SOCIETY FOR NEW AGE HERBALS

VIEWS & REVIEWS

No. 5 **DECEMBER** **2008**

SAFETY ASPECTS OF AYURVEDIC MEDICINES: AVAILABLE EVIDENCE AND NEED THEREIN

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INTRODUCTION

Survey indicated that about 70-80% of the world populations rely on non-conventional medicine mainly of herbal sources in their primary healthcare (Anonymous, 1996) and there are similar figures in India for percentage population which rely on traditional system of medicines (Lele *et al,* 1999). Traditional medicines comprise a wide range of therapeutic approaches that include diet, herbs, metals, minerals, precious stones and their combinations. In India, various systems of medicine - Ayurveda, Siddha, Unani and Homeopathy are practiced. Ayurvedic medicaments are made from herbs or mixtures of herbs, either alone or in combination with minerals, metals, and ingredients of animal origin.

Ayurveda forms an important component of health care in India. This is based upon its own centuries-old strong basic principles and philosophy coupled with prolonged documented observations and rich traditional wisdom. Ayurveda is the science of life and Ayurvedic products form only one component to fulfill the desire of achieving long and healthy life.

Charak Samhita, one of the first few documented treatises on Ayurveda starts from a conference of learned ancient physicians in the Himalayas.

Ayurveda operates on the precept that all the material on earth is made up of five basic elements- fire, water, air, earth and space. Therefore, there is synergy between humans and environment. The medicinal properties of these materials have been documented since ancient times to provide benefits in illness and/or help maintain good health. Despite general perceptions that all Ayurvedic medicines are safe, numerous adverse effects and interactions have been attributed to these medicines, based on variable levels of evidence ranging from historical use or anecdotes to

pre-clinical research or high quality clinical trials (Roche et al, 2005; Goel et al, 2006). Modern practitioners argue that simply following age-old Ayurvedic formulas is no guarantee of safety and the fundamental processes and concepts on which these ancient processes are based must be exposed to serious scientific scrutiny.

Since Ayurvedic product development was based upon wide ranging experiments and experiences, the need to validate the safety of these products was never felt. However, in the current times, quality of drugs has been affected due to several factors such as the problem of adulteration, contamination, short cuts being followed instead of following the recommended methods of producing Ayurvedic products by few individuals, and poor implementation of regulatory controls. These factors have led to the need for evidence of safety of Ayurvedic products.

In addition, global resurgence of Ayurveda, specially its herbal component has led to the need for its scientific validation both in terms of efficacy and safety. A few recent papers published in international journals have re-focused the attention on safety aspects of Ayurvedic products.

EVIDENCE OF SAFETY

1. Traditional use:

Ayurvedic medicines have been traditionally used for thousands of years in India. In 1998, as per statistics of Govt. of India, there were 609,400 physicians of Indian Systems of Medicine and Homeopathy in India, out of which, more than half belonged to the Ayurveda stream (ISM&H, 1999).

About 80% of the population in India depends on traditional medicine, out of which almost 70-75% depend on Ayurvedic medicines in one form or the other. That means, if approx. 250,000 Ayurvedic physicians see on an average 10 patients per day, it converts to 2.5 million patients per day. Almost equal numbers of people do not go to physicians and use these medicines on their own, which means that almost 5 million people use Ayurvedic medicines on daily basis in India in some form or the other. It is worthwhile to mention that though the Fourth estate enjoys full freedom in India, even then media reported incidents of side effects related to Ayurvedic medicines are almost nil. This is an important evidence of safety of Ayurvedic medicine going by their traditional usage pattern.

2. Regulatory Measures:

Ayurvedic medicines are regulated by Drugs and Cosmetic Act of India (D&C Act 1940). This Act has recognized the use of toxic substances in Ayurvedic medicine and has given a separate Schedule E1 for listing of such substances (Table 1). These toxic substances need to undergo a detoxification process referred to as ‘Shodhana Samskara’ in the Ayurvedic text books, before they can be used as an ingredient in an Ayurvedic formulation. All the Ayurvedic formulations

containing such substances need to carry a warning on their labels ‘to be taken under medical supervision only’.

Table 1- List of Poisonous substances under the Ayurvedic and Unani systems of Medicine

Drugs of vegetable origin	
Papaver somniferum	*Croton tiglium*
Cannabis sativa	*Hyoscyamus niger*
Abrus precatorius	*Strychnos nux-vomica*
Gloriosa superba	*Semecarpus anacardium*
Aconitum chasmanthum	*Datura metel*
Calotropis gigantea	*Nerium indicum*
Baliospermum montanum	*Euphorbia neriifolia*

Drugs & Cosmetics Act 1940 Schedule – E (1).

3. Generally Recognized As Safe (GRAS) list:

As mentioned earlier, Ayurveda uses holistic approach of treatment wherein food, medicine and non-therapeutic measures like exercise and behavior go together.

Ayurvedic formulations contain food ingredients as well as therapeutic food ingredients. Therefore, it is presumed that all other ingredients except published in Schedule E1 do fall under the list of GRAS i.e. Generally Recognized As Safe, though it has not been notified separately.

4. Adverse Drug Reaction Monitoring:

There is no formal system of ADR monitoring of Ayurvedic medicine in India. However, India has a free press and very active print and electronic media. So far, cases of adverse drug reaction of Ayurvedic medicine have not been reported

5. Toxicity studies:

Manufacturing of Ayurvedic medicine is controlled by Drugs and Cosmetic Act of India. However, there are certain conditions, which a manufacturer has to meet before being granted a manufacturing permission. But toxicity studies and clinical trials are not mandatory for grant of such license.

However, several Ayurvedic products have undergone toxicity studies at academic institutions as well as industries in India. Due to want of clear-cut guidelines, most of these studies have covered the following:

- Acute toxicity – LD_{50} in two species (mostly rats and mice)
- Sub acute & chronic toxicity – ranging from 28 days to 6 months studies by oral route in single species (mostly rats)
- Ames mutagenicity test in certain cases

NEED FOR CONDUCTING TOXICITY STUDIES:

1. Presence of Heavy Metals:

Some researchers have suggested that the potential source of toxicity of Ayurvedic medicines is their heavy metal content (Mitchell-Heggs *et al*, 1990; Keen *et al*, 1994; Olujohungbe *et al*, 1994; Roche *et al*, 2005). Significant levels of toxic heavy metals such as lead, mercury and arsenic were found in 20% of Ayurvedic preparations that were made in India and were available in US market (Saper *et al*, 2004). Similar studies performed in India, have confirmed these results (Parab *et al*, 2003).

However, it needs to be understood holistically and clearly that metals are integral to many Ayurvedic formulations and have been used for centuries after *shodhana* (detoxification), for medicinal purposes. There is no point in conducting safety and clinical trials on these products as they have been used safely and have been mentioned in the ancient texts. However, new combinations of these metallic ingredients should always be subjected to toxicity studies. Use of *in vitro* toxicity methods as part of standardization of metallic preparations may also resolve the issue of safety on these products.

2. Presence of pesticide residues and other microbial contaminants:

Excessive or banned pesticides and microbial contaminants may be related to the source of these herbal materials, if they are grown under contaminated environment or during collection of these plant materials. Chemical toxins may also come from unfavorable or wrong storage conditions or chemical treatment during storage.

3. Adulteration with synthetic medicines:

Other serious quality related safety problems include the deliberate addition of prescription medicines and toxic heavy metals to herbal products. The Medicine Control Agency, UK (MCA) reported the presence of: corticosteroids in creams intended for use in children with eczema; fenfluramine in a slimming product;and other prescription medicines (sildenafil, glibenclamide, warfarin, alprazolam) in herbal products (Gupta *et al*, 2000). Use of several herbs that have been labeled as toxic --- a recent example of the toxic *Aristolochia* species being used as a substitute in traditional Chinese medicines (TCM), which resulted in cases of serious renal toxicity and renal cancer --- has been reported from Europe, China and America.

4. Herb-Drug interactions:

Recently several reviews have reported herb-drug interactions with clinical significance (Zhou *et al*, 2004; Hu *et al*, 2005, Vanden *et al*, 2006**;** Kang-Yum *et al*, 2006; Ulbricht *et al*, 2006; Tirona & Bailey, 2006**).** The nature of herb-drug interactions is not a chemical interaction between a drug and a herb component to produce something toxic. Both pharmacokinetic and pharmacodynamic components may play a role in these interactions. The interaction may involve having a herb component cause either an increase or decrease in the amount of drug in the blood stream. A decrease in the amount of drug could occur by herb components binding up with the drug and preventing it from getting into the blood stream from the gastrointestinal tract, or by stimulating the production and activity of enzymes that degrade the drug and prepare it for elimination from the body. Besides, Ayurvedic or herbal medicine could affect the disposition of conventional pharmaceuticals through inhibition of human cytochrome P-450 (CYP) enzymes (Strandell *et al*, 2004).

MEASURES FOR MINIMIZATION OF AYURVEDIC/ HERBAL/ TRADITIONAL MEDICINE TOXICITY

Thus there is need to realize that all herbal/ traditional medicine may not be necessarily 'safe'. The 'safety' of traditional/ herbal medicine not only depends upon the Prescriber knowledge but also the several other factors including adulterations with other plant, synthetic drug, steroids, contamination with heavy metal, sub-standard/ poor quality formulation, improper method of formulation, storage of finished products, besides patients' knowledge. Usually an allopathic practitioner is not aware of or does not take full history about the herbal medicine taken by the patients or does not have the knowledge about the potential adverse effects of herbal medicine or herb-drug interactions. Updated knowledge on toxicity or adverse effects of plants, metals, gems, and shells used in traditional system of medicine, could largely help in this regard.

The clinical importance of herb-drug interactions depends on many factors associated with the particular herb, drug and patient. Herbs should be appropriately labeled to alert consumers to potential interactions when used concomitantly with drugs, and to recommend consultation with their medical practitioners before use (Hu et al, 2005). Herb-drug interactions may be avoided if patients are advised, as a matter of routine, to inform their physicians about drugs from any other systems that they may be taking. Practitioners should routinely take history of consumption of these medicines, and attempt to analyze the reasons why a particular patient may have opted for these medicines. Successful safety monitoring is possible only if adequate information is available to the practicing physicians.

Other formulation related factors can be controlled by implementing standard operating procedures (SOP) leading to Good Agricultural Practice (GAP), Good Laboratory Practice (GLP), Good Supply Practice (GSP) and Good Manufacturing Practice (GMP) for producing these medicinal products from herbal or natural sources. Advances in chemical and biomedical analysis will also help detect intentional and unintentional toxic contaminants in herbal substances (Chan K, 2003).

The widespread notion of herbal medicine products being inherently safe is naive at best and dangerous at worst. Also, most of the herbs under use are not being properly evaluated for their toxicity. More research is required to minimize the risk herbal/ traditional medicine products may pose to consumers' health (Ernst E, 2004).

CONCLUSION:

Ayurvedic/ Herbal medicines are widely used in several nations with approximately one quarter of adults reporting use of a herb to treat a medical illness within the past year. Although Ayurvedic/ herbal medicines are often believed to be "safe", these may contain potent bioactive substances and hence may cause many dangerous and lethal side effects including direct organ toxicity, allergic reactions, effects from contaminants, and interactions with drugs and other herbs. Literature suggests that herbal medicines have potential to cause serious toxicity (Ernst E, 2003a,b; Willett *et al*, 2004; Lenz *et al*, 2004) and also possibility of interaction (*Ginkgo biloba*, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, Garlic, Kava and *Ephedra* spp, etc.) with prescribed drugs (Zlotogorski & Littner, 2004). Until recently, an herb-drug interaction was only considered a possibility, but is now a reality. Although many herbal drugs have good safety profiles, it must be borne in mind that Ayurvedic or herbal medicines are intended to be taken over an extended period of time, which provides the opportunity for enzyme induction and other mechanisms of interaction to take effect (Williamson EM, 2003). The unreliable quality of these medicines poses a risk when Ayurvedic or herbal medicines are contaminated (e.g. with heavy metals) or adulterated (e.g. with prescription drugs). A new combination of herbal or other ingredients should always be subjected to toxicity studies. Use of *in vitro* toxicity methods as part of standardization of metallic preparations may also resolve the issue of safety of products.

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