and Chinese systems of medicine should note that they are used by at least two billion people. Our policy is that extensive utilization is a reason for public health observation and that safety and efficacy studies are therefore needed. It can be argued that safety levels are higher in well-tried systems of medicine that have been used for thousands of years. Our integrated skin care treatment carried a risk for dermatitis medicamentosa, particularly when the skin surface was compromised. However, we have seen irritant (Fig. 8) or allergic contact dermatitis develop in only four patients in over six years of officially running the OPD. The safety profiles of 542 patients who received two Ayurvedic internal medicines were normal for the whole period of their medicine intake. Along with these medicines, most patients intermittently received oral antibiotics and analgesics. They were also in regular receipt of topical medication at entry points. We did not detect any clinical abnormality during the three months of combined use of Ayurvedic oral medicine and biomedicine. The Ayurvedic oral medicines used were *Maha Manjistadi Kashaya* (MMK) and *Kanchanara Guggulu* (KG). The former is a herbal liquid preparation with 46 ingredients. The major herbs used are the roots of *Rubia cordifolia* Linn (*manjista*) and *Cyperus rotundus* Linn (*musta*). *Kanchanara* comes in tablet form and contains 11 ingredients, of which the major ones are *Bauhinia variegata* stem bark (*kanchanara twak*) and *Commiphora mukul* gum resin (*guggulu*). The American Botanical Council's translation of the complete *German Commission E Monograph Therapeutic Guide to Herbal Medicines*,[98] supposedly the most accurate source of information available on the safety and efficacy of phytomedicines, also lists several plants described in ISM classics.

We noted that, in recognition of the constraints imposed by poverty, health services must examine locally available sustainable and low-cost therapies that are utilizable at village level. We used lymphedema as a prototype disease for integrated treatment because there are more than 20 million cases of it in rural India. Its management largely involves skin care, and it should respond to low-technology maneuvers such as those practiced in Ayurvedic health centers.[18] Vitiligo is another stigmatizing and neglected disease occurring frequently in India. We were able to describe the clinical subtypes in relation to its prognosis and to compare clinical presentations in both dermatology and Ayurveda. However, responses to treatment could not be objectively assessed because of the lack of any tool in practice. Therefore, we are currently undertaking two important research programs. The Department of Science and Technology, New Delhi, has supported our work on developing protocols for systematic review in Ayurveda using vitiligo as the prototype (http://www.systematicreviewinayurveda.org). In another project, we are exploring the possibility of developing a tool to quantitatively and qualitatively measure repigmentation after treatment. This bioengineering project is being carried out in collaboration with the Indian Institute of Sciences, Bangalore, and is funded by the KSCSTE.

The principle guiding the integration of skin care treatments was the fact that each system of medicine recognizes the same disease, although their descriptions show minor differences. Each system of medicine prescribes topical and oral medications based on the pathophysiological understanding of the disease in its respective literature. The MSD team recognized that each therapeutic system has specific advantages. Dermatology offers facilities for confirmatory investigations, the control of infections and acute illness, and evidence-based analysis. Ayurvedic medicines have minimal side effects, are used for the management of chronic illness, and offer numerous therapeutic options. Homeopathy claims to cause no side effects, is based on symptomatology, includes well-developed management of the patient's mental resources, and is a low-cost therapy. We used the homeopathy approach for diagnosis and its methods to determine prognosis and to identify clinical subtypes in diseases. We did not use it for therapy except for its possible placebo effect when managing anxiety in patients with vitiligo.

In Ayurveda, the naming of the disease is less important than clinicopathological descriptions. Guidelines in classical Ayurvedic texts help in the selection of drugs. These assumptions were confirmed by the combined examination of patients by the MSD team. The outcome measures used were those of biomedicine. Therefore, judging by patient response assessed on the basis of outcome measures derived from biomedical dermatology, it is evident that integration at the level of therapeutics is possible, although the pathological basis of the disease differs according to the system of medicine. Irrespective of background understanding of the given disease, a mutually oriented MSD team was able to effectively use medications from more than one system of medicine to develop guidelines for their prescription and a patient care algorithm. This is a patient-

centered approach that has proven to be greatly appreciated, effective, and cost-effective.

Despite the existence of over 700,000 biomedical practitioners and equal numbers of AYUSH doctors, attempts to reflect this work in other centers within India may face resistance for non-scientific reasons. There is a great degree of ignorance among practitioners of one another's systems. Since the 18th century, many medical practitioners in India have adopted biomedicine by the transfer of knowledge, without understanding the philosophy and method of experiment behind its development. Had such an understanding been present, it might have enabled us to validate what was precious in our own medical inheritance and given us a powerful tool with which to initiate medical advancement.[36] The neglect of experiment obliged our practitioners of medicine to adhere to traditional Indian or Western texts depending on whether they practiced Ayurveda or biomedicine. Therefore, India provides patient care in the community by different avenues. However, given its membership of over 5,000 dermatologists, it is probable that the IADVL may lead the way forward. Its president, Professor H. R. Jarajani, has already offered associate membership of IADVL to practitioners of other disciplines. She has visited the IAD and plans to constitute an interest group on integrative dermatology to support the establishment of more MSD teams. In this context, we emphasize that any clinician interested in integrative dermatology must read all the references to this article before embarking on any new studies.

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