Ayurvedic Medicines: Some Potential Plants for Medicine from India

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Abstract
With the changing pattern of life style most of the diseases are now becoming lifestyle diseases. The traditional systems of medicine based on ancient cultures are primarily concerned with building the body strength which can help in healing the ailments and these systems rely largely on the nature cure. The Ayurvedic system has described a large number of such medicines based on plants or plant product and the determination of their morphological and pharmacological or pharmacognostical characters can provide a better understanding of their active principles and mode of action.

Introduction
Contribution of the traditional medicine to human health in the 21st Century is of paramount importance. A meeting of the International Forum on Traditional Medicine held recently (1999) at the Toyama Medical and Pharmaceutical University, Toyama, Japan, reviewed the potential of traditional medicines. WHO acting director Xhang emphasized that with the changing pattern of life style most of the diseases are now becoming lifestyle diseases. Natural medicines improve the inner strength of the body. The use of traditional medical systems has attracted so much attention that an International Health Center has been opened in July in the Toyama prefecture (Province).

Some of the oldest traditional medical systems include Chinese, Ayurvedic, Unani, Japanese and recently added homeopathy and chiropathy that is also around 200 years old. The use of traditional medicine includes (i) medication by use of medicinal plant, minerals, animal material and (ii) non medication: acupuncture and yoga.
Complementary medication includes acupuncture, herbal treatment, manual, spiritual and dietary treatments.

Toyama hospital utilizes vast amount of Chinese, Japanese and Ayurvedic medicine. Detailed studies in the areas of pharmacognosy and pharmacology are under progress (Annual report, TMPU, Toyama). Besides this the Research Center for Ethnomedicines with its Museum of Materia Medica is one of its own kind in the world under Professor Watanabe. Dr. Komatsu provides a wealth of information for all scientists engaged in the field all over the world. This includes identification, molecular characterization at DNA sequence level, chemical characterization, biotransformations and studies on effects on microorganisms to direct application in the hospital. To give an entire description will be attempted in another paper. Here a brief attempt is made to identify common goals of research in India and Japan, with an objective to attract attention of workers to the great potential that the vast bio-diversity of the Indian subcontinent and the wealth of Ayurvedic literature has to offer for future development of traditional medicines. However detailed future investigations are needed in this area to exploit the unexplored or poorly explored plant materials.

These traditional medicines have found practical application at clinical level in TMPU and over hundred cases of fissure have been cured in the hospital using a special thread prepared from latex of Euphorbia spp., thor of India (Euphorbia sp), haldi powder (Curcuma longa) and some herbal ingredients. The Euphorbia sp is a plant of the desertic region of India and different parts of the world. A large number of energy yielding desertic plants of India used in the Ayurvedic system have great potential as Ayurvedic medicine. Negative environmental effects of current agricultural practices, such as emission of greenhouse gases, nutrient leaching, decreased soil fertility, and erosion, may be reduced when traditional annual food crops are replaced by dedicated perennial energy crops and medicinal plants. As they are able to grow and produce valuable products under dessert conditions they have great potential for covering the global desert areas into green belts leading to environmental improvement on one hand and providing valuable Ayurvedic crude drugs in addition to supplementing the bio-energy resources as renewable fuels. However detailed studies on their pharmacognostical characterization and determination of chemical products obtained from them are lacking. Some of the investigations indicated their potential use in Human immuno deficiency (HIV) diseases (Hattori et al., 1995). Such bio-energy plants have not been explored in depth. Here an attempt shall be made to provide a brief outlook of the Indian scene and highlight some of the work being carried out at our place in Rajasthan along with the possible impact assessment for desertic plants for future research strategies.

Among the desert plants the value of Aloe vera (L.) was recognized more than 3000 years ago when the Egyptian and Greek civilizations used its extract for skin burns, cuts and wounds on the skin surface and found that it had a wonderful healing effects on the skin. It is claimed that even 3rd degree burns can be cured and healed by Aloe vera. The chemical compounds like Aloein, resins and a mixture of polysaccharides containing pectic acid are present. Modern investigations indicate that extracts of Aloe vera act on the dead epithelial cells of the skin, aiding their removal from the surface and stimulating
the growth of new cells. Thus Aloe is a great gift of traditional medicine for protecting
the smooth skin of human beings especially when radiation damage has assumed an
alarming situation due to stratospheric ozone depletion. Fresh juice of leaves are also
used in liver and spleen troubles and also for eye troubles, found useful in X-ray burns,
dermatitis, coetaneous and other skin disorders.

In India, Egypt and Sudan around 70 percent of the rural people use traditional medicine.
Similar situation exists in a large number of developing countries. In India and China 60
percent of the people affected with cholera and malaria are treated with herbal medicines.
In these countries the market for traditional medicines is US $ 500 million while Western
type medicine account for only 300 million US $. In Singapore 50 percent and in
Australia 60 percent of population uses alternative medicine. Around 17,000 herbal
products are registered in these countries. In Belgium 40 percent contemporary but 84
percent home medicines and 74 percent acupuncture medicine is utilized. In France 50
percent of the people take advantage of complementary medicine. In Germany 10,000 to
13,000 alternative medical practitioners are thriving well and 75 percent of them utilize
complementary medicines. 77 percent of pain clinics utilize acupuncture. In UK 90
percent of the complementary medical practitioners utilize osteopathy and acupuncture.
In US where in 1990 only 30 percent of the people were utilizing complementary
medicines, it grew to 40 percent in 1997.

Ayurvedic system of Medicine

Ayurveda is an offshoot of Atharva veda written over 3000 thousand years ago. The
Charak and Sushruta describe a large number of crude drugs and a large part of them has
origin to plants. However though some part of it has been translated from Sanskrit to
Japanese and the Japan Society of Ayurveda under Professor Dr. Namba is very active in
this field. But many of the crude drugs described remain to be identified to its plant
source in botanical terms and the Institute of Traditional Medicine is the prime center for
understanding the nature and morphology of crude drugs of Ayurvedic origin and their
identification to the plant level. The personal communication with Professor Watanabe
and Dr. Komatsu during my stay at Wakan Yaku as visiting Professor has contributed to
the stimulation of such studies back home and some of the important findings are
presented here. During my stay here I have worked on Nepalese crude drugs with support
and guidance from Dr. Komatsu and other members of this institute.

The basic philosophy of Ayurveda considers that man is an inseparable part of the
universe. The human body, mind and spirit continuum is an integral whole and the
individual is also linked to the family, society, environment and ultimately the universe.
The definition of health is that “It is state of complete psychosomatic equilibrium. It does
not mean only absence of diseases but a state in which the mind, senses and spirit are
pleasant and active”. That agrees with the definition of WHO “Health is a state of
complete physical, mental and social well being and not merely the absence of disease or
infirmity”
India with its varied climate, soils and agro-ecology possesses an immense plant diversity, with over 15,000 species of higher plants. Both our Indian civilization as well as our diverse tribal heritage have gone a long way in conserving the wild weedy species, native land races and primitive cultivars (Fig. 1). The Indian gene center is endowed with rich flora, especially with regard to several less known yet economically important plants, ca. 160 cultivar species of economic plants, plus 56 species of lesser known cultivated food plants. Further there are ca. 320 species of wild and weedy economic types (Paroda, 1979; Arora and Nayar, 1984; Kumar, 1998).

The unutilized and underutilized resources

Out of 2,50,000 plant species only 10,000 or so have been exploited during the course of human civilization. A large number of hydrocarbon yielding plants are able to grow under semi-arid and arid conditions and they also produce valuable hydrocarbons (up to 30 percent of dry matter) which could be converted into petroleum-like substances and used as fossil fuel substitute. They are rich in triterpenoids which are constituent to important drugs against HIV.

The potential plants

Certain potential plants were selected and attempts were made to develop agro-technology for their large scale cultivation (Kumar et al, 1995, Kumar, 1998, Kumar, 2000). A 50 ha bio-energy and medicinal plants cultivation demonstration center has been established on the campus of the University of Rajasthan to conduct the experiments on large scale cultivation of selected plants with the objective of developing optimal conditions for their growth and productivity, besides conserving the bio-diversity. Plantation of laticiferous plants and desert plants can be carried out, it could also lead to reclamation of marginal land that has already been abandoned in developed as well as developing countries. India alone has over 144 million hectare of marginal land which is about half of the total geographical area of the country. Touched only marginally by the green revolution, Africa suffers not only a dramatic nutritional problem but also an equally serious and interlinked problem of energy. Increasing scarcity of fuelwood, desertification, lack of water, food and medicines, excessive urbanization are all closely interdependent and rich biodiversity in developing countries has remained unutilized and underutilized for want of proper investigations.

There are surely opportunities for biomass of the medicinal plants in the south as well as in the north in wet climates and in dry ones but they will respond to very different schemes and strategies. There is not going to be a single unique recipe, rather multiplicity of solutions depending on climate, soil, availability of land, traditions as well as social and economic conditions. Technological improvements should lower production costs but they are unlikely to obtain significantly higher yields, as chemical and energy inputs must be reduced. The transformation of biomass into useful energy products and medicinal
compounds may however involve onsite industrial operations that could absorb at least part of the surplus man power.

As far as research is concerned we are all aware of the important progress being made in agricultural biotechnology. Genetic engineering for example is increasingly applied to crop plants for improving resistance to pests and diseases and for providing more favorable crop composition. There is a whole universe of possibilities in the use of advanced biotechnology to improve plants and processes. The natural medicine from plants has enormous possibilities for new and more effective means for curing the modern day ailments.

**Natural resource**

Total land area of Rajasthan is 3,42,239 sq km out of which 45.25 percent is characterized as wasteland. Large portions of this land were productive at a given time and due to man made deforestation, cattle pressure, water and wind based soil erosion, improper water management, they have turned out to be wastelands. (Kotia and Kumar, 2001a). A detailed survey on the weeds on wastelands yielded valuable data about the first colonizers. Out of the total weeds around 50 having important medicinal values while others produce related compounds. These regions are rich in bio-diversity and weeds were collected from different regions of the developing wastelands. (Kotia and Kumar, 2001b).

Some of the medicinally important plants of Rajasthan are listed by Ajanta and Kumar, (2001a) They include species listed in table 1:

<table>
<thead>
<tr>
<th>Plant species</th>
<th>Local name</th>
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<tbody>
<tr>
<td>1. Asparagus racemosus</td>
<td>Satavari</td>
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<tr>
<td>2. Chlorophytum arundinaceum</td>
<td>Safed musli</td>
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<tr>
<td>3. Curculigo orchioides</td>
<td>Kali Musali</td>
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<tr>
<td>4. Solanum surattense</td>
<td>Kantkari</td>
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<tr>
<td>5. Boerhaavia diffusa</td>
<td>Santhi,</td>
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<tr>
<td>6. Hamidesmus indicus</td>
<td>Anantmool</td>
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<tr>
<td>7. Sida cordifolia</td>
<td>Bala</td>
</tr>
<tr>
<td>8. Holarrhena antidysenterica</td>
<td>Indrajo</td>
</tr>
<tr>
<td>9. Curcuma aromatica</td>
<td>Vanhaldi</td>
</tr>
<tr>
<td>10. Oroxylum indicum</td>
<td>Shyonaka</td>
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<tr>
<td>11. Balanites aegyptiaca</td>
<td>Hingot</td>
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<tr>
<td>12. Withania somnifera</td>
<td>Ashwagandha</td>
</tr>
<tr>
<td>13. Aegle marmelos</td>
<td>Bael</td>
</tr>
<tr>
<td>14. Cassia fistula</td>
<td>Amaltas</td>
</tr>
<tr>
<td>15. Gymnema sylvestre</td>
<td>Gudmar</td>
</tr>
<tr>
<td>16. Terminalia arjuna</td>
<td>Arjuna</td>
</tr>
<tr>
<td>17. Butea monosperma</td>
<td>Palas</td>
</tr>
</tbody>
</table>
18. *Soymida febrifuga*  
Rohan

19. *Woodfordia fruticosa*  
Dhavri

20. *Tribulus terrestris*  
Gokhru

21. *Pedalium murex*  
Badagokhru

22. *Vitex negundo*  
Negad

23. *Dyerophytum indicum*  
Chhitral

24. *Plumbago zeylanicum*  
Chittrak

25. *Plantago ovata*  
Isabgol

26. *Colocynthes vulgaris*  
Indrayan

27. *Adhathoda vasica*  
Ardusta

28. *Allangium salvifolium*  
Aankol

29. *Caesalpinia bonducella*  
Tas

30. *Jatropha curcas*  
Ratanjot

31. *Eclipta alba*  
Bhringraj

32. *Aloe barbadensis*  
Gwarpatha

33. *Mucuna prurieta*  
Konch

34. *Terminalia bellerica*  
Baheda

35. *Tamarindus indica*  
Imli

36. *Azadirachta indica*  
Neem

37. *Achyranthes aspera*  
Aandhijhara

38. *Barleria caculea*  
Bajrandantis

39. *Barleria cristata*  
Bajradantip

40. *Barleria prinoitis*  
Bajradantip.

41. *Ocimum americanum*  
Bapchii

42. *Centella asiatica*  
Brahmibuti

43. *Datura metel.*  
Dhatura

44. *Convolvulus arvensis*  
Haranpadi

45. *Evolvulus alsinoides*  
Shankhpushpi

46. *Cassia occidentalis*  
Kasaundi

47. *Urginea indica*  
Kolikanda

48. *Andrographis paniculata*  
Kalmegh

49. *Helicteres ispara*  
Maroriphali

50. *Tinospora cordifolia*  
Nimgiloy

**Calotropis procera** (Ait.) R.Br. (Akanda, Alarka, Aak) : The plant is one of the important numbers of traditional herbal medicine in every home of India. Traditionally the leaves of aak are warmed and tied around any body organ in pain. It is practically useful in backache and in joint pains. Warm leaves also relieve from stomach ache if tied around. Inhalation of burnt leaf cures headache. The traditional folk healers use the milky latex of aak for several ailments. Leaf latex if applied on fresh cut, stops bleeding immediately. Recent investigations have found that the alkaloids calotropin, calotaxein and uskerin are stimulant to the heart. Flowers and roots are used in Ayurvedic medicine. The plant is anthelmintic, the ashes act as an expectorant. The leaves are applied hot to the abdomen to cure the pain inside. The flower is tonic, antisyphalagogue, used as appetizer and against stomach ache, and cures piles and asthma. Flowers are believed to have detergent properties so they are given in cholera. The fresh roots are used as a toothbrush and are considered by pathans to cure toothache. Alarka is an
alternative tonic and diaphoretic, in large dose emetic. Root bark is useful for treating chronic cases of dyspepsia, flatulence, constipation, loss of appetite, indigestion and mucus in stools. Leaves are used against guinea worms. Flowers are useful in asthma. Seed oil is geriatric and tonic. Green copra is given in asthma. Plant is used in spleen complaints, rheumatism, epilepsy, hemiplegia, sores, and smallpox and protracted labor.

**Calotropis gigantea** R.Br. (Arka) : Arka is purgative, anthelmintic alexipharmic.; cures leprosy, ulcers, leucoderma, tumors, piles, diseases of spleen, liver and abdomen. Juice is anthelmintic and laxative; cures piles and kapha. Dried and powdered plant is taken with milk and acts as a good tonic. Action is similar to Digitalis on the heart. Root bark and juice have emetic, diaphoretic, alternative and purgative properties. It is used in dysentery and as a substitute for Ipecacuantha. It is regarded as a great remedy in syphilitic afflictions and is called “Vegetable mercury”. In intermittent fevers it is used as antiperiodic and diaphoretic. It cures asthma and syphilis. In form of paste it is applied to elephantiasis. Tincture of leaves is used in intermittent fevers. Latex is bitter, heating, oleagenous and irritant, used in combination with *Euphrobia neerifolia* as purgative. Flowers are sweet, bitter, digestive, tonic, stomachic, anthelmintic, analgesic, astringent; cure inflammations, tumours, kapha and are good in ascites.

**Jatropha curcas** Linn. (Vyagrairanda) : Juice of Vyagrairanda is a well known purgative and is useful in whitlow, convulsions, syphilis, neuralgia, dropsy, anasarca, pleurisy and pneumonia. Root bark is applied externally in rheumatism and is used in sores. Leaves are galactagogue, rubefacient, suppurative, insecticidal and are used in foul ulcers, tumors and scabies, given internally in jaundice. Leaves are locally applied to breasts to increase secretion of milk. Leaves warmed and rubbed with castor oil and applied to boils and abscesses have supportive effect. Decoction of leaves is against diarrhoea, useful in stomach-ache and cough and also used for gargle to strengthen gums. Fresh stems are used as toothbrush. Fresh viscid juice flowing from stem is employed to arrest bleeding or hemorrhage from wounds. Stem bark is used for wounds of animal bites. Fruits and seeds are anthelmintic, useful in chronic dysentery, urinary discharges, abdominal complaints, anaemia, biliousness, fistula, and diseases of heart. Seeds are acro-narcotic, poisonous to human beings and cattle and used against warts and cancers and also to promote hair growth. Seeds and oil are purgative, more drastic than castor oil. Wood causes dermatitis. Drug is bitter, acrid, astringent and anthelmintic. It serves to cleanse the entire system through its purgative property. It is useful in chronic dysentery, thirst, abdominal complaints, biliousness, anemia, fistula, ulcer, and diseases of the heart and skin.

**Croton tiglium** Linn. (Jamaalagotta, Jayapala) : Jayapala seeds and oil are drastic purgative, diaphoretic, vasicant, vermifuge irritant, rubefaceint and cathartic. Its action is prompt. Croton oil when rubbed on skin acts as a rubefaceint and counter-irritant and vesicant. When administered internally it operates as a powerful hydrogue cathartic. It is found to be very useful in ascites, anascara, cold, cough, fever, asthma, constipation, calculus, dropsy and enlargement of abdominal viscera. It is given only when a drastic purgative is required as in dropsy and cerebral affections like convulsions, insanity and
other fevers, attended with high blood pressure. Wood is diaphoretic in small doses and purgative and emetic in large doses.

**Euphorbia hirta** Linn. (Dudhi, Cara) : Cara is demulcent, antispasmodic, anti-asthmatic pectoral, anthelmintic and local parasiticide. Plant is chiefly used in the affections of childhood, in worms, bowel complaints and cough, in postnatal complaints, failure of lactation, breast pain. Extract of plant has depressant action and action on cardiovascular system, a sedative effect on mucous membranes of the respiratory and urino-genitory tract. Juice of plant is given in dysentery and colic, and milk applied to destroy warts. Plant alkaloid is effective in respiratory system and produces dilation of bronchi. Decoction of plant is used in bronchial affections and asthma. Latex is vermifuge and used in diseases of urino-genitory tract and also in application for warts.

**Euphorbia tirucalli** Linn. (Vajraduhu, Satsala) :It is useful in biliousness, leucorrhoea, leprosy, dropsy, whooping asthma, enlargement of spleen, dyspepsia, jaundice, colic tumours, and stones in bladder. Milky juice is vesicant and rubifacient. In small doses a purgative but in large doses it is acrid, emetic and counter-irritant; application for warts, neuralgia, rheumatism, toothache, asthma, cough and earache. It is also a fish poison. Milky juice is applied to itch and scorpion bites. Decoction of tender branches and that of roots is administered in colic and gastralgia.

**Anti-HIV agents among desert plants**

Around 40million people are affected due to the Human Immuno-deficiency Virus globally. During the past decades, a large number of anti-viral screening experiments on medicinal plant extracts have been reported and have led to the selection of several extracts active towards herpes viruses. A promising result of a naturally occurring antiherpetic agent was given by n-docosanol (a natural 22 carbon saturated fatty alcohol) which is undergoing phase III clinical trials in patients. Clinical testing of the topical formulation, or systemic administration of drug suspensions has demonstrated a good therapeutic index, since high doses of n-docosanol do not elicit appreciable toxicity. The findings show that natural products are still potential sources in the search for new antitherpatic agents( Hattori et al., 1995.). Various plant extracts used in Ayurvedic medicine for inhibitory effects on HIV virus have been studied (Hattori et al., 1993 ; Kusumoto et al., 1995; Hattori, personal communication). A large number of such plants occur in semi-arid and arid climate of Rajasthan (Roy and Kumar, 1995).

Acquired immunodeficiency syndrome (AIDS), the great pandemic of the second half of the 20th Century, is still a threatening disease world wide. Many research approaches are currently aimed at developing novel agents to arrest the replication of HIV through various targets. These may include the inhibition of reverse transcriptase (RT), protease (PR), membrane fusion and integrase. HIV PR enzyme has been demonstrated to play an essential role in viral replication (Meek et al., 1990). It is considered as potential target for anti-AIDS therapy, as the inhibition of this enzyme produces immature, non-infectious virions (Mous et al., 1988; Huff, 1991; Robins and Platter, 1993). A range of
HIV PR inhibitors have been designed and applied in clinical trials such as Sanqunavir, Ritonavir and Indinavir. However, the development of drug resistance by virus, irrespective of the target, remains as an overwhelming problem in AIDS chemotherapy (El Farrash et al. 1994). Thus there is great need to search for and develop new and different anti-HIV candidates from plants and natural products are of considerable importance.

In search for anti-HIV active agents from natural products, many attempts at screening traditional medicines have been made (Chang and Yeung, 1989; Otake et al., 1995; Wan et al., 1996). However Indian and other tropical region plants with their vast diversity, have not been investigated for their antiviral activity. Hussein et al. (1999) investigated forty eight methanol extracts from Sudanese plants which were screened for their inhibitory activity on viral replication. Nineteen extracts showed inhibitory effects on HIV–induced cytopathic effects (CPE) on MT-4 cells. The extracts were further screened against HIV-1 protease (PR) using an HPLC assay method. Of the tested extracts, the methanol extracts of the desert plants Acacia nilotica (bark and pods), Euphorbia granulata (leaves), Maytenus senegalensis (stem-bark) and aqueous extracts of A. nilotica (pods) and M. senegalensis (stem-bark) showed considerable inhibitory effects against HIV-1 PR (Hussain et al., 1999). Some of the plants from Sudan are common within the Indian desert region of Rajasthan and generally they grow on the wastelands. They have potential use as bio-energy plantations (Kumar et al., 1995; Kumar, 1998). However a large number of them are used in the medicines of Ayurveda. They were also found effective against HIV-1. (Hussein et. al., 1999). A list of potential plants of this region is given here in table 1. However these plants have not been studied in detail and there is need to study them for their medicinal properties including anti-HIV properties. Some of the active principles against anti-HIV are triterpenoids which are abundant in laticiferous plants of Rajasthan. Besides, Ganoderma sp is very frequently met in Rajasthan attacking trees. Ganoderma lucidum has been described to contain triterpenes which have inhibitory effects against HIV-1 protease (Min et al., 1998). Besides this, several other plants like Abrus precatorius L., Leguminosae (Chao-mei et al., 1998), Datura stramonium L., Balanites aegyptiaca L. Delile etc. commonly found in Rajasthan show anti-HIV activity (Kawahata et al., 1996). In China, its seeds have been used as an insecticide and for skin diseases since ancient times.

A detailed survey of medicinally important plants has been carried out and important trees, shrubs and herbs have been listed and their characters studied in several publications from our laboratory. They included drugs for cure of urinary tract infection (Ajanta and Kumar, 2000b) anti-depressant herbal drugs (Ajanta and Kumar, 2000c), medicines for skin diseases (Shivani and Kumar, 2000), anticancer drugs (Sharma and Kumar, 2000); anti-diabetic drugs (Ritu and Kumar, 2000). Herbal drugs of Leguminosae from Rajasthan have been studied (Sapna and Kumar, 2000). Herbal crude drugs for anti-malaria (Anita and Kumar, 2001); anti-paralytic (Vandana and Kumar, 2001). Besides this, herbal crude drugs for cure of hepatic diseases (Santosh and Kumar, 2001) and diseases of the digestive system (Mamta and Kumar, 2001) have been studied for their characters and investigations on their morphological and pharmacognostical characterization are in progress.
Conclusion

The sustainable land utilization in the ecologically fragile climate of semi arid and arid regions has to be guided by the principal of optimal utilization of resources. It is a matter of great interest that a large number of plants of the arid and semi-arid regions of the world are effective as anti-HIV agents. They are also used in variety to herbal and traditional medicines as listed in this paper. Our previous work on their bio-energy production potential, if combined with their crude drug potential could yield bio-fuels on one hand and valuable crude drugs on the other. However a large number of tropical plants have not been studied in detail for their chemical constituents, pharmacological properties of the extracts, and their pharmacognostical characterization including DNA sequencing etc. If a joint collaboration could be established in this direction, valuable information could be generated with wide ranging practical applications. This could also provide alternative land use pattern for the rural poor thriving on marginal lands on one hand and help in eco-restoration on the other. The use of bio-energy plants in the herbal crude drugs has great potential and detailed investigations are planned with the help and cooperation of different agencies. This paper provided a brief outline of the work in the area for future suggestions and improvement.

Acknowledgement

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