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### Herbal drug toxicity and safety evaluation of traditional medicines

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#### Abstract

Medicinal herbs as potential source of therapeutics aids has attained a significant role in Health system all over the world for both humans and animals not only in the diseased condition but also as potential material for maintaining proper health. A major factor impeding the development of the medicinal plant based industries in developing countries has been the lack of information on the social and economic benefits that could be derived from the industrial utilization of medicinal plants. Except for the use of these plants for local health care needs, not much information has been available on their market potential and trading possibilities. The present review mainly focuses on some medicinal plants with their biological sources, chemical constituents, usual doses and adverse effects. Traditional medicines are generally considered safe due to long history of being in practice especially under the specified conditions for use reported in ancient literature. However, adverse effects in some individuals due long-term use of certain herbal drugs have been reported recently. The adverse effects range from liver failure (comfrey root) to abnormal heart rhythms (ephedra) to death (pennyroyal). World Health Organization advocates use of herbs that have long history of use only if no adverse events have been reported. In case of herbals where some adverse effects are reported, toxicity data in its dosage form is required using all toxicity bench –marks for conventional pharmaceuticals. Isolated active principles from herbals are to be treated like modern drug and subjected to rigorous testing as required by the regulatory authority of the country. Another concern related to safety of herbals is presence of contaminants such as heavy metals, persistent pesticides and aflatoxins.

**Keywords:** Herbal drugs, traditional medicines, herbal drug toxicity, authentication.

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#### Introduction

Herbs have created interest among the people by its clinically proven effects like immunomodulation, adaptogenic and anti mutagenic etc. the expanded use of herbal medicines has led to concerns relating to its safety, quality and effectiveness. In practice however, three

groups of herbs can be identified from a safety point of view. At first, a handful of herbs that contain near pharmaceutical concentration of poisonous constituents, which should not be taken internally. Example: Belladonna, Arnica and Digitalis. Second the herbs are with powerful action often causing nausea and vomiting. Example: Lobelia and Euonymus. At last there is an idiosyncratic grouping of herbs which have been alleged with some scientific support, they exhibit specific kinds of toxicity. Example: pyrrolizidine alkaloids containing comfrey, male fern, mistletoe and yohimbe. Toxicants can interrupt metabolism of carbohydrate, lipids, and proteins, alter synthesis release and storage of hormones. Some herbal alkaloids; Vincristine, Rutenecarpine, Evodamine, dehydroevodiamine, class of AQ, triterpenoids and flavonoids serve as substrates, inducers or inhibitors of CYP'S. Adverse drug reaction reports are a critical source of herbal drug safety information. *Artemisia absinthium* L contains an active narcotic derivative, which causes central nervous system disorders and generalized mental deterioration. *Heliotropium europaeum*, containing pyrrolidine alkaloids, potent hepatotoxins. *Valerian officinalis*, containing valepotriates, which acts as a sedative and muscle relaxant in laboratory animals. In the WHO database, there are presently 11, 716 suspected herbal plants case reports. The commonly reported reactions are; pruritus, urticaria, rash, erythematous rash, nausea, vomiting, diarrhoea, fever, abdominal pain, dyspnoea. The risk that the alkaloid Berberine in *chinese coptis* species elicits jaundice seems to be most substantial in infants who are deficient in glucose 6 phosphate dehydrogenase. The root of *Salvia miltiorrhiza* which has been used traditionally in China for the treatment of coronary disease can enhance the anticoagulant activity of warfarin, when both drugs are taken together. The World Health Organization (WHO) released guidelines for good agricultural and collection practices for medicinal plants, an industry estimated worth more than US \$60 billion. One of the major causes of adverse events is directly linked to the poor quality of herbal medicines, including raw medicinal plant materials, and to the wrong identification of plant species. Cultivating, collecting, and classifying plants correctly are therefore of the utmost importance for the quality and safety of products. Other species or plant parts through misidentification, accidental contamination or intentional adulteration, all of which may have unsafe consequences, may contaminate medicinal plants collected in the wild (Medicinal plants, 2004). Acute, subacute and chronic toxicity tests are required depending on the intended use of potential drug substance. Drugs intended for short-term use undergo acute toxicity (in mice and rats both sexes) and subacute toxicities studies in 2 species (both sexes) taking therapeutic dose [TD], 5 TD and 10 TD. The route of exposure is designed to stimulate anticipated route of administration. All the toxicity indicators like body weight, mortality, and complete hematological parameters at different time intervals are monitored and compared with control groups. Autopsy and hematological examination of all the vital organs is also required. Drugs for chronic ailments like diabetes, hypertension or age-related degeneration, need to undergo 2-year chronic administration to determine potential of a substance to induce chronic toxicity or carcinogenicity as suggested by NIEHS, USA under the National Toxicology Program. The safety evaluation of a potential drug also requires specific tests for target organ toxicity such as reproductive toxicity, neurotoxicity, nephrotoxicity or non-target organ adverse effects like genotoxicity or immunotoxicity. Development of harmonized guideline for the safety of herbal drugs will be a step forward in safe drug development from plant sources.

### ***Classifying therapies herbal drugs***

Complementary and alternative therapies differ in that the former are treatments that can work alongside and in conjunction with orthodox medical treatments, while the latter are those given

in place of orthodox medicine and whose effects may be negated by orthodox medicines (BMA, 1993). Classifying any treatment as one rather than the other, however, is open to debate. Thus, for example, the BMA (1993) classifies massage, acupuncture and aromatherapy as complementary therapies, and herbals as alternative therapies, while Dunning *et al* classify them all as complementary. Studies have shown that patients both consult their GP and use non-conventional therapies for the same illness episode. Therefore in the following discussion the term 'complementary' will be used throughout. There are a number of concerns in relation to complementary therapies. These include the problem that patients may see unqualified practitioners because, to date, only osteopathy has gained legislative power to sanction individuals guilty of malpractice. While patients are utilizing therapies other than orthodox ones, there is also a fear that they risk missed or delayed diagnosis, may waste money on ineffective treatments and may refuse or cease effective orthodox treatments. Furthermore, it is argued, the mechanisms of some therapies are so implausible that they cannot possibly be effective. These objections, however, are made from within an orthodox medical paradigm and are therefore open to question. Perhaps of greater concern is the belief that complementary therapies are universally safe. This is fallacious - all treatments have the potential to do harm as well as good; indeed, Vickers and Zollman (1999) suggest that herbal medicines present the greatest risk of adverse effects of all the complementary therapies. They will thus form the core of the following discussion, and Ernst's classification (1996b) will be used to structure this account.

### ***Use of herbal remedies***

The use of herbal remedies is common, with 35-45% of Americans using herbal products as medications (Cohen, 1998; Lee and Horne, 2001). In the UK spending on herbal products is now over £40 million a year (Vickers and Zollman, 1999). When 979 patients about to undergo surgery were asked about their use of herbal remedies and nutraceuticals (supplements not derived from plants), 170 (17.4%) reported taking such products (Larkin, 1999). The most frequently used herbs were ginkgo (*Ginkgo biloba*, 32.4%), ginseng (*Panax* and *Eleutherococcus* species, 26.5%), and garlic (*Allium sativum*, 26.5%).

### ***Toxicity***

Herbal remedies are plant-based, as in fact are many orthodox drugs - some 25% of present pharmaceutical preparations contain at least one active ingredient extracted from plant sources (Farnsworth, 1981). Moreover, thousands of our present drugs were originally derived from plants, including digitalis (foxglove), aspirin (willow and meadowsweet) and paclitaxel (Taxol). However, in the case of orthodox drugs the active ingredient is isolated from the plant, chemically standardized, subjected to critical clinical assessment and then often replaced with a synthetic analogue. In contrast, the herbalist uses mixtures of diverse herbal ingredients of varying potency. Potency depends on the part of the plant used - for example root, stem, leaves or fruits - the time of the year it is picked, and the actual species of plant used: for example, ginseng may refer to many *Panax* and *Eleutherococcus* species. Because potency refers to the amount of drug required evoking a response, if the potency of the formulation of the herbal remedy is unknown it is difficult to know what dose to prescribe to get the desired effect without causing problems of toxicity. An example of this problem is provided by mistletoe, the popular name for 1300 species of evergreen, including the European variety *Viscum album*. Mistletoe is used as an antispasmodic, diuretic and hypotensive, and some claim it has anti-cancer properties. Mistletoe extract contains at least three types of potentially toxic compounds: alkaloids - some of

which may be cytotoxic - viscotoxins and lectins, which have haemagglutin and mitogenic actions.

### ***Adverse reactions***

Modern drugs generally undergo extensive formal testing for therapeutic and adverse effects before being licensed. In this way drug regulatory bodies ensure that the risk of adverse effects is small and within acceptable limits. No such controls exist for the majority of herbal remedies, however. They do not come under the aegis of the regulatory bodies and are not required to undergo systematic testing. Consequently our knowledge of their potential adverse effects and interactions is limited. In the UK and the USA herbal remedies are considered as dietary supplements rather than as drugs. Consequently companies selling them cannot make any claims about their therapeutic effects and they give no advice about their adverse effects or contra-indications gives examples of some known medically serious adverse effects of herbal preparations.

### ***Allergic reactions***

Like orthodox drugs, herbal preparations can result in hypersensitivity reactions, which can range from dermatitis through to anaphylactic shock. For example, tea tree oil - widely used as a topical disinfectant - or chamomile can cause allergic reactions **Mutagenic reactions** Anthranoid laxatives such as aloe, cascara, rhubarb and Senna have Genotoxic potential and have been associated with colorectal cancer in epidemiological studies in humans. Chaparral may also be mutagenic. One case has been described where a patient developed cystic renal cell carcinoma after regularly drinking Chaparral tea.

### ***Drug interactions***

Most consumers believe herbal medicines are harmless, so they have no qualms with taking them in along with prescribed conventional medicines. In addition, many immigrants to the UK have their own traditional medicines, which they may combine with orthodox medical care (D'Arcy, 1993). Both these practices can lead to harmful herb-drug interactions. This problem is exacerbated because at least 30% of patients do not tell their doctor that they are using them (Eisenberg et al, 1993; Yoon and Horne, 2001). This is either because patients do not consider herbal remedies as 'drugs', and so when asked for a history of their medications do not mention them, or because they are reluctant to mention them for fear of a negative response from the practitioner. It is therefore vital that clinicians include questions about herbal remedies in their routine drug histories, and be informed rather than judgmental about their use.

### ***Contamination***

Herbal medicines are not required to undergo the same quality checks as conventional drugs and so they may be contaminated or adulterated. For example, many Asian and Indian herbal remedies have been found to contain heavy metals such as lead, arsenic and mercury. One of the worst examples of contamination causing adverse effects occurred in the USA in 1989, where there was an outbreak of eosinophilia-myalgia syndrome associated with the use of L-tryptophan, an over-the-counter dietary supplement used for weight loss (Anon, 1999). More than 1500 cases were reported, including 38 deaths. More than 95% of the cases were traced to an individual Japanese supplier. Researchers found some trace-level impurities, suggesting that a contaminated batch of L-tryptophan contributed to the outbreak.

***False authentication***

False authentication can occur inadvertently or deliberately. An example of this is Ginseng preparations. Only Asian ginseng contains the active compounds ginsenosides, but commercial preparations often do not make this clear. More seriously, ingredients may be included which are not identified, including potent orthodox drugs such as digitalis, steroids, active oestrogens, phenacetin and glibenclamide. Finally, one ingredient can be replaced with another. This led to an outbreak of fibrosing interstitial nephritis in Germany and France when 'Guang fangi' containing nephrotoxic aristolochic acids was substituted for the Chinese drug 'Fangji'. The use of herbal medications in the United States over the past decade has increased dramatically and there are over 29,000 products on the market. In the United States, as many as 65 percent of the population report the use of complementary and alternative medical (CAM) therapies. Women are more likely to use complementary medicine, and non-Hispanic whites are more likely than other racial groups. Use is highest in persons between the ages of 35 and 55 years. In 1997, the out-of-pocket cost for all complementary and alternative therapies was estimated to be \$27 billion while \$19 billion was spent for dietary supplements. Use of herbal medications can be traced back as far as ancient China, India, and Sumeria, and formulations have been expanded upon over the centuries. Many patients consider "natural" herbal remedies to be completely free of unwanted side effects. This is concerning since many herbal products have biological activity that can lead to severe toxicity. Fewer than 40 percent of patients disclose to their physician that they are using these products.

***Herbal aids for cancer treatment***

Cancer treatments are a paradox, on one hand delivering powerful toxicity to a tumor, but on the other spreading toxicity to the rest of the body. The side effects of such treatments may cause death even before the cancer does. Biological response modifiers (BRMs) are compounds that have a unique effect on physiology and can reduce the side effects of cancer treatments, while at the same time increasing their effectiveness. A BRM repairs damage to the body rather than targeting a pathogenic agent such as cancer. It typically acts by stimulating the immune system to restore optimal function. Many diseases and infections as well as AIDS result from immune surveillance failure. Because chemotherapy compromises the immune system, people receiving cancer treatments run an especially high risk of contracting and dying of infections. Cytokines, hormones naturally produced in the body, promote immunity and are often used clinically as BRMs—to treat disease, fight viral infections and augment chemotherapy. Three pharmaceutical cytokines currently in use include colony-stimulating factors that reduce the chance of infection and thus the need for antibiotics by stimulating bone marrow to produce more white blood cells; interferons that stimulate macrophages to ingest foreign particles and help the body produce antiviral chemicals; and interleukins that stimulate growth and activation of white blood cells. The therapeutic use of these cytokines, called immunotherapy, as a cancer treatment both with and without standard anti-cancer drugs is marginally successful. Side effects such as depression, nausea and chest pain, however, can limit the effectiveness of some pharmaceutical cytokines. Many herbs have long been known to affect the immune system, but only recently have scientists considered them as possible BRMs and adjunct cancer therapies. Such herbs often prompt the body's cells to secrete cytokines, which then enhance the immune response. The most promising of these herbs include black cumin, mistletoe, ginseng, astragalus, green tea, Echinacea and garlic.

### ***Black Cumin***

Black cumin (*Nigella sativa*) is related to a common garden flower that goes by several names including cinnamon flower, nutmeg flower and love-in-a-mist. In the Mediterranean and Middle East where nigella seeds are traditionally used, it is also referred to as black seed and is used for a variety of ailments including upper respiratory conditions, headaches, cancer, stomachaches and jaundice. Nigella seeds are traditionally eaten alone or ground with honey. Nigella is considered a BRM because studies show extracts from the seeds are toxic to cancer cells and, in mice, prevents blood cell toxicity caused by the anti-cancer drug cisplatin. The active components of nigella seeds are the volatile oils thymoquinoline and dithymoquinone, both of which inhibit tumor cells in laboratory experiments—even tumor cells resistant to anti-cancer drugs.<sup>2</sup> A recent cell study conducted at the International Immuno-Biology Research Laboratory in South Carolina showed that when incubated with nigella extract, cancer cells were unable to produce fibroblast growth factor and the protein collagenase, both necessary for blood-vessel growth into the tumor. Without a blood supply, a tumor cannot grow. Nigella also stimulates the immune system, as shown in an experiment conducted with human lymphocytic white blood cells. Cells treated with nigella-seed proteins produced greater amounts of cytokines, specifically interleukin-1-beta and tumor necrosis factor alpha. How and if this is important to treating cancer is not yet established. Another recent experiment indicates that thymoquinone may also prevent some toxic side effects of cancer treatments. Scientists from King Saud University in Saudi Arabia found that mice pretreated with thymoquinone were protected from carbon tetrachloride-induced liver toxicity. Carbon tetrachloride is a toxin that in small amounts can kill by causing the liver and kidney to atrophy. Liver toxicity was assessed by measuring the release of liver enzymes in the blood. Thymoquinone also demonstrated antioxidant activity, which may be how it protects the liver. According to U.S.D.A. Phytochemical and Ethnobotanical Databases compiled by James Duke, Ph.D., nigella seed also contains limonene. Found in high amounts in lavender, limonene is being investigated for use as a treatment for some types of cancer.

### ***Mistletoe***

European mistletoe (*Viscum album*) is an evergreen parasite that depends on a host, often an old apple tree. It has long been considered a sacred plant, partially because of its medicinal properties. Historically, mistletoe was used to treat nervous disorders, but some European clinics are now using it to treat cancer. Mistletoe may prove helpful for treating cancer because it stimulates the immune system, stabilizes DNA, inhibits blood vessel growth and is toxic to cancer cells. Many of these effects were documented in cell and animal studies in the 1970s and 1980s. Although small and poorly designed, some human studies show that mistletoe treatment also improves the quality of life and survival rates for people with cancer. The most common preparation of mistletoe is an injectable, fermented whole-plant extract called Iscador. Its active components include proteins such as ML-I and viscotoxins. Recent studies show that mistletoe's viscotoxins affect the immune system. Arndt Bussing from Krebsforschung Herdecke, University Witten/Herdecke in Germany showed that crude extracts of viscotoxin stimulated human granulocyte cells (a type of white blood cell) to destroy pathogenic cells.<sup>11</sup> This is especially important because cancer treatment stunts granulocyte activity, which in turn increases infection risk. Treatment with mistletoe must be administered only under the supervision of a health care provider.

### **Ginseng**

There are two types of ginseng, *Panax ginseng*, also known as Oriental, Asiatic, Chinese, Korean or Japanese ginseng, and *P. quinquefolius*, known as American ginseng. Siberian ginseng (*Eleutherococcus senticosus*) is a different plant genus entirely but shares many properties with true ginseng. All of the ginsengs are adaptogenic herbs, meaning they produce nonspecific resistance for the body. Although ginseng's energy-producing properties can benefit someone with cancer, scientific evidence indicates it has more specific uses.

A recent cell study by Tadahir Takeda from Kanazawa University in Ishikawa, Japan, showed that polysaccharides from panax boost production of the immune-stimulating cytokine interleukin-8. Both leukemic human monocytes (types of blood cells) and normal human monocytes were incubated with panax extracts for 24 hours. Researchers then measured the amount of IL-8 in the cells. The ginseng significantly increased the amount of IL-8 secreted from these cells compared to cells not incubated with ginseng. A purified polysaccharide of panax, called ginsan, has several immunomodulating effects on mouse cells that are similar to the effects of the naturally occurring cytokine interleukin-2. Ginsan activates T and B lymphocytes and macrophages and converts spleen cells into activated killer cells that destroy tumor cells. When ginsan was injected into mice with induced lung cancer, it significantly reduced the number of tumors—by 44 percent—compared with mice that did not receive ginsan. When mice were given ginsan in their drinking water, the tumors were also decreased, but only by 15 percent. Ginsan had no detectable toxicity. Customers should discuss using ginseng with their physician because the herb can decrease blood platelet clotting. When taken in conjunction with chemotherapy, bleeding problems may occur.

### **Astragalus**

In Chinese medicine, astragalus (*Astragalus membranaceus*) is considered an adaptogenic herb. A 1988 experiment indicated astragalus extract increased the ability of interleukin-2 to kill cultured tumor cells. A more recent study at the Hiroshima University School of Medicine in Japan showed that a water-based astragalus extract, when incubated with mouse spleen cells, had several immunopotentiating effects. It increased B cell growth, T cell activity, and interleukin-6, tumor necrosis factor and antibody production. Astragalus also protects the body against drug toxicity. In one animal study, a combination of astragalus and wintergreen (*Pyrola rotundifolia*) prevented damage to the kidney and to the cochlear nerves and hair cells of the inner ear caused by the antibiotic gentamicin, commonly prescribed for pneumonia and sepsis. Astragalus is included in a Chinese herbal medicine referred to as 10 significant tonic decoction or SQT (Shi-Quan-Da-Bu-Tang). It is a 10-herb combination recommended in conjunction with cancer therapy to protect the body from drug toxicity and increase immunity. According to Chinese research, astragalus prevents the adverse effects of the anti-cancer drugs mitomycin C and cisplatin as well as stimulates the immune system. The herb is more commonly used in Asia as an adjuvant to cancer treatments.

### **Green Tea**

Although it is better known as a cancer preventive, preliminary studies suggest green tea (*Camellia sinensis*) also may be a useful treatment for cancer or an adjuvant to chemotherapy.<sup>19</sup> Green tea contains catechins, antioxidantlike polyphenolic compounds, that can inhibit the spread of cancer. A recent animal study by Sadao Hirota from the University of

Shizuoka in Japan showed that, when taken with chemotherapy, steeped green tea also enhanced the therapeutic effects of the drugs. Mice with cancer were treated with the widely used anti-tumor drug doxorubicin and given green tea orally. After 18 days, tumor size in the green tea plus doxorubicin-group decreased 37 percent compared with 25 percent in the mice given only doxorubicin. Researchers found that the concentration of doxorubicin increased in the tumors of animals receiving the green tea but not in normal tissue, which may explain the drug's increased effectiveness.

### ***Echinacea***

Many laboratory studies document echinacea's (*Echinacea* spp.) traditional use as an immune stimulator. The active polysaccharide fraction of echinacea increases phagocytosis, or ingestion of foreign particles, and stimulates production of the cytokines interleukin-1, interleukin-6 and tumor necrosis factor. One human study by Wolfram Grimm of Philipps University in Marburg, Germany, showed that echinacea had some ability to prevent upper respiratory tract infections and shorten their duration. His double-blind study of 109 people showed that taking 4 mL of *E. purpurea* extract twice daily for eight weeks decreased the risk of infection by 22 percent and shortened the duration of colds by two days.<sup>23</sup> Although the improvement is modest, it may have important implications to someone on chemotherapy. Some herbalists, however, warn that using echinacea for long periods can decrease immunity. Herbalist Christopher Hobbs suggests using echinacea for only a week or 10 days at a time. Another study using cells from healthy volunteers, chronic fatigue syndrome patients and AIDS patients, showed that combined extracts of panax and echinacea enhanced natural killer cell function, an important component of cellular immunity. This was true for all the cells. Although echinacea is usually recommended for upper respiratory tract infections and there is little data on its use as an adjuvant to chemotherapy, it is reasonable to expect its immune-enhancing effects to decrease the risk of infection in people receiving cancer treatments.

### ***Garlic***

Garlic (*Allium sativum*) may be an effective adjuvant treatment for cancer because of its effects on the liver, tumor cells and the immune system. Its ability to reduce the side effects of cancer treatment was demonstrated in an animal study in which garlic given orally to rats significantly reduced liver damage caused by the cancer-causing aflatoxins found in molds. Researchers speculate that because garlic enhances the activity of glutathione S-transferase, a liver enzyme that helps detoxify and remove toxins from the body, it may detoxify aflatoxins before they cause damage. A more recent study by Dale Riggs at West Virginia University in Morgantown indicated aged garlic extracts are effective against bladder cancer. Garlic extracts were injected four times during a one-week period into mice with bladder cancer. The mice showed significant reduction in tumor growth compared with mice that did not receive injections. Garlic extract was also effective when given orally. High doses of garlic (greater than 12.5 mL per injection) caused toxicity, but effective doses (6.3 mL) did not cause side effects.<sup>27</sup> When garlic extracts were given orally in the animals' drinking water (29 mL/day), tumors decreased significantly with no side effects. In another experiment, a water-soluble extract of fresh garlic given orally to mice for five days prior to gamma-radiation treatment protected against the chromosomal damage caused by treatment. With luck, researchers will continue to find inexpensive and nontoxic BRMs. In addition to their usefulness as adjuvant to chemotherapy, such herbs may also help treat AIDS, chronic fatigue syndrome and other immune-depressing diseases. Although inferring

meaningful effects for humans from laboratory and animal studies is not easy, in most cases these herbs have few side effects when compared to pharmaceuticals and are generally safe to use. Advise customers to talk to their doctors before pursuing supplemental cancer treatments so that potential side effects, as well as therapeutic effects, can be monitored. Many of these treatments require injections that should be administered only by a qualified medical professional.

### ***Efficacy and safety of herbal remedies***

Dietary supplements, including vitamins, minerals, and herbal remedies, are not regulated by either state or federal agencies. They have been classified by the FDA as dietary supplements these products may be in the form of tablets, capsules, soft gels, gel caps, liquids, teas, or powders. Their use is often justified based upon experience from trial and error, not rigorous scientific scrutiny. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994; the FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market. As a general rule, supplement manufacturers do not need to register with the FDA, prove product safety, or get FDA approval before producing or selling supplements. The FDA monitors safety (eg, voluntary dietary supplement adverse event reporting) and product information, such as labeling and claims. The Federal Trade Commission regulates advertising of dietary supplements. Manufacturers must make sure that the product label is truthful and not misleading. They must list all ingredients contained in the product on the label and limit the claims (health claims, nutrient content claims, and structure/function claims) that can be made. Structure/function claims are those which claim that the nutrient is intended to affect normal structure or function in humans (ie, "calcium builds strong bones"). If a manufacturer makes a structure/function claim on the supplement label, DSHEA requires a disclaimer commenting: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease." The widespread use of mixed remedies and the lack of randomized, placebo-controlled clinical trials make any review of the safety and efficacy of herbal remedies troublesome. The popular use of herbal products in the general community raises concerns for potential herb–drug interactions. The risk of herb–drug interactions is increased if the herbal medicines are used concurrently with drugs which have a narrow therapeutic range, or are used in certain groups of patients, such as the elderly or those with impaired liver and renal functions. This short paper reviews some important concepts in herb–drug interactions and cases involving Chinese herbal medicines.

### ***Potential herb–drug interactions.***

Traditional herbal medicines have been widely used for thousands of years in many countries. Metals have been used in disease treatment since time immemorial. Gold in medicine was mentioned by Roman physician Pliny and Greek philosopher Dioscorides. Hippocrates, the father of modern medicine, explained the beneficial healing and anti-disease properties of silver. In olden days, people used silver bottles for storing water, wine and milk and to prevent spoiling. Siddha medicine is a form of South Indian medicine which is believed to have been developed by the Siddhars, the ancient supernatural spiritual saints of India. In siddha medicines, apart from gold and silver, mercury, sulphur, mica, arsenic, zinc and several other minerals, gems, shells, horns are treated with indigenous herbs and are given as bhasmas and chendurams. A bhasma means a fine ash obtained through incineration. Chendurams are prepared by the process of sublimation and they are much more potent than bhasmas. Siddha medicine has immense faith in

the miracles of mercurial drugs and in the prolongation of life through rejuvenating treatments and intense yogic practices. Silver, gold, zinc, copper and other metals, are well known to have anti-microbial effect in modern medicines have been used as wonderful life saving drugs against infectious diseases for thousands of years without any adverse effects. Role of these herbo-mineral preparations for curing skin diseases such as psoriasis, eczema, alopecia, diabetic ulcer, warts, vitiligo and leprosy are well studied. Most of the medicines are mixture of compounds and because of its synergistic action; toxicity is being diminished, thereby increasing bioavailability through the cells of the body. Treating the minerals with herbal juices may lead to reduction (trituration) in particulate size even up to nanolevels (less than 100 nm) enabling increased potency. These drugs are known to be effective even in low concentration. Various commercially available medicines such as Linga Chenduram, Poorna Chandrodaya Chenduram, Kshaya Kulanthaga Chenduram, Velli Parpam, Naga Chenduram and Naga Parpam which contain noble and other metals were used for analysis. These medicines are particularly used for treating infectious diseases. So far, nothing is known about the chemical composition of these medicines and the scientific basis of its application.

### ***WHO guidelines for quality standardized herbal formulations***

- a. Quality control of crude drugs material, plant preparations and finished products.
- b. Stability assessment and shelf life.
- c. Safety assessment; documentation of safety based on experience or toxicological studies.
- d. Assessment of efficacy by ethnomedical informations and biological activity evaluations.

The bioactive extract should be standardized on the basis of active principles or major compounds along with the chromatographic fingerprints (TLC, HPTLC, HPLC and GC). The standardization of crude drug materials include the following steps:

1. Authentication (Stage of collection, parts of the plant collected, regional status, botanical identity like phytomorphology, microscopical and histological analysis, taxonomical identity, etc.)
2. Foreign matter (herbs collected should be free from soil, insect parts or animal excreta, etc.)
3. Organoleptic evaluation (sensory characters – taste, appearance, odor, feel of the drug, etc.)
4. Tissues of diagnostic importance present in the drug powder.
5. Ash values and extractive values.
6. Volatile matter
7. Moisture content determination
8. Chromatographic and spectroscopic evaluation. TLC, HPTLC, HPLC methods will provide qualitative and semi quantitative information about the main active constituents present in the crude drug as chemical markers in the TLC fingerprint evaluation of herbals (FEH). The quality of the drug can also be assessed on the basis of the chromatographic fingerprint.
9. Determination of heavy metals – e.g. cadmium, lead, arsenic, etc.
10. Pesticide residue – WHO and FAO (Food and Agricultural Organization) set limits of pesticides, which are usually present in the herbs. These pesticides are mixed with the herbs during the time of cultivation. Mainly pesticides like DDT, BHC, toxaphene, aldrin cause serious side-effects in human beings if the crude drugs are mixed with these agents.

11. Microbial contamination – usually medicinal plants containing bacteria and molds are coming from soil and atmosphere. Analysis of the limits of *E. coli* and molds clearly throws light towards the harvesting and production practices. The substance known as aflatoxins will produce serious side-effects if consumed along with the crude drugs.

12. Radioactive contamination – Microbial growth in herbals are usually avoided by irradiation. This process may sterilize the plant material but the radioactivity hazard should be taken into account. The radioactivity of the plant samples should be checked accordingly to the guidelines of International Atomic Energy (IAE) in Vienna and that of WHO.

### *Limits for Microbial Contamination*

Microorganism	Finished product	Raw materials
<i>E. coli</i>	10 <sup>1</sup>	10 <sup>4</sup>
Salmonella	-	-
Total aerobic bacteria	10 <sup>5</sup>	-
Enterobacteria	10 <sup>3</sup>	-

Aflatoxins should be completely removed or should not be present

In order to obtain quality oriented herbal products care should be taken right from the proper identification of plants; season and area of collection, extraction, isolation and verification process.

Chemical and instrumental analyses are routinely used for analyzing synthetic drugs to confirm its authenticity. In the case of herbal drugs, however the scene is different especially for poly herbal formulation, as there are no chemical or analytical methods available. Therefore biological-screening methods can be adopted for routine checkup of herbal drugs and formulations. In the case of herbal drugs, the quality of raw materials and products can be furnished by regular pharmacognostic identifications and phytochemical analysis. The herbal formulations in general can be standardized schematically as to formulate the medicament using raw materials collected from different localities and a comparative chemical efficacy of different batches of formulation are to be observed. The preparations with better clinical efficacy are to be selected. After all the routine physical, chemical and pharmacological parameters are to be checked for all the batches to select the final finished product and to validate the whole manufacturing process.

The stability parameters for the herbal formulations, which includes physical parameters, chemical parameters, and microbiological parameters.

*Physical parameters* include color, appearance, odor, clarity, viscosity, moisture content, pH, disintegration time, friability, hardness, flow ability, flocculation, sedimentation, settling rate and ash values.

*Chemical parameters* include limit tests, extractive values, chemical assays, etc.

*Chromatographic analysis* of herbals can be done using TLC, HPLC, HPTLC and GC, UV, Fluorimetry, GC-MS, etc.

*Microbiological parameters* include total viable content, total mold count, total enterobacterial and their count. Limiters can be utilized as a quantitative or semiquantitative tool to ascertain and control the amount of impurities like the reagents used during abstraction of various herbs, impurities coming directly from the manufacturing vessels, impurities from the solvents, etc.

*Chemical decomposition* of substances present in the formulation also produces several toxic or impure compounds during storage in undesirable conditions. Contaminants may come directly from the atmosphere also. This includes mainly dust, sulfur dioxide, H<sub>2</sub>S, CO<sub>2</sub>, Arsenic, moisture, etc.

***The guidelines set by WHO can be summarized as follows:***

- a. Reference to the identity of the drug. Botanical evaluation – sensory characters, foreign organic matter, microscopical, histological, histochemical evaluation, quantitative measurements, etc.
- b. Reference to the physiochemical character of the drug. Chromatographic profiles, ash values, extractive values, refractive index, polarimetric readings, moisture content, volatile oil content, etc.
- c. Reference to the pharmacological parameters. Biological activity profiles, bitterness values, haemolytic index, astringency, swelling factor, foaming index, etc.
- d. Toxicity details – heavy metals like cadmium, lead, arsenic, mercury, etc. Pesticide residues.
- e. Microbial contamination – Total viable aerobic count, pathogenic bacteria like enterobacteria, *E. coli*, salmonella, *Pseudomonous aeruginosa*, *Staphylococcus aureus*, etc. and presence of aflatoxins etc.
- f. Radioactive contamination.

Maximum residue limits =

$$\frac{\text{Acceptable daily index} \times \text{body weight} \times \text{extraction factor}}{\text{Mean daily intake of drug} \times \text{safety factor} \times 100} \times \text{Therapeutic doses}$$

### ***Modern herbal ayurvedic monographs***

In the modern herbal ayurvedic monographs the standardization parameters are discussed in a comprehensive way. According to the modern ayurvedic monograph the quality control protocols include the following:

Title, synonyms, publications related to that plant, constituents present, analytical methods.

Descriptive evaluation: Description of the drug, phytomorphological, microscopical, organoleptic evaluations, foreign matter, foreign minerals, etc.

### ***Physicochemical parameters***

Identity: Physical and chemical identity, chromatographic finger prints, ash values, extractive values, moisture content.

Strength: Ethanol and water extractive values, volatile oil and alkaloidal assays, quantitative estimation protocols, etc.

### ***Biological Activity Evaluation***

Bitterness values, astringency, swelling factor, form index, hemolytic index, etc.

### ***Toxicological evaluation***

Pesticide residues, heavy metals, microbial contamination like total viable aerobic count, pathogens like *E. coli*, *Salmonella*, *P. aeruginosa*, *S. aureus*, Enterobacteria, etc.

### ***Aflatoxins***

The presence of aflatoxins can be determined by chromatographic methods using standard aflatoxins B<sub>1</sub>, B<sub>2</sub>, G<sub>1</sub>, G<sub>2</sub> mixtures. Aflatoxin is a product of the microbial strain *Aspergillus flavus*.

### ***Herbal medicine: safety of herbal medicine***

A major benefit of herbal medicine is its long history of safe use. Humans have been taking herbal medicine for thousands of years. This is like a huge experiment where thousands if not millions of people are utilizing plants to benefit their health and relieve symptoms, in some cases herbs like garlic have at least 3,000 years of safe use. Contrast this with many pharmaceuticals that have only a few years of studies and human use to support their safety. As it turns out, about 5% of drugs have to be pulled from the market after some years of use. In many cultures herbal medicines are added to food, and taken daily as tonics and restorative remedies. In European studies comparing herb preparations and pharmaceutical drugs, the side effects of the herbal remedies when compared with pharmaceutical drugs is typically one half, or equivalent to the rate of side effects for the placebo. As recently as the early 1980s, doctors, regulators, and even the news media were not much interested in the concept of herb safety. Why? Because most didn't believe herbs had any effect at all, much less pose a public safety threat. This all changed in the mid-1990s with the rise in popularity of St. John's wort, kava, ginkgo, and other top herbs. Enough high-quality studies were finally available to convince many skeptics that herbs in fact did have activity. Subsequent studies have shown that herbs have in some cases as much activity as pharmaceutical drugs. Since then, several factors have combined to bring herb safety to the forefront. In clinical trials, mostly from Europe, herbal products have shown similar activity to pharmaceutical drugs for relieving symptoms such as depression and anxiety. Modern herbal products can be highly concentrated. Some of the active constituents might be purified and then added back into extracts at up to 95% of the total! This high concentration makes the preparations that contain these extract more like drugs than herbs, at least in the traditional sense, and while these concentrations might increase the efficacy of the products in some cases, it also increases the risk of side effects and herb-drug interactions. The herb ephedra (ma huang), a traditional Chinese herb that contains substantial amounts of the alkaloid ephedrine became national news when it was linked to a number of adverse events and even deaths in the U.S. Many more people today are taking prescription drugs and herbs together—as many as 25 million people in the U.S. alone.

### ***Herbal safety***

Despite a huge upswing in the popularity and use of more concentrated herbal medicines worldwide, it is not easy to come up with any statistics or studies that show that herbs are not safe

when taken as generally recommended today on product labels, and doses given in popular herb books. The World Health Organization created one of the largest herb safety databases in the world. A thorough search of this database shows that very serious side effects or interactions have been reported internationally over the last xx years. [Give example from Artemisia search]. Very few reports of serious adverse events associated with herbal medicines can be found after a thorough search of databases and reports from government agencies such as the centers for disease control (CDC), and the food and drug administration (FDA), charged with monitoring the safety of the drugs and devices used in health care. A search of Toxline, one of the major sources of information on toxic substances, maintained by the National Library of Health, as part of the largest medical database in the world, PubMed, shows that herbs are inherently safe, with a few caveats: After reviewing numerous clinical trials with a total of thousands of patient volunteers, the most common side effect from taking herbs are digestive upset and headaches. These quickly resolve after reducing the dose or discontinuing the herbs. Herbs used in their whole form are usually safer than when used in highly refined forms. Some people are allergic to or react adversely to herbs that most people can use safely. People who have life-threatening diseases (particularly heart disease and liver disease) and are taking several to many prescription drugs should use caution when taking herbs. It is best to consult with professional health care providers such as licensed acupuncturists and professional herbalists, in concert with your physician. Herb-related adverse effects usually fall into the categories contraindications, side effects, and interactions. Most traditional systems of medicine, especially traditional Chinese medicine have defined conditions where specific herbs should not be taken. For instance when the patient has digestive weakness, or when they are taking other specific herbs. These potential interactions are not considered dangerous, but not following these contraindications could negate the positive effect of the treatment, or even lead to worsening of the condition or symptoms.

### ***Toxicity of traditional herbal drugs***

Herbs generally can cause either digestive upset or allergic reactions. Digestive upset can result from taking some herbs like ginkgo standardized extract, especially on an empty stomach. In their whole form, herbs have lots of crude fiber, and can be tough to digest for some people. Herb extracts are often easier to digest and usually cause less digestive upset, though even extracts can cause a feeling of nausea or fullness to occur in some cases. The possibility of digestive upset can be counteracted and the absorption enhanced by adding some spicy herbs like ginger to the formula, or taking the herbs with ginger tea. Using an herbal formula that is skillfully formulated by an experienced herbalist can reduce the possibility of side effects and increase the effectiveness because these factors are considered ahead of time. At home, add a little ginger, cinnamon, and other favorite spices to your herb teas to enhance the enjoyment and reduce digestive upset. Severe side effects of herbal preparations are unusual, when used as recommended on the product, but a few are best taken under the advice of an experience herbal practitioner because of reports of possible toxicity. Please consult the [Herbal Database] for specific information on 245 herbs.

### ***Interactions of herbal drugs***

Now that millions of people around the world are using herbs and pharmaceutical drugs together as part of their daily regime, interactions are certainly possible in some cases. Interactions can happen because herbs contain complex mixtures of many active compounds, and some of them

**Herbs with Potential for Side Effects or Toxicity**

<b>Herb</b>	<b>Use</b>	<b>Potential Side Effects or Toxicity</b>
Blue Cohosh (don't use during pregnancy)	Usually with black cohosh just before birth to stimulate contractions, but also in some "women's formulas."	Potentially toxic to the heart of the fetus, has other toxic compounds
Chaparral (Not for long-term use or excessive doses internally.)	Traditional remedy for colds, flu, infections, cancer, and more.	Liver toxicity reported in the literature without much evidence.
Comfrey (Not for long-term use or during pregnancy internally.)	Healing application for burns, cuts, skin trauma.	Liver toxicity reported in the literature with only moderate support.
Kava (Generally safe. Consult your health care professional if you have pre-existing liver disease. Caution using with alcoholic beverages or other sedative pharmaceuticals like benzodiazepines.)	Traditional social drink in Pacific Islands. Used today for muscle tension, anxiety, nervousness, insomnia.	Liver toxicity reported in the literature on some preparations containing stem extracts. For traditional root and rhizome extracts, moderate concentrations (below 20% kavalactones, teas, and tinctures less likely to cause problems. Any liver toxicity is likely to be due to rare allergic reactions.
Lobelia (Use in small amounts in formulas mostly safe.)	Antispasmodic for asthma, also used in stop-smoking mixtures	Can cause nausea in even moderate doses, but not considered dangerous by herbalists.
Mugwort (Internal use of the tea in moderate amounts is likely to be safe. Don't use during pregnancy.)	Used for digestive problems, poor digestion, flatulence, to stimulate menses.	Contains the potentially toxic compound thujone. Preparations made with alcohol should not be used more than a few days once in awhile. Teas contain very little thujone.
Poke (External use mainly, except under advice of an experienced herbalist.)	Used in cancer treatment protocols externally and internally. Also for lymphatic congestion and swellings, and venomous bites.	Can definitely cause nausea and vomiting in even small amounts when used internally. I recommend internal use under guidance of an herbalist.
Sassafras (The use internally in tea form for short periods is likely to be safe.)	Used in spring tonic teas and formerly to flavor root beer.	Some animal studies show one of its constituents, safrole, to be a potential carcinogen and mutagen. Very little safrole in teas.
Scullcap	Used as a general nervine or nerve tonic or relaxing herb. Sometimes as an antispasmodic.	Scullcap itself is not considered toxic, but it is commonly adulterated in commercial products with the potentially liver-toxic herb germander. Fortunately, <i>this adulteration is very unlikely with organically-grown herb.</i>
Wormwood	Used for digestive problems, poor digestion, flatulence, to stimulate menses. Also as a worm remedy.	Contains the potentially toxic compound thujone. Preparations made with alcohol should not be used more than a few days once in awhile. Teas contain very little thujone.

have the potential to change the way pharmaceutical drugs are absorbed, metabolized, distributed throughout the body, and eliminated. The major site of this potential interaction might be the liver. When you swallow a drug, the chemical compound is affected by enzyme systems in the liver in some way. It is often altered, and can be changed to compounds that are more easily eliminated by the body, as is necessary with all potentially toxic compounds. Some common herbs, most notably, St. John's wort, have been shown by human studies to lower the concentrations of common drugs in the blood system. When these drugs are potentially life-sparing, like the anti-rejection drugs taken after organ transplants, antiviral drugs (for HIV infections), or chemotherapeutic drugs used in the treatment of cancer, then a problem could occur. Herbalists often recommend that if you are in poor health *and* taking pharmaceutical drugs, Despite a few documented cases of herb-drug interactions, it is remarkable that with 25 million people in the U.S. alone taking herbs and drugs together, as is estimated, so few actual clinical reports of interactions have been published in the scientific literature. This seems to indicate that herb-drug interactions are not a very important public health safety problem. Nevertheless, we are learning more about the actions of herbs, and the pharmacology of their major active compounds is becoming increasingly known. Because of this new knowledge, many books and articles on herb-drug interactions do make *theoretical* statements about interactions. Hopefully, these sources will make sure to state whether an interaction they list is theoretical or actually reported in humans. Studies on interactions using animals are not very reliable because each animal species metabolizes herbs and drugs differently.

### ***Herbal safety guidelines***

Before taking any medication or herbal supplement you are unfamiliar with, explore its medicinal properties. Research the ingredients thoroughly and/or consult with an appropriately qualified practitioner or expert. If you are taking prescription drugs or have a medical condition, check with an appropriately qualified practitioner before using a herbal product medicinally. There is overwhelming evidence to suggest that that herbal remedies really do work. Remember that just because a small amount works well does not mean that a larger dosage will be even more effective. As individuals we all have different constitutions, sensitivities, allergic reactions and possible health conditions. The following are merely guidelines and relate to all the herbal product supplements offered on our websites. Any possible interactions and contraindications with prescription medicine need to be discussed with your physician.

*Caution:* do not use any of cloud nine lifestyle's products if you are pregnant, nursing, or suffer from one or more of the following conditions: high blood pressure, heart disease, thyroid disease, glaucoma, or diabetes. Do not use any of cloud nine lifestyle's products if you have difficulty urinating due to prostate enlargement, or if you are currently taking a prescription monoamine oxidase inhibitor (maoi) or for two (2) weeks after you have stopped taking a maoi drug (maoi drugs are sometimes used in the treatment of depression, psychiatric or emotional conditions, and parkinson's disease). If you are uncertain whether your prescription drug contains an maoi, consult a physician before taking any cloud nine lifestyle product. Do not exceed recommended dosage. This is a good idea, especially for certain population groups. Dietary supplements may not be risk-free under certain circumstances. If you are pregnant, nursing a baby, or have a chronic medical condition, such as, diabetes, hypertension or heart disease, be sure to consult your doctor or pharmacist before purchasing or taking any supplement. While vitamin and mineral supplements are widely used and generally considered safe, you may wish to check with

your doctor or pharmacist before taking these or any other dietary supplements. If you plan to use a dietary supplement in place of drugs or in combination with any drug, tell your health care provider first. Many supplements contain active ingredients that have strong biological effects and their safety is not always assured in all users. If you have certain health conditions and take these products, you may be placing yourself at risk. Some supplements may interact with prescription and over-the-counter medicines. Taking a combination of supplements or using these products together with medications (whether prescription or otc drugs) could under certain circumstances produce adverse effects. Be alert to advisories about these products, whether taken alone or in combination. For example: coumadin (a prescription medicine), ginkgo biloba (an herbal supplement), aspirin (an otc drug) and vitamin e (a vitamin supplement) can each thin the blood, and taking any of these products together can increase the potential for internal bleeding. Some supplements can have unwanted effects during surgery. It is important to fully inform your doctor about the vitamins, minerals, herbals or any other supplements you are taking, especially before elective surgery. You may be asked to stop taking these products at least 2-3 weeks ahead of the procedure to avoid potentially dangerous supplement/drug interactions -- such as changes in heart rate, blood pressure and increased bleeding - that could adversely affect the outcome of your surgery. Do not be used during pregnancy, or if you are nursing: alkanet, aloe, angelica, anise, anise star, arnica, ashwaganda, barley grass, barberry, basil, bitter melon, black cohosh, bladderwrack, blessed thistle, blood root, blue cohosh, blue flag, blue vervain, borage, buckthorn, california poppy, cascara sagrada, catnip, celandine, celery, chervil, cinnamon, club moss, comfrey, coltsfoot, cubeb, dong quai, elecampane, ephedra, false unicorn, fenugreek, feverfew, ginger, golden seal, gravel, guarana, gymnema, horehound, horsetail, hyssop, juniper, lemongrass, licorice, lobelia, lovage, lungwort, mace, motherwort, mugwort, muira puama, myrrh, neem, oregon grape, osha, parsley, pennyroyal, pleurisy, prickly ash, red clover, rhodiola, rosemary, rue, sage, sassafras, sarsaparilla, senna, shepherds purse, spikenard, turkey rhubarb, turmeric, uva ursi, vitex, watercress, white sage, wormwood, yarrowroot for persons with history of kidney stones, liver disorders, renal dysfunction or inflammation. Cubeb, essiac, horsetail, hydrangea, juniper berries, kava kava, parsley root, pennyroyal, sheep sorrel, shepherds purse, suma, sumac, uva ursi, yellowdock, yohimbenot recommended for person currently taking blood thinning medications: alfalfa, angelica, cramp bark, cubeb, dong quai, ginkgo, meadowsweet, red clover, sarsaparilla, yohimbenot for persons with stomach inflammation/ulcers serious digestion and/or liver problems. May cause gastrointestinal upset: black haw, blue flag, chaparral, club moss, crampbark, devils claw, eucalyptus, elecampane, essiac, gentian, ginger, licorice, lobelia, parsley root, pleurisy, pygeum, solomons seal, tribulus, turmeric, yohimbenot for long-term use: bilberry leaf, black walnut, blessed thistle, borage, cascara sagrada, comfrey, coltsfoot, chaparral, elecampane, ephedra, flax, horsetail, gentian, goldenseal, guarana, juniper berries, licorice, lobelia, lungwort, mullein, nettle root, rhubarb, sage, sassafras, sarsaparilla, senna, sheep sorrel, wild cherry, wormwood, uva ursi, yohimbe To be used only under the supervision of an expert qualified in the appropriate use of this substance: calamus, horse chestnut, lobelia, licorice, mandrake, poke, tornado not use if you have abdominal pain or diarrhea, discontinue if these occur. Consult health practitioner prior to use if pregnant, nursing, and taking medication or have a medical condition. Do not exceed recommended dose. Not for long term use: aloe, buckthorn, cascara sagrada, senna, turkey rhubarb, yohimbemay cause photo toxicity in some individuals at high dosage. Avoid long exposure to sun if using internally: angelica, celery seed, orange peel, rue, st. Johns wort seek advice from health practitioner prior to use if pregnant, nursing, have high blood pressure, heart or thyroid disease, diabetes, difficulty in urination due to prostate

enlargement, or if taking mao inhibitor or other prescription drug. Reduce/discontinue use if nervousness, tremor, sleeplessness, loss of appetite or nausea occur. Do not exceed recommended dose. Keep out of reach of children: ephedra, st. Johns wort, yohimbeseek advice from a health practitioner before use if you have/may have had kidney or liver disease. Discontinue use if nausea, fever, fatigue or jaundice (dark urine, yellow discoloration of eyes) should occur: boldo, chaparralstatements made by cloud nine lifestyle llc have not been evaluated by the food and drug administration. The fda does not evaluate or test herbs. These products are not intended to diagnose, treat, cure or prevent any illness or disease. Consult with your physician for diagnosis or treatment. Use herbs as per instructions and always watch for any allergic reactions.

### ***Safe herbs to take during pregnancy***

While anyone can experience mild allergic reactions to an herb or herbal preparation, or even extremely rare life-threatening allergic reactions, these 10 herbs are very unlikely to interact with drugs that you are taking. These herbs are all generally considered safe to take during pregnancy as well.

- ❖ Chamomile—a good-tasting tea to drink throughout the day, or as needed, for mild nervousness, and many digestive upsets such as intestinal cramps, mild nausea, or a feeling of general digestive discomfort. Chamomile is also used for relieving menstrual cramps and pain.
- ❖ Nettle leaf—a popular mineral tonic to take during pregnancy, or anytime. Reported to help “build the blood,” and also help maintain good urinary tract health.
- ❖ Lemon balm—safe for infants and young children. A mild calming tea to give during teething, digestive upset and colic. Administer 1-3 droppers full of the mild, good-tasting tea. Good for teenagers and adults too by the cup.
- ❖ Elder berry, elder flower—a great herb to help lower fevers, and it has antiviral effects, being one of the best-studied herbal remedy to help counteract flu.
- ❖ Andrographis—another well-studied anti-flu herb.
- ❖ Peppermint—makes a good-tasting tea for relieving digestive pain due to gas, upset stomach, and nausea.
- ❖ Linden—a great-tasting tea for relieving mild nervousness and sleep disturbances.
- ❖ Echinacea leaf and flower—a classic traditional herbal remedy to shorten symptoms of colds and flu, and other kinds of infections. Some scientific studies show that children get fewer colds during the winter season when using the herb regularly, off and on.
- ❖ Hawthorn—A famous heart “tonic.” Some human studies show beneficial effects for people with mild heart weakness, and hypertension. Herbalists respect the herb for the herb’s strengthening effect on the heart.
- ❖ Shiitake—one of the best-studied immune tonics, used in traditional Chinese cooking for thousands of years. Today, it is known to have antiviral and anticarcinogenic effects.

### ***Efficacy of herbal medicine***

You may be surprised to know that today many herbal medicines have substantial scientific evidence demonstrating their safety and efficacy. The news media sometimes reports on negative studies or safety issues involving herbs, but rarely reports on the successes or the long safety record that stands behind many herbal remedies. In Europe, herbal medicine takes a more scientific path, relying on extensive scientific investigation, testing, and clinical trials before it can be licensed for sale to consumers or patients. Few would say that herbal medicine is

inherently dangerous, or a public health and safety concern, yet how effective is herbal medicine? Citing European clinical trials involving as many as 10,000 to 20,000 people, one generally finds that herbal medicine is equally effective for relieving symptoms of a number of common ailments than the equivalent pharmaceutical drug. This is especially true when one considers some of the best-known and most widely used herbal remedies. These include ginkgo (for dementia), St. John's wort (depression), saw Palmetto (prostate hyperplasia), Elderberry (flu), garlic (blood cholesterol), and kava (mild to moderate anxiety). A major question that has to be asked is if some herbal medicines have strong scientific support for efficacy and safety, are turning out to be as effective as pharmaceutical drugs in some human trials, at one quarter of the cost in half the safety problems, then why aren't they more commonly recommended by physicians and included on hospital formularies? We might suspect that the answer to this is obvious, political and economic. It is also likely to be due in part to the human beings resistance to change and new ways of doing things. Today there is getting to be enough solid science, economic and environmental reasons to choose herbal medicine over pharmaceutical drugs, especially as the first line of treatment. Why start off with something that is likely to be less safe, more expensive, harder on the environment and possibly our body, yet have no proof that it is any more effective? If you are looking for herbs with positive human studies, start with this list of ten top herbs.

#### ***Current regulatory issues for herbal medicines***

There are several regulatory concerns in relation to research applications and commercialization of herbal medicines.

#### ***Standardization of herbal drugs***

For safe and effective use of herbal drugs, consistency in composition and biologic activity are essential requirements. However, herbal drugs frequently fail to meet this standard, as there are problems such as 1) difficulties in identification of plants, 2) genetic variability, 3) variations in growing conditions, 4) diversity in harvesting procedures and processing of extracts, and 5) the lack of information about active pharmacologic principles. The use of chromatographic techniques and marker compounds for the standardization of herbal products can ensure batch-to-batch consistency; however, this does not ensure consistent pharmacologic activity or stability. With herbal medicines what is on the label and what is in the bottle may differ considerably. In a study of ginseng preparations, the amount of ginsenosides varied from 11.9-327.7% of the amount on the label. Medical letter cautions, "Their (herbal medicines) potency may vary and their purity is suspect,"<sup>9</sup> Australian medicines regulatory body the Therapeutic Goods Administration, suspended production license of Pan Pharmaceuticals after an audit, which revealed problems with company's quality control standards. The Lack of standardization of herbal drugs would be a serious problem for a researcher as he would not be able to rely on commercially available herbal products for his research studies.

#### ***Quality of herbal preparations***

If an herbal remedy is effective, quality assurance is needed to ensure that the product has the expected effects. Even in the absence of data on efficacy, quality assurance is important, as quality is a critical determinant of safety as well. Adulteration of plants is serious problem. Some of the common adulterants are: botanicals, toxic metals, microorganisms, microbial toxins, pesticides, and fumigation agents. A US investigation reported that 32 percent of marketed Asian

patent medicines contained undeclared pharmaceuticals or heavy metals.<sup>2</sup> The drugs most frequently found were ephedrine, chlorpheniramine, methyltestosterone, and phenacetin; 10 to 15 percent contained lead, mercury, or arsenic. The incidence of heavy metal contamination is not known, but one study showed that 64% of samples collected in India contained significant amounts of lead (64% mercury, 41% arsenic and 9% cadmium). This can cause serious harm to patients taking such remedies and could confound the assessment of safety in a clinical trial. Quality has to be assured at all stages – herbal raw materials, processing of herbals and finished herbal medicines

### ***Evidence of Clinical Efficacy***

Scientific evidence from randomized clinical trials is only strong for many uses of acupuncture, some herbal medicines and for some of the manual therapies. Only a small fraction of the thousands of medicinal plants used worldwide has been tested rigorously in randomized, controlled trials. Even if the animal studies or anecdotal clinical experiences are promising and use of an herb is widespread, such observations cannot predict the results of well designed randomized, controlled trials. A recent review concluded that evidence-based studies on the efficacy and safety of traditional Indian medicines are limited. The data available is mostly experimental or in animals.

Most trials do not report hard efficacy endpoints and duration of observation periods is generally short. The clinical relevance of the observed effects is not always clear. For instance, most Indian trials of hepato-protective agents are open and uncontrolled. As most acute liver conditions have a natural recovery, it is difficult to link the improvement to the herbal product. The essential ingredient in most formulations is not precisely defined. High quality studies are necessary to evaluate and compare the value of traditional Indian drugs to modern medicine. A fundamental problem in all clinical research of herbal medicines is whether different products, extracts, or even different lots of the same extract are comparable and equivalent. For example, Echinacea products can contain other plant extracts; use different plant species (*E. purpurea*, *pallida* or *angustifolia*), different parts (herb, root, both), and might have been produced in quite different manners (hydro- or lipophilic extraction). Even different species may be known by the same name in local language. Brahmi refers to *Centella asiatica* and *Bacopa monniera*. The herbal industry is not required to conduct clinical trials, and the industry professionals argue that it would be not be possible to recover the high research costs, as herbal products can not be patented as easily as new chemical entities. Nevertheless, randomized, controlled trials are the best way to demonstrate the efficacy of any medicine, herbal or conventional.

### ***Global regulatory scene***

The above issues have led to an increasing regulatory focus on herbal products in US and Europe.

### **US FDA Guidance for Botanicals**

The US FDA has issued draft guidance for botanical products.<sup>6</sup> The regulatory approach is based on 1) intended use of botanical – as dietary supplement, cosmetic or drug and 2) status of botanical – marketed in US, marketed outside US or not marketed at all. The guideline is fairly exhaustive and pragmatic. The data requirements depend on several factors,

Some of the general guidelines are:

- Traditional herbal medicines or currently marketed botanical products, because of their extensive though uncontrolled use in humans, may require less preclinical information to support initial clinical trials than would be expected for synthetic or highly purified drugs.
- Requirements for Investigational New Drug (IND) applications of botanicals legally marketed in the United States as dietary supplements or cosmetics
  - Very little new chemistry manufacturing and controls (CMC) or toxicologic data are needed to initiate early clinical, if there are no known safety issues associated with the product and it is used at approximately the same doses as those currently or traditionally used or recommended.
  - As the product is marketed and the dose thought to be appropriate and well tolerated is known, there should be little need for pilot or typical Phase 1 studies. Sponsors are allowed to initiate more definitive efficacy trials early in the development program. If there is doubt about the best dose of the product tested, a randomized, parallel, dose-response study may be particularly useful as an initial trial.
- Requirements for botanical product that has not been previously marketed in the United States or anywhere in the world
  - Certain additional information (CMC, toxicology, human use) is required to assist FDA in determining the safety of the product for use in initial clinical studies.
  - If the product is prepared, processed, and used according to methodologies for which there is prior human experience, sufficient information may be available to support such studies without standard preclinical testing.
- Clinical trials of botanical products
  - There may be special problems associated with the incorporation of traditional methodologies, such as selection of doses and addition of new botanical ingredients based on response, which will need to be resolved.
  - The credible design for clinical trials studies will be randomized, double blind, and placebo-controlled (or dose-response). For most conditions potentially treated by botanical drugs (generally mildly symptomatic), active control equivalence designs would not be credible.
  - For expanded i.e., Phase 3 clinical studies on a botanical drug product, more detailed information on CMC and preclinical safety is necessary as compared to the information required for a Phase 1 or Phase 2 study. This additional information should be provided regardless of whether the product is currently lawfully marketed in the United States or elsewhere as a dietary supplement.
  - All study data should conform to standard ethical guidelines of good clinical practice (informed consent, approval from ethics committee) for all clinical trials.
- Documentation for early trials (IND)
  - Description of Product and Documentation of Human Use
    - Description of Botanicals Used
    - History of Use
    - Current Investigational Use
  - Chemistry, Manufacturing, and Controls
    - Botanical Raw Material

- Botanical Drug Substance
  - Botanical Drug Product
  - Placebo
  - Labelling
  - Environmental Assessment or Claim of Categorical Exclusion
  - Pharmacology/Toxicology Information
- Exclusive marketing rights
    - US FDA has a provision to grant exclusive marketing rights for 3-5 years even in the absence of patent protection. During the period of exclusivity, FDA will not approve, or in some cases even review, certain competitor products unless the second sponsor conducts all studies necessary to demonstrate the safety and effectiveness of its product.

### ***European guidelines on herbal medicinal products***

The data requirements in the European Guidelines depend on the nature and level of indication and available clinical literature.<sup>7</sup> The guidelines provide grading of recommendations based on previous clinical trial data. The level of safety must correspond to the indication claimed for the product. The review of literature should identify the current level of evidence for safe and effective use of herbal medicine. For minor indications, a low level of evidence (expert opinions or clinical experience of respected authorities) is acceptable if there is support from experimental data. Description of traditional use without supporting clinical or experimental data is not sufficient to establish a sufficient level of efficacy. The guideline also covers the good agricultural practices (GAP) in growing and processing of all medicinal plants.

The international regulatory authorities would expect that the data generated (pre-clinical, CMC and clinical) meet the global good laboratory practices (GLP), good clinical practices (GCP) and good manufacturing practices (GMP).

### ***Indian scenario in traditional medicine***

The domestic turnover of traditional medicine industry in India is over Rs 4000 crore. The domestic market largely focuses on over the counter (OTC) sales of patent and proprietary (P & P) medicines.

The P & P formulations include the ingredients cited in traditional medicine's authoritative texts, but are not formulated as per the traditional formulae. National Policy on Indian Systems of Medicine of 2001 has identified a need for efficacy trials for the therapeutic claims of P & P medicines.

Indian exports are around \$ 100 million, which are quite low compared to Chinese figures of \$ 3 billion. Group-II of Task Force on "Pharmaceuticals and Knowledge Based Industries" 1999 has concluded that Indian exports of herbal products is rather low due to several factors like 1) issues related to non-availability of scientific data, 2) price competitiveness, 3) packaging 4) timely delivery schedule, 5) lack of proper documents, 6) government authority to provide certificate confirming compliance of good manufacturing practices, 7) availability of free sale certificate, 8)

certificate of analysis and 9) the quality of the products. There is an urgent need for Indian research to focus on the areas of quality, documentation, standardization and clinical evidence. In 2001, the Central Drugs Standard Control Organisation of Directorate General of Health Services has recently issued GCP guidelines. These guidelines recommend the approach to clinical trials of herbal remedies and medicinal plants

The guidelines divide the herbal products into different categories based on the whether the use and formulation of product are as per the traditional medicine literature or are not as per the traditional documentation.

- For the herbal remedies and medicinal plants that are to be clinically evaluated for use in the Allopathic System and which may later be used in allopathic hospitals, the procedures laid down by the office of the Drugs Controller General of India for allopathic drugs should be followed.
- When an extract of a plant or a compound isolated from the plant has to be clinically evaluated for a therapeutic effect not originally described in the texts of traditional systems or, the method of preparation is different, it has to be treated as a new substance or new chemical entity (NCE) and the same type of acute, sub acute and chronic toxicity data will have to be generated as required by the regulatory authority before it is cleared for clinical evaluation.
- An extract or a compound isolated from a plant, which has never been in use before and has not ever been mentioned in ancient literature, should be treated as a new drug, and therefore, should undergo all regulatory requirements before being evaluated clinically.

The document also provides general guidelines on clinical trials of herbals, toxicity studies, need for standardization, and compliance with GCP in all clinical trials.

Some of the recommendations are:

- Plants and herbal remedies should prepared strictly in the same way as described in the literature while incorporating GMP norms for standardization
- For herbal remedies, it may not be necessary to undertake Phase 1 studies
- If there are reports suggesting toxicity or when the herbal preparation is to be used for more than 3 months, toxicity studies (4-6 weeks toxicity study in 2 species of animals) are needed for phase 2 trials.
- For Phase 3 trial toxicity studies (4-6 weeks toxicity study in 2 species of animals) are needed.
- Clinical trials should be carried out with herbal preparations only after standardization and identification of markers to ensure that the substances being evaluated are always the same.
- Ethical guidelines (patient information, informed consent, protection of vulnerable populations etc) for biomedical research should be followed.
- Clinical trials should to be approved by the appropriate scientific and ethical committees of the concerned Institutes.

- Clinical trials should be carried out only when a competent Ayurvedic, Siddha or Unani physician is a co-investigator

### **Conclusions**

Although there is a global interest in traditional herbal medicines, there are concerns about use of untested and unregulated medicines. The scientific community is concerned about the quality, standardization, clinical safety and efficacy of herbal remedies. The experience of allopathic industry suggests that regulations are necessary in order to support science and quality of research. Time has to come to accept the same for herbal remedies. Unless the research data on Indian herbal remedies meet the local and global regulatory standards, our traditional systems will find it difficult to compete with Chinese efforts. The golden dictum for herbal medicines is “Effective Regulations Improve Research” Herbal medicines are generally considered comparably safer than synthetic drugs. While this may be probably correct, case reports show that severe side effects and relevant interactions with other drugs can occur. For instance, the herb Ephedra marketed as a dietary aid in USA, led to at least a dozen deaths, heart attacks and strokes. Other well-known safety issues have been hepatotoxicity of kava and renal effects of aristolochic acid. Besides, drug interactions of herbal drugs are of a serious concern. For example, hypericum extracts can decrease the concentration of a variety of other drugs by enzyme induction. Serious adverse effects have been reported when the addition of St. John's wort caused serum levels of cyclosporine and antiretroviral agents to fall to sub therapeutic levels. Garlic is reported to increase clotting time in patients taking warfarin. Lack of regulatory standards regarding the efficacy and safety of herbal products did not arouse much concern in the past, as these products were often perceived as so safe that even if they were ineffective, little harm resulted. However, the situation is changing now and there is an increasing body of literature on the side effects and interactions of herbal medicines. Besides the direct risks of adverse effects and drug interactions there is an indirect risk that an herbal remedy without demonstrated efficacy may compromise, delay, or replace an effective form of conventional treatment. WHO has urged the governments to establish regulatory mechanisms to control the safety and quality of products. Herbal preparations have a role to play in modern medicine, and there is clear evidence of their therapeutic benefits. However, as with any therapy, herbal preparations have the potential to do harm as well as good. To prevent harm, nurses must be aware of the risks and benefits of herbal remedies. During admission procedures they must enquire about the herbal remedies the patient is using, together with prescribed orthodox drugs and over-the-counter medications. Finally, they must be non-judgmental in their attitudes to complementary therapies, accepting that patients have the choice to make their own decisions regarding treatment. The nurse's role is to ensure that this is an informed decision.

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