Wisdom of Ayurveda in perceiving diabetes: Enigma of therapeutic recognition

Ashok K. Tiwari

Diabetes mellitus is described as 'Madhumeha' in ancient Indian Sanskrit literature dealing with health care systems, and is duly acknowledged in modern medical texts. However, detailed descriptions of the disease process and therapeutics prescribed in these classics could not get proper recognition, because of the fact that modern medical science those days was at its budding stage. Nevertheless, recent advances in modern science in understanding pathophysiology of diabetes mellitus, its complications and therapeutic requirements, are providing a better platform to interpret and understand centuries-old Ayurvedic knowledge. Furthermore, scientific analyses of medicines prescribed therein, reveal that they possess enormous therapeutic capabilities that modern medicine is searching for. This article provides a general account of these understandings, and an analysis that may provide insights for future study and development of Ayurvedic medicines in modern scientific perspective.

UNVEILING ancient sculptures and inscriptions by modern society has replenished several valuable directions and descriptions. However, there are yet several unexplained and inadequately exhumed gems of immense relevance for acquisition. While the polyuric states, clinically resembling diabetes mellitus, were described as early as 1550 BC, in the ancient Egyptian papyrus discovered by George Ebers, the sweet taste of diabetic urine associated with polyuria were noted and clinically described first in 5th–6th century AD in Sanskrit literature by Indian physicians Susruta and Charaka[1], followed by Thomas Willis in the 17th century[2]. Susruta and Charaka described urine of certain polyuric patients tasting like honey (madhu). The Indian description of that period distinguished two forms of diabetes, one affecting the older and obese, and the other affecting thin people who did not survive long; the fortuitous parallel with the present-day subdivisions of diabetes into insulin-dependent and non-insulin-dependent types[1]. Furthermore, the same Hindu physicians described the classical clinical syndrome of severe thirst, profuse urination, and bodily wasting followed by coma and death, many centuries ago before the central role of glucose was recognized[3]. Beyond these acknowledgements, however, detailed descriptions pertaining to etiology, pathophysiology, and therapeutics could not be understood in modern medicine. This may be due the fact that efforts of modern medicine towards understanding pathophysiology and therapeutic development were beginning to grow.

In Western literature though, the word 'diabetes' (Ionian Greek; meaning to pass through) was first used by Aretaeus of Cappadocia in the 2nd century AD as a generic description for conditions causing increased urine output[1]. It was the English physician John Rollo (1809) who introduced the adjective 'mellitus' (Latin-Greek; meaning honey) to distinguish the conditions from other polyuric diseases in which glycosuria does not occur and the urine is tasteless[4]. Later, Matthew Dobson made it clear that serum as well as urine of a diabetic patient contained a sweet-tasting substance[5] and that it was sugar. He explained that the kidney was drawing a large proportion of the alimentary nutritious matter, before it is perfectly assimilated and applied to the purpose of nutrition and that diabetes was a systemic disease condition. Since then, research, understanding and the struggle to manage this dreaded disease has continued. However, despite the fact that several significant achievements have been made in the past to treat and control diabetes and its complications; it is taking the shape of an epidemic[6–9].

The efforts of modern medicine in delineating the pathogenesis of diabetes are paving ways to understand and interpret descriptions of diabetes mellitus and its complications in Ayurvedic texts. Similarly, evaluation of medicines prescribed in Ayurvedic classics utilizing modern scientific tools and techniques, reveals the fact that they are amazingly relevant even today and have the capabilities to take global care of the disease. In the light of recent advances in modern science, this article analyses (i) understanding of diabetic pathogenesis in both Ayurvedic and modern medicine, (ii) therapeutic approach for prevention and treatment, and present views as how therapeutics prescribed in Ayurvedic medicines are still relevant in taking care of preventive as well as therapeutic aspects of this dreaded disease and finally, (iii) challenges posed to traditional medicines like Ayurveda, that have to be addressed

Ashok K. Tiwari is in the Pharmacology Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India.
e-mail: astiwari@yahoo.com

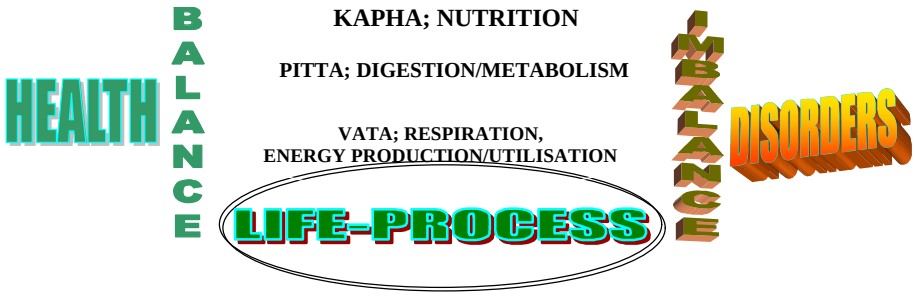

Figure 1. Ayurvedic philosophy describes Kapha, Pitta and Vata as three important factors of life. Their appropriate balance is important to lead and live a healthy life. However, their inappropriate distribution causes imbalance in biochemical/physiological homeostatic processes that leads to different disorders/diseases. In such circumstances, these factors become doshas (culprits) responsible for genesis of various pathological states. In diagnosis of diseases, Ayurveda considers vitiation in these doshas (Tridosha) together. Therefore, the therapy incorporates and prescribes multiple ingredients possessing the capacity to bring the vitiated homeostatic phenomenon back to normalcy.

seriously in order to place the gems of Ayurveda in proper perspective.

Fundamental principles of Ayurvedic philosophy and description of diabetes

Basic principles of Ayurvedic philosophy revolve around three important factors (doshas) of life, viz. Kapha, Pitta and Vata. At macro- or molecular levels, *Kapha* represents nutritious regimens and may be either of dietary origin or nutritious substances at systemic and/or tissue level. *Pitta* designates factors responsible for digestion, absorption, and/or metabolism of nutritious substances at any level of physiological processes and may be regarded as enzymatic activities, etc. Further, *Vata* represents processes like respiration, oxygen (vayu) responsible for combustion/burning of nutritious substances during metabolic activities to release and mobilize energy. Ayurvedic philosophy enforces the qualitative as well as quantitative appropriateness and balance of all these factors to maintain normal physiological fuel homeostasis in order to live a healthy life. Therefore, it emphasizes that any vitiation either due to exogenous or endogenous over-consumption/accumulation and vice versa in these three factors (Tridoshas) creates an imbalance in normal biochemical/physiological processes. This disturbance inappropriately activates the inbuilt defence and self-sustaining mechanisms, leading to either disproportionate accumulation or depletion of factors responsible for maintenance of normal biochemical/physiological homeostasis. In the absence of appropriate corrective measures therefore, vitiated homeostasis leads to disorderliness in normal physiological functions and hence favours multiple disease (Figure 1).

Hence, as a remedy, Ayurveda recommends multiple herbo-mineral preparations incorporating appropriate characteristics to manipulate risk factors (doshas) in order to bring physiological homeostasis back into the state of equilibrium. In Ayurvedic classics, diabetes mellitus and its complications have been described in Sanskrit in detail, and more than twenty types of diabetic descriptions are available[10]. Ayurveda recognizes beginning of this disease condition primarily as Prameha (increased frequency and turbidity of urine), which in due course of time may turn out to become Madhumeha[10] (diabetes mellitus). In such a situation the disease becomes incurable:

SARVA YEVA PRAMEHASTU KALENAPRATIKARINAH MADHUMEHATVAMAYANTI TADA ASADHYA BHAVANTI HI (Su. Ni. 6)[10].

Ayurvedic literature describes symptoms of Prameha, where there is rapid urge and frequent passage of urine:

PRACHURAM VARAM VARAM VA MEHATI MUTRATYAGAM KAROTI YASMIN ROGE SA PRAMEHA (Ma. Ni.)[10].

Susruta describes that day time sleeping; lack of exercise and laziness; too much of cold, sweet, lipidemic and alcoholic foods and beverages as the caustive factors for development of diabetes later in life:

DIVASWAPANAM VYAYAMALASYA PRASAKTAM, SHEETASNIGDHA, MADHURDRVYAPANASEVINAM PURUSAM JANEEYAT PRAMEHI BHAVISHYTEETA (Su. Ni. 6)[10].

Furthermore, Charaka adds that excess of newly harvested foodgrains, jaggery preparations and factors responsible for elevation of Kapha, may contribute to the development of diabetes:

…..…NAVANNAPANAM GUDVAIKRITAM CHA PRAMEHAHETU KAPHAKRICCHASARVAM (Ch. Chi. 6)[10].

It is envisaged in Ayurvedic descriptions that vitiation in oxidative processes, and disturbances in digestive or metabolic system may lead to the accumulation of carbohydrate and/or fat metabolites that in due course may generate diabetes:

VATA PITTA MEDOBHIRANVITAHA SHLESMA MEHANJANAYATI (Su. Ni. 6)[10].

It had already been described by observations made in late 18th century by Dobson[5], that the disease originates due to imperfect application, assimilation and utilization of nutritious substances. Ayurveda further adds that if adequate care is not taken in time to correct these disturbances, the over accumulation or lack of proper nutrients at a systemic or tissue level fans the flames of Vata (oxidative stress) that complicates the disease (diabetes mellitus). Thereafter, treatment becomes difficult:

UPECCHAYA HI PITTAKAPHAJANAMAPI MADHUMEHATVAM PRADARSHAYITUMAH SARV YETEYADI DHATUCCHAYAVARANABHYAM KUPIT VATEN MADHUMEHAASAMBHAVABHAH (Ma. Ni)[10].

Ayurveda advocates that diabetes mellitus aggravated with oxidative stress is a condition difficult to treat:

….*VATAJASHCHATVARO MEHASTE POORVAROOPRAHITA API NAHI SADHYAH* (Ch. Ch. 6)[10].

Many centuries ago, Charaka had made pathogenic staging of the disease as due to dietary followed by metabolic inappropriateness and then aggravated by oxidative stress:

SAPOORVAROOPAH KAPHA PITTA MEHAH KRAMENA YE VATKRITASCH MEHA (Ch. Chi. 6)[10].

It emphasized that improper dietary habits, imperfect digestion, metabolism and utilization of nutrients from carbohydrates and lipids at tissue level are the cause of diabetes mellitus. Accumulation in systemic circulation, and lack of nutrients at the tissue and cellular level aggravates oxidative stress that complicates diabetic pathogenesis.

Current developments of understanding disease pathogenesis in modern medicine and relevance to Ayurvedic descriptions

Like the Ayurvedic concept of 'Tridosha theory' which advocates imbalance in different doshas (factors) producing various disorders and diseases, it is now increasingly being realized in modern medicine that an imbalance in physiological homeostasis generates several diseases. Simultaneously, it is also being accepted that development of disease depends on individual susceptibility. This concept of 'altered homeostatic theory' asserts that multiple acquired (environmental) and genetic factors (risk factors) move the basic homeostatic balance in an action direction, which inappropriately activates defence mechanism in favour of multiple diseases[11]. Therefore, therapeutic regimens containing opposite qualities may help improve and correct the imbalanced physiological homeostasis. Modern science also recognizes that life is based on a complex and finely tuned network of reduction–oxidation (redox) reactions that are under homeostatic control. Cells or organisms are constantly subjected to factors that can alter this redox balance, often resulting in overt generation of free-radicals (oxidative stress)[12]. Therefore, imbalance in oxidant and antioxidant defence in the body is being recognized as the causative/fostering factor for development of a number of diseases like diabetes, atherosclerosis, cancer, neurodegenerative diseases and disorders of ageing, etc. All these diseases are now being observed to share common pathophysiological platforms, irrespective of their source of origin[13,14]. Ayurveda also recognized Vata-Vriddhi (oxidative stress) as the cause of majority of diseases if corrective measures to manipulate, modulate or improve the disorderliness in disturbed physiological processes are not taken up in time[10]. The realization of oxidative stress as the cause of majority of diseases in modern medicine has, therefore, initiated several global programmes to harness and harvest natural antioxidant-rich resources[13–18] and boost antioxidant defence by various means.

Descriptions in Ayurvedic classics teach that carelessness of disturbed nutrition and related metabolic mechanisms are the reasons that later appear as diabetes:

UPECHHAYA HI PITTAKAPHAJANAMAPI MADHUMEHATVAM PRADARSHAYITUMAH (Ma. Ni. 23–26)[10].

Prolonged negligence, therefore, causes lack of passable nutrients for the preservation of proper physiological functions. Continuous burden on physiological processes to maintain normal physiological functions, therefore, aggravates the redox system leading to oxidative stress that may terminate as diabetes mellitus:

DHATUCHHAYAVARNABHYAM KUPIT VATEN MADHUMEHASAMBHAVAH (Ma. Ni. 23-26)[10].

In accordance with these centuries-old Ayurvedic descriptions about diabetes, modern medicine also recognizes that diabetes mellitus culminates in a disglycemic state, where metabolic homeostasis of carbohydrates and lipids is improperly regulated by insulin and other governing factors (refs 19 and 20 and references cited therein). Therefore, if this inappropriateness in metabolic homeostatic disturbance is not managed properly and on time, prolonged hyperglycaemia results in the generation of free radicals, ultimately leading to oxidative stress in a

variety of tissues[21]. In the absence of an appropriate endogenous compensatory response from the antioxidant network, the system becomes overwhelmed (redox-imbalance), leading to the activation of stress-sensitive intracellular signalling pathway causing cellular damage and ultimately being responsible for the late diabetic complications[21] (Figure 2).

These recent scientific understandings of cause and course of development of diabetes mellitus, and consequently its complications are in fact not different from what has been described in classical Ayurvedic texts centuries ago. It seems likely therefore that therapeutics described in Ayurvedic literature may also find relevance in the management and treatment of the cause and course of diabetes as a whole.

Modern therapeutic approach and Ayurvedic medicine in management of diabetic syndrome

Multi-factorial pathogenesis of diabetes as discussed above, therefore, demands a multi-modal therapeutic approach[19]. Progress in understanding metabolic staging of this disease and its complications in modern science has advanced several therapeutics for it.

In order to manage carbohydrate-related metabolic disturbances at various levels, several medicines have been developed. For example, to manage post-prandial hyperglycaemia at digestive level, modern medicine has *a*-glucosidase inhibitors (acarbose, miglitol and voglibose); to tackle insulin insufficiency at systemic level, it has insulin preparations; for insulinotrophic action at *b*-cells of pancreas, it has sulphonylurea (glypizide, glibenclamide); to inhance glucose uptake through multiple pathways at tissue/cellular levels, it has biguanides (metformin); and in order to tackle the problems of insulin resistance, it has developed insulin sensitizers (the glitazones). Therefore, as knowledge of understanding advanced, drugs were developed to tackle different aspects of the pathogenic steps.

Now based on recent advances and involvement of oxidative stress in complicating diabetes mellitus, efforts are on to find suitable antioxidant therapy[19–25]. For modern biomedical researchers dealing with the cause of diabetes, antioxidants are becoming essential tools in investigating oxidative stress-related diabetic pathologies[20] and therapies[21]. Therefore, it is being realized that identification of molecular basis for the protection afforded by a variety of antioxidants against oxidant-induced damage might lead to the discovery of pharmacological targets for novel therapies to prevent, reverse, or delay the onset of resultant pathologies[21].

It is important to note here that multiple defects in pathophysiology of diabetes in modern medicine are still being unravelled. Furthermore, arguments are also being forwarded not to isolate a single drug target to the reversal of all or majority of the aspects of the disease[25], since biological systems are too complex to be fully understood through conventional and isolated experimentations, as they are not always linear. Also, there are several factors that are not obvious from biological considerations alone. Therefore, therapeutic approach of several traditional medicines is rather more holistic. Majority of fundamental concepts of these medicinal systems still cannot be explained using modern tools. Traditional medicine preparations contain a variety of herbal and non-herbal ingredients that incorporate synergistic, potentiative, agonistic, antagonistic pharmacological agents, and hence act on a variety of targets by various modes and mechanisms[19]. It has also been accepted by modern biologists that a plethora of compounds present in traditional medicines represent essentially the raw materials with which our body is made of. Supply of various phytochemicals that mimic natural vibrations of our biochemistry, boosts metabolic pathways positively. Phenolics boost antioxidant defence; antimicrobials provide microbe-free environment within the body to protect tissues from invaders and therefore, bring all the functions/pathways of the body back on the track[26].

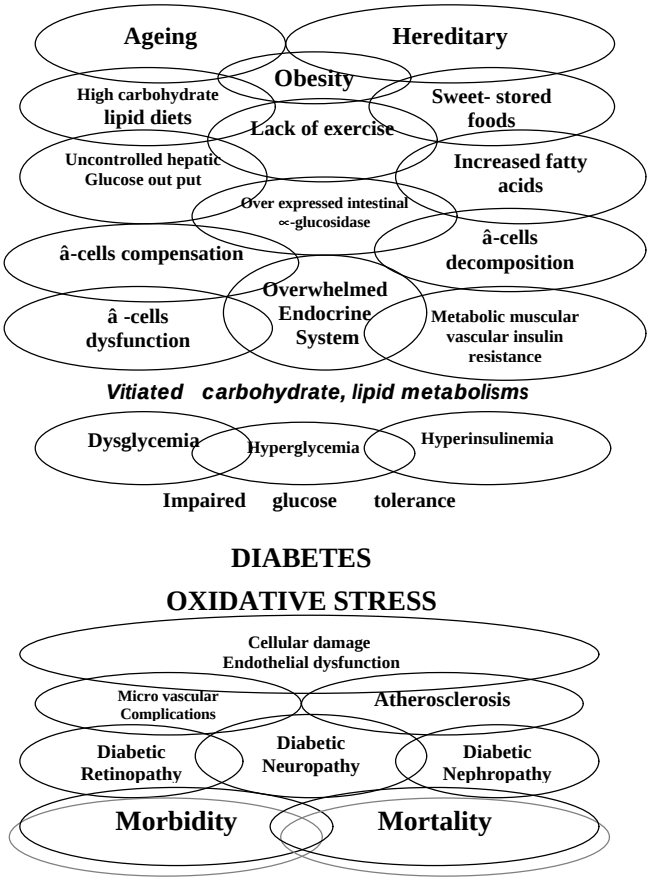

Figure 2. Summary and sequence of events dealing with cause, course and complex interplay among various aspects which are either of natural, environmental, or hereditary origin, or the disturbances at various physiological and/or biochemical levels that direct development of diabetic syndrome, ultimately responsible for morbidity and mortality due to the disease (details in text).

Utilizing modern tools and techniques, medicinal plants described in Ayurvedic texts for diabetes and related disorders have been observed to possess disease modifying therapeutic potentials within themselves. Intestinal brush border carbohydrate hydrolases (e.g. α-glucosidase, sucrase, maltase, etc.) are observed overtly expressed in diabetic animals[27,28], increasing the absorption of sugars and amino acids. Therefore, they may play an important role in aggravating post-prandial hyperglycaemia. The α-glucosidase inhibitors are observed to not only mitigate post-prandial hyperglycaemic excurtions[29], but they also reduce triglyceride levels[30], post-prandial insulin levels[31] and reduce the cardiovascular mortality due to diabetes. Post-prandial hyperglycaemia may be managed by the α-glucosidase inhibitory activities[32–34] and glucose absorption delaying properties of Ayurvedic medicinal plants[35,36]. The enzyme inhibitory (α-glucosidase) activity of these medicinal plants may be interpreted as their Pitta-Nasak property. Similarily, the resultant reduction in post-prandial hyperglycaemic excurtion can be understood as Kaph-Nasak (antihyperglycaemic) activities.

Insulin is the master regulator of glucose and lipid metabolism[37]. Its insufficiency and resistance play a key role in pathogenesis of several human diseases like diabetes, obesity, hypertension and cardiovascular diseases[38]. The active principles present in Ayurvedic medicinal plants have been observed to possess pancreatic β-cells regenerating[39–42], insulin releasing[43,44], secretory[45,46], sparing[47] and even ameliorating the problem of insulin resistance[48]. Furthermore, they are reported to affect various key metabolic enzymes involved in diabetogenesis[49], correcting the imbalanced glucose metabolic homeostasis[50], improving glucose uptake[51], inhibiting gluconeogenic enzymes[52,53], and modulating glycolytic and lipolytic pathways in diabetic conditions[54]. In diabetic complications, these medicinal plants have been observed to attenuate renal hypertrophy, urine volume, albuminuria[55], and ameliorate diabetic neuropathy and gastropathy[56]. Various ingredients in medicinal plants hence play an important role to manipulate, modify and correct the factors causing vitiation in normal/healthy homeostatic biochemical–physiological processes at various molecular, cellular and tissue levels, and hence the organism as a whole, in order to bring back the vitiated homeostasis to normalcy.

In experimental animal models, diabetes is produced frequently by inducing oxidative stress. Streptozotocin, is a commonly used chemical to induce diabetes in animals. It damages pancreatic β-cells through production of free radicals[57]. It is impotant to note here that pancreatic islets are poorly equipped to bear oxidative-insult, as inherently they have low expression of antioxidant enzymes[58,59]. This might be the reason they fall easy prey to oxidative stress of different origins, resulting in disturbed insulin synthetic and secretory processes. Stressful modern lifestyle may also contribute to the havoc of diabetic epidemic in modern society. Therefore, free-radical scavengers/antioxidants are found effective in preventing diabetes in such animal models[60]. Grover *et al*.[61] have recently reviewed forty-five traditional medicinal plants of India with antidiabetic potential. Majority are advocated in Ayurvedic medicine for antidiabetic activities. Most of them are used either as vegetables, fruits or culinaries. A significant proportion of these medicinal plants has been observed to possess potent antioxidant activities and therefore, antidiabetic properties in streptozotocin-induced animal models[61]. Not only in Ayurveda, but also in several other traditional medicines utilizing plants for antidiabetic activity also possess strong antioxidant/free-radical scavenging properties[17].

Descriptions in preceding paragraphs and Figure 2 signify the role of oxidative stress in complicating the disorder of diabetes mellitus which culminates in different diseases. Therefore, it becomes important to have therapeutics addressing oxidative stress in concurrence with modifying or eliminating the cause of hyperglycaemia in order to check the outbreak of various diseases of diabetic complications. This might have been the reason that Ayurvedic physicians chose medicinal plants that possessed apart from Kapha (e.g. antidysglycaemic and antidyslipidemic properties) and Pitta (enzyme inhibitors/modulators) modifying activities, strong Vata-Nasak (antioxidant) properties also, in order to address holistically, the cause and complications of diabetes mellitus.

Devdaru (*Cedrus deodara*) has been advocated in Ayurvedic classics especially to tackle the causes of oxidative stress (Vata), heart disease (Hrid-rog) and diabetes (Prameha):

DEVADARUSAMAYUKTAM NAGRAM PARIPESHITAM
HRIDVATAVEDANAMARTASTU PEETVA
SUKHAMVAPNUYAT
(Bha. Pra. Chi 24)[62].
PRAMEHAPINASHLESHMAKASAKANDUSAMEE-RANUT (Bha. Pra) [62].
AMDOSHVIBANDHARSAHPRAMEHAJWARANAS-ANAM (Ra. Ni) [62].
DEVADARU RASETIKTAM
SNIGDHAMSLESHMAVATAJIT (Dha. Ni)[62].

Multiple-active lignans in substantial yields have been isolated by us from this medicinal plant as antioxidants (anti-Vata)[63], and antiatherosclerotic (anti-cardiovascular disease)[64] compounds. These molecules have also been reported to possess antidyslipidemic (anti-Sleshma, meda), effective in cardiovascular disorders (hrid-rog) and have been found to be effective in both types of diabetes[65,66].

Similarly, Veerataru (*Dichrostyches cinerea*) has been described to be effective in treating Vata (oxidative stress), mutrkrichha (urinary problems), trisna (polydypsea), Kapha mobilizing (e.g. antidysglycaemic) activities and diseases of sarkara (sugar):

NISSESHAVATAROGAGHNO MUTRKRICHHARUJAPAHAH (Ma. Ni)[67].
VELLANTARO RASEPAKETIKTATRISNAKAPHAPAHAH (Bha. Pra)[67].
VEERARTADIRITYESHA GANO VATAVIKARANUT ASHMARY SARKARAMUTRAKRICHHGHATRUJAP-AHAH (Su. Su. 38.13)[67].

In the course of our study, we were able to isolate in bulk yields, (–)-epicatechin and its enantiomer, as a new isomer of mesquitol[68] from *D. cinerea*. The new enantiomer of (–)-epicatechin, (–)-mesquitol was observed to possess more than double potency for inhibition of enzyme *a*-glucosidase (Pitta modifying, Kapha mobilizing and hence antihyperglycaemic property, i.e. anti-sarkara) along with multiple free-radical scavenging/antioxidant properties. Further modification of this compound not only improved its *a*-glucosidase inhibitory property without changing antioxidant potential, but could also incorporate xanthine oxidase inhibitory property[68]; an enzyme responsible for overt generation of free-radical in oxidative stress-related disorders[69]. The natural compound (–)-epicatechin is well known for its antidiabetic activity[39–42,70].

Furthermore, Tuvaraka (*Hydnocarpus wigthiana*) has been proposed to be a potent medicinal plant for treatment of madhumeha (diabetes mellitus)[62]:

ARUSKARAMTAUVARKAM KASAYAM KATUPAKI CHA USHNAM KRIMIJWARONAMAHAMEDORVANTANA-SHANAM (Su. Su. 46)[62, 67].
MAHAVEERYA TUVARAKAH KUSTHAMEHAMAHAPA-RAH (Su. Chi. 13.20)[62].
VATAKAPHAKUSTAMEDOMEHAKRIMIPRASAMANE UBHAYOKTO BHAGDOSHAHARE CH (Su. Su. 42)[62].

Study of this plant led us to isolate in bulk quantities from its seed hulls compounds luteolin and flavolignans[71]. These compounds also displayed strong multiple antioxidant (anti-Vata) along with potent *a*-glucosidase inhibitory activity that may lead to their antihyperglycaemic and antihypertriglyceridemic (anti-meha and meda) properties[71], as described in Ayurveda. Luteolin and its glycosides have been reported in literature to possess *a*-glucosidase, *a*-amylase inhibitory[72] and antidiabetic activities[73] in various experimental models.

Diabetic patients have been observed to be immunocompromised as one of its marker *N*-acetyl-*b*-D-glucosaminidase enzyme has been noticed to be increased in such patients[74,75]. Furthermore, increased level of this enzyme has been linked to microangiopathy in type-I diabetes[76], diabetic retinopathy and nephropathy[77], renal tubular dysfunction[78], and hyperfiltration[79] in diabetic complications. Inhibitors of this enzyme have been observed as immunomodulators, potentiate cellular-immune response, reactivate depressed-immune response and enhance the delayed-type hypersensitivity[80]. The extract luteolin and its flavolignans isolated from *H. wigthiana* showed varying degrees of inhibitory potential for this enzyme[71]. These descriptions made in laboratories provide at least in part enough evidence and scientific justification to convince us about the holistic therapeutic approach of Ayurvedic medicines.

Impediments preventing future growth

Diabetes and its complications, hypertension, obesity and cardiovascular diseases share more or less a common platform. They are taking the shape of a worldwide epidemic. Unfortunately, discovery of affordable, effective, safe and innovative new drugs is becoming a global crisis, because of the prohibitive costs involved in developing such drugs (which is approximately more than US$ 800 million)[81]. Also, some of the world's richest nations are driving the hardest bargain, despite the fact that the benefits of treatment are global[81] and by advising that to develop the much-needed research capacity, developing countries should no more rely on the industrialized world, but find their own specific solutions[82]. Diplomatically, developing countries are being categorized by developed nations as the consumer market and the under-developed world as their experimental platform. Therefore, a sense of insecurity may develop in the under-industrialized world.

Ayurveda was discovered, nurtured and perfected in India. This science of longevity provides a framework defining cause and conditions of sickness and connects them with healing practices. In its golden days, Ayurveda was practised by vaidyas (physicians) who had knowledge about nature and medicines. Furthermore, they used to prepare medicines themselves, as a source of livelihood and self-esteem. The period when this science flourished was the era of professional truthfulness, faith and belief. But the modern period is the era of globalization and cultural Copernicanism. Furthermore, nature and its habitat are being bricked and concretized. The fundamentals of truth, faith and belief are becoming words of the past. Today we need proof, scientific validation, testing, and rather more lucidity in the system, because only based on these facts can modern medicine revolutionize the global healthcare system. Their fundamentals are based on scientific research, active principles, mechanism of action, validation, testing, standardization and controlled clinical trails. Evidences provided by modern medicine are such that it is becoming difficult for vaidyas to convince the common man about the real efficacy of their medicinal preparations. Common man is moving towards modern medicine because it has strict scientific foundation and the ability to adequately manage symptoms of chronic and terminal diseases. The modern medicines are monitored vigilantly through systematic reviews and meta-analysis. At this juncture unfortunately, traditional medicines in

this era are finding themselves poorly equipped to respond to these challenges, even though they may have superior therapeutic potential.

Twenty-three systematic reviews of rigorous clinical trails of traditional medicines are available[83]. Eleven yielded positive results, nine promising and three negative. These facts encourage trust on scientific data and not merely anecdotes. Though the market for herbal medicines is booming[84] and evidence for their effectiveness is growing, it is also being simultaneousy counter-balanced by inadequate regulations[85]. One of the major problems with many of the traditional medicines is that the active ingredients are not well defined. It is important to have molecular/chemical fingerprints of the components of active extracts from medicinal plants. This will not only help analyse therapeutic efficacy of the product, but also help standardize the product in terms of active principles as markers. Lack of this exercise encourages biopiracy and hence develops distrust that divides the rich and the poor nations[86]. The relative paucity of basic scientific research, standardization, validation, and rigorous clinical trails in Ayurvedic medicines is also squelched due to the fact that (i) compared to modern multinational pharmaceutical sectors, the traditional herbal industries (like Ayurvedic) are small and hardly equipped to bear the cost[83], and (ii) due to human greed, many of the wild plants are being harvested to the point of extinction. This results in demolishing the natural habitat, and health of millions of people in the developing world[87].

Traditional systems of medicine like the Ayurveda prominently prescribe in their preparations, the vegetation available in and around human habitat, and used by the people in their daily life. Dissemination of knowledge about the importance and medicinal properties of such vegetation by researchers is creating awarenesss among people. Nowadays patients are treated as customers, and hence the ultimate users of these scientific developments. Industries translate these developments in products. Unfortunately, lack of proper industries, accountability about the authenticity, genuineness and quality of the products, and healthy collaboration with academic and scientific institutions in developing countries are the factors hampering the therapeutic benefits of research to the common man. It is important to remember that the success stories of global herbal giants like China, Japan, Korea, and even South Africa are due to their collaborations with government academies and institutions[88]. Therefore, unless these challenges are addressed seriously, the gems of Ayurveda will remain illusive as they are at present.

1. MacFarlance, I. A., Bliss, M., Jackson, J. G. L. and Williams, G., The history of diabetes mellitus. In *Textbook of Diabetes* (eds Pickup, J. and Williams, G.), Blackwell, London 1997, 2nd edn, vol. I, pp 1.1–1.21.
2. Willis, T., *Pharmaceutica Rationales Siva Diatriba de Medicamentorium Operationitus in humano Corpore*, London, 2 vols, pp. 1674–1675.
3. Frank, L. L., Diabetes mellitus in the text of old Hindu medicine. *Am. J. Gastroenterol.*, 1957, **27**, 76–71.
4. Rollo, J., An account of two cases of the diabetes mellitus, with remarks as they arose during the progress of the cure. C. Dilly, London, 1797.
5. Dobson, M., Experiments and observations on the urine in diabetes. *Med. Obs. Inq.*, 1776, **5**, 298–316.
6. Marx, J., Unraveling the cause of diabetes. *Science*, 2002, **296**, 686–689.
7. Ramachandran, A. *et al*., For the Diabetes Epidemiology Study Group in India (DESI). High prevalence of diabetes and impaired glucose tolerance in India; National Urban Diabetes Survey. *Diabetologia*, 2001, **44**, 1094–1101.
8. Mohan, V., Shanthirani, C. S. and Deepa, R., Glucose intolerance (diabetes and IGT) in a selected south Indian population with special reference to family history, obesity, and lifestyle factors – The Chennai Urban Population Study (CUPS 14). *J. Assoc. Physicians India*, 2003, **51**, 771–777.
9. Pradeepa, R. and Mohan, V., The changing scenario of the diabetes epidemic; implications for India. *Indian J. Med. Res.*, 2002, **116**, 121–132.
10. Upadhyaya, Y. (ed.), In *Madhavnidanam of Sri Madavakara, Part. II*. The Kashi Sanskrit Series 158, Chaukhambha Sanskrit Sansthan, Varanasi, 1993, 22nd edn, pp. 1–27.
11. Hellstrom, H. R., The altered homeostatic theory: A holistic approach to multiple diseases, including atherosclerosis, ischemic diseases, and hypertension. *Med. Hypotheses*, 1999, **53**, 194–199.
12. Nedelcu, A. M., Marcu, O. and Michod, R. E., Sex as a response to oxidative stress: a two-fold increase in cellular reactive oxygen species activates sex genes *Proc. R. Soc. London, Ser. B*, 2004, **271**, 1591–1596.
13. Tiwari, A. K., Antioxidants: New-generation therapeutic base for treatment of polygenic disorders. *Curr. Sci.*, 2004, **86**, 1092–1102.
14. Tiwari, A. K., Imbalance in antioxidant defense and human diseases: Multiple approach of natural antioxidants therapy. *Curr. Sci.*, 2001, **81**, 1179–1187.
15. Wu, X., Beecher, G. R., Holden, J. M., Haytowitz, D. B., Gebhardt, S. E. and Prior, R. L., Lipophilic and hydrophilic antioxidant capacities of common foods in the United States. *J. Agric. Food Chem.*, 2004, **52**, 4026–4037.
16. Fenglin, H., Ruili, L., Bao, H. and Liang, M., Free radical scavenging activity of extracts prepared from fish leaves of selected Chinese medicinal plants. *Fitoterapia*, 2004, **75**, 14–23.
17. McCune, L. M. and Johns, T., Antioxidant activity of medicinal plants associated with the symptoms of diabetes mellitus used by the indigenous peoples of the North American Boreal forest. *J. Ethnopharmacol.*, 2002, **82**,197–205.
18. Vahabzadeh, F., Mehranian, M. and Mofarrah, E., Antioxidant activities of Pistachio hulls. *JAOCS*, 2004, **81**, 621–622.
19. Tiwari, A. K. and Rao, J. M., Diabetes mellitus and multiple therapeutic approaches of phytochemicals: Present status and future prospects. *Curr. Sci.*, 2002, **83**, 30–38.
20. Laight, D. W., Carrier, M. J. and Anggard, E. E., Antioxidants, diabetes, and endothelial dysfunction. *Cardiovasc. Res.*, 2000, **47**, 457–464.
21. Evans, J. L., Goldfine, I. D., Maddux, B. A. and Grodsky, G. M., Oxidative stress and stress activated signaling pathways; A unifying hypothesis of type 2 diabetes. *Endocrine Rev.*, 2002, **23**, 599–622.
22. Dhalla, N. S., Liu, X., Panagia, V. and Takeda, N., Sub cellular modeling, and heart dysfunction in chronic diabetes. *Cardiovasc. Res.*, 1998, **40**, 239–247.
23. Jain, S. K., McVie, R. and Smith, T., Vitamin E supplementation restores glutathion and malonaldhyde to normal concentrations in erythrocytes of type-I diabetic children. *Diabetes Care*, 2000, **23**, 1389–1394.

24. Perkiner, B. *et al.*, *In-vivo* treatment with stobadine prevents lipid peroxidation, protein glycation and calcium overload but does not ameliorate Ca++ –ATPase activity in heart and liver of streptozotocin-diabetic rats: Comparison with vitamin E. The ADIC (Antioxidants in Diabetes Induced Complications) Study Group. *Biochim. Biophys. Acta*, 2002, **1588**, 71–78.
25. Bailey, C. J., Potential new treatments for type-2 diabetes. *Trends Pharmacol. Sci*., 2000, **21**, 259–265.
26. Daniel, M., The impediments preventing India from becoming a herbal giant. *Curr. Sci*., 2004, **87**, 275–276.
27. Wen, D., Henning, S. J. and Hazolwood, R. L., Effect of diabetes on development of small intestinal enzymes in infant rats. *Proc. Soc. Exp. Biol. Med*., 1988, **187**, 51–57.
28. Caspary, W. F., Rhein, A. M. and Creutzfeldt, W., Increase of intestinal brush border hydrolase in mucosa of streptozotocin-diabetic rats. *Diabetologia*, 1972, **8**, 412–414.
29. Mooradian, A. D. and Thurman, J. E., Drug therapy of postprandial hyperglycemia. *Drugs*, 1999, **57**, 19–29.
30. Lebowitz, H. E., *a*-Glucosidase inhibitors as agents in treatment of diabetes. *Diabetes Rev.*, 1998, **6**, 132–145.
31. Johnston, P. S., Caniff, R. F., Hoogwerf, B. J., Santiago, J. V., Pi-Suryer, F. X. and Krol, A., Effect of carbohydrase inhibitor miglitol in sulfonylurea-treated NIDDM patients. *Diabetes Care*, 1994, **17**, 20–29.
32. Asano, N., Oseki, K., Tomioka, E., Kizu, H. and Matsui, K., N-containing sugars from *Morus alba* and their glycosidase inhibitory activities. *Carbohydr. Res.*, 1994, **259**, 243–255.
33. Mastuda, H., Murakami, T., Yashiro, K., Yamahara, J. and Yashikawa, M., Antidiabetic principles from natural medicines IV. Aldose reductase and alpha-glucosidase inhibitors from roots of *Salacia oblonga* Wall (Celastraceae): Structure of a new friedelane-type triterpene, Kotalagenin 16-acetate. *Chem. Pharm. Bull*., 1999, **47**, 1725–1729.
34. Yashikawa, M., Murakami, T., Yashiro, K. and Matsuda, H., Kotalanol, a potent alpha glucosidase inhibitor with thiosugar sulfonium sulfate structure, from antidiabetic Ayurvedic medicine *Salacia reticulata*. *Chem. Pharm. Bull.*, 1998, **46**, 1339–1340.
35. Jaglekar, G. V., Chaudhary, N. Y. and Aiaman, R., Effect of Indian medicinal plants on glucose absorption in mice. *Indian J. Physiol. Pharmacol.*, 1959, **3**, 76–77.
36. Yashikawa, M., Murakami, T., Kadoya, M., Liu, Murakami, N., Yamahara, J. and Matsuda, H., Medicinal food stuffs: IX, The inhibitors of glucose absorption from the leaves of *Gymnema sylvestre* R. BR (Asclepiadaceae): Structure of gymnemoside a and b. *Chem. Pharm. Bull*., 1997, **45**, 1671–1676.
37. Saltiel, A. R., Putting the breaks on insulin signaling. *N. Engl. J. Med*., 2003, **349**, 2560–2562.
38. Nandi, A., Kitamura, Y., Koh, C. R. and Accili, D., Mouse models of insulin resistance. *Physiol. Rev*., 2004, **84**, 623–647.
39. Chakravarthy, B. K., Gupta, S., Gambhir, S. S. and Gode, K. D., Pancreatic beta cell regeneration. A novel antidiabetic mechanism of *Pterocarpus marsupium* Roxb. *Indian J. Pharmacol*., 1980, **12**, 123–127.
40. Chakravarthy, B. K., Gupta, S. and Gode, K. D., Functional beta-cell regeneration in the islets of pancreas in alloxan induced diabetic rats by (–) epicatechin. *Life Sci.*, 1982, **31**, 2693–2697.
41. Chakravarthy, B. K., Gupta, S. and Gode, K. D., Antidiabetic effect of (–)-epicatechin. *Lancet*, 1982, **2**, 272–273.
42. Sheehan, E. W., Zemaitis, M. A., Slatkin, D. J. and Schiff, Jr. P. L., A constituent of *Pterocarpus marsupium*, (–) epicatechin, as a potential antidiabetic agent. *J. Natl. Prod*., 1983, **46**, 232–234.
43. Welihinda, J., Arvidson, G., Gylfe, E., Hellman, B. and Karlsson, E., The insulin releasing activity of the tropical plant *Momordica charantia*. *Acta Biol. Med. Ger.*, 1982, **41**, 1229–1240.
44. Ivorra, M. D., Paya, M. and Villar, A., Hypoglycemic, and insulin releasing effect of tormentic acid: a new hypoglycemic natural product. *Planta Med.*, 1988, **54**, 282–286.
45. Sauvaire, Y. *et al.*, 4-Hydroxyisoleucine: A novel amino acid potentiator of insulin secretion. *Diabetes*, 1998, **47**, 206–210.
46. Augusti, K. T. and Shella, C. G., Antiproxide effect of S-allele cysteine sulfoxide, an insulin secretogague in diabetic rats. *Experientia*, 1996, **52**, 115–120.
47. Kumar, R. V. and Augusti, K. T., Insulin sparing action of a leucocyanidin derivative isolated from *Ficus bengalensis* Linn. *Indian J. Biochem. Biophys.*, 1994, **31**, 73–76.
48. Tominaga, M. *et al.*, Effect of seishin renshi-in and *Gymnema sylvestre* on insulin resistance in streptozotocin induced diabetic rats. *Diabetes Res. Clin. Practice*, 1995, **29**, 11–17.
49. Grover, J. K., Vats, V. and Rathi, S. S., Antihyperglycemic effect of *Eugenia jambolana* and *Tinospora cardifoia* in experimental diabetes and their effects on key metabolic enzymes evolved in carbohydrate metabolism. *J. Ethnopharmacol*., 2000, **73**, 461–470.
50. Okabayashi, Y. *et al.*, Effect of *Gymnema sylvestre*. R. Br. on glucose homeostasis in rats. *Diabetes Res. Clin. Practice*, 1990, **9**, 143–148.
51. Chattopadhyaya, R. R., Chattopadhyaya, R. N., Nandy, A. K., Poddar, G. and Maitra, S. K., The effect of fresh leaves of *Azadiracta indica* on glucose uptake and glycogen extent in the isolated rat hemi diaphragm. *Bull. Calcutta Sch. Trop. Med*., 1987, **35**, 8–12.
52. Hossain, M. Z., Shibib, B. A. and Rahman, R., Hypoglycemic effects of *Coccinia indica*; Inhibition of key gluconeogenic enzyme, glucose-6-phosphatase. *Indian J. Exp. Biol.*, 1992, **30**, 418–420.
53. Shibib, B. A., Khan, L. A. and Rahman, R., Hypoglycemic activity of *Coccinia indica* and *Momordica charantia* in diabetic rats: Depression of hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase and elevation of both liver and red-cell shunt enzyme glucose-6-phosphatase dehydrogenase. *Biochem. J.*, 1993, **292**, 267–270.
54. Kamble, S. M., Kamlakar, P. L., Vaidya, S. and Bambole, V. D., Influence of *Coccinia indica* on certain enzymes in glycolytic and lipolytic pathway in human diabetes. *Indian J. Med. Sci*., 1998, **52**, 143–146.
55. Grover, J. K., Vats, V., Rathi, S. S. and Dawar, R., Traditional Indian antidiabetic plants attenuate renal hypertrophy, urine volume and albumin urea in streptozotocin-induced diabetic mice. *J. Ethnopharmacol.*, 2001, **76**, 233–238.
56. Grover, J. K., Rathi, S. S. and Vats, V., Amelioration of experimental diabetic neuropathy, and gastropathy in rats following oral administration of plant extracts. *Indian J. Exp. Biol*., 2002, **40**, 273–276.
57. Rakieten, N., Rakieten, M. L. and Nadkarni, M. V., Studies on diabetogenic action of streptozotocin. *Cancer Chemother. Rep.*, 1963, **29**, 91–98.
58. Lenzen, S., Drinkgren, J. and Tiedg, M., Low antioxidant enzyme gene expression in pancreatic islets compared with various other mouse tissues. *Free Radic. Biol. Med*., 1996, **20**, 463–466.
59. Tiedge, M., Lortz, S., Drinkgren, J. and Lenzens, S., Relation between antioxidant enzyme gene expression and antioxidant defense status of insulin producing cells. *Diabetes*, 1997, **46**, 1733–1742.
60. Miyake, Y., Yamamoto, K., Tsujihara, N. and Osawa, T., Protective effects of lemon flavonoids on oxidative stress in diabetic rats. *Lipids*, 1998, **33**, 689–695.
61. Grover, J. K., Yadav, S. and Vats, V., Medicinal plants of India with anti-diabetic potential. *J. Ethnopharmacol*., 2002, **81**, 81–100.
62. Sharma, P. V., *Classical Uses of Medicinal Plants*, Haridas Ayurveda Series 4, Chaukhambha Visvabharati Publication, Varanasi, 1996, p. 169.
63. Tiwari, A. K., Srinivas, P. V., Praveen Kumar, S. and Rao, J. M., Free-radical scavenging active components from *Cedrus deodara***.** *J. Agric. Food Chem*., 2001, **49**, 4642–4645.
64. Rao, J. M., Tiwari, A. K., Srinivas, P. V., Yadav, J. S. and Raghavan, K. V., Use of two plant phenols in the treatment of arteriosclerosis. United States Patent No. (2002) 6458831.

65. Cornwell, T., Cohick, W. and Raskin, I., Dietary phytoestrogens, and health. *Phytochemistry*, 2004, **65**, 995–1016.
66. Westcott, N. D. and Muir, A. D., Overview of flax lignans. *Int. News Fats, Oils, Related Mater.* (*INFORM*), 2000, **11**, 118–121.
67. *Medicinal Plants of India*, Arya Vaidyasala, Kotakkal (India) (eds), Orient Longman, 1995, vol. 2, p. 330, and vol. 3, p. 185.
68. Rao, R. J., Tiwari, A. K., Sampath Kumar, U., Reddy, S. V., Ali, A. Z. and Rao, J. M., Novel 3-0-acyl mesquitol analogues as free-radical scavengers and enzyme inhibitors; synthesis, biological evaluation and structure activity relationship. *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2777–2780.
69. Borges, F., Fernandes, E. and Roleira, F., Progress towards the discovery of xanthine oxidase inhibitors. *Curr. Med. Chem.*, 2002, **9**, 195–217.
70. Ahmad, F., Khalid, P., Khan, M. M., Rastogi, A. K. and Kidwai, J. R., Insulin-like activity in (–) epicatechin. *Acta Diabetol. Lat.*, 1989, **26**, 291–300.
71. Reddy, S. V., Tiwari, A. K., Kumar, S. P., Rao, R. J. and Rao, J. M., Free-radical scavenging, enzyme inhibitory constituents from antidiabetic traditional Indian medicinal plant *Hydnocarpus wightiana* Blume. *Phytother. Res.*, 2004, **18**, in press.
72. Kim, J. S., Kwan, C. S. and San, K., Inhibition of alpha-glucosidase and amylase by luteolin, a flavonoid. *Biosci. Biotechnol. Biochem.*, 2000, **64**, 2458–2461.
73. Zarzuelo, A., Jimenez, I., Gamez, M. J., Utrilla, P., Fernandez, I., Toroes, M. I. and Osuno, I., Effect of luteolin-5-O-*b*-rutinoside in streptozotocin induced diabetic rats. *Life Sci.*, 1996, **58**, 2311–2316.
74. Reglero, A., Carretero, M. I. and Cabezas, J. A., Increased serum L-fucosidase and *â-N*-acetylglucosaminidase activities in diabetic, cirrhotic and gastric ulcer patients. *Clin. Chem. Acta*, 1980, **103**, 155–158.
75. Alhadeff, J. A. and Holzinger, R. I., Characterization of *b*-hexosaminidase from liver and sera of diabetic patients and control. *Biochem. Med.*, 1982, **27**, 214–225.
76. Agardh, C. D., Agardh, E., Isaksson, A. and Huttberg, B., Association between urinary *N*-acetyl-*b*-D-glucosaminidase and its isoenzyme pattern and microangiopathy in type-I diabetes mellitus. *Clin. Chem.*, 1991, **37**, 1696–1699.
77. Mandic, L. J. and Filipovic, D., Changes in isoenzymes of serum *N*-acetyl-*b*-D-glucosaminidase in relation to different types of diabetes. *Biochem. Mol. Biol. Int.*, 1998, **45**, 545–554.
78. Schutltz, C. J., Dalton, R. N., Neil, H. A. W., Bahu-Konopelska, J. and Dunger, D. B., Markers of renal tubular dysfunction measured annually do not predict risk of microalbuminurea in first few years after diagnosis of type-1 diabetes. *Diabetologia*, 2002, **44**, 224–229.
79. Muller, D., Sievers, E. and Eggest, P., Influences of hyperfiltration on the measurement of urinary *N*-acetyl-*b*-D-glucosaminidase. *Pediatr. Nephrol.*, 1999, **13**, 519–523.
80. Aoyagi, T. *et al.*, Nagstatin, a new inhibitor of *N*-acetyl-*b*-D-glucosaminidase, produced by *Streptomycese amakusaensis*. MG-846-fF3. Taxonomy, production, isolation, physico-chemical properties, and biological activities. *J. Antibiot.*, 1992, **45**, 1404–1408.
81. Tanne, J. H., FDA chief wants other rich countries to share drug development cost. *Br. Med. J.*, 2003, **327**, 830.
82. Iaccarino, M., Mastering science in the South. *EMBO Rep.*, 2004, **5**, 437–441.
83. Ernst, E., Herbal medicines put into context their cure entails risk, but probably fewer than with synthetic drugs. *Br. Med. J.*, 2003, **327**, 881–882.
84. Brevoort, P., The booming US botanical market. A new overview. *Herbalgram*, 1998, **44**, 33–46.
85. Ernst, E., Herbal medicines: Where is the evidence? *Br. Med. J.*, 2000, **321**, 395–396.
86. Verma, I. M., Biopiracy: Distrust widens the rich–poor divide. *Mol. Ther.*, 2002, **5**, 95.
87. Edwards, R., No remedy in sight for herbal ransacks. *New Sci.*, 2004, **181**, 10–11.
88. Bruke, M., Herbal healing. *Chem. Br.*, 2003, **39**, 27–29.

ACKNOWLEDGEMENTS. I thank Dr J. S. Yadav, Director, IICT, Hyderabad for encouragement and support; Dr G. P. Dubey, BHU, Varanasi, for teaching Ayurvedic philosophy; and Dr J. Madhusudana Rao, IICT for support and collaboration in understanding and delineating the chemistry of Ayurvedic medicinal plants. I also thank the referee(s) for their comments to modifying this article. Thanks are also due to Dr P. V. Diwan, Head, Pharmacology Division, IICT for laboratory support and Mrs A. Z. Ali for technical assistance. This is IICT communication No. 041202.

Received 24 September 2004; revised accepted 14 December 2004