Chapter 12
Safety Aspects of Ayurvedic Drugs

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12.1 Introduction

Ayurveda, the science of life, prevention, and longevity, is the oldest and most holistic or comprehensive Indian medical system. This is based upon its own centuries old strong basic principles and philosophy coupled with prolonged documented observations and rich traditional wisdom. Ayurvedic products form only one component to fulfill the desire of achieving long and healthy life. As per Ayurvedic concepts, every material on earth is made up of five basic elements, which are *prithvi* (earth), *jal* (water), *tej* (fire), *vayu* (air), and *aakash* (space). This is true for both plants as well as human beings, thus providing interface between them.

ASU (Ayurvedic, Siddha, and Unani) drugs include herbals, minerals, and metals, intended for internal (except injectables) or external use for or in the diagnosis, treatment, mitigation, or prevention of disease or disorder in human beings or animals, the ingredients of which are described in the authoritative books of Ayurveda as specified in the first Schedule of Drugs and Cosmetics Act 1940 [1].

Though the safety evaluation of modern (allopathic) medicines was being done for a long time, no such procedure existed to evaluate the Ayurvedic medicines. It was usually the view that these medicines have no or minimal adverse effects. However, in the year 1993, the *World Health Organization* (*WHO*) stated that "inappropriate use of traditional medicines or practices can have negative or dangerous effects" and that "further research is needed to ascertain the efficacy and safety" of several of the practices and medicinal plants used by traditional medicine systems [2].

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In the present scenario, safety of a medicine has gained utmost importance due to growing global interest, competition, and scientific discovery along with changing regulatory requirements. In USA, Europe, and also in India, many new regulatory notifications have come in recent years, which itself is a regulatory challenge in the field of herbals.

Ayurvedic medicines contain ingredients of plants, minerals, metals, or animal origin. There may be potential risk of toxicity due to contamination or improper manufacturing processes, etc. Saper et al. (2004) questioned the safety of Ayurvedic medicines contaminated with heavy metals [3]. Subsequently, in 2005, *Health Canada* and *UK* banned few Indian Ayurvedic medicines consequent to which the Government of India made testing of heavy metals mandatory for exported Ayurvedic products. These were the triggers which actually led to the setting of heavy metal limits for herbals by Government of India. Herbal materials can be crude herbs or herbal extracts like aqueous extracts, hydroalcoholic extracts, etc. As per a recent notification by Government of India (*GSR 663* (*E*) *August 2010*), other solvent extracts have also been permitted with the condition of safety studies [4].

Evaluation of safety of Ayurvedic medicines is a complicated task. The first question is what to evaluate: the crude formulation or its individual ingredients? While many protagonists of modern medicine are of the view that individual ingredients must be evaluated for safety, followers of Ayurvedic system may argue that separation of ingredients may destroy the basic character of these medicines. We may actually evolve a middle path to avoid any such confrontation—let the multi-ingredient finished product be evaluated first for safety of the Ayurvedic medicines and if found safe, be put to clinical use. The individual ingredients can be studied later in case adverse drug reactions are reported.

Modern medicines may contain potentially harmful chemicals, due to which, a number of safety procedures have been adopted for their evaluation. Phase I of the clinical studies evaluates the intended drug for its safety only. Only after a chemical substance is found safe for clinical use, further studies can be conducted for its clinical applications.

With the Ayurvedic system of medicine, as with all other forms of traditional medicines, no such check point(s) has been suggested till date. This does not imply that Ayurvedic system is not aware of the adverse drug reactions (ADR) associated with these medicines. The pharmacovigilance system for Ayurvedic products has been put in place with functioning ADR monitoring headquarters at Jamnagar (Gujarat) and others at all tertiary Ayurvedic hospitals. However, currently, the process of an ADR data bank of Ayurvedic drug is very much in the offing and is expected to be completed within a few years.

As a result of WHO promotion of traditional medicine, countries have been seeking the assistance of WHO in identifying safe and effective herbal medicines for use in national health-care systems. In 1991, the Director-General of WHO, in a report to the 44th World Health Assembly, emphasized the great importance of medicinal plants to the health of individuals and communities [5]. Earlier, in 1978, the 31st World Health Assembly (WHA) had adopted a resolution (WHA31.33) that called up on the Director-General to compile and periodically update a therapeutic

classification of medicinal plants, related to the therapeutic classification of all drugs [6]. Subsequently, resolution of WHA40.33, adopted in 1987, urged member states to ensure quality control of drugs derived from traditional plant remedies by using modern techniques and applying suitable standards and good manufacturing practices [7]. Resolution WHA42.43 of 1989 urged member states to introduce measures for the regulation and control of medicinal plant products and for the establishment and maintenance of suitable standards [8]. Moreover, the International Conference on Primary Health Care, held in Alma-Ata, USSR, in 1978, recommended, inter alia, the accommodation of proven traditional remedies in national drug policies and regulatory measures [9].

WHO (1993) has published guidelines in order to define basic criteria for evaluating the safety and efficacy of herbal medicines aimed at assisting national regulatory authorities, scientific organizations, and manufacturers in this particular area. Originally, WHO guidelines for GCP have been adapted from ICH guidelines. These guidelines specify the requirements for clinical trial protocol and protocol amendment(s), background information about the name and description of the investigational product(s), trial objectives and purpose and trial design selection and withdrawal of subjects, treatment of subjects; assessment of efficacy and safety, statistics, direct access to source data/documents, quality control and quality assurance, description of ethical considerations relating to the trial, data handling and record keeping, financing and insurance if not addressed in a separate agreement, publication policy if not addressed in a separate agreement, pharmaceutical assessment of preparations, and stability and safety aspects [2].

12.2 Department of AYUSH (Ayurveda, Yoga, Unani, Siddha, and Homeopathy), India

Government of India formed department of AYUSH under Ministry of Health and Family Welfare to coordinate its various facets like education, research, and health care through Indian Systems of Medicine, Ayurveda, Homeopathy, Naturopathy, Siddha, and Yoga. This department funds several extramural projects besides having a research council called Central Council for Research in Ayurveda sciences, dedicated to research in Ayurveda, through its several labs. In order to lay down standards on medicinal plants, Department of AYUSH has prepared 540 monographs on individual medicinal plant parts and 152 Ayurvedic formulation monographs, through Ayurvedic Pharmacopoeia Committee [10, 11].

Ayurvedic medicines are regulated by Drugs and Cosmetics Act of India. This Act has recognized the use of toxic substances in Ayurvedic medicines and has given a separate Schedule E (1) for listing of such substances. These toxic substances need to undergo a detoxification process referred to as "*Shodhana Samskara*" in the Ayurvedic textbooks 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."

The following preclinical safety evaluation requirements for Ayurveda, Siddha, and Unani drugs and other traditional medicine have been prescribed through the Gazette of India [4].

Safety data required for various ASU products categories in India are summarized below:

1. *Patent or propriety drugs*
   ASU drugs with any of the ingredients of Schedule E (1) (list of poisonous substances under the Ayurvedic (including Siddha) and Unani Systems of Medicine) of Drugs and Cosmetics Act, 1940 with existing indication
2. *ASU drugs for Balya and Poshak*
   If any of the ingredients specified in the Schedule E (1) of Drugs and Cosmetics Act, 1940
3. *ASU drugs for Saundarya Prasadak*
   If any of the ingredients specified in the Schedule E (1) of Drugs and Cosmetics Act, 1940
4. *Medicines based on extracts of medicinal plants* (*dry or wet*)

Hydroalcohol extract for new indications and extracts other than aqueous/hydroalcoholic

For herbal Ayurvedic preparations, only subchronic studies are required except herbal extracts other than aqueous and hydroalcoholic where acute, chronic, mutagenicity, and teratogenicity toxicity studies should be done.

12.3 Evidence of Safety of Ayurvedic Products

Since Ayurvedic product development was based upon wide-ranging experiments and experiences, 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 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.

12.3.1 Traditional Use

Ayurvedic medicines have been traditionally used for thousands of years in India. In 1998 as per statistics of Government of India, there were 609,400 physicians of Indian Systems of Medicines and Homeopathy in India, out of which, more than half belonged to the Ayurveda stream [12].

About 80% of the population in India depends on traditional medicine, out of which, almost 70–75% depends on Ayurvedic medicines in one form or the other.

That means if approx. 250,000 Ayurvedic physicians see on an average ten patients per day, it converts to 2.5 million patients per day. Almost equal numbers of people do not go to physician 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 also includes home Ayurvedic remedies, though.

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.

12.3.2 Method of Preparation

The herbomineral products are processed in a way that eliminates the toxic properties of the metals. Most of the minerals/metals are used only after they are converted into *bhasma* by Marana. Prior to Marana, the minerals/metals are thoroughly purified by classical process called Shodhana. By Shodhana processes, minerals/metals lose the physical impurities present in them and become available in pure form for further processing. Apart from getting purified, they are certain modifications done in the properties of these minerals/metals. Specific types of processes with specific materials are advocated in classical texts for each mineral/metal [13].

12.3.3 Adverse Drug Reaction Monitoring

There was no formal system of ADR monitoring of Ayurvedic medicines in India previously. However, recently, Government of India started pharmacovigilance program for ASU drugs. It is yet to see what data are being collected through this formal system of adverse drug reaction monitoring, basis which it will be possible to comment authentically about the safety of Ayurvedic medicines in India. Moreover, 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.

12.3.4 Toxicity Studies

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

The major issue with the Ayurvedic/herbal medicines is that there is very less scientific data available on their safety. However, it is also a fact that it is difficult to evaluate

polyherbal medicines using the conventional array of toxicological methods since these materials consist of hundreds of active ingredients. There are several publications, which state the potential toxicity of the phytomedicines. Contamination of these products by pesticides, herbicides, naturally occurring toxins, microbes, or adulteration by means of synthetic substitutes is a cause for concern. Toxicity manifestations include hepatotoxicity (most prominent—mild elevations of liver enzymes to fulminant liver failure), nephrotoxicity, and neurotoxicity, hematological, mutagenic, and cardiovascular toxicities. Hence, there is a need for a fundamentally different approach for toxicological studies that need to be adopted for Ayurvedic and herbal products. In light of the above stated facts, an integrated approach for safety assessment focused on the hazard identification is imperative. The type, nature, and extent of effects obtained during toxicity studies can help in adequately classifying herbal medicines as nontoxic, moderately toxic, or severely toxic on selected biological systems [14].

It is essential that the literature sources should be reviewed for the toxicities of the herbal products in prior human experiences or existing animal data. The need for additional preclinical studies prior to clinical trials depends on the following considerations:

- Similarities between the new and old preparations, in terms of product characteristics, and usages in clinical settings
- Scale and exposure (dosage/duration) of the proposed new clinical studies
- Frequency and severity of any known toxicity

Thus, in general, requirements for preclinical studies may range from none for early phase, small, studies using the same preparations that have been used extensively and without known safety problems, to a complete set of conventional toxicology studies for relatively new products in large phase III trials. For many herbal products, certain preclinical studies may be necessary but can be conducted concurrently with the proposed clinical trials.

Following preclinical toxicity studies used for conventional medicines may be adopted to suit the needs of traditional medicine on case-to-case basis.

12.3.4.1 Acute Toxicity [15]

Table 12.1 OECD Test Guideline 425 [15]

Species	Rats (female nonpregnant) for oral and inhalation tests
Age	Young adults
Number of animals	5 rats for each sex per dose level
Dosage	3 dose levels recommended; exposures are single doses or fractionated doses up to 24 h for oral and 4-h exposure for inhalation studies
Observation period	≤14 days

12.3.4.2 Subacute Toxicity [16]

Table 12.2 OECD Test Guideline 412 [16]

Species	Rats for oral/diet/drinking water tests
Age	Young adults
Number of animals	5 rats per dose level
Dosage	3 dose levels recommended; exposures are single doses or fractionated
Observation period	14–28 days

12.3.4.3 Subchronic Toxicity [17]

Table 12.3 OECD Test Guideline 413 [17]

Species	Rodents (usually rats) preferred for oral and inhalation studies; rabbits for dermal studies; nonrodents (usually dogs) recommended as a second species for oral tests
Age	Young adults
Number of animals	10 of each sex for rodents, 4 of each sex for nonrodents per dose level
Dosage	3 dose levels plus a control group; includes a toxic dose level plus NOAEL (no observed adverse effect level); exposures are 90 days
Observation period	30–90 days

12.3.4.4 Chronic Toxicity [18]

Table 12.4 OECD Test Guideline 452 [18]

Species	2 species recommended: rodent and nonrodent (rat and dog)
Age	Young adults
Number of animals	20 of each sex for rodents, 4 of each sex for nonrodents per dose level
Dosage	Three dose levels recommended; includes a toxic dose level and NOAEL; exposures generally for 12 months
Observation period	12–24 months

12.3.4.5 Carcinogenicity [19]

Table 12.5 OECD Test Guideline 451 [19]

Species	Testing in two rodent species, the rat and mouse preferred due to relatively short life spans
Age	Young adults
Number of animals	Each dose group and concurrent control group should therefore contain at least 50 animals of each sex
Dosage	Three dose levels recommended; highest should produce minimal toxicity and NOAEL; exposure periods are at least 18 months for mice and 24 months for rats
Observation period	18–24 months for mice and 24–30 months for rats

12.3.4.6 Developmental and Reproductive Toxicity [20, 21]

Table 12.6 OECD Test Guideline 415 and 416 [20, 21]

Species	Rat, dog is recommended
Age	Young adults
Number of animals	20 pregnant females of each sex per dose level
Dosage	Three dose levels recommended; highest dose should produce toxicity but not mortality in parents; lowest dose should not produce toxicity and NOAEL
Observation period	28 days depending on the animal species

12.4 Heavy Metals in Ayurvedic Products

Heavy metals are commonly defined as those having a specific density of more than 5 g/cm. The main threats to human health from heavy metals are associated with exposure to lead, cadmium, mercury, and arsenic. Although adverse health effects of heavy metals have been known for a long time, exposure to heavy metals continues and is even increasing in some areas [22].

Herbs-based Ayurvedic products were the only therapeutic options available to Ayurvedic physicians up to 1000 AD. The dose of such herbal products was very high, the efficacy was low, shelf life was low, and availability of the materials throughout the year was also a problem. These factors were responsible to look for the need of those products, which can be used in low dose, should be quick acting, and for which round the year availability could be ensured. This was the genesis for use of metallic products (*Rasaushadhi*) in Ayurveda.

It is generally believed that herbal and natural products are safer than the synthetic or modern medicines, but some Ayurvedic products may contain heavy metals as essential ingredients. The ever increasing popularity of Ayurvedic medicine has led to concerns relating to its safety, quality, and effectiveness especially for *bhasmas* as these are usually made of metals like mercury (Hg), copper (Cu), iron (Fe), tin (Sn), zinc (Zn), gold (Au), silver (Ag), and arsenic (As). Cadmium (Cd) and nickel (Ni) are not used as starting material, but may come as contaminant.

All these preparations are not recommended for all the patients. The indications, dose, to whom to give and to whom not to give, what should be the vehicle, what are the diseases, where they are not recommended, etc., are major factors always considered by the physician before they recommend these Ayurvedic metallic products to the patients.

Heavy metal limits for true herbal products as followed in some countries have been enumerated in Table 12.7.

The Ayurvedic Pharmacopoeia of India has specified the following permissible limits of heavy metals in Ayurvedic products [10] (Table 12.8).

Most of Rasaushadhis, by design of preparations, form a ligand of organic/inorganic substances; and free metal is converted into organic/inorganic compound. The current method of analysis of heavy metals by atomic absorption spectroscopy involves heating the test substance around up to 700°C to convert the compound into free metal before testing. However, the art of converting toxic metal into nontoxic metal-based Ayurvedic formulation gets lost in the current methods of heavy metal analysis. Therefore, there is a need to develop nondestructive analytic method for testing of such products before branding them toxic merely because of presence of metals. Alternatively, let the finished product be subjected to toxicity studies, and if then it is found to be nontoxic, it should be accepted for clinical use. The toxicity study results of few of Ayurvedic Rasaushadhi products of Dabur India Limited are given in Table 12.9.

Ayurvedic formulations do contain toxic substances, metals etc., which, if not used following Ayurvedic principles, may show symptoms of toxicity. Järup (2003) has elaborated hazards of heavy metals [22]. Some of them are given in Table 12.10.

12.5 Factors Responsible for Side Effects of Ayurvedic Medicines

The following factors are responsible for toxicity of Ayurvedic medicines:

- Known side effects
- Medication errors

Table 12.7 Heavy metal limits in few countries [23]

		Arsenic (As)	Lead (Pb)	Cadmium (Cd)	Chromium (Cr)	Mercury (Hg)	Copper (Cu)	Total toxic metals as lead
For herbal medicines								
Canada	Raw medicinal plant materials	5 ppm	10 ppm	0.3 ppm	2 ppm	0.2 ppm		
	Finished herbal products	0.01 mg/day	0.02 mg/day	0.006 mg/day	0.02 mg/day	0.02 mg/day		
China	Medicinal plant materials	2 ppm	10 ppm	1 ppm		0.5 ppm	20 ppm	
Malaysia	Finished herbal products	5 mg/kg	10 mg/kg			0.5 mg/kg		
Republic of Korea	Medicinal plant materials							30 ppm
Singapore	Finished herbal products	5 ppm	20 ppm			0.5 ppm	150 ppm	
Thailand	Medicinal plant material, finished herbal products	4 ppm	10 ppm	0.3 ppm				
WHO recommendations			10 mg/kg	0.3 mg/kg				
For other herbal products								
National Sanitation Foundation draft proposal (raw dietary supplement)		5 ppm	10 ppm	0.3 ppm	2 ppm			
National Sanitation Foundation draft proposal (finished dietary supplement)		0.01 mg/day	0.02 mg/day	0.006 mg/day	0.02 mg/day	0.02 mg/day		

Table 12.8 Heavy metal limits in Ayurvedic products [10]

Heavy metal	Permissible limits in Ayurvedic product
Arsenic	3 ppm
Lead	10 ppm
Cadmium	0.3 ppm
Mercury	1 ppm

Table 12.9 Summary of toxicity studies conducted by Dabur on Ayurvedic Rasaushadhis [24]

Product name	Type of study	Species/dose	Observation
Vasant Kusumakar Rasa	Acute oral Undue toxicity	Albino mice/oral (2.5, 5, 7.5 g/kg bw); (500 mg/kg IP)	No sign of toxicity or mortality
Laxmi Vilas Ras	Subchronic (90 days) oral Dose-range-finding study (14 days repeated feeding)	Male and female rats/500 mg/kg bw/day; 31.2, 62.5, 125, 250, 500 mg/kg bw	No significant changes
Vasanta Kusumakar Ras	Chronic (180 days) oral	Male and female Sprague Dawley rats/0, 20, 100, 300 mg/kg/day	NOEL 20 mg/kg bw; no significant changes/findings. Incidental findings and not treatment related were liver round cell infiltration, acute lung inflammation, acute kidney inflammation and abscess
Vasant Malati Ras	Acute oral	Male and female Sprague Dawley rats	LD50>2,000 mg/kg body wt in rats and mice
	Repeated dose oral (90 days)		NOEL at 80 mg/kg body wt
Swarna Bhasma	Acute oral	Male and female Sprague Dawley rats	LD50>2,000 mg/kg body wt in rats and mice
	Repeated dose oral (90 days)		NOEL at 10 mg/kg body wt
Siddha Makardhawaj	Acute oral	Male and female Sprague Dawley rats	LD50>2,000 mg/kg body wt in rats and mice
	Repeated dose oral (90 days)		NOEL at 80 mg/kg body wt
Ras Raj Ras	Acute oral	Male and female Sprague Dawley rats	LD50>2,000 mg/kg body wt in rats and mice
	Repeated dose oral (90 days)		NOEL at 160 mg/kg body wt
Chandraprabha Vati	Acute oral	Male and female Sprague Dawley rats	LD50>2,000 mg/kg body wt in rats and mice
	Repeated dose oral (90 days)		NOEL at 1,000 mg/kg body wt

(continued)

Table 12.9 (continued)

Product name	Type of study	Species/dose	Observation
Medohar Vidangadi Lauh	Acute oral	Male and female Sprague Dawley rats	LD50>2,000 mg/kg body wt in rats and mice
	Repeated dose oral (90 days)		NOEL at 1,000 mg/kg body wt
Mahayograj Guggulu	Acute oral	Male and female rats	LD50 b/w 300 and 2,000 mg/kg body wt in rats and mice
	Repeated dose oral (30 days)		Tolerance of 10 times of therapeutic dose (875 mg/kg/day)
Mahalakshmivilas Ras	Acute oral	Female Wistar rats and female Swiss mice	LD50 b/w 300–2,000 mg/kg body wt in rats and mice
	Repeated dose oral (30 days)	Female Wistar rats	Tolerance of 10 times of therapeutic dose (175 mg/kg/day)

Table 12.10 Toxicity of heavy metals [22]

Heavy metal	Toxicity signs and symptoms
Cadmium	Inhalation of cadmium fumes or particles can be life threatening, and although acute pulmonary effects and deaths are uncommon, sporadic cases still occur. Cadmium exposure may cause kidney damage. The initial tubular damage may progress to more severe kidney damage. Animal experiments have suggested that cadmium may be a risk factor for cardiovascular disease, but studies of humans have not been able to confirm this
Mercury	Acute mercury exposure may give rise to lung damage. Chronic poisoning is characterized by neurological and psychological symptoms, such as tremor, changes in personality, restlessness, anxiety, sleep disturbance, and depression. The symptoms are reversible after cessation of exposure. Metallic mercury may cause kidney damage. Metallic mercury is also an allergen, which may cause contact eczema. Methyl mercury poisoning has latency of 1 month or longer after acute exposure, and the main symptoms relate to nervous system damage. High doses may lead to death, usually 2–4 weeks after onset of symptoms. However, the general population does not face significant health risks from methyl mercury exposure with the exception of certain groups with high fish consumption
Lead	The symptoms of acute lead poisoning are headache, irritability, abdominal pain, and various symptoms related to the nervous system. Lead encephalopathy is characterized by sleeplessness and restlessness. Children may be affected by behavioral disturbances and learning and concentration difficulties. In severe cases of lead encephalopathy, the affected person may suffer from acute psychosis, confusion, and reduced consciousness. People who have been exposed to lead for a long time may suffer from memory deterioration, prolonged reaction time, and reduced ability to understand. Recent research has shown that long-term low-level lead exposure in children may also lead to diminished intellectual capacity. Acute exposure to lead is known to cause proximal renal tubular damage

Table 12.10 (continued)

Heavy metal	Toxicity signs and symptoms
Arsenic	Inorganic arsenic is acutely toxic, and intake of large quantities leads to gastrointestinal symptoms, severe disturbances of the cardiovascular and central nervous systems, and eventually death. In survivors, bone marrow depression, hemolysis, hepatomegaly, melanosis, polyneuropathy, and encephalopathy may be observed. Ingestion of inorganic arsenic may induce peripheral vascular disease, which in its extreme form leads to gangrenous changes. Populations exposed to arsenic via drinking water show excess risk of mortality from lung, bladder, and kidney cancer, the risk increasing with increasing exposure. There is also an increased risk of skin cancer and other skin lesions, such as hyperkeratosis and pigmentation changes

- Improper manufacturing process
- Contaminants
- Irrational use of Ayurvedic medicine
- Quality of Ayurvedic medicine
- Abuse/adulteration

12.5.1 Known Side Effects

Almost every drug is known to have side effects. An ideal drug should be free from side effects and should not give rise to any other disease. It is hard to achieve targets; however, we should make efforts to keep the undesirable effects as minimum as possible. *Kashyapa* described the minimum side effects of the drugs as *Alpadosa*, *Mandaglaapana*, and *Naatiglapanam* [25].

12.5.2 Improper Manufacturing Process

Certain products contain metallic ingredients which have to be prepared strictly as per the classical Ayurvedic textbooks which include methods to render them nontoxic. Sometimes unscrupulous manufactures may use short cuts, and safety problems may arise. However, if Ayurvedic drugs are prepared properly, this problem does not arise.

To give an example, one of most commonly used Ayurvedic product is *Swarna Vasant Malti*, which contains gold, besides mercury, sulfur, etc. Sharma et al. (2001) published the results of studies with this formulation in 20 volunteers. Blood chemistry profile of these volunteers before and after 3 months of therapy with this drug has shown no statistically significant changes in blood urea, creatinine, bilirubin, SGOT, SGPT, CPK, LDH, and hemoglobin [26].

Government of India has issued guidelines on Good Manufacturing Practices for Ayurvedic medicines, which are already in vogue. This regulatory measure is generally quite effective to tackle with the problem related to improper procedure of manufacturing.

12.5.3 Contaminants

Saper et al. (2008) have reported that 14 out of 70 Ayurvedic products tested were containing heavy metals [3]. Though in some of the medicines mentioned in this chapter had heavy metals present as contaminants, in certain other cases, they are Rasaushadhis prepared as per the Ayurvedic textbooks. The following points need intense scientific debate on this issue:

(a) Various methods used to test heavy metals involve process of digestion, which converts bound metal into free metals, which are then tested using various techniques. Do these products undergo the same process inside the human body and actually release metals from bound to free form?
(b) Does mere presence of heavy metals in plant make it toxic or the presence of heavy metals in plants may be contributing to therapeutic activity as well?
(c) There is a need to conduct a comparative study of a plant material containing heavy metals from the soil vs. the plant material which does not contain heavy metals from the soil, but the similar quantity of heavy metals is added from outside. Both these samples should be subjected to compare their toxicity to answer the above two questions.
(d) In India, we do not have any systematic study basis which the limit of heavy metals can be decided. It is recommended therefore to first screen the plant materials available in India for heavy metal presence from various geographical locations and then decide the limits.

It is also possible that sometimes these heavy metals may come as contaminant during processing in improper vessels or from the water used. These are probable sources of contamination and the Good Manufacturing Practices should be able to take care of it.

12.5.4 Irrational Use of Ayurvedic Medicines

The following factors are very important with respect to rational consumption of Ayurvedic medicines:

(i) **The vehicle**, e.g., honey, water, etc.
(ii) **Relationship with food**
There are ten different timing of taking the medicine as per Ayurveda which are given below:
1. *Abhukta* (early morning empty stomach)
2. *Pragbhukta* (immediately before food)
3. *Adhobhukta* (immediately after food)
4. *Madhyabhukta* (mid way in the meal)
5. *Antarabhukta* (between morning meal and evening meal)
6. *Sabhukta* (with food or mixed in food)

7. *Samudagbhukta* (before and after intake of light meal)
8. *Muhur-muhur* (with food or without food, infrequent intervals)
9. *Sagras* (with every bite or with some of the bites)
10. *Grasantar* (between subsequent bites)

(iii) **Improper dose**

(iv) **Incompatible formulations**

Though Ayurvedic physicians always take care for any incompatible formulations, however, this possibility cannot be overruled in over-the-counter products.

(v) **Individualized medicines**

As per Ayurvedic concepts, one medicine is not suitable for all. To give an example, three patients of common cold will be prescribed different medicines by same physician depending upon their psychosomatic constitution (*prakriti*). The application of this principle of individualized medicines by the trained Ayurvedic physicians is extremely important factor and helps to take care of safety-related aspect of the products as well. With this approach, the patient receives only those products, which are suitable to him.

12.5.5 Quality of Ayurvedic Medicine

Maintaining quality of Ayurvedic medicine is of paramount importance. After almost 30 years of effort, Government of India has developed Ayurvedic Pharmacopoeia of India giving the quality standards of certain raw materials. Since Ayurvedic medicines cover a large number of ingredients and formulations, generation of quality specifications of all the ingredients and formulations is an uphill task and will take its own time. In the meantime, most of the Indian Ayurvedic industries use their own in-house standards to maintain the quality. However, presence of unscrupulous manufacturers cannot be ruled out. GMP guidelines for Ayurvedic medicines in India have recommended implementation of quality control measures as well.

12.5.6 Abuse/Adulteration

The Charaka Samhita has classified physicians into three categories: genuine physician, feigned physician, and pseudo physician. Due to socioeconomic reasons, quackery in the name of indigenous system practitioners is also one important factor in certain parts of India.

Gupta et al. (2000) reported the presence of corticosteroids in some of the Ayurvedic preparations prescribed by the so-called traditional medicine physicians in India. In this study, almost 42% Ayurvedic medicine samples were found to be adulterated with corticosteroids [27].

In another study, Gogtay et al. (2002) reported the presence of phenytoin and phenobarbital in the Ayurvedic tablets given to the patients of epilepsy. This is to be noted that these kinds of malpractices usually happen at the end of the physician rather than at the end of manufacturer [28].

Ayurvedic products sometimes are adulterated with similar-looking cheaper alternatives also. This practice, though not common, can easily be controlled by strict GMP norms implementation.

As mentioned earlier, Ayurveda uses holistic approach of treatment where food, medicine, and nontherapeutic measures like exercise and behavior go together. The use of medicines since thousands of years, without noticeable side effects, should become a criteria for classifying Ayurvedic medicines as generally recognized as safe. The data presented above also suggest that whenever properly processed and manufactured Rasaushadhis were subjected to safety studies, these medicines came out to be safe.

12.6 Issues in Safety Evaluation of Ayurvedic Drugs

In the last 3,000 years, many things have changed, but the basic rules of safety were embedded in the formulae itself as per the classical Ayurvedic texts on herbals, and we are following the same even today. But today, can we say that because of traditional use and because of the formulation being mentioned in the classical texts, toxicity study should not be done? We need to understand that the plants used centuries ago on which the data are available in classical texts might not be the same today because of changes in geographical and climatic conditions; even the inherent genetic makeup of the plants might have changed.

How are modern drugs evaluated for their safety? Can the same parameters be applied to Ayurvedic drugs also or they need a separate form of safety evaluation? These questions need to be answered for developing a safety evaluation procedure for these drugs.

Modern medicines are evaluated for their safety by doing animal studies first. The lethal dose that kills 50% of the animals (usually mice) is called LD_{50}. From this, the effective dose can be calculated using a hit-and-trial method. Toxicity studies are carried out in animals using short and medium tenures (long-term treatment is not recommended in small animals). If the drug is found to be useful, it is then evaluated clinically using human volunteers—normal healthy subjects first and then patients. The drug then enters the market for clinical use, but for the next 5 years, yearly safety evaluation called phase IV or postmarketing evaluation is mandatory. This is done to eliminate any risk that arises after long-term therapy and could not be evaluated at the time of clinical studies.

Can the same parameters be applied to Ayurvedic medicines also? The question is gradually gaining ground, and more and more Ayurvedic physicians are now of the view that they should be applied. The main reason for this is the scientific credibility that it will provide to the Ayurvedic system of medicine as safe and effective

drugs. Moreover, today the patient consciousness and legal issues involved make it safe for the practicing physician also to be sure that the medicine he/she is prescribing is a scientifically proven safe medicine.

Herbs are different from chemicals. Single plant has more than one active component or alkaloid or chemicals, which might have different biological activities when used separately. Different compounds have different actions. These chemicals may have synergistic actions. The individual chemicals may counteract the adverse drug reactions of each other. They may have effects on the bioavailability and help in absorption of the other active ingredients of the formulation. So even taking a single plant would mean taking number of chemical constituents, and hence, it becomes a challenge to identify them.

Ayurvedic products differ in their consistency too, e.g., the bulk density, specific gravity, physical form, etc., having direct impact on dose. The dose of Ayurvedic formulations also depends on the fact whether crude herb or herbal extract is used in the formulation. Like the pure chemicals may have a dose range from mcg to mg, the plant as a whole may have a dose range from mg to gm, and the large dose of herbals itself poses logistic challenges for conducting toxicity/safety studies.

Different parts of a single plant might have different actions and might have different toxicity profiles too. The uniformity of the samples used in the formulation is required for standardization of the final formulation. Hence, the selection of the parts of plants itself is a challenge for the safety of the formulation.

Secondary metabolite plays a major role in determining the action of the product. Berberine, an antimicrobial product, has poor absorption when given alone, while extract of Berberis aristata having berberine as major constituent resolves this issue, and bioavailability of berberine gets enhanced. Each extract might have different metabolites, and the absorption of the extract will also depend on it.

The absorption, distribution, metabolism, and excretion of herbs are not fully known. Hence, it remains a mystery how these herbs are acting inside the body. This lack of facts regarding pharmacokinetics itself poses a challenge to determine the safety of the formulation.

As per Schedule Y of Drugs and Cosmetics Act, if a product is used up to 2 weeks, a toxicity study of 4 weeks is required. So, the duration of toxicity studies is linked with durations of its use. According to the OECD guidelines, the NOAEL limitations are 2,000 mg per kg. Moreover, these guidelines are applicable for allopathic medicines. Therefore, these guidelines if used as such for herbal medicines might not actually be giving the validated safety outcomes.

Ayurvedic treatment follows few strict principles and ideologies, which cannot be extrapolated by modern method of toxicity study. Ayurvedic treatment regime typically includes diet, drug, vehicle, and behavioral modalities, but a part of treatment cannot be evaluated by any kind of toxicity. In Ayurveda, not all medicines are prescribed to be taken with water; some are prescribed with honey, and some are given with other vehicles like juices, etc. The herbal practitioner follows the ethics by giving the treatment as described and taught. So, while conducting the toxicity studies, should the medicine samples be given with honey or water, etc.? Therefore, in this complex scenario in herbals, it is advisable, if possible, that one sample

should be given with standard vehicle and another sample without standard vehicle, and only then some conclusion about the safety of regime can be drawn. But the concept cannot be established by current methods of toxicity studies. More importantly, Ayurvedic physicians are having their own unique way to prescribe the medicines. One may prescribe different products concomitantly along with some other things like aahar, vihar, and anupana to different patients with same disease depending upon their psychosomatic constituents. Modern toxicity methods would not be able to capture this variable.

Along with the oral preparation, topical formulations are also being described in Ayurveda. There are appropriate methods available to find out the rate of absorption, the depth of absorption, and methods to study whether the topical formulations go and accumulate somewhere inside the skin or do they accumulate in some other organs of the body. By and large, only few toxicity studies such as dermal irritation test and mucosal irritation test are conducted on these products. Therefore, there is a need for some elaborate discussions on the desirability of toxicity and safety studies on topical herbal products.

Allopathic medicines may have a short onset of action, while the onset of action of herbs is not definitely known, and it actually might be much longer say in days or weeks. Therefore, herbal formulation that does not produce effect within a short time, it may not actually produce any toxicity too in a model that has been chosen basis the concept of toxicity studies on Allopathic formulations. Therefore, there is a need to look at a different paradigm, and the guidelines for the toxicity studies in herbals need to be changed accordingly.

To cite the example of lead, if it takes 6 months to produce the clinical symptoms, and while conducting toxicity study on Ayurvedic formulations having lead as an ingredient, it may not actually show any toxicity if the studies are conducted just for 1 month or 3 months. So the question arises then how are we conducting the toxic study with it? Therefore, there is a need to have total new modern protocol for that, but this needs a lot of discussions, because other considerations will be required.

12.7 Way Forward for Safety Evaluation of Ayurvedic Drugs

According to the Drugs and Cosmetics Act and Rules of India, the clinical trials were not mandatory keeping in view the traditional use and the reference of Ayurvedic textbooks. In Ayurvedic literature, a list of toxic substances has been mentioned, which should be used only after detoxification processing. Therefore, the law has been amended in India recently, which says that if the formulations are known to have any of these herbs, which are known to be toxic, the toxicity studies need to be conducted.

Another guideline, which is yet to be published, mentions that a 28-day toxicity study needs to be conducted, and if the product is to be given for a longer period, a 90-day toxicity study is required. And also, if any of the products contains these

listed toxic ingredients, then it needs to be mentioned on the label itself as "To be taken under medical supervision only."

According to ICMR (Indian Council of Medical Research) guidelines, every product needs to undergo toxicity study if the product is reported to contain Schedule E (1) drugs, or it is to be given for more than 3 months [14]. The available guidelines for toxicity studies are WHO guidelines, ICH guidelines, OECD guidelines, Schedule Y guidelines, etc. The basic methodologies in almost all these guidelines are more or less same, which revolve around the principles of safety of allopathic medicines.

Nowadays, C. elegans model is also used as a tool of predictive toxicity. This may be useful for herbal drugs as well. Therefore, instead of doing the studies in rat, mice, followed by monkey, which is usually done for unknown medicines, these in vitro models may give fast and expedited results at least from safety screening purpose, and then the herb which is passing in the screen can be subjected to animal models to evaluate its safety. Ayurvedic medicines are not unknown substances, as these have been used since hundreds of years. So, if we still have to conduct toxicity studies in rat, mice, and monkey, probably, we need to find a way and need to debate and discuss on this issue.

As per the recent amendment notification by Government of India dated August 10, 2010 for the manufacturing license requirement, the special class of products, e.g., herbal extracts other than aqueous extracts, need to undergo toxicity studies, or a total safety profile needs to be established [5].

So there is a need to find out alternative means, alternative methods of toxicity safety evaluations other than documented use of traditional practice. One can also use pharmacovigilance as a tool of clinical safety basis documentation of actual clinical practice.

Ayurvedic formulations contain food ingredients, as well as therapeutic food ingredients. Therefore, it is presumed that all other ingredients except published in Schedule E (1) do fall under the list of GRAS, i.e., generally recognized as safe though it has not been notified separately.

A quick review of approx. 100 classical Ayurvedic products reveals that there are several ingredients which are common in more than ten formulations. Such ingredients can also be declared as generally recognized as safe (GRAS). The representative list of few such ingredients is given below. Thorough review of formulations mentioned in the Ayurvedic textbooks shall lead to more than 250 such ingredients (Table 12.11).

Therefore, there is a need to arrive at a criterion to declare a list of generally recognized as safe (GRAS) ingredients as well as products.

Sanjeev Sarmukaddam et al. (2010) proposed "equivalent trials" using modern medicine benchmark as a comparator and a "safety/tolerability index" on this perspective. They proposed that the trials on Ayurvedic medicines can be designed with the hypothesis that Ayurveda interventions are equivalent to conventional medicine for efficacy and superior in terms of safety. The safety index proposed by Sanjeev Sarmukaddam et al. was in light of the hypothesis that equivalence generally pertains to efficacy, but it would be desirable to match the safety and tolerability of the

Table 12.11 Frequency of occurrence of few medicinal plants in classical Ayurvedic medicines

Name of the plant	No. of products
Zingiber officinale	65
Tinospora cordifolia	59
Hedychium spicatum	50
Adhatoda zeylanica	39
Commiphora wightii	32
Mesua ferrea	31
Solanum xanthocarpum	27
Curcuma longa	25
Withania somnifera	25
Nardostachys jatamansi	23
Picrorhiza kurroa	20
Nymphaea stellata	19
Solanum indicum	17
Oroxylum indicum	17
Stereospermum suaveolens	14
Gymnema sylvestre	12
Premna integrifolia	11
Vitex negundo	10

investigational drug with that of comparator. They proposed safety index was to capture the burden of adverse events at any point in a trial subject. This type of safety index will allow making comparison between two arms for adverse events more methodological and robust. It might be difficult to establish the validity criteria for such an index as there are no gold standards to compare with, but it is not impossible. As safety is of paramount importance and an inherent strength of Ayurveda, such an index may be explored in real-life drug evaluation system [29].

12.8 Conclusions

The interest of consumers has been increasing in Ayurvedic/herbal products over the decades. One of the reasons is increasing awareness of the consumers about the side effects of the traditional medicines and chemical ingredients. Consumers perceive Ayurvedic/herbal options safer, though may not be validated scientifically due to their traditional use among the large masses, especially in traditional-medicine-rich countries like India and China. However, this increasing interest of consumers has also invited scientific scrutiny of these products, not so much for efficacy but certainly for safety. Probably, this was the reason that Saper et al. (2004, 2008) tested some of the Ayurvedic products available in US market for the presence of heavy metals and published in the *Journal of American Medical Sciences* [3, 30]. Being negative, these articles were picked up by the media with a view to shatter the miss of safety around these products. One of the points, however, missed by the authors of these articles was the Ayurvedic process of detoxification of some of the

poisonous substances including heavy metals used in Ayurvedic medicines. The biggest drawback of this negative publicity was the reaction of the Western Government in banning the use of some Ayurvedic products. However, it needs to be addressed that "does mere presence of certain heavy metals in these products which are consumed at very very low dose makes them toxic" Some of the Indian companies have conducted toxicity studies of herbometallic products following OECD guidelines, and their data are contrary to the views put forward by Saper et al. to scrutinizing the safety of these products. The issue of safety of traditional medicines be it Ayurvedic, herbal, or traditional Chinese medicine products needs to be viewed with caution, and centuries of their safe use cannot be discarded. As far as certain reports of toxicity of lead due to Ayurvedic medicines are concerned, it appears that out of millions of consumers, only one to two such cases have been reported. Therefore, unless blood levels of controlled population are compared with the blood levels of patients consuming these products, reaching any conclusion shall be premature and should not be supported by the scientists.

One area of concern of proving safety of Ayurvedic drugs by traditional use is lack of system of pharmacovigilance. Government of India has initiated an action in this regard in 2009 by documenting the actual use of Ayurvedic medicines. The data have yet to come, and whenever they come, they will provide the directions of the level of safety of such products. Till that time, there is a need of developing optimum scientifically validated methods of safety evaluation of such products being used in the holistic manner as they were in actual clinical practices along with their do's and don'ts.

References

1. Malik V (2010) Drugs & Cosmetics Act, 1940 and Rules 1945. In: Law relating to Drugs & Cosmetics. Eastern Book Company, Lucknow
2. WHO Research guidelines for evaluating the safety and efficacy of herbal medicines (1993) World Health Organization, Geneva
3. Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, Phillips RS (2004) Heavy metal content of Ayurvedic herbal medicine products. JAMA 292:2868–2873
4. GSR 663(E) (2010) Gazette notification of Government of India
5. WHO report of the 44th World Health Assembly (1991) World Health Organization, Geneva
6. WHO report of 31st World Health Assembly (1978) World Health Organization, Geneva
7. WHO report of the 40th World Health Assembly (1987) World Health Organization, Geneva
8. WHO report of the 42nd World Health Assembly (1989) World Health Organization, Geneva
9. The International Conference on Primary Health Care (1978) Alma-Ata, USSR
10. The Ayurvedic Pharmacopoeia of India. Part I; Volumes I–VII. Government of India, Ministry of Health and Family Welfare, Department of Ayurveda Yoga & Naturopathy Unani Sidha and Homeopathy (AYUSH), New Delhi
11. The Ayurvedic Pharmacopoeia of India (formulations). Part-II; Volumes I–III. Government of India, Ministry of Health and Family Welfare, Department of Ayurveda Yoga & Naturopathy Unani Sidha and Homeopathy (AYUSH), New Delhi
12. Indian Systems of Medicine and Homeopathy in India (1999) Planning and evaluation cell, Department of ISM & H, Ministry of Health & Family Welfare, Government of India, New Delhi
13. Bhaishajaya Ratnavali (1961) Ed. Rajeshwar Dutt Shastri. Chowkhamba Sanskrit Sansthan, Varanasi

14. Ethical Guidelines for Biomedical Research on Human Subjects (2006) Indian Council of Medical Research, New Delhi
15. OECD (2001) Guidelines for testing of chemicals: Test No. 425. Acute oral toxicity
16. OECD (2009) Guidelines for the testing of chemicals, section 4: health effects, Test No. 412: Subacute inhalation toxicity: 28-day study
17. OECD (2009) Guidelines for the testing of chemicals, section 4: health effects, Test No. 413: Subchronic inhalation toxicity: 90-day study
18. OECD (2008) OECD guideline for the testing of chemicals test guideline 452: Chronic toxicity studies
19. OECD (2008) OECD guideline for the testing of chemicals test guideline 451: Carcinogenicity studies
20. OECD (1983) Test guideline 415. One-generation reproduction toxicity study. In: OECD guidelines for the testing of chemicals. Organisation for Economic Cooperation and Development, Paris
21. OECD (2001) Test guideline 416. Two-generation reproduction toxicity study. In: OECD guidelines for the testing of chemicals. Organisation for Economic Cooperation and Development, Paris
22. Järup L (2003) Hazards of heavy metal contamination. Br Med Bull 68:167–182
23. WHO Guidelines for assessing quality of herbal medicines with reference to contaminants and residues (2007) World Health Organization, Geneva
24. Data on Dabur R&D Files, Dabur India limited, Sahibabad, Ghaziabad, India
25. Savarikar SS, Safety of Ayurvedic Drugs (2011) Ayurvedic perspective in relation to current drug safety design. International conference on recent advances in safety and efficacy of Ayurvedic formulation: 33–44
26. Sharma DC, Jha J, Sharma P (2001) Evaluation of safety and efficacy of a gold containing Ayurvedic drug. Indian J Exp Biol 39:892–896
27. Gupta SK, Kaleekal T, Joshi S (2000) Misuse of corticosteroids in some of the drugs dispenses as preparations from alternative systems of medicine in India. Pharmacoepidemiol Drug Saf 9(7):599–602
28. Gogtay NJ, Bhatt HA, Dalvi SS, Kshirsagar NA (2002) The use and safety of non-allopathic Indian medicines. Drug Saf 25(14):1005–1019
29. Sarmukaddam S, Chopra A, Tillu G (2010) Efficacy and safety of Ayurvedic medicines: recommending equivalence trial design and proposing safety index. Int J Ayurveda Res 1(3):175–180
30. Saper RB, Phillips RS, Sehgal A, Khouri N, Davis RB, Paquin J, Thuppil V, Kales SN (2008) Lead, Mercury, and Arsenic in US- and Indian-Manufactured Ayurvedic medicines sold via the internet. JAMA 300(8):915–923