STANDARDIZATION AND QUALITY CONTROL – THE MANDATORY REQUIREMENT OF HERBAL DRUG INDUSTRIES

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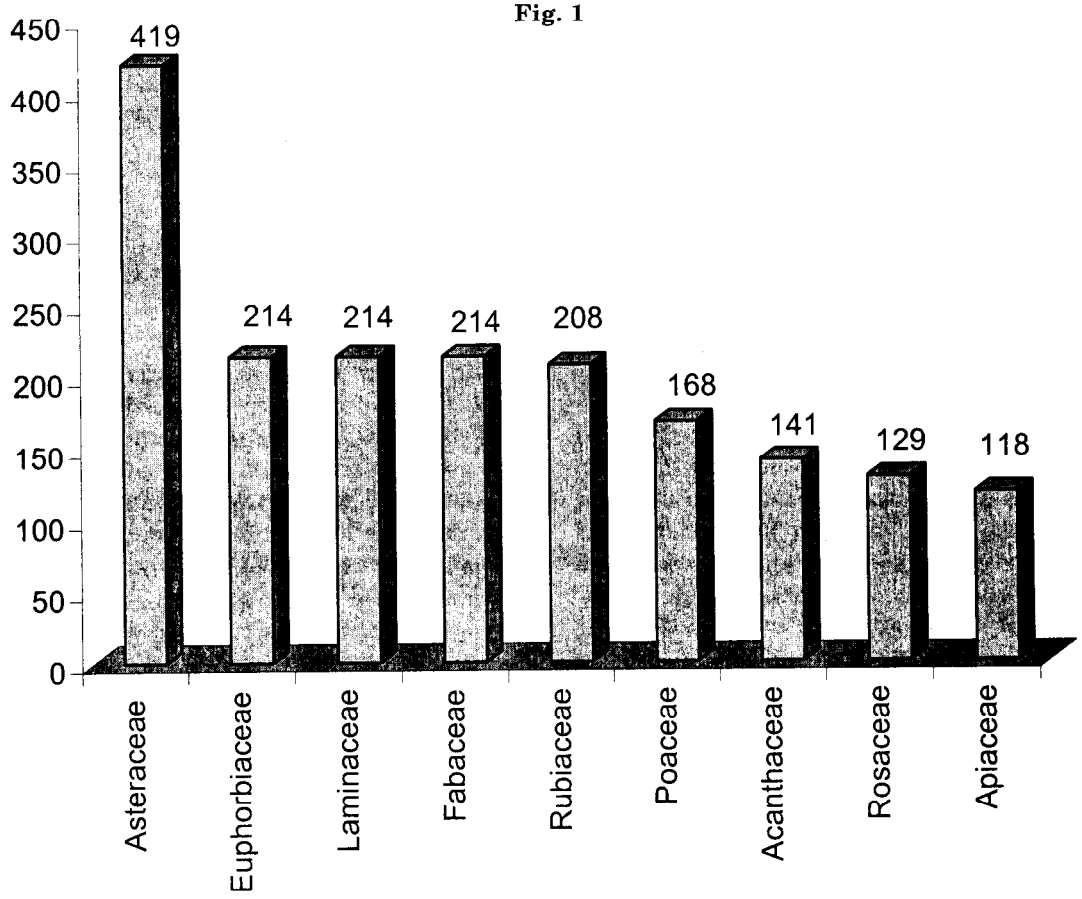
Introduction

Complementary and Alternative Medicine (CAM) as it is called outside India and traditional medicine as it is referred to by the World Health Organization, is rapidly growing in economic importance worldwide. In many parts of the world, people are becoming concerned about the adverse effects of chemical drugs and the escalating cost of conventional health care. Longer life expectancy and life style related problems have brought with them an increased risk of developing chronic, debilitating diseases such as heart diseases, cancer, diabetes and mental disorders. Although new treatments and technologies for dealing with them are plentiful, but more and more patients are now looking for simpler, gentler therapies for improving the quality of life and avoiding iatrogenic problems. According to WHO, a significant percentage of people are using traditional medicine and expenditure on traditional medicine is increasing day by day. The world market for herbal medicine including herbal products and raw materials, has been estimated to have an annual growth rate of between 5 and 15%. In a wider context, there is a growing demand for plant-based medicines, health products, pharmaceuticals, food supplements, cosmetics etc. in the national and international markets. The global market in herbal products is over US $ 60 billion per year. India at present exports herbal material for medicines to tune of Rs 446.3 crores only which can be raised to Rs. 3,000 crores by 2005. China and India are two great producers of medicinal plants, having more than 40% of global biodiversity. In India, more than 1,800 plants belonging to different familiès of Angiosperms are used for their therapeutic efficacy (Fig.1). China, besides meeting its domestic requirement, is earning US $ 5 billion per year from herbal trade but unfortunately India's share in the global trade of herbals is very poor due to lack of quality control and standardization measures. If India wants to emerge as a major player in global herbal products based medicine, it requires a grand strategic plan particularly in standardization and quality control of herbal drugs to boost the export to Rs. 10,000 crores by 2010 and can minimize the import. Medicinal plants are traded mostly as bark, roots, twigs, leaves, flowers, fruits and seeds (Fig. 2).

Adulteration - Unintentional and deliberate

The chances of adulteration – both deliberate and uninternational – are very high. A survey of the raw herbal drug

Fig. 1

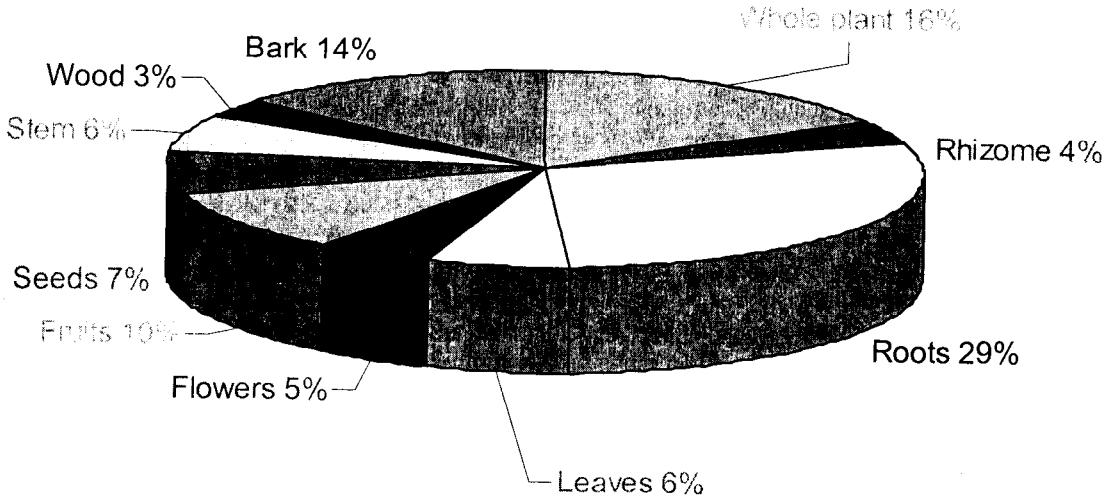


Distribution of major medicinal plants in different families

markets of the country shows that sometimes different plant species are sold as same drug in different parts of country viz. in case of 'Daruharidra', in northern part of India different *Berberis* spp. are being sold as 'Daruhaldi' but in southern part of our country an all together different plant *Coscinium fenestratum* is being used. Thus, detailed Pharmacognostic evaluation is highly essential and is a necessary prerequisite. The Ministry of Health and Family Welfare (Department of ISM&H) New Delhi has notified on 23rd June 2000 that the Ayurveda, Siddha and Unani/ Pharmacopoeial Industries should get the certificate of GMP under '155-B in schedule I certified of GMP of ASU drugs' in order to get the license for manufacturing. This rule will be enforced from July 2003. Hence due to the implication of this law the quality evaluation and standardization will be mandatory for all manufacturing units of ASU drugs.

Another area of concern is the deliberate substitution with a cheaper material that resembles the required part from therapeutically important plants.

Fig. 2



Medicinal Plants for forest conservation and healthcare (FAO - Anon., 1997)

Here, it is not an inadvertent mistaking of a non-medicinal plant for a medicinal species but one of deliberate adulteration and fraud. To cite some common examples : bark from *Pterocarpus* sp., *Toona ciliata* and *Gluta travancorica* is used to substitute that of *Caesalpinia sappan*; bark of *Wrightia tinctoria* is regularly adulterated with that of *Holarrhena antidysenterica,* and *Saraca asoca* bark is replaced with the cheaper substitute from *Trema orientalis*. Deliberate adulteration is not limited to substitution of one plant for another. Various traditional medicines have been found to contain undeclared synthetic materials such as aminopyrine, phenylbutazone, hydrochlothiazide, diazepam and corticosteroids.

In all such cases, efficacy and even the safety of the preparation may be compromised. The popular perception that herbal preparations are relatively harmless is often misplaced because several plants are known to be potentially hazardous. Therefore, there is a need for standardization of raw materials in terms of correct identity and nomenclature.

Efforts towards standardization

The Pharmacognosy Section of National Botanical Research Institute (NBRI) is engaged in standardization and authentication of herbal drugs in order to have the quality assurance of raw material for maintaining the desire therapeutic efficacy of the final product from the last two decades. Further, this will not only help in maintaining the credibility of the Indigenous Systems of Medicine but also assume importance for the effective enforcement of the provisions of the Act of detection of substitution and authentication in pharmacopoeial herbal drugs. Consequently this will assure the interests of the profession and public

health at large. Hence, the main objectives of the studies are:-

- To carry out detailed Pharmacognostic studies which include correct taxonomic identification of plants and its parts, macro- and microscopical details and histological analysis of the plant parts used as medicine. The SEM studies are also under taken for the identification/authentication of those commercial samples, which are available in broken or small pieces.

- To develop physico-chemical standards viz. foreign matter, total ash, acid soluble and insoluble ash, water and alcoholic extracts, total phenolics, tannins, sugars, starch and protein etc. of crude as well as finished herbal drugs/products.

- To develop chemical markers for the identification, quality assurance and batch to batch consistency of herbal drugs with the help of HPTLC, HPLC, GLC & DNA finger printing etc.

- To estimate concentration of heavy metals and pesticide residues in herbal drugs as per WHO guidelines

- To detect the microbial contamination including the detection of mycotoxins in herbal drugs (raw as well as in finished) in accordance with the latest WHO guidelines. In this context different parameters are being used for quality evaluation of herbal drugs (Fig. 3).

Thus, some of the work carried out in the Section on standardization and quality evaluation using different parameters has been discussed in the paper.

Work carried out at Pharmacognosy Section, NBRI

More than 150 herbal drugs were studied. Besides, identification of their substitutes and adulterants were also made. Some of the drugs studied are 'Ashoka' bark, 'Bala' root, 'Banafsha' 'Bhavya' fruit, 'Bhuamliki' whole plant, 'Brahmi', 'Hansraj' whole plant, 'Daruharidra' root and stem, 'Dronpushpi' aerial part, 'Kapikachhu' seed, 'Ratanjot', aerial part, 'Sapan', 'Satawar' root tuber, 'Vidarikand' root tuber. In this chapter, one example of each activity carried out in the division has been taken up.

Quality Evaluation of herbal drugs : 'Talishpatra' is an important crude drug of indigenous systems of medicine, used in number of herbal formulations, attributable to leaves of *Abies spectabilis* and *Taxus wallichiana*. Morphologically the leaves and leaf fragments of both *Abies* and *Taxus* have close similarties, thereby making it difficult to authenticate the drug. Realizing the problem, an attempt has been made to lay down some diagnostic markers for the authentication and standardization of the drug. Moreover, the necessity for the correct identification of the leaves of *Taxus wallichiana* gained much importance as the leaves are being extracted for taxane derivatives which are used for synthesis of an anticancer compound taxol.

Seasonal variation studies on 'Kalmegh' – Andrographis paniculata : *Andrographis paniculata* is an important official IP drug and very good hepatoprotective agent. Several indigenous formulations reputed to have liver protective properties contain 'Kalmegh' as one of the main ingredients. The whole plant is also used singly in

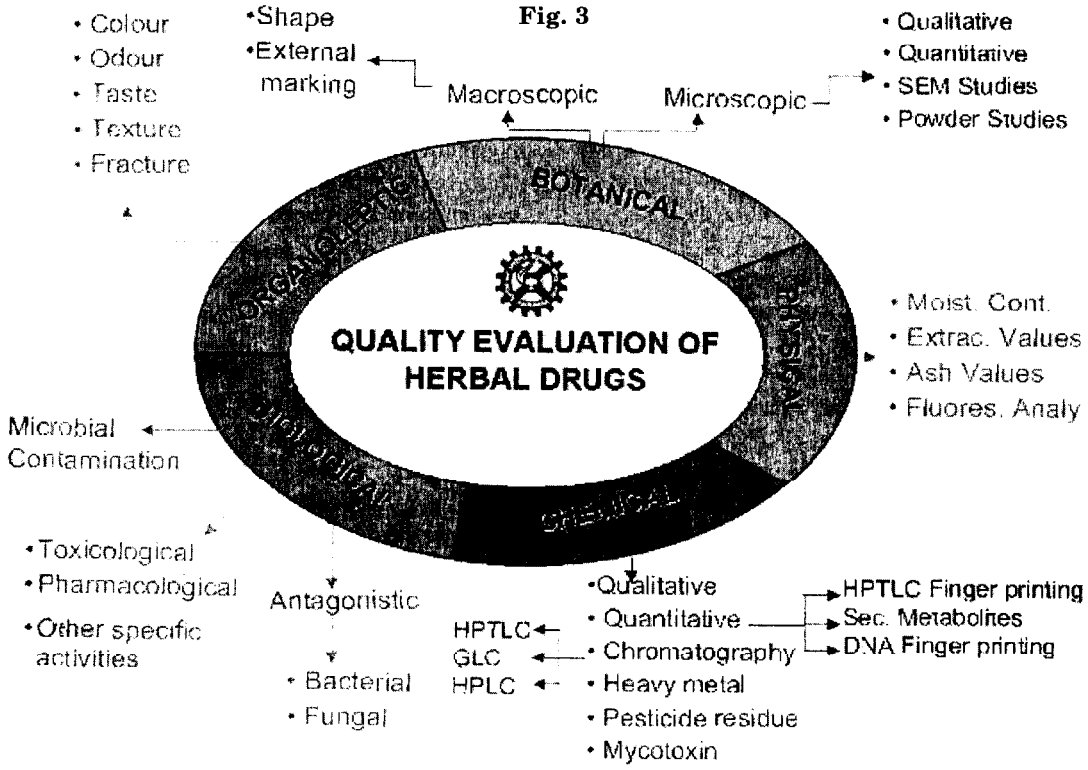


Fig. 3

Standardization and Quality Evaluation of Herbal drugs

various ailments viz. spleen complaints, colic, strangulation of intestine, constipation, cholera etc. The drug contains bitter crystalline diterpene lactone named as andrographolide, flavonoids and phenols.

The present investigation was carried out with a view to see the effect of seasons on total' andrographolide content responsible for the therapeutic uses for ascertaining the proper time of collection of this plant. The whole plant of *Andrographis paniculata* was collected from Banthra Research Station in the month of March, May and November (1993-1995). The percentage of andrographolide was higher (1%) in May and was 0.5% in March and November suggesting thereby that the plant should be collected in the month of May.

Scanning electron microscopic studies on Swertia spp. : Scanning electron microscopy can play an important rate in identification of different species which can be used as adulterant or substitute. Thus SEM studies were done on *Swertia chirata* Karst. Which is a popular medicine of traditional systems of medicine and an ingredients of various hepatoprotective and antipyretic compound formulations. The commercial drug is obtained from wild plants of *Swertia chirata* and due to scarcity of this drug in India, several other species of *Swertia* are being sold in the market in the name of 'Chiraita' . It is in this context that the scanning electron

microscopic studies of nine species of *Swertia* viz. *S. alternifolia, S. bimaculata, S. chirata, S. ciliata, S. cordata, S. corymbosa, S. petiolata, S. thomsonii* and *S. tetragona* have been carried out to lay down parameters for the genuine 'Chiraita' plant. The leaf of *S. chirata* can be identified from other species, by bold striations and irregular folds on the surface of epidermal cells and slit like inner stomatal ledges.

Shelf life studies of Picrorhiza kurrooa with respect to the percentage of 'Picroliv' : Shelf-life of crude drug is very important factor and very little work has been on record. Thus a study on the shelf-life of an important plant *Picrorhiza kurrooa* – from which a wonder drug 'Picroliv' has been released by Central Drug Research Institute (CDRI) – was undertaken. This was carried out in order to see whether there is any difference in concentration of 'Picroliv' (picroside-1 and kutkoside) after storing it for two years. Percentage of Picroliv was calculated in fresh, six months and one and a half year old materials. The study revealed that its percentage got reduced with the storing time.

Antimicrobial activity of some important essential oil : Essential oils from *Elsholtzia flava, Nardostachys jatamansi, Ocimum vulgare, Rhododendron antopogon, Tanacetum gracile* were extracted and different dilutions of these oils were tested against human pathogenic bacteria viz. *Bacillus subtilis, Escherchia coli, Klebsiella* sp., *Samonella typhi, Salmonella paratyphi* (A), *Staphylococcus aureus* and *Streptococcus faecalis* along with the known antibiotics. Oils of *Ocimum vulgare* and *Elsholitzia flava* show promising activity against *Bacillus subtilis* and *Salmonella typhi* responsible for intestinal and throat infections respectively.

Effect of 'Shodhan Sanskar' on 'Gunja' : In Ayurvedic literature it has been mentioned that certain toxic plants can be used in medicine after processing or 'Shodhan'. In this context the effect of 'Shodhan Sanskar' on seeds of *Abrus precatorius* which is an important member of the Upavisha-verga in Ayurveda has been studied with the objective to study the effect of Shodan on concentration of various phyto-constituents resulting in acute toxicity of Gunja and at the same time to find out which of the Shodhan processes is more effective. A comparative physico-chemical values profile revealed that the percentage of total ash got significantly reduced in 'Shodhit' material as compared to the 'Ashodhit' ones. For instance it was 1.5, 3.7, 1.7% in Milk Shodhit and 1.8, 5.7 and 2.1% in Kanji Shodhit material while it was 3.1, 9.5 and 5.2% in Ashodhit seeds of white, red and black variety of Gunja respectively. This is due to the leaching of some amount of inorganic salts during the Shodhan process. Like-wise, the percentage of protein in Ashodhit and Shodhit material was 18, 11, 14% (Ashodhit) 14.0%, 4.3, 11.0 (Milk Shodhit) 6.4, 2.8, 6.2% (Kanji Shodhit) in white, red and black kernels respectively. The decrease in total protein percentage was due to the dissolution of water soluble proteins in shodhit material and denaturalisation of toxic protein during heating. Similarly, the protein percentage of pericarps in all the three types of seeds also decreased with the shodhan process. The decrease was more in Kanji as compared to the Milk.

During HPLC studies of alkaloids, it was observed that in Shodhan process there was an increase in abrine percentage,

while percentage of hypaphorine decreased from 11.789% to traces. It is presumed that during Shodhan process, major part of hypaphorine might have undergone some changes and got converted in to abrine. This transformation seems to be quite possible after observing their chemical structure. The tertiary amino group of hypaphorine got reduced to primary amino group changing hypaphorine into abrine. This can be very well supported by the fact that during the Shodhan, total percentage of alkaloids remained unchanged while the ratio of hypaphorine and abrine changed considerably. The aforesaid changes in the percentage of proteins and hypaphorine got reflected in the pharmacological behaviour of the Shodhit seeds with regards to their pharmacological action and toxicity. For example the toxic effect got reduced with the processing – the LD_{50} and LD_{100} were found 1:2 in unprocess material and it increases with the processing viz. 2:5 in Milk Shodhit and 20:30 in Kanji Shodhit seeds.

Validation of Ethnobotanical claims by Pharmacological evaluation : The hepatoprotective activity of a popular ethnomedicine *Boerhaavia diffusa* L. Roots was tested pharmacologically on experimental animals. The roots of *Boerhaavia diffusa* L. commonly known as 'Punarnava', are used by a large number of tribes in India for the treatment of various hepatic disorders. In the present study, the effect of seasons, thickness of roots and form of does (either aqueous or powder) were studied for their hepatoprotective action to prove the claims made by the different tribes of India. The hepatoprotective activity of roots of different diameters collected in three seasons, rainy, summer and winter, was examined in thioacetamide in toxicated rats. The results showed that an aqueous extract (2ml/kg) of roots of diameter 1-3 cm, collected in the month of May (Summer), exhibited marked protection of a majority of serum parameters, i.e. GOT, GPT, ACP and ALP, but not GLDH and bilirubin, thereby suggesting the proper size and time of collection of *B. diffusa* L. roots for the most desirable results. Further, the studies also proved that the aqueous form of drug (2ml/kg) administration has more hepatoprotective activity than the powder form. This is probably due to the better absorption of the liquid form through the intestianl tract.

Standardization of Compound formulation 'Kalmeghasava' : A compound hepatoprotective formulation containing 18 herbal drugs was prepared in the laboratory and standardized. Besides, the change in physico-chemical properties of sugar, variation in total amount of sugars, their composition and amount of alocohol formation were also studied and it was observed that the amount of alocohol formation varied significantly from traces at 0 day to highest 6.4% at 20th day. The changes in the different physico-chemical properties was found to be directly related with the amount of sugar or its consumption.

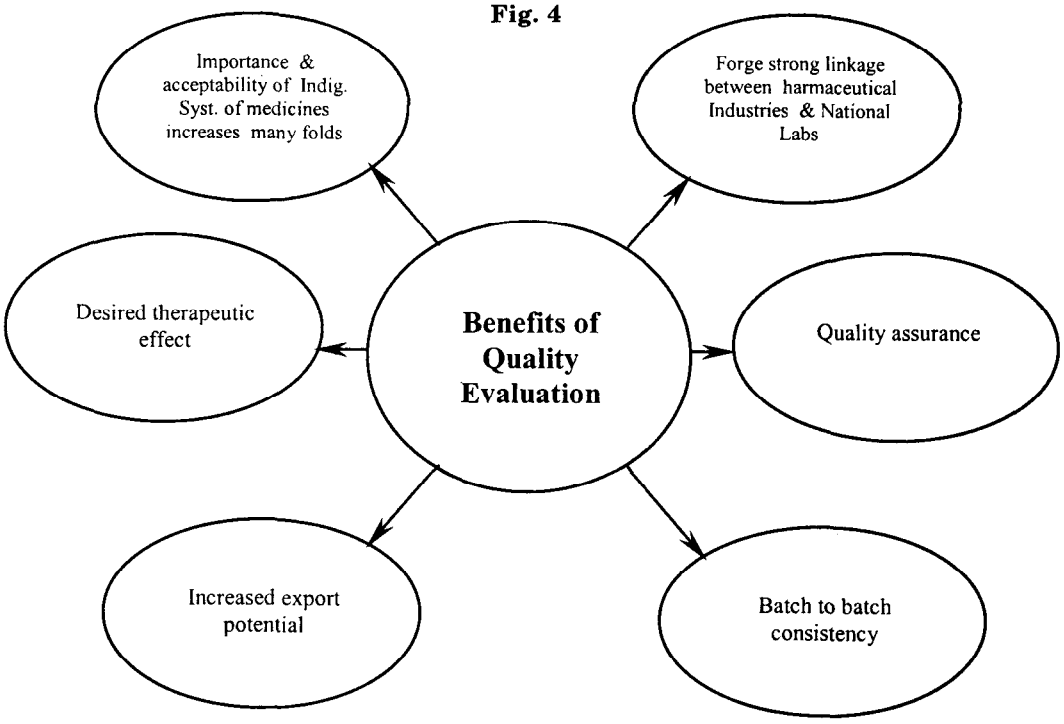
Its hepatoprotective action was also studied in collaboration with CDRI and it exhibited marked protection 40-87% of majority of serum parameters like SGOT, SGPT and SALP.

Quality evaluation of adulterants / substitute of Daruharidra : Adulteration and substitution of genuine herbal drug material are predominating in the herbal drug markets of the country and cause

serious problem with regard to their desired therapeutic efficacy of a particular drug. In certain cases, more than one plant source, those belonging to the species of the same genera, is being used as substitute. Thus all the four species of *Berberis* sold in the crude markets under the trade name 'Daruharidra' have berberine as a major alkaloid, but the concentration varies in different species. In context, these four species of *Berberis* viz. *Berberis aristrata, B. asiastica, B. chitria* and *B. lycium* were collected from Dehra Dun and Dhanaulti region for detailed Pharmacognostical studies. The berberine alkaloid was isolated in two species, *B. aristrata* and *B. asiatica*. These two species can be differentiated on the basis of some anatomical feature like number of pericyclic fibres which are more in *B. aristata*. On the contrary the percentage of tannin, ash values and water and alcohol soluble extractives are higher i.e. 1.75, 2.7, 0.25, 14.5 and 12.0 respectively in *B. asiatica* while these are 0.616, 2.2, 0.05, 14.0, 9.5 in *B. aristata*. The concentration of Berberine was also calculated and it was found that highest percentage of Berberine was in roots of *B. chitria*.

Detection of hevay metals concentration in some medicinal plants : Detection of heavy metals concentration viz. Cd, Pb, Cu, Zn in some important medicinal plants like *Alpinia galanga, Artemisia parviflora, Butea monosperma, Coleus forskohlii, Curcuma amada, Euphorbia prostrata, Pueraria tuberosa* was analyzed by atomic absorption spectrophotometer. The study

Fig. 4



Importance of Quality Evaluation of Herbal Drugs

revealed that all the metals were accumulated to a greater or lesser extent by all the nine species studied. The average bio-accumulation of metals irrespective of plant species were 22.84 (2.92-99.33), 0.47 (0.8-1.41), 1.33 (2.0-28.58), 49.23(8.75-144.28) ppm respectively for Pb, Cd, Cu and Zn. It is interesting to note that *Artemisia parviflora* leaves sample obtained from Junagarh has maximum concentration of Pb, Cd and Zn i.e. 99.33, 1.41 and 144.28 ppm, while the samples collected from hilly region of Uttar Pradesh have lesser accumulation of heavy metals. For instance, Tarikhet samples of *Artemisia, Coleus, Euphorbia* and *Microstylis* have lesser conc. of heavy metals in comparison to other samples of some species collected from different other localities. This shows the trend that hilly area, due to lesser environmental pollution and industrial activities accumulate lesser amount of heavy metals.

Identification and estimation of microbial contamination in herbal drugs : During survey of some important Indian herbal drug markets were observed that majority of the plant material being sold as herbal medicines are contaminated with bacteria like *Salmonella* spp., *Pseudomonas aeruginosa, Staphylococcus aureus* etc. and fungi like *Aspergillus, Penicillium, Mucor, Rhizopus* spp. etc. As per WHO suggestions, the raw or herbal drugs should be free from microbes which can alter the quality of drugs and can also produce toxins, which may be harmful to human beings. Further, this international body also emphasized for laying down standard limits of microbial contamination in herbal drugs, which are being used for Pharmaceutical preparations. In this context, NBRI has introduced this programme in its work on quality evaluation of herbal drugs. At present, samples of *Alpinia galanga* and *Pueraria tuberosa* and *Tinospora cordifolia* have been collected/procured from different parts of the country and the study revealed that majority of samples were found to be contaminated with *Aspergillus* spp. and *Enterobacteria*.

Conclusion

Thus one of the major impediments in the herbal drugs industries in India is the lack of quality control which reduces the reliability of herbal products. In this connection Pharmacognosy & Ethnopharmacology Division of National Botanical Research Institute is one of the oldest in the country engaged since the last three decades in standardization and quality evalution of crude herbal drugs and their products. It has now grown into a full fledged division of modern pharmacognosy with the latest state of art infrastructure and instrumentation facilities with experienced manpower. Hence, the quality control measures which include taxonomical, anatomical, phytochemical and pharmacological aspects are highly essential for each and every raw drugs and its products. Besides, all the claims mentioned in the classical literature should be validated scientifically which may enhance not only the commercial value of the products but credibility of our ancient claims will also be recognised throughout the world. In this way there are many benefits of quality evaluation of herbal drugs and their products viz. importance and acceptability of Indigenous Systems of Medicine would be increased many folds, desired therapeutic efficacy would be obtained and batch to batch consistency of the products would be assured (Fig. 4).

SUMMARY

The Ministry of Health and Family Welfare (Department of ISM&H) New Delhi has notified on 23rd June 2000 that the Ayurveda, Siddha and Unani/Pharmacoepial industries should get the certificate of GMP under '155-B in Schedule I certified of GMP of ASU drugs' in order to get the license for manufacturing. This rule will be enforced from July 2003. Hence due to the implication of this law the quality evaluation and standardization will be mandatory for all manufacturing units of ASU drugs. A significant percentage of people are using traditional medicine, and the expenditure on these medicine is increasing day by day. Although global market in herbal drugs is over US$ 60 billion per year but India's share is very poor, due to lack of quality control and standardization measures. If India's share has to be increased, a grand strategic plan, particularly in standardization and quality control of herbal drugs should be introduced which may boost up the export to Rs. 10,000 crores by 2010. Thus detailed pharmacognostic evaluation is highly essential and is a necessary prerequisite. In this context the National Botanical Research Institute is engaged in standardization and quality control of herbal drugs using different parameters viz. botanical, physical, phytochemical and biological. Besides, other aspects like seasonal variations studies, assessment of microbial loads, shelf life studies, detection of heavy metals and validation of classical and ethnobotanical claims have also been undertaken and more than, 150 single herbal drugs and 20 herbal formulations have been evaluated by the NBRI.

शाकीय एवं औषध निर्माण उद्योग की वैधानिक आवश्यकता – प्रतिमानीकरण एवं गुणवत्ता नियन्त्रण

शांता मेहरोत्रा

सारांश

चूंकि स्वास्थ्य एवं परिवार कल्याण मंत्रालय (भारतीय चिकित्सा एवं स्वास्थ्य प्रणालियां विभाग) नई दिल्ली ने 23 जून 2000 को यह विज्ञापित कर दिया है कि औषधि निर्माण प्राप्त करने के लिए आयुर्वेद - सिद्ध - यूनानी औषधियों का नियम 155 - बी की अनुसूची i में सभी सामान्य औषधियों का जीएमपी (सामान्य औषधियां) प्रमाणपत्र आयुर्वेद, सिद्ध और युनानी औषधियां बनाने वालों को भी प्राप्त करना होगा । यह नियम जुलाई 2003 से लागू होगा । अतः इसके निहितार्थो के कारण सभी आयुर्वेद - सिद्ध - यूनानी औषधियों को बनाने वाली इकाइयों के लिए गुणवत्ता का मूल्यांकन और प्रतिमानीकरण करना कानूनी तौर पर बाध्यकर होगा । विश्व स्वास्थ्य संगठन के अनुसार लोगों का काफी बड़ा प्रतिशत पारम्परिक औषधियां उपयोग करता है और इन औषधियों पर होने वाला खर्च दिन प्रतिदिन बढ़ता जा रहा है । हांलाकि जड़ी बूटियों से बनी दवाइयों का विश्व बाज़ार 60 बिलियन अमेरिकी डालर वार्षिक से ज्यादा है किन्तु भारत का इसमें हिस्सा गुणवत्ता नियन्त्रण न किया जाने तथा प्रतिमानीकरण उपायों का आभाव रहने से बहुत कम है । यदि भारत का यह हिस्सा हमें बढ़ाना अभीष्ट है तो हमें एक विशाल समरनीति, विशेषतः जड़ी बूटियों से बनने वाली औषधियों के प्रतिमानीकरण और गुणवत्ता नियन्त्रित रखने की, आरम्भ करनी चाहिए, जिससे हमारा इनका निर्यात बढ़कर 2010 तक 10,000 करोड़ रुपंयों तक पहुंच जाए । अतः विस्तृत भैषज्य ज्ञान होना अत्यधिक अनिवार्य है और यही हमारी सबसे पहली आवश्यकता है । इसी संदर्भ में राष्ट्रीय वनस्पति अनुसन्धान संस्थान विभिन्न परिमाण जैसे वानस्पतिक, भौतिक, पादप रसायनिक और जैवकीय उपयोग में लाकर जड़ी बूटियों से बनाई जाने वाली औषधियों के प्रतिमानीकरण और गुणवत्ता निर्धारण कार्य में लगा हुआ है । इसके अलावा, अन्य पक्ष, जैसे मौसमी विभिन्न होने के अध्ययन, अणुजीवी भार का आकलन, भण्डारणकाल अध्ययन, भारी धातुएं मिली होने का पता लगाना तथा आर्ष होने और जातीय वनस्पति रहने के दावों की वैधता जांचने के कार्य भी हाथ में लिए हुए हैं और अब तक 150 अकेली जड़ी बूटियों से बनाई औषधियों और 20 जड़ी बूटियों से बनाई मिश्रित से ज्यादा औषधियों का इस संस्थान द्वारा मुल्यांकन किया जा चुका है ।