Pharmacologic Properties and Therapeutic Efficacy of Herbal Medications

Number of Contact Hours – 5

Audience RN

Pharmacology Hr : 5.0

CERP : A

Goals and Objectives

Goals

The goal of this article is to review the global trends, developments and prospects of the strategies and methodologies concerning the conservation and sustainable use of medicinal plant resources

Objectives

Discuss the global prevalence of herbal medicines

Discuss the evolving role of natural products in drug discovery

Identify three factors associated with the recent resurgence of public interest in herbal remedies

Describe the role of complementary therapies in health promotion

Discuss the toxicological challenges associated with the use of herbal medicines

Introduction

More than two-thirds of the U.S. population has used complementary and alternative medicine (CAM), defined as healthcare systems, practices and products not currently considered part of conventional medicine. Most Americans use CAM as an adjunct to, rather than a substitute for, conventional medical care. Yet, 63−72% of CAM users do not discuss use with doctors; and CAM disclosure is particularly low among racial/ethnic minorities. CAM utilization can affect treatment outcomes, including adverse herb–drug interactions, underscoring the need for patient–provider communication about CAM.

Medicinal plants are globally valuable sources of new drugs. There are over 1300 medicinal plants used, of which 90 % are harvested from wild resources; in the United States, about 118 of the top 150 prescription drugs are based on natural sources. Furthermore, up to 80 %

of people in developing countries are totally dependent on herbal drugs for their primary healthcare, and over 25 % of prescribed medicines in developed countries are derived from wild plant species. With the increasing demand for herbal drugs, natural health products, and secondary metabolites of medicinal plants, the use of medicinal plants is growing rapidly throughout the world.

A highly conservative estimate states that the current loss of plant species is between 100 and 1000 times higher than the expected natural extinction rate and that the Earth is losing at least one potential major drug every 2 years. According to the International Union for Conservation of Nature and the World Wildlife Fund, there are between 50,000 and 80,000 flowering plant species used for medicinal purposes worldwide. Among these, about 15,000 species are threatened with extinction from overharvesting and habitat destruction and 20 % of their wild resources have already been nearly exhausted with the increasing human population and plant consumption. Although this threat has been known for decades, the accelerated loss of species and habitat destruction worldwide has increased the risk of extinction of medicinal plants.

The conservation and sustainable use of medicinal plants have been studied extensively. Various sets of recommendations have been compiled regarding their conservation, including the establishment of systems for species inventorying and status monitoring, and the need for coordinated conservation practices based on both in situ and ex situ strategies. For medicinal plants with increasingly limited supplies, sustainable use of wild resources can be an effective conservation alternative. [1, Rank 5]

The Global Prevalence of Herbal Medicines

The use of herbal medicines and phytonutrients or nutraceuticals continues to expand rapidly across the world with many people now resorting to these products for treatment of various health challenges in different national healthcare settings. This past decade has obviously witnessed a tremendous surge in acceptance and public interest in natural therapies both in developing and developed countries, with these herbal remedies being available not only in drug stores, but now also in food stores and supermarkets. It is estimated that up to four billion people (representing 80% of the world's population) living in the developing world rely on herbal medicinal products as a primary source of healthcare and traditional medical practice which involves the use of herbs being viewed as an integral part of the culture in those communities.

The use of herbal remedies has also been widely embraced in many developed countries with complementary and alternative medicines (CAMs) now becoming mainstream in the UK and the rest of Europe, as well as in North America and Australia. In fact, while places like the UK have a historical tradition of using herbal medicines, the use is also widespread and well established in some other European countries. In these developed countries, the most important among many other reasons for seeking herbal therapy is the belief that it will promote healthier living. Herbal medicines are, therefore, often viewed as a balanced

and moderate approach to healing and individuals who use them as home remedies and over-the-counter drugs spend huge amount of money (in excess of billions of dollars) on herbal products. This explains in part the reason sales of herbal medicines are booming and represents a substantial proportion of the global drug market.

As the global use of herbal medicinal products continues to grow and many more new products are introduced into the market, public health issues, and concerns surrounding their safety are also increasingly recognized. Although some herbal medicines have promising potential and are widely used, many of them remain untested and their use also not monitored. This makes knowledge of their potential adverse effects very limited and identification of the safest and most effective therapies as well as the promotion of their rational use more difficult. It is also common knowledge that the safety of most herbal products is further compromised by lack of suitable quality controls, inadequate labeling, and the absence of appropriate patient information. It has become essential, therefore, to furnish the general public including healthcare professionals with adequate information to facilitate better understanding of the risks associated with the use of these products and to ensure that all medicines are safe and of suitable quality. [9, Rank 4]

Disclosure of Use of Natural Health Products

Reasons patients give for nondisclosure of CAM use include doctors not asking about CAM use, beliefs that doctors do not need to know or would not understand, and doctors' potentially negative responses to CAM. Perceived legitimacy of CAM treatments also affects disclosure. In a qualitative study of self-treatment practices originating from popular, folk and professional sectors, patients most likely discussed treatments from the professional sector with physicians because they were perceived as legitimate and medically acceptable. Research suggests disclosure differs by type of CAM used, but a systematic examination of disclosure rates for specific CAM modalities, provider based and self-care, has not been conducted. Patients may more willingly disclose use of provider-based CAM (e.g., chiropractic or acupuncture) relative to self-care CAM (e.g., vitamins and herbal medicine) if the former is perceived as more legitimate. [2, Rank 3]

The Evolving Role of Natural Products in Drug Discovery

Patients may have an easier time discussing provider-based CAM treatments because of a perception that they are more legitimate and acceptable to a conventional medical provider. Domains with >50% disclosure have licensing requirements (e.g., acupuncture and chiropractic) or greater perceived integration with conventional medicine (e.g., biofeedback, chelation therapy) that likely add to their perceived validity.

Disclosure of self-care CAM ranged from fewer than a quarter of those using relaxation therapies to nearly half of those using megavitamins. Self-care is the most widely used CAM. Simultaneous use of vitamins, herbs and homeopathic remedies with over-the-counter and prescription medications is common, but often users are unaware of possible

interactions between drugs and biologically based CAM therapies. Patients may consider it unimportant to report using herbs and other treatments readily available over the counter, as they often do not discuss pharmaceutical over-the-counter medications, such as analgesics, cold and allergy products and antacids. Low patient disclosure of yoga, tai chi, qi gong and relaxation therapies is not surprising since patients may not see the use of these therapies as interacting with medical treatments and may not consider the medical encounter as a good source of information about these practices.

Corroborating previous research, studies found that African Americans, Latinos and Asian Americans were less likely to disclose any CAM use to healthcare providers relative to non-Latino whites. Racial/ethnic differences in disclosure are mitigated by access and quality of conventional healthcare was partially confirmed. Using 2 national data sets, researchers examined specific factors of access to and quality of conventional care and patient disclosure of CAM use. When sociodemographics were considered, access issues such as insurance and cost were not associated with disclosure. Factors indicative of higher-quality care—including better source of usual conventional care in the NHIS and having a regular doctor and higher patient–provider relationship ratings—were positively associated with greater disclosure and mitigated the effects of race/ethnicity. It is not surprising that sequential opportunities and familiar relationships, especially if combined with culturally competent care, foster communication. Findings indicate a need for improved quality of conventional medical care vis-á-vis patient–provider communication for minority populations.

In studies, race/ethnicity contributed to nondisclosure regardless of access to and quality of conventional care, suggesting impediments to open communication between minority patients and their health providers. Differential treatment at the medical encounter based on patients' race/ethnicity, such as more information provided to and better questions asked of white patients than of African-American patients, is likely to contribute to limited disclosure of CAM in minority groups. For some minorities, distrust of conventional medicine - resulting from racial/ethnic injustices, such as the Tuskegee syphilis study and overuse of avoidable invasive procedures in minority populations - motivates CAM use as a sociopolitical alternative to the shortcomings of the healthcare system. If CAM and conventional treatments are polarized along sociopolitical lines, patients may withhold information about treatments they are using when they visit medical doctors. For immigrants, disclosure may be further impeded by unavailability of providers who speak their preferred language, different communication norms of medical systems in the country of origin, fear about immigration status and unfamiliarity with the American healthcare system.

Being female, having lower health status, a greater number of health conditions, living in the northeast and being married were also associated with increased likelihood of disclosure. Compared to men, women have more medical encounters, have longer appointments and are more engaged at them, which provides more opportunity for

disclosure. Poor health often translates to more frequent medical interactions and perhaps more active medication management, the two conditions that could invite discussion of CAM use. In fact, when women use CAM and see a medical health doctor for the same health concern, disclosure rates are particularly high, ranging from 52−96% depending on the health condition. The associations of place of residence and marital status with disclosure are less clear. [3, Rank 4]

Review of the Use of CAM

Health promotion and illness prevention are important strategies for maintaining and improving health, particularly with increasing age. Health promotion is the process of enabling people to increase control over their health and its determinants, and thereby improve their health. Illness prevention is concerned with avoiding disease and involves health promotion behaviors that prevent disease and improve the overall quality of life. Hence, promotion and prevention are overlapping activities.

The desire to promote health has been suggested as a major reason for the increased use of complementary therapies. As early as 1990, it was found that 58% of adults used complementary therapies for health promotion. Ongoing research has documented the importance of complementary therapies for health promotion. The use of complementary therapies for health promotion has been tied to a changing worldview in which individuals take greater responsibility for their own health and are more cautious in accepting direction from conventional health care providers, such as allopathic physicians. For example, older adults report the use of herbs such as Echinacea to prevent colds, saw palmetto to prevent prostate problems, and ginkgo biloba to maintain memory. Studies have reported that older adults report the use of home remedies, such as vinegar and honey for health promotion.

Complementary therapy use is prevalent among older adults. Among older adults, the general use of complementary therapies varies by gender, ethnicity, age, and education. More women than men use complementary therapies. Although about equal proportions of African American and White older adults use complementary therapies, more African American than White older adults use home remedies. Complementary therapy use is associated with increasing education. Although a decline in use of complementary therapies is often reported for older adults compared to middle aged adults, closer analysis has shown that the decline in use is among those 75 and older.

Investigations focused on the factors related to the use of complementary therapies for health promotion are rare; more conceptually driven investigations of complementary therapy use for health promotion are needed. Several recent investigations have touched on this topic. Many adults with chronic conditions use complementary therapy practitioners, putting these practitioners in an ideal position to advise these adults on health promotion. Researchers, both using data collected by the 2002 National Health Interview Survey, show those who use complementary therapies are more likely to use specific preventive medical care practices, including pneumonia vaccination and influenza

vaccination. They use data from the 2007 National Health Interview Survey to examine whether complementary therapies were used by adults for health promotion or for treating illness. They report that more adults use complementary therapies for health promotion (24.7%) than use them for treating illness (17.4%). They found that the Mind-Body domain, which includes mediation, tai chi, and yoga, was the most common form of complementary therapy used for health promotion. Researchers found that older adults who used complementary therapies for health promotion had lower mental health related quality of-life than those who did not; these older adults did not differ in physical health-related quality-of-life.

The behavioral model of health services provides a framework for the analysis of complementary therapy utilization for health promotion and illness prevention. This model proposes that health care behavior is influenced by three sets of factors: predisposing, enabling, and need. Predisposing factors exist prior to a disease; they influence whether a person uses a service. They include demographic characteristics, education, and health beliefs. Enabling factors are resources that affect a person's ability to access a health care service. They include income, insurance, and social support. Need factors are a person's health or illness characteristics that require the use of services. [4, Rank 4]

The Role of Complementary Therapies in Health Promotion

The older adults use complementary therapies for health promotion, and they use some of these complementary therapies frequently. Almost all of these older adults pray for health promotion, and they do so almost every day. Most also use OTC medicine. At least half use supplements and vitamins for health promotion, and they use these for about 3 days out of every 5, and more than half use exercise but do so on fewer than 2 of 5 days. Other complementary therapies used by many participants for health promotion include specific food or beverages and being active. Few of the participants use home remedies for health promotion. The types of complementary therapies used for health promotion among these older adults reflect the general literature on complementary therapy among older adults in the general population.

The analysis also reflects previous research documenting the associations of enabling and predisposing factors with the use of complementary therapies, although this analysis focused on the use of complementary therapies for health promotion. The enabling factors of being married, having money to treat yourself after bills are paid, and having no problems with access to health care were each associated with the use of a few complementary therapies for health promotion. Having money to treat yourself after bills are paid was also associated with the use of home remedies and supplements. None of the need factors was associated with use of complementary therapies for health promotion. This is not surprising. These need factors were measures of current health problems, while the focus in using these therapies was on prevention.

Consistent with previous research, individuals differ in their use of complementary therapies in terms of predisposing factors, gender, ethnicity, and education. For example, gender was related to the use of supplements; this probably reflects, in part, the use of calcium by women to prevent osteoporosis. Other analyses have also shown that African American older adults make greater use of home remedies. In the bivariate analysis, drinking alcohol was associated positively with the use of several complementary therapies, including herbs, supplements, vitamins, and exercise, but negatively associated with the use of prayer for health promotion. The residents of the study counties are generally conservative Christians, for whom drinking alcoholic beverages is prohibited. The use of alcohol in this context is often a marker for more liberal attitudes.

The predisposing factor most associated with use of the most complementary therapies for health promotion was health information seeking. Those who sought more information about health were more likely to use food and beverages, herbs, supplements, and vitamins for health promotion. They were more likely to exercise. However, they were less likely to pray. Other analyses have not examined the associations of health information seeking with complementary therapy use for health promotion.

The use of complementary therapies is part of a changing worldview in which individuals take greater responsibility for their own health. The use of complementary therapies for health promotion is part of a wellness lifestyle. The importance of health information seeking among the participants who use complementary therapies for health promotion reflects a changing health worldview and wellness lifestyle in which individuals take greater responsibility for their own health. The components of the health information measure indicate the degree to which some of these older adults are taking responsibility for their health. Forty-one percent reported regularly reading newspapers, magazine or books about health, 44.2% reported reading food labels, 37.5% reported watching television or listening to radio programs about health, 24.5% reporting seeking advice from family or friends about health issues, and 13.5% had attended a health fair or wellness program.

Although a small number, that 15 (7.5%) participants reported using the Internet to find health information indicates the growing importance of the Internet in rural populations. However, it is not clear whether older adults' health information seeking efforts represent actual improvements in their health or health behaviors. Older adults, especially those with low health literacy, may not be making a careful and clear critique of the information they access. This may be a concern particularly for older adults who use less valid information or credible sources to promote health without consulting their physicians or other health care providers.

These data were collected from a relatively small sample of older adults residing in a few counties in North Carolina. A random selection procedure was not used. Therefore, caution should be used in generalizing results. Although several categories of complementary therapies were used, the specific types of therapies were too diverse to include in the

analysis. All predisposing, enabling, and need factors that might be related to complementary therapy use could not be included in this analysis. Therefore, the analysis may not specify potentially important associations with complementary therapy use for health promotion. Finally, the multivariate analysis included nine separate models; this could have inflated Type I error. However, the study did engage 200 older adults, with most of them participating over 6 months. The participants provided information on the complementary therapies they used specifically for health promotion at each of the six follow-up contacts.

Older adults are using several complementary therapies for health promotion on a regular basis. The use of complementary therapies for health promotion is associated most consistently with health information seeking, indicating a wellness lifestyle. This health self-management for health promotion may have positive effects on future medical expenditures. However, the self-prescription of some health promotion therapies may increase the out-of-pocket costs for individuals. Future research on health self-management and use of complementary therapies should focus on issues surrounding health promotion. This research should also investigate how health information seeking and wellness lifestyles affect the inclusion of complementary therapies in health promotion and health self-management. [15, Rank 4]

Toxicological Challenges Associated with the Use of Herbal Medicines

With the burst in the use of herbal medicinal products (HMPs) globally, either for primary treatment or as complementary and alternative medicine, safety and efficacy of herbal medicine have become a public health concern. Till date, it has been difficult to make reliable estimates of ill health caused by herbal products particularly because (i) the perception that “natural” equates to “safe” and therefore herbal medicine users would not realise that a herbal remedy may be responsible for adverse symptoms they have experienced; (ii) the lack of communication between patients and medical practitioners regarding the use of herbal medicine; (iii) the presence of low-grade herbal products on the market, and (iv) the supply of counterfeit products.

The World Health Organisation (WHO) estimates that 80% of Asian and African populations rely on traditional medicine as the primary method for health care needs. The scenario in developed countries is very similar with 70% to 80% of the population using some form of complementary and alternative medicine. Whilst conventional medical science has powerful methodologies for proving efficacy, ensuring quality, standardising good manufacturing practices, testing for safety, and conducting postmarketing surveillance for adverse effects, similar guidelines are lacking for herbal products; the same has not been extended to traditional herbal medicines despite these having been embraced by different cultures and regions.

It must, however, be acknowledged that a number of protocols documents on safety and toxicity testing of HMPs have been put forward by the Union of Pure and Applied Chemistry,

the European Medicines Agency (EMEA), and the European Food Safety Authority though they are not followed by all countries. In addition, with the rising demand of medicinal plants from developed countries, international trade particularly via the Internet has ascended. However international trade in medicinal plants is not well regulated, with limited data available on the product identity, on the true demand and supply, and on the price of the unprocessed raw materials and the processed HMPs. Although there exists the WHO certification scheme to regulate the quality of HMPs in international commerce, noncompliance with this certification further accentuates the problems of adverse reactions. [22, Rank 4]

Adverse health effects associated with herbal products exist since time immemorial though and could be attributed to both the inherent toxic effects of herbal medicine and toxicities induced by adulterants/contaminants. The low incidence of adverse reports associated with HMPs in developing countries may be explained by the fact that consumers generally regard them as safe and therefore believe their symptoms are not attributable to the use of those products. In addition, the reluctance to indicate the concomitant use of HMPs to health care professionals, the impression that the adverse effects are known, forgetfulness, unwillingness to report based on suspicion alone, pressures of clinical practice, and uncertainty about the reporting process are key factors which if addressed can certainly help in risk mitigation. Whilst evidence-based studies indicating the efficacy of herbal drugs are still being unveiled, increasing evidence, regarding side effects of herbal medicine, has highlighted the demand for and consequently the necessity of toxicological studies for herbal products.

With the increased discussion on safety assessment of herbs, toxicology constitutes an essential role in the development of herbal medicines and advancements of analytical techniques and molecular technology, in particular the “-omic-” technology comprising transcriptomics, proteomics, and metabonomics, can make a significant contribution to the predictive and preclinical toxicology assessment of herbal medicine.

Apart from the toxicity of the intended herb(s) itself, the lack of a stringent and harmonised quality control and effective monitoring system imposed on herbal medications may lead to contamination or adulteration that could prove harmful to humans. Possible contaminants/adulterants such as heavy metals, pesticides, toxic herbs, and conventional drugs are commonly encountered toxicological concerns in herbal preparations. Nevertheless, strategies in devising suitable toxicological examination protocols to deal with the wide panoply of components in herbal drugs stand as a challenge to toxicologists. [29, Rank 3]

Heavy metal contaminants like cadmium (Cd), arsenic (As), and lead (Pb) can be a risk factor in contributing to the toxicity of these herbal products. The WHO maximum permissible limits of As, Cd, and Pb are 1.0, 0.3, and 10 ppm, respectively, with agricultural practices and industrial emissions being accounted as indirect contributors. Hence, a recent study showed

the level of arsenic in ready-to-use aqueous-based antimalaria herbal medicine in Ghana to be above the WHO permissible levels. Plant material may also be contaminated with pesticides and subsequent poor manufacturing practices may lead to contamination with bacteria, fungi, and other microorganisms. In addition, an increasing number of herbal supplements have been found to be adulterated with active pharmaceutical products.

Case reports have played a crucial role in alerting the scientific community on the adverse effects of therapeutic interventions. This is particularly true for herbal medicines, many of which have a long traditional use but without ever having been submitted to formal tests of safety compared to conventional medicines. Moreover, despite their importance, case reports are often of poor quality, a fact that can seriously limit their value. Hence, many of the case reports in the developing countries are not properly recorded, limiting appropriate conclusion thereby contributing to increasing adverse clinical effects of herbal remedies.

Pharmacokinetics and Pharmacodynamics of Herbal Medications

Toxicological problems associated with the use of herbal medicines are complex but have been regularly associated with serious adverse fatalities ranging from cardiovascular problems to psychiatric to neurological effects to liver toxicity or malfunction to hematologic and renal toxicity. The diagnoses of herbal toxicity are usually made after consideration of the temporal relationship between exposure to the herb and the occurrence of the adverse event and by excluding other causes. However, causality assessment using appropriate tools for ascertaining herbal toxicity in a number of cases has failed to show any causal effects or has indicated only weak causal relationship. For instance, the report of toxic liver injury due to consumption of the herb Greater Celandine (*Chelidonium majus* L.) in patients from various European countries has been a matter of concern.

Moreover, although weak or no causality of herbal toxicity could be shown in many instances, a number of studies still have reported the potentially toxic nature of herbal drugs. In 1992, in Belgium, consumers of a herbal weight-loss preparation containing *Aristolochia* spp. exhibited severe renal disease manifested by interstitial fibrosis, which rapidly progressed to renal failure. Moreover, Aristolochia spp. also used as an aphrodisiac, as an anticonvulsant, as an immune stimulant, and to treat arthritis, gout, rheumatism, eczema, wound treatment, allergic gastrointestinal colic, and gallbladder colic have been subsequently reported to impair renal function due to the presence of aristolochic acid.

In 1995, in Southern Taiwan and Japan, the use of *Sauropus androgynus* in weight control was associated with an outbreak of *Sauropus androgynus*-related obstructive lung disease. The use of blue cohosh herbal medication was associated with profound neonatal congestive heart failure. The effect could be attributed to the presence of vasoactive glycosides and to an alkaloid known to produce toxic effects on the myocardium. Furthermore, blue cohosh has sympathomimetic and direct cardiotoxic effects, which can

cause coronary vasoconstriction and decrease oxygen flow to the heart, thereby leading to morbidity and mortality in the foetus or in newborn infant exposed via maternal ingestion. Similarly, cardiac glycosides have been linked with hyperkalaemia, a side effect observed in a patient taking a long list of herbal medicinal drugs.

Similarly, in 2005, clinical problems arising from the use of herbal medicines were reported in Hong Kong and *Aristolochia* species was found responsible for acute renal failure (*n* = 1), with aconite roots causing aconitine poisoning, the *Datura* species causing anticholinergic poisoning, and "yulan" (*Stephania sinica*) causing tetrahydropalmatine poisoning. Likewise, in 2007, a systematic survey in Swiss hospitals indicated 10 cases implicating Herbalife, a herbal product sold for promoting "wellness" and weight reduction, as a possible cause of potentially severe hepatotoxicity. However it should be noted that the causality assessment in these cases was conducted by the WHO global introspection method, which is not liver-specific and therefore not a reliable tool to ascertain causality in presumed hepatotoxicity cases. Causality assessment of hepatotoxicity cases requires the Council for International Organisations of Medical Sciences (CIOMS) methods. Thus, for the 10 cases, a number of parameters for a valid causality assessment were not reported and there was also a case of hepatitis E explaining the presence of liver disease. [32, Rank 2]

The diagnosis of herbal-drug-induced hepatotoxicity continues to be a challenge despite the availability of causality assessment tests. There are only limited number of clinical studies with HMPs reported in the literature despite the fact that they have been used for centuries. Thus postmarket pharmacovigilance providing interesting source of safety information and causality assessment indicates a link between an observed adverse event to a suspected HMP. Although there is no universally accepted method for causality assessment, the existing methods rely on algorithmic, probability-based, and expert analyses as well as on the quality of adverse reactions reports. Unless causality is established, narrative reports remain less convincing of any herbal adverse reactions.

Cases with severe intoxications in humans have also been reported after consumption of essential oil rich in thujone. Thujone or thujone-containing products have been reported to cause central nervous system disturbances which can lead to convulsions and ultimately to unconsciousness and death. Similarly, licorice (*Glycyrrhiza glabra*) commonly used for inflammation of the upper respiratory tract and gastric and duodenal ulcers has been reported to cause suppression of the renin-aldosterone system, resulting in sodium and water retention, hypokalemia, hypertension, cardiac arrhythmias, and myopathy in cases of prolonged use. Also, 10 deaths and 13 permanent disabilities from Ephedra-containing herbal drugs were reported to the FDA and the effects with ascribed to its sympathomimetic effects. Overall, it is seen that while, on one hand, the toxic effects of herbs have been widely reported in developed countries, the same has not received an equivalent depth of scrutiny in developing countries.

The toxicity of herbs may also result from the generation of reactive intermediates through metabolic activation of herbal constituents via phases I and II reactions within the human body. The resultant reactive intermediates can bind covalently to DNA and proteins, leading to organ toxicity, mutagenicity, and even carcinogenicity. For instance, aristolochic acids in *Aristolochia* spp. used in a number of Chinese traditional medicine undergo reduction of the nitro group by hepatic CYP1A1/2 or peroxidases in extrahepatic tissues generating highly reactive cyclic nitrenium ions. The latter can react with DNA to form promutagenic DNA adducts such as 7-(deoxyadenosin-N6-yl) aristolactam I and 7-(deoxyguanosin-N2-yl) aristolactam I as well as protein, resulting in activation of H-ras and myc oncogenes and gene mutation in renal cells and finally carcinogenesis of the kidneys. In vitro studies have also indicated the role of herbal reactive intermediates in irreversibly inhibiting various cytochrome enzymes (CYPs). However, the discrepancy of effects between in vitro, animal, and human studies reflects the significance of herbal dosing in the modulation of CYPs.

Other factors compromising safety may result from herbs harvested from polluted sites or poor farming practices, medicinal plant products contaminated with pesticides and microbial contaminants, heavy metals, toxic substances, and adulterants which can be toxic to the consumer. [38, Rank 5]

Evidence Based Drug Herbal Reactions

The contemporary use of herbal medicine is widespread but the challenge that society faces with its use is whether a patient will divulge to his or her medical practitioner, the concurrent use of herbal products with conventional pharmacotherapy. A number of observational studies have shown the negative or conflicting interactions of drugs and herb though theoretically herb-drug interactions could also be positive or neutral. Herbal drugs usually contain a multitude of pharmacologically active ingredients, a fact that greatly increases the possibilities of interactions. In many instances, the likelihood of herb-drug interactions could be higher than drug-drug interactions.

Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects via the pharmacokinetic herb-drug interactions caused by one medicine interfering with the elimination, metabolism, or absorption of another medicine and the pharmacodynamic herb-drug interactions caused by two different medicines working in the same or opposite directions and ultimately affecting the dose response and any mechanisms of therapeutic or toxic effects. For example, St-John's Wort, a well-known cytochrome P450 inducer, may affect systemic bioavailability of many conventional drugs

Common examples of herb-drug interactions have been found when cardiovascular medications with a narrow therapeutic index, such as digoxin and warfarin, are coadministered with herbs. For instance, concomitant use of warfarin with St. John's Wort decreases prothrombin time, which may result in reduced anticoagulant effect and need for increased warfarin dose. Other examples of interactions include St. John's Wort with cyclosporine and grapefruit juice with felodipine and lovastatin.

The current evidence that herbal medicine may interact with conventional drugs is mainly based on case reports of patients, case series, and a limited number of clinical studies. Drug-herbal interactions are difficult to evaluate because of the lack of compositional reliability of the herbal products though a number of interactions, amongst which are drug-metabolizing enzymes and drug transporter systems, as well as pharmacodynamic interactions can be involved. However since the pharmacokinetic and pharmacodynamic characteristics of most herbal medicine or supplements are not completely recognized, potential interactions cannot be predicted.

In a clinical study involving 313 patients, herbal drugs used alone were relatively safe, but the risk for adverse reactions may increase when herbal and conventional drugs are taken concurrently. The results indicated a 2.3% incidence of liver injury in the combined group of Korean patients. Concomitantly, rutaecarpine, an alkaloid found in *Evodia rutaecarpa*traditionally used in combination with Chinese traditional medicine, had profound effects on the hepatic drug processing enzyme gene expression, CYP enzyme genes and UDP-glucuronosyltransferase, and increased the expression of hepatic uptake and efflux transporters. The authors speculated that all these effects could play an integrated role in rutaecarpine-increased metabolism and elimination of caffeine, theophylline, and acetaminophen. [41, Rank 2]

From evidence-based herb-drug interaction in cancer chemotherapy, most of the available information, both positive and negative, came from basic in vitro experiments or trials testing the use of a single herb along with chemotherapy drug when in practice most of the herbs are used in mixtures. It is not reasonable to discard the potential usefulness of the traditional wisdom of herbal medicine, which has the backing of thousands of years of clinical experience. However, this statement should be taken with some level of skepticism particularly since clinically relevant pharmacokinetic interactions between anticancer drugs and CAM have already been reported between the frequently used St. John's Wort and the anticancer drugs irinotecan and imatinib.

Regulations Concerning The Use of Herbal Medicines in Developing Countries

Due to the wide use and easy availability of herbal medicines, herbal toxicity and herb-drug interactions have become an issue of global concern. While companies provide opportunities for complementing the armoury of existing drugs, for their purportedly preventive and therapeutic purposes, the major problem with the use of herbal-based treatments is the lack of definite and complete information about the composition of extracts, resulting mainly from the trade secrecy of a number of herbal practitioners. Despite the fundamental role that traditional medical practitioners play in the provision of health services in developing countries, trade secrecy has been observed and is currently encroaching on the proper assessment of local herbal drugs.

Hence, in many developing countries involved with the active production and use of regulations distinct from the one for food and drugs are warranted. The existence of such

regulation can emphasise a premarket system, which provides market authorisation for each based on evidence that the product is safe under the recommended conditions of use without a prescription, effective for the proposed claims, and of high quality, and is mandatory. In addition, a licence issued on the basis of evidence of compliance with Good Manufacturing Practices to importers, manufacturers, packagers, and labellers will certainly aid in reducing health-related risks.

There is also a strong need for scientific evidence of the pharmacological qualities and safety of herb-derived remedies employed for centuries as traditional medicines in these countries. This is particularly because sound knowledge of the mechanisms of actions and interactions is essential for a clinical risk assessment. In addition, the design of an appropriate postmarket pharmacovigilance system will help address the fatalities of herbal drugs. Surveillance for HMP-related adverse responses should consist mainly of prompting voluntary reporting from consumers and health care practitioners. It should be noted that even if the interactions between medicinal herbal products and drugs may be clinically insignificant, susceptibility to them may be enhanced by a wide variety of patient-related factors, such as the presence of multiple diseases, other pharmacotherapies, or genetic predisposition.

At the same time, it would be helpful to set up a national and/or regional accessible database to document the use of herbal medicines. Concurrently, efforts should be made to educate both healthcare professionals and patients about the use of herbal medicine. It should also be emphasised that besides its role in primary healthcare, traditional medicines have been and continue to be a strategic option in drug discovery.

The previously mentioned long-term strategies could certainly help to address the toxicological concern of herbal drugs in developing countries. But more immediate actions are also warranted and should be geared towards (1) greater communication between patients and physicians about the use of herbal medicine, (2) health care professional should be aware of herb-drug interactions and encourage patients to discuss herbal medicine use, (3) physicians should question patients about their use of herbal medicines, and (4) surveillance of adverse responses should be monitored. In the meantime, preclinical and clinical studies should be conducted to ascertain herb-drug interactions and government regulatory authority should put more efforts into natural health product regulations. [55, Rank 5]

Factors Responsible for Increased Patronage of Herbal Medications

Essentially, herbal remedies consist of portions of plants or unpurified plant extracts containing several constituents which are often generally believed to work together synergistically. The recent resurgence of public interest in herbal remedies has been attributed to several factors some of which include (i) various claims on the efficacy or effectiveness of plant medicines, (ii) preference of consumers for natural therapies and a greater interest in alternative medicines, (iii) erroneous belief that herbal products are

superior to manufactured products, (iv) dissatisfaction with the results from orthodox pharmaceuticals and the belief that herbal medicines might be effective in the treatment of certain diseases where conventional therapies and medicines have proven to be ineffective or inadequate, (v) high cost and side effects of most modern drugs, (vi) improvements in the quality, efficacy, and safety of herbal medicines with the development of science and technology, (vii) patients' belief that their physicians have not properly identified the problem; hence the feeling that herbal remedies are another option, and (viii) a movement toward self-medication.

The increasing utilization of herbs for self-medication by patients or individuals is also attributed to a number of other reasons such as (i) patients being uncomfortable about discussing their medical problems and fear lack of confidentiality in handling their health information, (ii) fear of possible misdiagnosis and wrong treatment by patients with non-specific symptoms or general malaise, and (iii) lack of time to see a physician; this is usually a reason where prior visit did not yield any positive experience. Furthermore, patients' freedom of choice of a practitioner is also encouraging their utilization of alternative treatments and herbal remedies, although many select herbal medicines from a deductive approach based on anecdotal information. So also, because of the influence of religion and greater level of spiritual consciousness, many individuals tend to be increasingly disposed to accepting therapeutic value of a treatment based on faith or intuition rather than scientific reasoning. Herbal medicines, therefore, become particularly alluring when the body's natural capacity for self-repair, given appropriate conditions, is emphasized.

In addition to all these above-mentioned factors, the marketing strategies and efforts by various manufacturers of herbal medicines and their sales representatives have seriously projected these products into greater limelight. Various advertisements in the mass media including television and radio programmes have significantly increased consumers' awareness and given the herbal products undue respectability and credibility. These advertisements are carefully presented to attract the different age groups of people that exist in the society. Children are encouraged to use herbs for their nutritional values to facilitate normal or healthy growth and development; young persons for their euphoric effects, supply essential ingredients to help them cope with daily stress and to prevent or slow the onset of aging; older persons for their anti-aging or rejuvenating effects and women for slimming and beauty enhancing effects. [67, Rank 4]

Influence of Regulatory Policies on Safety of Herbal Medicines

It has been observed that most of the problems associated with the use of traditional and herbal medicines arise mainly from the classification of many of these products as foods or dietary supplements in some countries. As such, evidence of quality, efficacy, and safety of these herbal medicines is not required before marketing. In the same vein, quality tests and production standards tend to be less rigorous or controlled and in some cases, traditional health practitioners may not be certified or licensed. The safety of traditional and herbal

medicines has therefore become a major concern to both national health authorities and the general public.

Until 2011, there were three possible regulatory routes by which an herbal product could reach a consumer in the US. The unlicensed herbal remedy is the commonest route which does not have to meet specific standards of safety and quality neither is it required to be accompanied by safety information for the consumer. Recently, the European Union (EU) implemented a directive after a 7-year transition period to harmonize the regulation of traditional herbal medicine products across the EU and establish a simplified licensing system in order to help the public make informed choices about the use of herbal products. This requires that all manufactured herbal products either gain a product license of the type needed to manufacture “conventional” products or become registered as a “traditional herbal medicinal product”.

Like conventional medicines, licensed herbal medicines hold a product license based on safety, quality, and efficacy. Hence, it is compulsory that they are accompanied by comprehensive information such as indications, precautions, how to use the product, side effects, how to store the product and regulatory information, for safe use. This information is usually provided on a leaflet inserted into the product package. On the other hand, due to insufficient evidence of reproducible efficacy to meet regulatory standards, license cannot be obtained for some herbal medicines to sell these products. This led to the creation of a new category of traditional herbal registration (THR) with a transition period of seven years.

In line with this, the Traditional Herbal Medicines Registration Scheme, which is a “simplified registration scheme,” was introduced in the US. In this scheme, herbal medicinal products are required to meet specific standards of safety and quality, agree upon indications for use based on their traditional use and also provide information in a leaflet to promote safe use of the product by the purchaser. However, this is not the case in many other parts of the world, especially in the developing countries where many unregistered and poorly regulated herbal products are sold freely on the market with little or no restraint. Furthermore, the common misconception that natural products are not toxic and are devoid of adverse effects often lead to improper use and unrestrained intake and this has also resulted in severe poisoning and acute health problems. This misconception is not limited to the developing countries. It also exists in highly developed countries, where the general public often resorts to “natural” products without any proper awareness or information on the associated risks, particularly in the event of excessive or chronic use. [73, Rank 4]

Toxicity and Adverse Health Effects of Some Common Herbal Medicines

In most countries, herbal medicines and related products are introduced into the market without any mandatory safety or toxicological evaluation. Many of these countries also lack effective machinery to regulate manufacturing practices and quality standards. These herbal

products are continuously made available to consumers without prescription in most cases and the potential hazards in an inferior product are hardly recognized.

It is important to reiterate the staggering rate at which interest and use of herbal medicines is expanding. Over the past decade, the use of herbal medicines represents approximately 40% of all healthcare services delivered in China while the percentage of the population which has used herbal medicines at least once in Australia, Canada, USA, Belgium, and France is estimated at 48%, 70%, 42%, 38%, and 75%, respectively. In spite of the positive perception of patients on the use of herbal medicines and alleged satisfaction with therapeutic outcomes coupled with their disappointment with conventional allopathic or orthodox medicines in terms of effectiveness and/or safety, the problem of safety of herbal remedies continues to remain a major issue of concern.

The general perception that herbal remedies or drugs are very safe and devoid of adverse effects is not only untrue, but also misleading. Herbs have been shown to be capable of producing a wide range of undesirable or adverse reactions some of which are capable of causing serious injuries, life-threatening conditions, and even death. Numerous and irrefutable cases of poisoning have been reported in the.

Study revealed that this herbal formula was capable of elevating plasma levels of liver enzymes and inducing hypokalemia following 30 days administration in rats. From our observation, the potassium loss (which is capable of predisposing to dangerous arrhythmias) was a greater risk associated with this herb during this sub-acute exposure or toxicity study. Prior to this study, we had evaluated the safety of “super B blood purifier” and “super B seven keys to power” mixtures in experimental model over a decade ago. These herbal mixtures were marketed by a registered Nigerian company which cultivated medicinal plants and manufactured medicinal herbal preparations. The herbal blood tonics were well patronized by common folks who claim their efficacy according to the manufacturer’s stipulation that “they are safe, give strength and cleanse the blood and body of infection.” Researchers obtained the herbal constituents (*Entandrophragma utile*and *Anacardium occidentalis*) and investigated the individual plant extract as well as the herbal tonics made from them.

Although, all the extracts and tonics proved safe during acute toxicity study, chronic toxicity testing revealed splenic enlargement in 10% of mice that received *E. utile* or either of the two tonics and one case of lung tumor. Recently, researchers reported an association between traditional herbal medicine use and the development of liver fibrosis among study participants in Uganda. A number of Chinese herbal medicines and other herbal medicines from different parts of the world have also been implicated in cases of poisoning. Many of them have been shown to contain toxic compounds which are capable of reacting with cellular macromolecules including DNA, causing cellular toxicity, and/or genotoxicity. For the purpose of brevity and other obvious constraints, adverse reactions of only a few commonly used herbal medicines are described below.

ARISTOLOCHIC ACIDS AND ***Aristolochia*** SPECIES

Following the discovery of the nephrotoxic and carcinogenic potentials of aristolochic acids, several studies confirmed their genotoxic activity demonstrated the presence of aristolochic acids-related DNA adducts in renal tissues of patients. These mutagenic adducts when formed are usually poorly repaired and are capable of persisting for years in DNA. Aristolochic acids I and II have been identified in different Asian medicinal plants and also reported to be present in slimming products.

Misidentification of medicinal plants and mislabeling herbal medicinal products are sometimes responsible for some of the observed adverse events or interaction and that is the reason it is important to assess herbal medicines for possible presence of adulterants. In the UK and many other countries *Aristolochia fangchi*was linked to the development of subacute interstitial fibrosis of the kidney referred to as "Chinese herbs nephropathy". Also, recently a 75-year-old man was reported to have died in Australia from kidney failure associated with a toxic preparation containing the root of *Aristolochia fangchi* which he purchased over the internet for psoriasis. This case report suggested the chronic use of aristolochic acid-containing herbal product as the most likely cause of the patient's death. Similar cases had previously been reported. Consumption of aristolochic acid-containing Chinese herbal products has also been demonstrated in several studies to be associated with increased risk of urothelial cancer.

A few years back, poisoning that was attributed to Fang-Ji (*Stephania tetrandra* S. Moore) in a weight-loss preparation was actually caused by Guang-Fang-Ji (*Aristolochia fangchi*;). The presence of aristolochic acids in the latter produced dramatic adverse reactions which led to nephrotoxic and carcinogenic events in more than 100 women using this weight-loss preparation. In this instance, the similarity in the names of the two herbal products was responsible for the confusion and the unfortunate events.

Ephedra sinica

Ephedra is a very popular herb with long history of traditional use in respiratory conditions. This herb, whose efficacy has been demonstrated in a number of randomized double-blind clinical trials, is currently included in the Chinese Pharmacopoeia for therapeutic use and classified as non-toxic. It is an ingredient in commonly used formulary preparations such as Xiaoqinglong Heji for common cold and Zhisou Dingchuan Koufuye for asthma. *Ephedra* has been marketed in the US as a weight-loss dietary supplement and its use associated with a number of serious cardiovascular and central nervous systems (CNSs) adverse effects. Several case reports have also linked the use of *Ephedra sinica* and *Ephedra*-containing dietary supplements to adverse events such as hepatotoxicity, neurotoxicity and transient blindness.

Aconitum SPECIES

Aconitum carmichaeli and *Aconitum kusnezoffii* are used traditionally for pain relief. The toxicity of the medicinal plants derives primarily from the presence of diester diterpene alkaloids such as aconitine, mesaconitine, and hypaconitine in them. These medicinal plants constitute important ingredients in some commonly used herbal preparations like Sini Tang, Fuzi Lizhong Wan, and Guifu Dihuang Wan for stroke and heart failure, diarrhea and diabetes, respectively. Poisoning due to homemade medicated liquor containing aconite and traditional medicine containing *A. carmichaeli* were reported in China between 1999 and 2008.

Severe cases of cardiac toxicity from consumption of aconitine-containing herbal preparation manifesting as ventricular tachycardia and fibrillation and eventually leading to death have been reported. In other studies bradycardia and hypotension were observed. Clinical cases of aconitine poisoning from *A. kusnezoffii* consumption have also been reported. Furthermore, the toxic effect of the combination of *A. kusnezoffii* and *A. carmichaeli*overdose which manifested as bradycardia and hypotension was also reported in a case study.

Tussilago farfara

Traditionally, *Tussilago farfara* has been used effectively for thousands of years for the treatment of acute and chronic cough and it is generally regarded as non-toxic. Total alkaloids and senkirkine isolated from this plant, on the other hand, have been demonstrated to be hepatotoxic. Recently, the potential health effects of the pyrrolizidine alkaloids found in *T. farfara* was reviewed and hepatic veno-occlusive disease and cirrhosis were suggested as the major potential disease outcome in human. However, restrictions in intake of pyrrolizidine-containing herbs and further investigations were recommended because of paucity of data on toxicity assessment in human.

GARLIC (***Allium sativum***)

Garlic has found relevance for management of hypertension and hypercholesterolemia besides its use as a food or food additive. It is known to contain alliin, which on crushing or chopping in the absence of heat or acid becomes activated by alliinase to allicin. Adverse effects associated with garlic extract including burning sensation in the gastrointestinal tract, nausea, diaphoresis, and lightheadedness have been reported. This extract may also cause contact dermatitis and morbid spontaneous spinal epidural hematoma has been attributed solely to excess garlic ingestion.

Ginkgo biloba AND ***Ginseng***

Ginkgo biloba has found widespread use in a variety of conditions and several products such as elixirs, extracts, tea, as well as capsules and tablets that may differ in terms of content,

have been made from the dried root. The whole root which contains ginsenosides is usually used because these compounds possess specific pharmacologic effects that may oppose each other. Over 30 ginsenosides have been identified and these compounds are being investigated for their ability to inhibit cell proliferation, tumor cell invasion, and/or metastasis. Recently, the ability of ginsenosides to modulate signaling pathways involving cell cycle, inflammatory, or growth factor pathways, was demonstrated. The leaf extracts of ginkgo had also been demonstrated to contain active compounds that had found usefulness in improving circulation and cognition.

The plant extracts appear to be relatively safe, although headache, dizziness, restlessness, nausea, vomiting, diarrhea, and dermal sensitivity are the most common side effects that have been observed. *Ginkgo* has been demonstrated to be capable of inhibiting platelet-activating factor and altering bleeding times. Therefore, cautious use had been advised in individuals or patients on anticoagulants therapy. The ability of ginkgo to induce liver cancer in experimental model was reported recently and genotoxic mechanisms were suggested to play some role in the carcinogenic process.

Similar observation was made in the thyroid gland and further studies are required to determine whether the mechanisms for the ginkgo-induced thyroid tumors are also found in humans. In addition to the carcinogenic effects in the liver and thyroid, ginkgo has also been shown to be capable of inducing tumorigenesis in the nasal cavity. The pathogenesis of the nasal lesions was suggested to be related to toxic metabolites of ginkgo reaching the nasal cavity from the systemic circulation. Some other authors, however, have attributed the nasal lesions to gastric reflux/post gavage reflux through the nasopharyngeal duct.

Although, *Ginseng* products as well as the published descriptions rarely report or specify the species, *Ginseng* used as herbal remedies has different botanical sources generally obtained from several *Panax*species including *Panax quinquefolius, Panax Ginseng*, and *Panax pseudoginseng*. In large or excessive doses, *Ginseng* has been reported to cause agitation, insomnia, and elevation of blood pressure while mastalgia and vaginal bleeding have been observed at recommended doses.

Other adverse effects that have reported include transient nervousness, excitation, insomnia, inability to concentrate, headache, epistaxis, and allergies. A case of severe but non-fatal Stevens–Johnson syndrome was reported following a 3-day *Ginseng* administration. Also, spontaneous bleeding from the iris into the anterior chamber of the eye was linked to the use of *G. biloba* extract.Separate case reports had also linked the use of *G. biloba* to the development of bilateral subdural hematomas and subarachnoid hemorrhage.

KAVA (*Piper methysticum*)

Kava is known for its CNS depressant activity and it is commonly used as an anxiolytic agent. Commonly reported side effects of this medicinal plant include headache, dizziness,

gastrointestinal discomfort, and localized numbness after oral ingestion. Large dosages has been shown to be capable of giving rise to dry, scaly skin, and yellowish discoloration of the skin and nails, photosensitivity and redness of the eye. Excessive consumption of kava may also lead to photophobia and diplopia.

The muscle relaxant and anticonvulsant effects of this plant have been attributed to its active pyrones constituent. Significant interaction of kava with other CNS depressants which may lead to a comatose state has been reported and as such concurrent use with these agents is usually not advised.

In 2002, the US Food and Drug Administration received several reports of liver-related injuries alongside that of a previously healthy young female who eventually required liver transplantation following consumption of kava-containing products. This prompted the FDA to alert consumers on the potential risk of severe liver injury associated with the use of kava-containing dietary supplements. This liver-related risks also prompted regulatory agencies in other countries including Germany, Switzerland, France, Canada, and the UK to warn consumers about the potential risks of kava use and also went on to consider the withdrawal of kava-containing products from the market. In over 25 reports of adverse events outside the US, kava-containing products were associated with liver-related injuries like hepatitis, cirrhosis, and liver failure with some of the affected patients eventually requiring liver transplants.

ST. JOHN'S WORT

Hypericum perforatum, popularly known as St. John's wort, contains active compounds, such as hypericin, hyperforin, and melatonin. It was once used against viral infections but has gained increased use for mild depressive symptoms. Adverse effects reportedly associated with its use include allergic reactions, headache, dizziness, restlessness, fatigue, dry mouth, nausea, vomiting, constipation, and photosensitivity. Hyperesthesia and a syndrome of dyspnea and hyperventilation with flushing headache, mydriasis, nausea, palpitations, and tremor, have been reported along with a hypomanic episode in a patient with a history of panic disorder who took St. John's wort tincture for 10 days. The hypomanic episode, however, resolved within 2 days of discontinuing the herbal remedy. Interaction of St. John's wort with antidepressants and anticoagulants has been demonstrated and the herbal remedy is usually not recommended in pregnancy because of its uterotonic activity. [82, Rank 2]

Challenges Associated with Monitoring Safety of Herbal Medicines

With the enormous global consumption of herbal products and medicines, it is high time they were included in pharmacovigilance systems. In terms of population exposure alone, it is essential to identify the risks associated with the use of herbal medicines, and in this regard, the safety of these products has become an issue of great public health importance. There is no doubt that the increasing cases of poisoning associated with the use herbal

medicines in many parts of the world in recent times, is necessitating the need to ensure thorough toxicity assessment alongside active pharmacovigilance on these products in order to promote their safe use and protect public health.

The development as well as implementation of the regulation of traditional or herbal medicines in different parts of the world is often confronted with several challenges. Challenges often encountered and common to many countries are those related to regulatory status, assessment of safety and efficacy, quality control, safety monitoring and inadequate or poor knowledge about traditional, complementary/alternative, and herbal medicines within national drug regulatory authorities.

CHALLENGES RELATED TO THE REGULATORY STATUS OF HERBAL MEDICINES

The definition and categorization of herbal medicines vary from one country to another. Depending on the regulations applying to foods and medicines, a single medicinal plant may be categorized as a food, a functional food, a dietary supplement, or a herbal medicine in different countries. This introduces serious difficulty in the definition of the concept of herbal medicines for the purposes of national drug regulation while at the same time also confusing patients and consumers.

In the United States, for example, natural products are regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994. By definition, a dietary supplement is a product that is ingested and is intended to supplement the diet and contains a “dietary ingredient.” The dietary ingredients in these products may include vitamins, minerals, herbs, or other botanicals. Under the DSHEA, additional toxicity studies are generally not required if the herb has been on the market prior to 1994. In this regard, the FDA bears the burden to prove that a herbal medicinal product or “dietary ingredient” is toxic or not safe for use. Additional major challenge in many countries is the fact that regulatory information on herbal medicines is often not shared between regulatory authorities and safety monitoring or pharmacovigilance centers.

CHALLENGES RELATED TO THE ASSESSMENT OF SAFETY AND EFFICACY

There is no gainsaying the fact that the requirements as well as the research protocols, standards and methods needed for the evaluation of the safety and efficacy of herbal medicines are much more complex than those required for conventional or orthodox pharmaceuticals. A single herbal medicine or medicinal plant may contain hundreds of natural constituents, and a mixed herbal medicinal product may contain several times that number. Suppose every active ingredient were to be isolated from individual herb from which the herbal medicine is formulated or produced, the time and resources required would be tremendous. Such an analysis may practically be impossible especially where an herbal product is a mixture of two or more herbs.

CHALLENGES RELATED TO QUALITY CONTROL OF HERBAL MEDICINES

The quality of the source materials used in the production of herbal medicines determines to a large extent the safety and efficacy of these herbal remedies. Generally, the quality of source materials is dependent not only on intrinsic (genetic) factors, but also on extrinsic factors like environmental conditions, good agricultural, and good collection practices (GACP) for medicinal plants, including plant selection and cultivation. It is the combination of these factors that makes it difficult to perform quality controls on the raw materials of herbal medicines. According to good manufacturing practice (GMP), correct identification of species of medicinal plants, special storage, and special sanitation and cleaning methods for various materials are important requirements for quality control of starting materials.

One of the major challenges often encountered in the quality control of finished herbal medicinal products, especially mixture herbal products, is the difficulty in ascertaining the inclusion of all the plants or starting materials. Thus, the general requirements and methods for quality control of finished herbal products remain far more complex than for other pharmaceuticals. To ensure safety and efficacy of herbal medicines, therefore, WHO continues to recommend the institution of quality assurance and control measures such as national quality specification and standards for herbal materials, GMP for herbal medicines, labeling, and licensing schemes for manufacturing, import and marketing, in countries where herbal medicines are regulated.

CHALLENGES RELATED TO SAFETY MONITORING OF HERBAL MEDICINES

In recent years, issues relating to increasing use of herbal products in developed countries, dependence of many people living in developing countries on plants as a major source of medicines coupled with absence or weak regulation of herbal medicines in most countries and the occurrence of high-profile safety concerns, have increased awareness of the need to monitor safety and deepen understanding of possible harmful as well as potential benefits associated with the use of herbal medicines. Adverse events arising from consumption of herbal medicines are attributable to several factors among which include the use of the wrong species of plant by mistake, adulteration of herbal products with other, undeclared medicines, contamination with toxic or hazardous substances, overdosage, misuse of herbal medicines by either healthcare providers or consumers and use of herbal medicines concomitantly with other medicines.

Although, the assessment of the safety of herbal medicines has become an important issue for consumers, regulatory authorities, and healthcare professionals, analysis of adverse events related to the use of these products is much more complex than in the case of conventional pharmaceuticals. It is also recognized that evaluation of safety is complicated by factors such as the geographical origin of plant material, different processing techniques, route of administration, and compatibility with other medicines. Furthermore, there is lack of the knowledge and/or poor emphasis on the importance of taxonomic botany and

documentation by most manufacturers of herbal medicines and this poses peculiar challenges during identification and collection of medicinal plants used for herbal remedies.

In order to eliminate the confusion created by the common names, it is necessary to adopt the most commonly used binomial names (including their binomial synonyms) for medicinal plants. For example, *Artemisia absinthium* L., which contains an active narcotic derivative and capable causing CNS disorders and generalized mental deterioration, has at least 11 different common names. Seven of the common names bear no resemblance to its botanical name. Because common names are mainly used, *Heliotropium europaeum* (heliotrope), which contains potent hepatotoxic pyrrolidine alkaloids, is often confused with *Valerian officinalis* (garden heliotrope), known to contain valepotriates with sedative and muscle relaxant properties. This explains why it is important to provide the exact scientific name of the plant, the plant part used, and the name of the manufacturer when reporting adverse drug reactions of herbal medicines. Therefore, effective monitoring of safety of herbal medicine will require effective collaboration between botanists, phytochemists, pharmacologists, and other major stake-holders. [96, Rank 5]

The Association Between Health Risk Factors and Use of CAM

Physical activity has been shown to exert a protective effect on health even in those with generally poor health behaviors. In addition, physical fitness has been associated with younger age, better education, higher income, greater internal (versus external) health locus of control, and higher sense of coherence, which is also consistent with CAM use in this report.

Associations between CAM use and smoking status were not observed in earlier surveys of health fair participants, individuals attending geriatric clinics, and members of managed care and health maintenance organizations. Although participants in these surveys appeared to be healthier than our NHIS participants, in our analysis, adjusting for the number of health conditions and physician visits, and the use of pharmaceutical drugs had little effect on the odds ratios for the effect of smoking status on CAM use. Because researchers performed a cross-sectional analysis, the direction of causality, whether these individuals stopped smoking or used CAM first, cannot be directly assessed.

However, several converging lines of evidence suggest the possibility of a time sequence. First, unpublished data from the NHIS suggest that a sizable number of CAM users do so for self-management of addictive behaviors. Second, in our data, CAM was more strongly associated with former smoking than with current smoking. This is consistent with smokers deciding to quit as part of a move to a healthier lifestyle that could involve CAM. If people first used CAM then quit smoking, we would expect more of an association between CAM and current smoking. Longitudinal analyses will be needed to answer this question definitively.

Previous reports have not agreed on whether, and to what extent, alcohol consumption is associated with CAM use, with some finding an inverse association, some a positive association, and some no significant relationship. After adjustment for potential confounds, we found CAM use to be highest among those who consumed light to moderate amounts of alcohol. Of note, some research has identified linkages between light to moderate alcohol consumption and a number of positive health behaviors, including regular physical activity, having a healthy weight, not smoking, and getting influenza vaccinations. Taken together, these findings suggest that people make clear lifestyle choices that encompass a range of health-related activities, including CAM use.

Researchers identified a set of noteworthy associations between select measures of health status, healthcare access and utilization, and sociodemographic measures and the use of CAM independent of the relationships between respondents' health behaviors and CAM use. Similar to other reports they found a particularly strong association between use of CAM and a number of factors indicative of poorer health, such as the number of reported health conditions and the number of reported doctor visits. However, CAM use was also associated with improved health status and increased use of self-care indicators such as LTPA. The latter suggests that while CAM use is most likely among those with current chronic health problems, a subset of CAM users may be healthier (or more health-conscious) than those who do not use CAM. The association between CAM use and frequent physician visits could also be interpreted to reflect more active involvement in care. This is consistent with the concept that a significant portion of CAM use is for prevention, health promotion, and wellness, rather than solely treatment of illness.

The variables being investigated were self-reported. The scientific literature suggests that most people tend to under-report negative health behaviors. Hence, the effects of alcohol consumption, for example, may have been diminished in this study. Flu shots are very different than the other health behavior indicators we used in that flu shots require contact with a health care provider. As such, obtaining a flu shot is influenced by many factors other than an individual's motivation such as access to care or availability of vaccine, potential confounders we could not account for in our analyses.

This might have resulted in underestimating the association between CAM use and obtaining a flu shot seen by others. These data reflect a cross-sectional set of associations. Longitudinal assessments might have identified cohort and secular trends in the associations between health behaviors and CAM use that were not evident in cross-sectional analysis. Fourth, it is possible that additional respondent health behaviors (as well as other unexplored factors) explain more of the observed relationships. However, the five measures employed are important modifiable factors contributing to fatal diseases and morbidity, and can be seen as standard measures of a healthy lifestyle. Finally, because primary focus was to identify factors associated with the use, versus nonuse, of CAM, a dichotomous dependent variable was utilized. By doing so, information on the number and type of CAM therapies used and frequency of their use was lost. It may be that substantial differences

exist between heavy and light users of one or more CAM modalities. It has been found that the use of specific types of CAM therapies is associated with specific personality styles. These associations might confound our results if specific personality styles (e.g., "openness" or "control") are also related to adoption of positive health behaviors. [95, Rank 5]

An Evidence Based Review of Some of the Commonly Used Herbal Medications

Saw Palmetto

The efficacy of saw palmetto (also known as *serenoa repens*) is currently the subject of active investigation by several research groups. An updated systematic review of saw palmetto for BPH found that most, but not all, published studies showed some modest benefit in overall lower-urinary tract symptoms and nocturia, but that much of the available research suffered from serious methodologic problems. Researchers recently reported the efficacy results of a year-long clinical trial of a saw palmetto extract in men with at least moderately severe BPH that addressed many of the shortcomings of earlier studies. This trial, the Saw palmetto Trial for Enlarged Prostates (STEP) study, found no evidence of efficacy of saw palmetto for either BPH symptoms or objective measures of urinary function.

Despite the substantial quantity of clinical research performed on saw palmetto, there are few data regarding potential adverse effects associated with its use. Most trials were of short duration; few described any systematic attempt to assess adverse effects, and with rare exception, laboratory testing was not performed to test for asymptomatic toxicities of saw palmetto. This information is of great public-health consequence given the large numbers of men who self-medicate with saw palmetto for extended periods of time. Since it is well known that most individuals who take dietary supplements do not inform their physicians about their use of these products, most men who take saw palmetto will not be monitored for potential adverse effects. Understanding the risks of using saw palmetto, therefore, is of great importance for patients, clinicians, and regulatory authorities.

Consumption of this saw palmetto extract, at a dose of 160mg twice daily over a period of one year, was associated with any clinically important adverse effects. Relatively few participants suffered serious adverse events, and these were more common in the placebo-allocated participants. Non-serious adverse events were nearly equally distributed between the saw palmetto and placebo groups, both in total number and in the proportion of participants who suffered at least one adverse event.

Only one of the five domains on the O'Leary sexual-functioning instrument (the perception-of-problems domain) showed a significant difference between treatment groups; however, this difference was small (approximately 1/3 of a point difference on a 12-point scale). Finally, we found little evidence of toxicity of saw palmetto among the laboratory analyses performed: while there were a small number of significant results, the large number of tests conducted would be expected to generate a small number of significant differences due to

chance. Further evidence suggesting that these differences are most likely due to chance is the fact that no other liver-function tests besides the total bilirubin showed significant differences and that the greater source of the observed difference in potassium levels was due to a small decline in the placebo group, not a rise in the saw palmetto group; the significant difference in glycosuria was due to an increase in urine glucose in placebo-allocated participants.

With the growing popularity of dietary supplements, it is imperative that better data on their potential toxicities be generated. Several dietary supplements have been shown to have serious toxic effects and have been removed from the market in the U.S. and some European countries. There is a compelling need to better understand potential adverse effects of other widely used dietary supplements, so that consumers can make more informed decisions about risks and benefits.

The efficacy of saw palmetto extracts for the treatment of BPH is still a matter of controversy and higher-quality studies of this phytotherapeutic are now beginning to appear. Regardless of the ultimate outcomes of these studies, saw palmetto extracts will likely continue to be used widely by men who feel that they benefit from its use. Prior studies suggested that side effects of saw palmetto may include headache, dizziness, nausea, and constipation but assessment of adverse effects of saw palmetto has often been incomplete and unsystematic. The STEP trial data are reassuring in that no important toxicities of this extract were identified among the group of patients studied.

These reassuring results, however, must be viewed within the context of the study limitations. The statistical power to detect important clinical differences was limited for some variables, given the sample size of the study. The follow-up phase was one year, so no conclusions regarding use over a longer time period can be made. Whether the favorable safety profile of the extract used in this study is typical of other extracts cannot be determined, as there is variation in the extraction techniques and final product composition among the marketed products. Finally, rare but serious adverse effects of saw palmetto cannot be assessed in a trial of this size and, like pharmaceutical agents, will require large-scale post-marketing studies to adequately assess this possibility. While case reports do not establish causality, there are case reports suggesting that serious idiosyncratic toxicity of saw palmetto may exist: one patient developed cholestasis after taking an herbal blend that contained saw palmetto, another developed transient hepatitis and pancreatitis, and one patient suffered excessive intra-operative bleeding and prolonged bleeding time from saw palmetto.

Overall, the data from the STEP trial do not support the concern of serious clinical adverse effects of this saw palmetto extract over a period of one year. While these results are reassuring, further data are needed to more definitively address toxicity issues and will likely emerge from ongoing investigations of saw palmetto as well as population-based toxicity studies. [101, Rank 1]

St. John's Wort

In Europe and the United States herbal preparations of St John's wort (SJW) can be bought over-the-counter to treat a variety of conditions. SJW products may also be prescribed in some European countries. As individuals view these treatments as safe they rarely inform their clinicians of their use or possible undesirable effects. However, recent reports indicate that SJW interacts with a number of different medicines, which could result in potentially serious adverse reactions.

Extracts of SJW have been used for their medicinal properties since ancient times. SJW (also known as Hypericum) is *Hypericum perforatum*, a member of the Hypericaceae family. Traditionally, SJW has had a number of different uses including applying it externally as a treatment for wounds and burns, or taken internally as an infusion or herbal tea to treat fevers and nervous conditions including depression.

Currently, subject to certain conditions, unlicensed herbal medicines may be sold or supplied as herbal remedies in the US, exempt from licensing requirements, under Section 12 of the 1968 Medicines Act. No specific safety or quality requirements apply to unlicensed herbal remedies. In addition, no written indications about the intended use of the product may be given when the product is sold under this exemption.

SJW extract has been shown to inhibit the uptake of serotonin, noradrenaline and dopamine. Extract of SJW has been shown to have a potent affinity for the adenosine, serotonin $5HT_1$, benzodiazepine and γ-aminobutyric acid (GABA) receptors and to weakly inhibit monoamine oxidase. It has also been postulated that SJW's antidepressant activity may be a result of its effect on interleukin-6. The constituent hyperforin is perhaps the most likely candidate to be responsible for the antidepressant activity and may be critical to the therapeutic effects of SJW. This reflects the fact that only the effect on GABA receptors by hyperforin appears to be of sufficient magnitude to elicit an antidepressant effect at therapeutic doses of SJW. However, the exact mechanism responsible for the therapeutic effects of SJW remains unclear.

Despite the fact that the pharmacology of the different constituents of SJW is not fully known, the hypericin concentration is commonly used to standardize the various SJW products. However, the amount of hypericin varies widely in different parts of the plant, under different growth conditions, and at different times of the year. In addition, hypericin is probably not the only relevant constituent. It is therefore likely that different preparations vary in their content of substances contributing to the antidepressant effects of SJW. Therefore there is a potential for different SJW products to have different levels of efficacy and possibly different adverse reaction profiles. [120, Rank 1]

Adverse Reaction

Herbal remedies can produce adverse reactions, some of which can be serious and even potentially fatal. Individuals experiencing adverse reactions may not associate these with

their use of herbal preparations. This is further complicated by the fact that the majority of herbal preparations are self-prescribed and never mentioned when consulting a doctor. Therefore adverse reactions associated with herbal preparations are likely to be under reported.

The most commonly reported adverse reactions for SJW are gastrointestinal symptoms, allergic reactions, dizziness/confusion, tiredness/sedation and dry mouth. The majority of these reactions were generally considered to be mild, moderate or transient.

Photosensitivity reactions affecting the skin are potentially serious adverse reactions associated with SJW. Recent data suggest that photosensitivity reactions are dose related, with increased sensitivity associated with higher doses. However, the main body of evidence comes from anecdotal evidence in animals, particularly pale skinned cattle, which apparently gorge on *Hypericum perforatum* resulting in photosensitivity reactions presenting as severe sun burn. [122, Rank 2]

The available evidence suggests that SJW extracts are effective in treating patients with mild and moderate MDD compared to placebo and comparable to antidepressants. Observed adverse events were fewer than compared to antidepressants, however, adverse event assessments were limited.

The existing evidence base indicates that SJW is a herbal alternative to antidepressant medication with fewer adverse events without compromising effectiveness in symptom improvement in mild and moderate depression. Improvements in depression symptoms were shown for treatment response rates and on standard clinical scales. Translating the shown effect size estimates into clinically meaningful units, the average response rate, i.e. participants showing a marked response to treatment, was 56 % for SJW compared to a response rate in patients treated with a placebo of 35 %. The mean standardized effect size estimate seen across studies is equivalent to a 3-point reduction on the HAMD scale compared to placebo treatment.

While studies were consistently favoring SJW over placebo, the size of the treatment effect estimates varied substantially across included studies. Despite a large number of meta-regressions and subgroup analyses, we were unable to identify significant sources of differences between studies that could explain the heterogeneity shown in the pooled results. Therefore, findings have to be interpreted with caution. Future research may provide more insights for which patient group SJW is particularly effective or which intervention characteristics are associated with larger treatment effects.

Review also addressed the outcome remission using study authors' definitions, which usually corresponded to a HAMD score of less than seven or eight and indications that no further treatment was required. While remission rates were lower among participants using SJW compared to a placebo, these results were not statistically significant and the quality of evidence was low due to mixed study quality and differences in results across studies. The

average proportion of patients in remission was 38 % in SJW treatment groups and 27 % in placebo groups.

The evidence base indicated that SJW was not less (or more) effective than antidepressants in treating major depressive disorder in patients with mild and moderate depression. Treatment response rates and depression severity did not differ between patients administered SJW and antidepressants, including studies that were explicitly designed to detect statistically significant differences between the treatment groups. Remission rates were also not significantly different but given the lack of effect shown in placebo trials and the limited quality of the identified studies this result has to be interpreted with caution. Remission rates were low in SJW as well as antidepressant arms (average 38 and 33 %, respectively); of note, the follow-up times in the included studies were relatively short (range 4–12 weeks).

Patients taking SJW were not more likely to experience adverse events than patients receiving a placebo across all assessed adverse events. Serious adverse event rates did not differ between the groups, but users of SJW experienced more adverse events related to the nervous system or to eye, ear, liver, renal, and reproductive organ systems. Conversely, SJW treatment was associated with fewer adverse events overall than antidepressants, and specifically for adverse events related to the gastrointestinal and nervous systems. Serious adverse events did not differ significantly between the two treatment groups, but only a few studies reported on adverse events and the identified RCTs were not designed to address rare adverse events. The quality of evidence of adverse event effect estimates was downgraded given that the rigor of assessments varied and the studies were not designed to detect rare events.

Although all but one study reported on adverse events, the assessment and reporting varied considerably. Studies varied in particular on which adverse events they reported on; the presence or absence of serious adverse events was only addressed in a small proportion of studies. SJW has been linked to specific rare events such as hypertensive crisis and induction of mania, but the adverse event reporting in identified studies was often generic and concentrated on gastrointestinal aspects and tolerability. In order to advance our knowledge of the effects of SJW, empirical evidence of the presence and the absence of adverse events is critical and should be addressed in future research. [150, Rank 4]

<u>Ginkgo</u>

The name *Ginkgo* is derived from a wrong transcription of the Japanese name Yin-Kwo (silver fruit), while the epithet *biloba* refers to the bilobed shape of leaves; the English name “maidenhair tree” is due to a resemblance of the leaf shape and veins to maidenhair fern. It is regarded as a “living fossil” because of the species’ uninterrupted existence for 270 million years without changes and for being the oldest tree in the world, with no living

relative in existence. Its relationship with other plants is uncertain. As a result, it is classified in its own division: Ginkgophyta, having the extant species *G. biloba*.

The distinguishing feature of the ginkgo from conifers is its multiflagellated sperm cells, as in cycads, on vegetative anatomy, and partial molecular analysis of its genome suggests a much closer relationship to cycads than to conifers. Vigorous young growing trees show distinct pyramidal growth with a principal central leader and spaced whorls of lateral branches growing out in diagonal orientation to the trunk, but with progression in maturity, increase in height slows, accompanied by the formation of a spreading crown due to the filling out of the branched, juvenile structures

This dioecious tree bears clusters of fan-shaped, deciduous, alternate, simple leathery leaves (2-5 cm long) with forking parallel venation; and the leaves turn bright yellow, then fall within 15 days during autumn. The tree shows extremely slow growth with very poor regeneration through seeds; vegetative propagation through cuttings is the most appropriate propagation method. The ginkgo's sprouting ability enabled it to persist on mountains with eroded slopes and played a role in its survival with morphological stability. Male and female plants occur in 1:1 ratio, with rare reports of monoecious individuals. The plant shows high resistance to environmental stresses, microbial diseases (fungal, viral, and bacterial), other pests, and gaseous pollutants ozone and SO_2, making it suitable and relevant for planting in urban areas. Indeed, it can act as a model to study disease resistance and stress in plants.

Wild species native to China are believed to be members of mixed mesophytic forests that at one point covered the hill country along the Yangtze River valley border. The ginkgo has tremendous medicinal, spiritual, and horticultural importance in Chinese culture. The supplements are bestselling herbal medications with a long history of use in traditional medicine to treat blood disorders; these are known to improve memory and offer the best-known way to keep the mind sharp. Leaves and seeds of *G. biloba* have been used in Chinese herbal medicine for thousands of years.

Modern research focuses on the standardization of *G. biloba* extract from the dried green leaves. The tree produces biflavones, constituents in its leaves: the terpene trilactones (ginkgolides A, B, C, J, P, and Q, and bilobalides) many flavonol glycosides, proanthocyanidins, alkylphenols, simple phenolic acids, 6-hydroxykynurenic acid, 4-O-methylpyridoxine, and polyphenols. *Ginkgo* leaf extract is used in medicine due to its therapeutic actions in regulating cerebral blood flow, protection against free radicals, and delaying the progress of dementia and diabetes. The standard extract is developed by pharmaceutical companies in the USA and Europe, with billions of doses sold in the last 40 years. [167, Rank 2]

G. biloba is the most valued and ancient among medicinal plants, its use dating back to 1505 AD. Despite its existence for over 200 million years, the real value of the species was recognized again in the last 40 years due to the discovery of the increasing importance of

the tree's pharmacological compounds and their therapeutic effects. The therapeutic effect and pharmacological action are due to the joint effect of multiple components, and no individual component is regarded to solely exert the effect

The tree's leaves and fruit are used in Chinese traditional medicine to treat many diseases. *Ginkgo* leaf extract has been developed for pharmaceutical purposes in Germany since 1965, but the first commercially available extract registered for human use was in France in 1974 under the name EGb761 and is among the bestselling herbal medications worldwide. The extract has been shown to improve memory function and enhance motivation in a monoaminergic, in particular dopaminergic role associated with the underlying mechanism of clinical effect in *G. biloba*. In USA, pharmaceutical products from *G. biloba* are produced, and the leaf extract is one of the five top-selling herbal supplements. The standardized extract is administered in Europe at a clinical daily dosage of 120-240 mg for at least 8 weeks and is composed of at least 24% ginkgo flavone glycosides and 6% terpene lactones.

The advancing age of the population worldwide has necessitated the increase in research on disorders primarily affecting older people, such as dementia and cognitive decline. Using observational data, some authors have suggested that up to 50 % of dementia might be preventable, and it has been shown that people with higher levels of education are at lower risk of dementia. The reasons for this difference remain unclear. Additionally, the concept of “successful aging” has become increasingly important in an aging society. Cognition plays a crucial role in the definition of this concept, as the maintenance of cognition allows elderly people to remain actively involved in society.

Understanding self-contained strategies to prevent cognitive impairment and dementia and to engage in successful aging has become increasingly important in societies of advancing age of the population. A high level of education is not only associated with a lower risk of dementia but also with higher rates of health conscious behavior. Health-conscious behavior is determined by behavioral factors and factors related to knowledge and awareness. Indeed, to engage in high levels of health-conscious behavior, people must know and be well aware of factors that could either promote or impair health. Furthermore, they must be convinced that they are responsible for their own health and can influence their health using certain strategies. Beyond that, they must be willing to influence their own health positively in the areas of nutrition, lifestyle, physical exercise (sports), etc..

However, the basis from which such knowledge is obtained by elderly people and how they choose which behaviors will, in their opinion, actually lead to successful aging remains unclear. Integral parts of the concept of successful aging are the use of food supplements, natural remedies, and other over the counter (OTC) drugs. *Ginkgo biloba* supplements have a leading position in this market and are commonly considered to be effective in preventing cognitive decline; thus, they represent a strategy that is not evidence-based to prevent cognitive impairment and dementia.

G. biloba is one of the oldest living tree species in the world and is an integral part of the Asian culture and traditional medicine. *G. biloba* extracts contain high concentrations of flavonoids and terpenoids which have, among other (possible) advantages, antioxidative effects. Further assumed mechanisms of action are only partially evidence-based thus far and include the following: neuroprotection via anti-apoptotic effects, inhibition of β-amyloid-aggregation, and changes in gene expression.

G. biloba supplements are currently one of the most popular herbal drugs in the world. In Germany, pharmaceuticals containing *G. biloba* essence are approved for the therapy of peripheral arterial disease, tinnitus, vertigo, and "dementia related syndrome". More than 20 different pharmaceutical companies provide *G. biloba*, the most common OTC drug, in Germany. The effectiveness of these supplements, however, remains unclear.

Numerous randomized placebo-controlled trials and meta-analyses have investigated the (pro-) cognitive effects of *G. biloba*. The large majority of studies suggest that *G. biloba* does not have procognitive effects in younger or older subjects or in those with or without cognitive impairment or dementia. While there is no evidence that reliably shows that *G. biloba* has a positive impact on cognition, this supplement also has minimal relevant side effects and can be used with little concern. Several studies have shown the lack of positive effects on particular cognitive domains, such as vigilance, attentiveness, reaction time, memory or mood, regardless of whether *G. biloba* extracts are used once or over a period of several months. [182, Rank 2]

the prevalence of *G. biloba* use in a population of 1,672 highly educated people was 15.3 %. Although there was a significant difference between users and non-users with respect to age, there were no differences between the groups with respect to education, current professional situation, family status, or health insurance.

Regarding the types of substances used to increase cognition, the most recent study about cognitive enhancement among 2,600 students using a specialized technique shows a 1-year prevalence of 20 % for the nonmedical use of prescription and illicit drugs for cognitive enhancement. Furthermore, an online poll conducted by the journal "Nature" demonstrated a lifetime prevalence of 20 % for the use of stimulants, modafinil, or beta blockers for cognitive enhancement purposes. Compared to *G. biloba*, these so-called "smart pills" seem to play a more important role among regular students and employed persons than *G. biloba* . However, substance use to increase cognition among regular students is captured by the "Cognitive Enhancement" paradigm, which suggests that to increase academic performance and enhance their position, students are often prepared to take high risks.

Regarding educational status, the majority of participants in our study had a university degree (63.8 %, *n* = 338), which highlights the high educational status of the surveyed population. Although we did not aim to include participants with considerably different education statuses, we can demonstrate a relatively high prevalence of *G. biloba* use among

this group of highly educated participants. In this respect, the study of Adusumil and colleagues compared participants' educational status and revealed higher prevalence of *G. biloba* use among participants with higher educational status which underlines our findings.

With respect to recommendations regarding the use of *G. biloba*, more than 50 % of participants in our study were advised to use *G. biloba* by a physician, which is one of the most important findings of this study and certainly explains, at least in part, the high prevalence of *G. biloba* use. This observation confirms results of a previous US study which revealed that 38 % of surveyed US geriatricians recommend the use of *G. biloba* to their patients. One can only speculate as to why physicians recommend *G. biloba*—especially given that the use of *G. biloba* does not conform to treatment guidelines, which have shown the lack of efficacy of *G. biloba* and advise against the recommendation of *G. biloba* to patients.

One of the most important reasons for primary care physicians to recommend such drugs to patients (and for subjects asking for preventive strategies against cognitive decline) may be the patients' expectation of a solution and their desire for a prescription. This may increase pressure among physicians to prescribe "lifestyle" or "herbal" medicine such as *G. biloba* . In addition, physicians may feel the need to prescribe a drug with (nearly) no side effects, which may at least offer a "placebo" effect to healthy subjects.

A further explanation for the high prevalence of *G. biloba* use is the users' assumed "knowledge" about *G. biloba* and its scientifically proven procognitive effectiveness. In this respect, a physicians' recommendation is quite important. Further sources of knowledge available to users include the internet, healthcare magazines, and patient brochures containing information about *G. biloba* and other herbal products from unknown sources. The pharmaceutical industry may have a significant influence over the distribution of this information to patients and healthy subjects searching for preventive strategies against cognitive decline. Therefore, it seems particularly difficult to inform oneself objectively about *G. biloba* and further herbal products which are marketed for cognitive well-being and the prevention of cognitive decline. [190, Rank 3]

<u>Ginseng</u>

As the genus name *Panax*, meaning 'cure all' in Greek, implies, ginseng has been referred as a panacea and prescribed for many serious symptoms. Ginseng is basically a tonic or adaptogenic herb that improves the basal level of health, body balance, and restoration capacity. Beyond its health-improving and self-healing functions, the pharmacological activities of ginseng span a broad range of protections to direct therapeutic effects on various organs and diseases.

Numerous compounds, from small molecules to macromolecules, have been isolated from and identified in ginseng, including triterpenesaponins, polyacetylenes, alkaloids, phenolics, polysaccharides, peptidoglycans, and proteins. Ginsenosides, the triterpene glycosides

(saponins), are the unique and active constituents in ginseng. More than 100 ginsenosides have been isolated from all parts of the *Panax* species. Protopanaxadiol and protopanaxatriol are the main structural features of the aglycone moiety of ginsenosides in *P. ginseng*. Excessive steaming results in modification of the ginsenoside structure, characterized by deglycosylation of the sugar moieties and double bond formation following dehydroxylation at C20. Less polar ginsenosides with this aglycone structure are the unique and biologically active ingredients in red ginseng and sun ginseng . Finally, polysaccharides are the other major and biologically interesting constituents in ginseng. Many polysaccharides, including panaxans, ginsenans, and pectins, have been isolated from ginseng and characterized. Ginseng polysaccharides show anti-diabetic, immune-modulating, anti-cancer, and anti-infection activities.

Ancient pharmacists created transformed herbal medicines through steaming, roasting, or fermenting. Processing leads to changes in the component phytochemicals, thereby expanding the chemical diversity and bolstering the overall efficacies. Processing is now gaining interest in an effort to create new medicinal recourses having diverse chemical pools, and many new advanced techniques are currently being examined and applied.

Traditionally, ginseng refers to the root, and the other parts of ginseng, such as the leaves and berries, are rarely used. The ginseng preparations described below follow this traditional notion. Fresh ginseng refers to immediate harvest without any additional processing. Because of problems during storage or circulation, in most cases, fresh ginseng is turned into white or red ginseng. White ginseng refers to dried ginseng, while red ginseng is the transformed ginseng created by traditional processing with successive steaming and drying. Our research group developed a new processed ginseng (called sun ginseng) from *P. ginseng*through steaming under optimized high temperature and pressure conditions.

Sun ginseng contains increased levels of biologically active, less polar ginsenosides and enhanced pharmacological activities compared to those of white and red ginseng. This processing method has also been applied to different *Panax* species and other natural medicines . Other types of processed ginseng have been developed using modified steaming, explosive puffing, or fermentation with specific microorganisms, such as intestinal microbial flora. Black ginseng is prepared by repeated cycles of atmospheric steaming and sun-drying . Puffed ginseng is prepared by applying an optimized puffing pressure and residual moisture content in ginseng . Fermentation with intestinal microbial flora leads to structural modification of the ginsenosides. Compound K, the intestinal metabolite of ginsenoside, is a representative bioengineered ginsenoside that shows potent anti-cancer effects. [203, Rank 1]

Recently, traditional herbal medicines have been gaining attention as the therapeutic candidates for many chronic or degenerative diseases caused by multifactorial causes in modern society . Single or simple mixtures of active compounds are no longer considered to be the best therapeutic choices for treating these diseases. Formulations of natural

medicines composed of diverse phytochemicals may be potential alternatives in preventing or overcoming incurable diseases through their ability to modulate multiple targets, enhance self-healing and adaptogenic capacity as described in the ethnopharmacological literature.

Low toxicity and reliable efficacy in humans that has been verified through a long medicinal history are other advantages of natural medicines that are encouraging the development of herbal medicines in modern therapeutics. However, the main problem in natural medicine development is quality control, as the quality can be influenced by many factors, including differences in cultivation methods, environment, and the genetic background of plant species. Validated analytical methods for herbal medicines are important not only to establish drug standards, including species authentication and quality assessment, but also to understand drug targets and pharmacokinetic properties . Analytical methods will therefore play an essential role in the discovery of innovative herbal medicine therapeutics.

Ginseng is a best-selling herbal medicine and has been a top-ranked subject of many fields of scientific research worldwide. The medicinal history of ginseng can be traced back over approximately 2,000 years to one of the first descriptions in ancient Oriental medical literature . The English name ‘ginseng’ is derived from Chinese word meaning man-shaped root. Owing to this shape, ginseng is considered sacred in oriental medicine. Together with various beneficial activities, ginseng is known as a noble, miraculous medicine and is prescribed to treat many symptoms. More than 5,000 research papers have been published in authoritative scientific journals on the secrets of ginseng, which have traditionally been transmitted by word-of-mouth.

Ginseng research must draw on aspects of natural product chemistry, pharmacognosy, pharmacology, plant bioengineering, and analytical sciences. With particular respect to analytical methodologies of ginseng, many researchers have developed methods (in terms of metabolomics) of single or multiple phytochemical analyses using sophisticated chromatographic tools as well as total extract or plant material analyses using both spectroscopic techniques and statistics . The ‘ginseng analysis’ should be the professional term used to refer to analytical approaches for ginseng, and is a representative model for other natural medicines.

Echinacea

Herbal medicines derived from several species of the indigenous *Echinacea* genus were in use throughout the plains of NorthAmerica long before the introduction of European medicines, primarily as treatments for various infectious diseases and wounds. Nine discrete species were classified subsequently by botanists, although medical records suggest that considerable interchange between uses of designated species occurred and consequently the association of a specific species with particular treatments has to be viewed with caution. Even in recent years there have been revisions in the taxonomy of the genus. Nevertheless it is generally agreed that *Echinacea purpurea*, the purple coneflower, was

widely used by Native peoples and later by the Eclectic practitioners of North America, possibly because it was so widespread, and also because it was apparently effective in a number of diseases. Current herbal preparations, which have become very popular in North America, Europe, and elsewhere, have tended to favor this species over the others, and the majority of the basic scientific studies have focused on this one. Accordingly, this review is restricted primarily to discussion of *E. purpurea*(abbreviated EP), with occasional reference to alternative species.

Acute respiratory infections in humans are usually caused by one or more of a group of well-known viruses, which includes over 100 rhinoviruses ("common cold" viruses), influenza viruses A and B, parainfluenza viruses, corona viruses, respiratory syncytial virus, and certain adenoviruses. Influenza virus A deserves special consideration because of its unique capacity for genetic reassortment between animal and human strains and consequent production of epidemics. In addition the recent application of more sensitive molecular detection techniques has revealed the presence of other viruses, such as metapneumoviruses and bocaviruses, which might also be involved in the generation of respiratory symptoms.

Clearly various families of viruses, with different structures and replication schemes, and consequently bearing different potential molecular targets, are involved in respiratory symptoms, and many of them are susceptible to *Echinacea* extracts. Among the possible viral targets are: (i) the virion itself (membrane components); (ii) cellular attachment or entry; (iii) one or more of the many stages in virus replication and development, particularly those that involve virus-specific enzymes; (iv) egress of progeny virus from infected cells. However, because of the variety of replication schemes among these viruses the chances of success for a single therapeutic drug are low, especially considering that in the majority of respiratory infections specific virus information is lacking. [215, Rank 4]

In respiratory infections, the invading virus initially encounters epithelial tissues, which are composed largely of epithelial cells and occasional dendritic cells and macrophages. These cells respond by means of the various antimicrobial strategies that make up the innate immune system, including defense peptides (antimicrobial peptides) and the secretion of various proinflammatory cytokines and other mediators of inflammation. Other molecules such as kinins are released and are probably responsible for some of the early symptoms. Rhinoviruses have also been shown to induce kinin gene expression, although this effect is more likely a delayed effect of virus infection. In response to all these mediators phagocytic cells and various types of inflammatory cell may then be attracted to the site of infection. In addition the redox balance of the cells may be adversely affected, either by the virus infection itself or as a consequence of the proinflammatory response.

Since most of the symptoms reflect this common nonspecific host response to infecting agents, rather than to the direct cytolytic or cytopathic effects of a specific virus, then a more rational therapeutic approach would be the application of anti-inflammatory agents,

especially if the intention of the therapy is to ameliorate symptoms. If a potential safe anti-inflammatory agent also contains multiple antiviral activities, then this would provide a bonus. Several herbal extracts have been shown to possess a combination of bioactivities that could be useful in the control of respiratory infections, and these *Echinacea* extracts have become very popular, although, because of the variation in their chemical composition, not all of them are necessarily beneficial.

Influenza viruses are ubiquitous and produce significant annual morbidity and mortality throughout the world, with potentially devastating consequences for human and animal health, and the global economy. Thereare three types of influenza virus, A, B, and C the latter two being confined mainly to humans, in which they produce relatively mild seasonal outbreaks. However the greatest impact derives from Influenza A virus, which has been associated with several well-known human pandemics during the last century and an increasing number of epidemics (epizootics) in domestic birds. It is believed that influenza A virus originated in wild birds, possibly waterfowl such as ducks and geese and that these birds act as reservoirs and vectors for the many known subtypes (strains) of influenza A virus.

The classical symptoms of human influenza include cough, malaise, and fever, often accompanied by sore throat, nasal obstruction, and sputum production, which resolve spontaneously in most healthy individuals, although immune compromised and elderly individuals tend to be more vulnerable. Complications may include bronchitis and pneumonia, and exacerbation of asthma, and chronic obstructive pulmonary disease (COPD). [224, Rank 4]

Streptococcus pyogenes (Group A streptococcus, or GAS) is responsible for widespread infections, ranging from hundreds of millions of relatively mild cases of pharyngitis globally, to more severe toxic shock syndromes and necrotizing fasciitis (“flesh-eating disease”), the more severe symptoms being ascribed to inflammatory cytokines (“cytokine storms”). In addition several *Streptococcal* gene products or virulence factors have been described which aid the bacteria in persistence in oral epithelia and saliva and dissemination to other tissues. Consequently the dual actions of EP in killing the bacteria and reversing their proinflammatory activities could be a significant aid in combating such infections.

Hemophilus influenzae is part of the normal naso-pharyngeal flora. Recently additional pathogenic strains have been associated with otitis media, chronic bronchitis, and pneumonia. Initial interaction with epithelial cells can result in proinflammatory cytokine secretion, via toll receptors and other mediators. EP can kill this organism readily and also inhibit the cytokine induction in bronchial epithelial cells.

Legionella pneumophila, associated with Legionnaires' disease and sometimes more severe cases of pneumonia, is widely distributed in water and soil, from which the organism can be inhaled as an aerosol and once inside alveolar macrophages localizes in a relatively resistant

vacuole, in which it replicates. The organism is however very sensitive to EP, and its induction of proinflammatory cytokines is inhibited by EP treatment.

Staphylococcus aureus has long been recognized as part of the normal skin flora, but Methicillin-resistant (MRSA) strains have been associated in recent years with increased frequency of hospital-acquired infections, resulting in severe pneumonia. Preparations of EP had relatively little effect on growth of MRSA or MSSA (methicillin sensitive *S. aureus*) but were very effective in inhibiting the proinflammatory response to the bacteria, indicating at least partial benefits in counteracting the detrimental effects of MRSA infection. *Klebsiella pneumoniae*, often associated with antibiotic resistant pneumonia, was also relatively resistant to the bactericidal effects of EP, as were *Mycobacterium smegmatis* and several other bacterial opportunists.

Several conclusions were drawn from these results: (i) EP and other *Echinacea* extracts were selective in their antibacterial activities; (ii) different organisms showed significant differences in their patterns of sensitivity; (iii) there were no correlations between chemical composition of extracts, in terms of known marker compounds, and their corresponding antibacterial activities; (iv) different preparations of *Echinacea* showed markedly different effects on bacteria, indicating that EP has distinct mechanisms of action against each bacterium; (v) in general EP can reverse the stimulation of proinflammatory cytokines regardless of the inducing bacterium or virus.

Several studies have reported the effects of *Echinacea* preparations on cellular gene expression in uninfected human cells relevant to the immune system. Changes in NK cells and cell surface antigens were described for blood cells taken from humans treated with EP. Many dendritic cell genes were affected, either upregulated or downregulated. Modulation of several cytokines by EP extract was also reported for cultured mouse dendritic cells. None of these studies included infected cells, but they clearly confirmed that EP produces multiple gene effects in immune cells.

Many groups during the last 20 years have investigated the effects of *Echinacea* preparations on immune functions in cell cultures of mouse origin. In general, incubation of peritoneal, alveolar, or spleen monocyte/macrophage/lymphocyte preparations with EP resulted in stimulation of phagocytosis and cytokine secretion. This was in contrast to the studies described above for infected airway epithelial cells and fibroblasts, in which EP generally acted as an anti-inflammatory agent, via numerous changes in gene expression. In studies with partially purified EP polysaccharides (derived from *in vitro* EP plant cultures), stimulation of phagocytic activity in macrophages was also observed, whereas isolated *Echinacea* alkylamides, individually or in groups, invariably displayed immune suppression in various cultured cells.

Unfortunately the earlier studies gave rise to a popular belief that *Echinacea* acted as a general “immune stimulant” or “immune booster”, statements that persist today on many commercial labels and web site descriptions. More recent studies however refer more

appropriately to immune modulation rather than generalized immune stimulation. Thus the net result of interactions between EP and cells *in vivo* will likely be influenced by the composition of the extract and the nature and location of the cell type.

Researchers reported that several preparations of EP showed minimal effects on production of cytokines in mouse cultures, unless the extracts were first exposed to a simulated gastric and intestinal digestion protocol, whereupon they acquired the ability to stimulate cytokine secretion. This result is clearly relevant to normal consumption of *Echinacea*, but remains unexplained. [235, Rank 2]

Kava

Kava, prepared from the rhizome of the kava tropical shrub plant, *Piper methysticum* Forst F., is a traditional beverage used for many centuries, especially at ceremonial activities in the South Pacific. During recent years, kava has been used in Europe for treatment of anxiety and nervous disorders such as stress and restlessness, and in the United States as a natural alternative to anti-anxiety drugs and sleeping pills.

Kava (*Piper methysticum* G. Forster) is a recreational Pacific herb consumed worldwide. The beverages prepared from its rhizomes/roots are also used for cultural purposes by Pacific Island communities, and in Australia, the tablet or capsule form is used for the treatment of anxiety. Considerable global interest emerged when reports of toxic liver injury appeared, possibly related to Western acetonic and ethanolic kava extracts. In 2002, this led to kava withdrawals from various European countries; to Food and Drug Administration (FDA) consumer advice in the USA; and to a practitioner alert, consumer advice and voluntary recall in Australia.

Since 2005, aqueous kava products have again become available in Australia as a Therapeutic Goods Administration approved over-the-counter product. In New Zealand, consumer advice was issued in 2002, with aqueous and solvent-based kava products remaining on the market. In the USA, there is no particular solvent specification issued by the FDA for kava extracts; consequently, production and use of hydro-ethanolic kava products are not restricted.

Although initially questioned, the subsequent use of the structured, quantitative and liver-specific assessment method of the Council for International Organizations of Medical Sciences, in the updated form, established causality for kava in a few patients with liver injury. The appearance of these cases was unexpected and created concern, because the mechanistic understanding of causation was not identified. [240, Rank 1]

In 2003, when the Pacific kava paradox was first proposed, the first case reports appeared showing hepatotoxicity due to kava use prepared traditionally as water extracts rather than by organic solvents. In two cases from New Caledonia, severe hepatotoxicity was described following the use of traditional aqueous extracts derived from kava imported from Vanuatu,

with clinical features akin to those detailed for the corresponding German and Swiss cases of patients who used acetonic and ethanolic extracts.

Similar reports of single cases came from other countries: Australia, the USA and Germany. In all these reports, causality for kava has been established by the structured, quantitative, liver-specific and updated scale of the Council for International Organizations of Medical Sciences that was also applied to cases of patients with liver disease due to acetonic and ethanolic extracts. In 2007, the World Health Organization (WHO) kava hepatotoxicity study listed five cases due to aqueous kava extracts; three were coded for kava with a causality of possible and two probable; two were from traditionally prepared kava. The WHO report also referred to other cases of patients with liver disease, but a relation to the use of traditional aqueous kava extracts was not established using the WHO scale. Essentially, the WHO kava report confirmed that traditional aqueous kava extracts may exert rare potential hepatotoxicity similar to acetonic and ethanolic extracts. These observations have cast doubt on the Pacific kava paradox.

In a recent study, typical features of kava hepatotoxicity caused by aqueous, acetonic and ethanolic extracts were compared. Clinical characteristics included assessment of gender, age, daily use of kavalactones, daily kava overdose, duration of kava use, co-medication with synthetic drugs and other herbs including use of herbal mixtures, outcome and requirement for a liver transplant. The assessed features were fairly comparable with respect to all used extracts, substantiating that the solvents employed to prepare the various kava extracts are not causally related to the development of liver injury in these cases.

In 2003, cases of hepatotoxicity in connection with the use of Western acetonic and ethanolic kava products were reported; at the same time, it was observed that liver toxicity had not been documented with traditional water-based kava extracts used in Pacific countries, such as the South Pacific Islands and Australia. In support of this proposed Pacific kava paradox, three Australian studies involving Aborigines in Arnhem Land who consumed traditional aqueous kava extracts prepared with kava raw material imported from Pacific Islands did not report cases of hepatotoxicity. A fourth and a fifth study also supported the proposed Pacific kava paradox. The fourth report concerned inhabitants of New Caledonia who consumed traditional aqueous kava beverages prepared from plants imported from Vanuatu, and the fifth study provided data of a predominantly Tongan population of Hawaii, consuming traditional aqueous kava extracts prepared from plants of Hawaii.

In the first Australian study, published in 1988, heavy use of traditional aqueous extracts caused greatly increased levels of γ-glutamyltranspeptidase (γGT) and a concomitant decrease of bilirubin, but values for alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP) were lacking. In the two other Australian reports concerning traditional aqueous extracts, published in 2003, serum γGT and ALP levels were increased, with normal values of ALT and bilirubin, but AST data were lacking. In 2003, the fourth study, from New Caledonia, showed that heavy users of

traditional aqueous extracts had marginally elevated ALT and AST activity in a few cases, but there were high serum γGT levels in most heavy users, with a lack of ALP values. Finally, in 2007, the fifth study, from Hawaii, revealed elevated activities of γGT and ALP and unchanged ALT and AST values in consumers of the traditional aqueous beverages. [76, Rank 3]

Kavalactones (alpha-pyrones) of the kava compounds have the highest pharmacological activity. The six major kavalactones are yangonin, methysticin, dihydromethysticin, dihydrokawain, kawain, and demethoxyyangonin. When kavalactones were tested individually, they did not exhibit biological activity similar to that found in the whole kava extract.

Lipid extracts of kava produce higher pharmacological activities than aqueous kava extracts. Synergistic effect between kavalactones and other amino butyric acid-active sedatives was observed. Similar to methenesin, kava can cause muscle relaxation without depressing CNS function. Both yangonin and desmethoxy-yangonin possess weaker central nervous activity than kava extract. The other alpha-pyrones exhibit markedly enhanced activity.

Both aqueous extracts and lipid soluble extracts (kava resin) used for intoxicating beverage kava exhibit analgesic effects in mice. Among the eight purified alpha-pyrones contained in lipid soluble extracts, kawain, dihydrokawain, methysticin and dihydromethysticin were found to be very effective in producing analgesia, which was shown to occur via non-opiate pathways.

Yangonin and methysticin showed moderate antioxidant activities in a free radical scavenging assay, but demethoxyangonin, dihydrokawain, kawain, dihydromethysticin, and methysticin did not exhibit antioxidant activities. [287, Rank 3]

Although the potential hepatotoxicity of kava has long been reported, no epidemiological and case studies on the association of exposure to kava and cancer risk in humans has been reported. On the other hand, kava has been implicated in a number of human liver failure cases in recent years. Standardized kava extracts produced in Europe caused many serious health problems including death.

In Europe, there have been more than 30 cases of liver damage possibly associated with kava intake, although this remains controversial. The types of liver damage include hepatitis, cirrhosis, liver failure, and death. It is not clear what doses were used and the period of use associated with the risk of liver damage. Both chronic and heavy use has been associated with cases of neurotoxicity, pulmonary hypertension, and dermatologic changes.

Use of kava at frequent high doses causes kava dermopathy. The heavy use of kava appeared to be related to malnutrition and weight loss, liver damage (causing elevated serum *γ*-glutamyl transferase and high-density lipoprotein cholesterol levels), renal dysfunction, rashes, pulmonary hypertension, macrocytosis of red cells, lymphocytopenia, and decreasing platelet volumes. Acute kava usage caused reversible anesthesia of the

mouth and skin, euphoria, sedation, muscle weakness, ataxia and, eventually, intoxicationKava is a spinal depressant, causing transient ataxia or uncoordinated walk.

The underground parts of the *Piper methysticum* shrub, which contain high quantities of kavalactones, are used to prepare the kava beverage. However, some kava herbal supplements may contain pipermethystine, which is an ingredient from aerial stem peelings. Pipermethystine was found to decrease cellular ATP levels and mitochondrial membrane potential and induce apoptosis as measured by the release of caspase-3 in cultured human hepatoma cells, HepG2. These results suggest that pipermethystine, rather than kavalactones, is capable of causing cell death.

In the United States, kava is still commercially available, although the U.S. Food & Drug Administration (FDA) has issued warnings to consumers and physicians. The U.S. FDA stated in 2002 that "Kava-containing products have been associated with liver-related injuries—including hepatitis, cirrhosis, and liver failure—in over 25 reports of adverse events in other countries. Four patients required liver transplants. The FDA has received a report of a previously healthy young female who required liver transplantation, as well as several reports of liver-related injuries".

Case 1

In May 2001, a 45-year old woman who took kava-containing dietary supplement one tablet twice daily for about 8 weeks felt nausea and weakness. Several days after stopping taking the kava-containing supplement, the patient was hospitalized with jaundice and hepatitis. Liver biopsy found subfulminant hepatic necrosis. Liver transplantation was performed in July 2001, and the patient since recovered.

Kavalactones require hepato cytochrome P450 enzymes for clearance by the liver. Since both herbal medicines and therapeutic drugs require metabolizing enzymes for metabolism, the use of herbal remedies and therapeutic drugs simultaneously can raise the potential of herb-drug interactions, causing an adverse response. It is important to note that inhibition of metabolizing enzymes, such as cytochrome P450 (CYP) activities, is not a toxic effect; the inhibition can lead to modulation of drug metabolism. As such, the effect on enzyme inhibition is not expected to produce a clear dose-dependent increase in adverse events.

<u>Garlic</u>

Dietary factors play a key role in the development of various human diseases. Across cultures, there are many different dietary patterns which are believed to promote human health. Despite cultural differences, there are some shared characteristics of healthy dietary patterns. Perceiving plant foods as beneficial diet is advised by the folklore of many cultures over centuries.

Garlic (*Allium sativum* L.) has acquired a reputation in different traditions as a prophylactic as well as therapeutic medicinal plant. Garlic has played important dietary and medicinal

roles throughout the history.Some of the earliest references to this medicinal plant were found in Avesta, a collection of Zoroastrian holy writings that was probably compiled during the sixth century BC. Garlic has also played as an important medicine to Sumerian and the ancient Egyptians. There is some evidence that during the earliest Olympics in Greece, garlic was fed to the athletes for increasing stamina.

Ancient Chinese and Indian medicine recommended garlic to aid respiration and digestion and to treat leprosy and parasitic infestation.In the medieval period, garlic was also played an important role in the treatment of different diseases. Researchers recommended garlic as a useful compound in treatment of arthritis, toothache, chronic cough, constipation, parasitic infestation, snake and insect bites, gynecologic diseases, as well as in infectious diseases (as antibiotic). With the onset of Renaissance, special attention was paid in Europe to the health benefits of garlic.

Garlic has attracted particular attention of modern medicine because of widespread belief about its effects in maintaining good health. In some Western countries, the sale of garlic preparations ranks with those of leading prescription drugs. There is appreciable epidemiologic evidence that demonstrates therapeutic and preventive roles for garlic. Several experimental and clinical investigations suggest many favorable effects of garlic and its preparations. These effects have been largely attributed to *i*) reduction of risk factors for cardiovascular diseases, *ii*) reduction of cancer risk, *iii*) antioxidant effect, *iv*) antimicrobial effect, and *v*) enhancement of detoxification foreign compound and hepatoprotection.

Garlic is a bulbous plant; grows up to 1.2 m in height. Garlic is easy to grow and can be grown in mild climates (Figure). There are different types or subspecies of garlic, most notably hardneck garlic and softneck garlic. Allicin (allyl 2-propenethiosulfinate or diallyl thiosulfinate) is the principal bioactive compound present in the aqueous extract of garlic or raw garlic homogenate. When garlic is chopped or crushed, allinase enzyme is activated and produce allicin from alliin (present in intact garlic). Other important compounds present in garlic homogenate are 1 -propenyl allyl thiosulfonate, allyl methyl thiosulfonate, (E,Z)-4,5,9-trithiadodeca- l,6,11-triene 9- oxide (ajoene), and y-L-glutamyl-S-alkyl- L-cysteine. The adenosine concentration increases several-fold as the homogenate is incubated at room temperature for several hours. [293, Rank 1]

Garlic and its preparations have been widely recognized as agents for prevention and treatment of cardiovascular diseases. The wealth of scientific literature supports the proposal that garlic consumption have significant effects on lowering blood pressure, prevention of atherosclerosis, reduction of serum cholesterol and triglyceride, inhibition of platelet aggregation, and increasing fibrinolytic activity. Both experimental and clinical studies on different garlic preparations demonstrate these favorable cardiovascular effects.

In *in vivo* animal experiments, intravenous administration of garlic extracts produced slight reductions in both systolic and diastolic pressures and oral ingestion of garlic extract in hypertensive animals brought the blood pressure back to the normal level. Several clinical

studies showed that garlic reduced blood pressure in more than 80% of patients suffering from high blood pressure. In one trial, investigation on 47 hypertensive patients showed that garlic significantly decreased the mean systolic blood pressure by 12 mmHg and the mean supine diastolic blood pressure by 9 mmHg versus placebo. The authors stated that garlic was free from side effects and no serious complication was reported.

Many *in vitro* and *in vivo* studies have suggested possible cancer-preventive effects of garlic preparations and their respective constituents. Garlic has been found to contain a large number of potent bioactive compounds with anticancer properties, largely allylsulfide derivatives. Different garlic derivatives have been reported to modulate an increasing number of molecular mechanisms in carcinogenesis, such as DNA adduct formation, mutagenesis, scavenging of free radicals, cell proliferation and differentiation as well as angiogenesis. The growth rate of cancer cells is reduced by garlic, with cell cycle blockade that occurs in the G2/M phase.

In 1990, the U.S. National Cancer Institute initiated the Designer Food Program to determine which foods played an important role in cancer prevention. They concluded that garlic may be the most potent food having cancer preventive properties. Garlic has a variety of anti-tumor effects, including tumor cell growth inhibition and chemopreventive effects. In rodents, garlic and its constituents have been reported to inhibit the development of chemically induced tumors in the liver, colon, prostate, bladder, mammary gland, esophagus, lung, skin, and stomach in both rodent and human studies. Diallyl trisulfide (DATS), an organosulfur compound isolated from garlic, has been shown anticancer activity both in *in vitro* and *in vivo* investigations..

Possible anticarcinogenic mechanisms of garlic and its constituents may include the inhibition of carcinogen activation, the enhancement of detoxification, excretion, and the protection of DNA from activated carcinogens. Furthermore, DATS reduced tumor mass and number of mitotic cells within tumors. DATS reduced mitosis in tumors, decreased histone deacetylase activity, increased acetylation of H3 and H4, inhibited cell cycle progression, and decreased pro-tumor markers. Garlic components have been found to block covalent binding of carcinogens to DNA, enhance degradation of carcinogens, have anti-oxidative and free radical scavenging properties, and regulate cell proliferation, apoptosis, and immune responses. Ajoene, a garlic stable oil soluble sulfur rich compound and garlic-derived natural compound, have been shown to induce apoptosis in leukemic cells in addition to the other blood cells of leukemic patients. Ajoene induced apoptosis in human leukemic cells via stimulation of peroxide production, activation of caspase-3-like and caspase-8 activity. Garlic synergizes the effect of eicosapentaenoic acid, a breast cancer suppressor, and antagonizes the effect of linoleic acid, a breast cancer enhancer.

Although garlic is believed to be a safe substance, long-term trials of reasonable duration would provide insights into the possible side-effects of different garlic extracts. The safety of garlic should be tested especially in pregnant or breastfeeding women as well as in young

children. Long-term and large trials are also needed to evaluate the differences in mortality, serious adverse events, and morbidity of cancer and cardiovascular diseases after garlic therapy.

A recent increase in the popularity of alternative medicine and natural products has renewed interest in garlic and their derivatives as potential natural remedies. This review may be useful to increase our knowledge of garlic therapeutic effects and improve our future experimental and clinical research plans. Although it is shown that garlic may have a significant clinical potential either in their own right or as adjuvant therapy in different disorders, however, due to some issues, such as methodological inadequacies, small sample sizes, lack of information regarding dose rationale, variation between efficacy and effectiveness trials, the absence of a placebo comparator, or lack of control groups more standard experiments and researches are needed to confirm the beneficial effect of garlic in various diseases. Future trials on the effect of garlic should include information on the dosage of active ingredients of standardized garlic preparations for better comparison of trials. It would also be interesting to explore the effect of different forms of garlic extract on standard drug therapy, especially when used as adjuvant therapy. [292, Rank 2]

Valerian

Valerian “can interfere in an unwanted way with the oncological cancer therapy” or valerian “can diminish the efficacy of cancer therapeutics.” Statements like these can be found in published features on complementary medicine for cancer patients. It is further stated that cancer patients often have difficulties to sleep and are restless, so that they can use herbal drugs such as valerian in order to avoid chemically defined sedatives and hypnotics as they fear becoming addicted. However, they state that warnings that valerian (*Valeriana officinalis*) may stimulate CYP 3A4.

This would reduce the effect of several cytostatic substances. For tamoxifen, the plasma level is reduced by CYP3A4 inductors, while inhibitors of CYP2D6 can lower the level of active metabolites, both leading to reduced efficacy. In case of cyclophosphamide, metabolic activation by CYP2D6 is necessary that is increased by inductors of this isoenzyme. The plasma level of several other cytostatic substances is lowered by CYP3A4 inductors. Examples are the epipodophyllotoxin derivative teniposide, camptothecin, tyrosine kinase inhibitors like imatinib, taxanes like paclitaxel and docetaxel, and vinca alkaloids like vincristine. CYP3A4 inductors also may reduce the activity of alkylating substances like ifosfamide and some antitumor antibiotics.

In several websites directed to patients, the use of valerian in cancer is also questioned due to its interaction potential. By the way, Scientific American elected the latter website just a year after foundation as one of the best five US medicinal websites.

More than 70% of all cancer patients are very interested in herbal drugs. However, many of them do not inform their oncologist about their use. As 19 to 75% of all cancer patients

suffer from sleep disturbances, warnings against the use of valerian preparations have a high impact on these patients. However, it has to be ascertained that warnings that valerian may cause interactions with other medicines are backed by valid evidence supporting such an assumption and that they are therefore scientifically correct. [291, Rank 2]

The clinical relevance of acute as well as chronic sleep disorders is obvious: epidemiological data show that they affect approximately one-third of the adult population. Treatment is indicated in about 15% of these cases. Insomnia, defined as insufficient quantity or quality of sleep resulting in compromised daytime alertness and activity, is a common condition. It can result in serious adverse consequences, including attention and memory impairment, depression, falls, and perceived reduced quality of life.

To the most common treatments of insomnia belong drugs, this however bears some problems. Benzodiazepines and imidazopyridines offer only short-term relief, while data on their long-term efficacy are scarce. Both drug classes have significant adverse effects such as serious psychomotor symptoms, behavioral aberrations, memory impairment resulting in injuries, respiratory depression, rebound insomnia, and paradoxical agitation. Especially for benzodiazepines, the potential for abuse is high. Therefore, the National Institutes of Health consensus conference strongly discouraged chronic treatment of insomnia with benzodiazepines already in 2005.

Sedating antihistamines, such as diphenhydramine, the active ingredient in most over-the-counter sleep aids, are associated with cognitive impairment, daytime drowsiness, and anticholinergic effects. There is no evidence-based data available on their efficacy improving insomnia or prolonging sleep. It therefore was recommended that they should be avoided in the elderly. Finally, antidepressants used for treating insomnia, such as trazodone, can produce dangerous and life-threatening adverse events due to their anticholinergic, cardiovascular, and neurologic actions.

Herbal substances improving insomnia, such as valerian, hops, or passion flower, are well-known sleep aids. While marketed as food in the US, they are authorized or registered as medicines in Europe and many other regions, being mostly used in self-medication and holding widespread appeal, presumably because of their lower cost and higher range of safety when compared to chemically defined pharmaceuticals. Among these, the roots of valerian (*Valeriana officinalis* L.) are the most familiar ones, especially in Europe. They improve the subjective experience of sleep when taken in the evening over a period of one or two weeks. The constituents of valerian root include, among others, valepotriates (iridoids) and volatile oil, including monoterpenes and sesquiterpenes (valerenic acids). Commercially available extracts are free from valepotriates

Several controlled clinical trials with various valerian extracts are available, and also a meta-analysis on eighteen randomized placebo-controlled trails was published. Its qualitative results suggest that valerian would be effective for a subjective improvement of insomnia, although its effectiveness could not be demonstrated with quantitative or objective

measurements. In a study conducted in cancer patients, an improvement in the primary variable, a sleep quality index based mainly on objective parameters, could not be demonstrated; however, fatigue and sleep problems were significantly improved.

The clinical studies available show an excellent short-term tolerability, and from several decades of clinical use within the frame of pharmacovigilance systems no data questioning its long-term safety have evolved, while prospective data are missing. In contrast to classical sedatives, valerian extracts did not impair the ability to drive or to use machines, neither after single nor after repeated doses. Reports of putative adverse reactions are extremely rare and include one case of hepatic symptoms after prolonged treatment and one case of cardiac symptoms after discontinuation of a long-term treatment with very high doses, which were interpreted as a withdrawal reaction. In both case reports, outcome was benign, causality was questionable, and characteristics of the extract preparations were not provided. [173, Rank 5]

Chamomile

Chamomile (*Matricaria chamomilla* L.) is one of the important medicinal herb native to southern and eastern Europe. It is also grown in Germany, Hungary, France, Russia, Yugoslavia, and Brazil. It was introduced to India during the Mughal period, now it is grown in Punjab, Uttar Pradesh, Maharashtra, and Jammu and Kashmir. The plants can be found in North Africa, Asia, North and South America, Australia, and New Zealand. Hungary is the main producer of the plant biomass. In Hungary, it also grows abundantly in poor soils and it is a source of income to poor inhabitants of these areas. Flowers are exported to Germany in bulk for distillation of the oil.

In India, the plant had been cultivated in Lucknow for about 200 years, and the plant was introduced in Punjab about 300 years ago during the Mughal period. It was introduced in Jammu. There is no demand for blue oil as such at present in India. However, flowers of chamomile are in great demand.

Chamomile has been used in herbal remedies for thousands of years, known in ancient Egypt, Greece, and Rome. This herb has been believed by Anglo-Saxons as 1 of 9 sacred herbs given to humans by the lord. The chamomile drug is included in the pharmacopoeia of 26 countries. It is an ingredient of several traditional, unani, and homeopathy medicinal preparations. As a drug, it finds use in flatulence, colic, hysteria, and intermittent fever. The flowers of *M. chamomilla* contain the blue essential oil from 0.2 to 1.9%,which finds a variety of uses.

Chamomile is used mainly as an antiinflammatory and antiseptic, also antispasmodic and mildly sudorific. It is used internally mainly as a tisane (infuse 1 table-spoonful of the drug in 1 L of cold water and do not heat) for disturbance of the stomach associated with pain, for sluggish digestion, for diarrhea and nausea; more rarely and very effectively for inflammation of the urinary tract and for painful menstruation. Externally, the drug in

powder form may be applied to wounds slow to heal, for skin eruptions, and infections, such as shingles and boils, also for hemorrhoids and for inflammation of the mouth, throat, and the eyes. Tabulated products from chamomile flower extracts are marketed in Europe and used for various ailments. Chamomile tea eye washing can induce allergic conjunctivitis. Pollen of *M. chamomilla* contained in these infusions are the allergens responsible for these reactions.

Antonelli had quoted from writings of several doctors of ancient time of the 16th and 17th century that chamomile was used in those times in intermittent fevers. It was found in general that the patients fell into deep sleep after taking the beverage. Infusion prepared from *M. chamomilla* exercised a marked stimulatory action on the secretary function of the liver. Studies reported toxicity of acetone-extract of *M. chamomilla* against larvae of *Gulex pipens* L. The other pharmacological properties include antiinflammatory, antiseptic, carminative, healing, sedative, and spasmolytic activity. However, *M. chamomilla* has exhibited both positive and negative bactericidal activity with *Mycobacterium tuberculosis, Salmonella typhimurium*, and *Staphylococcus aureus*.

The international demand for chamomile oil has been steadily growing. As a result, the plant is widely cultivated in Europe and has been introduced in some Asian countries for the production of its essential oil. *M. chamomilla* L., *Anthemis nobilis* L., and *Ormenis multicaulis* Braun Blanquet and Maire belonging to the family Asteraceae is a natural and major source of “blue oil” and flavonoids. The oil used as a mild sedative and for digestion besides being antibacterial and fungicidal in action.

In addition to pharmaceutical uses, the oil is extensively used in perfumery, cosmetics, and aromatherapy, and in food industry. Researchers studied that the essential oil present in the flower heads contains azulene and is used in perfumery, cosmetic creams, hair preparations, skin lotions, tooth pastes, and also in fine liquors. The dry flowers of chamomile are also in great demand for use in herbal tea, baby massage oil, for promoting the gastric flow of secretion, and for the treatment of cough and cold. The use of herbal tea preparations eliminated colic in 57% infants. Because of its extensive pharmacological and pharmaceutical properties, the plant thus possesses great economic value and is in great demand in the European countries. [120, Rank 3]

There is a great demand for chamomile in the world market because of its extensive medicinal values and impeccable pharmacological properties. Also, there has been an increase in the use of natural substances instead of synthetic chemicals because many herbal medicines are free from side effects, easy to obtain, considered healthy, and create income. It is a well-established fact that chamomile plant diversity is being threatened by unregulated harvesting of natural populations and expansion of urban centers.

So it is advisable to cultivate chamomile for better quality control of the target bioactive components. This approach also allows for the production of uniform plant material at predetermined intervals in the required quantities. A strong need is felt to screen the

different chemotypes of chamomile growing at different phytogeographical locations. Similarly, biodiversity studies at morphologic, biochemical, and genetic levels will enable the research community to realize the extent of variability within the existing germplasm of chamomile, and hence help in the conservation of the plant. However, there is still a wide scope for exploring different aspects of chamomile.

Soy

Soy, *Glicine max* (L.), is a plant of Asian origin belonging to Fabaceae family. Worldwide producers of soy bean are USA, Brazil, Argentina, China and India with world production volumes of 35%, 28%, 17%, 4% and 3%, respectively. In the soy industry, after oil extraction, a consistent fraction is used for the production of fodder for livestock.

Soy is a basic food ingredient of traditional Asian cuisine used for thousands of years. In Western countries, soybeans have been introduced about a hundred years ago and recently they are mainly used for surrogate foods production. Soy and soy foods are common nutritional solutions for vegetarians, due to their high protein content and versatility in the production of meat analogues and milk substitutes. However, there are some doubts about the potential effects on health, such as the effectiveness on cardiovascular risk reduction or, conversely, on the possible disruption of thyroid function and sexual hormones. The soy components that have stimulated the most research interest are isoflavones, which are polyphenols with estrogenic properties highly contained in soybeans.

Shift from omnivore to vegetarian diet implies the intake of nutrients from plant sources with sustainable and well-planned dietary schemes. Some supplements are needed to ensure adequate nutrition if the diet falls to guarantee correct essential nutrients. Overall, the most important and accepted supplement is the vitamin B12 supplementation, scarcely represented in plant foods. Also protein quality has often been a cause for debate because of different amino acid pattern of plant foods in relation to animal ones, which has been speculated to affect protein synthesis; this concept led to the definition of “high quality protein” referred to proteins from animal foods. However, increasing variety and quantity of plant foods may overcome this issue and may guarantee the intake of all essential amino acids needed for an adequate nutrition plan. Essential amino acid consumption needs more emphasis in children and individuals engaging in sport activity, with specific increased turnover in body proteins.

Increasing interest over the last years has been paid to protein from plant sources: there is evidence that individuals consuming foods high in vegetable proteins (i.e., legumes) have lower risk of cardiovascular disease and other metabolic disorders. Among others, protein quality of soy beans is one of the most attractive reasons for the interest in soy and soy foods among vegetarians. With the growing adoption of vegetarian lifestyles, a great variety of soy-based food products have become more available in grocery stores; besides the market request, a reason for such popularity may depend on the nutritional and versatile properties of soy beans, which are suitable for food technological transformations. Soy

beans are used for the production of several analogues and surrogates of meat and dairy products that might be used as alternatives especially during transition to vegetarian diet. [175, Rank 5]

Ginger

The current mode of treatment based on synthetic drugs is expensive and also causes genetic and metabolic alterations. However, safe and sound mode of treatment is needed to control the diseases development and progression. In this regards, medicinal plant and its constituents play an important role in diseases management via modulation of biological activities. Ginger, the rhizome of the *Zingiber officinale*, has shown therapeutic role in the health management since ancient time and considered as potential chemopreventive agent. Numerous studies based on clinical trials and animal model has shown that ginger and its constituents shows significant role in the prevention of diseases via modulation of genetic and metabolic activities.

Although, allopath based treatment is effective in diseases cure but also alters the various metabolic and molecular pathways. Since ancient time, medicinal plants and its constituents have been used for diseases management. Medicinal plants and its constituents such *curcumin*, black seed, olive fruits/leaves and dates shows a therapeutic role in diseases control via modulation of biological activities. Herbs and its constituents have important value in diet and treatment of various diseases and Prophet Mohammed (PBUH) used various herbs including dates and *Nigella sativa* and also recommended various medicinal plants in the diseases cure.

Medicinal plants and their constituents show a vital effect in the diseases cure especially with properties of being antioxidant, anti-inflammatory, anti-diabetic and anti-tumour effect. Ginger, the rhizome of the *Zingiber officinale* is commonly consumed dietary condiments, generally considered to be safe and used to cure various diseases. It also shows a role in cancer prevention by inactivating and activating various molecular pathways. In this review, we summarized the therapeutics role of ginger in diseases management via modulation of biological activities including anti-inflammatory and anti-oxidative activities together with regulation of genes mechanism of action. Antioxidants are substances that play a role in the neutralization of free radicals and oxidative stress. The free radical production is balanced by the antioxidative defense system of our body.

Any alterations between reactive oxygen species (ROS) generation and its neutralization by antioxidant defense cause oxidative stress. Several plants and their constituents are rich source of antioxidant and play a significant role in prevention of disease progression process. Ginger is a source of a large number of antioxidants and also plays an important role in the reduction of the lipid oxidation and inhibits the pathogenesis of diseases. Previous study reported that ginger extract possesses antioxidative characteristics and shows a role in scavenge superoxide anion and hydroxyl radicals and gingerol, inhibited ascorbate/ferrous complex induced lipid peroxidation in rat liver microsomes. [99, Rank 3]

Peppermint

Mentha piperita essential oil was bactericidal in order of *E. coli*> *S. aureus* > *Pseudomonas aeruginosa* > *S. faecalis* > *Klebsiella pneumoniae*. There was 38.3% decrease in WBCs count, while platelet count showed increased levels of 214.12%. Significant decrease in uric acid level and cholesterol/HDL and LDL/HDL ratios were recorded. The volatile oil displayed high cytotoxic action toward the human tumor cell line. The results of this study deserve attention with regard to antioxidative and possible anti-neoplastic chemotherapy that form a basis for future research. The essential oil of mint may be exploited as a natural source of bioactive phytopchemicals bearing antimicrobial and antioxidant potentials that could be supplemented for both nutritional purposes and preservation of foods.

Supplementation of human diet with herbs, containing especially high amounts of compounds capable of deactivating free radicals, besides the fruits and vegetables recommended as optimal sources of antioxidant activity, may have beneficial effects. The benefits resulting from the use of natural products rich in bioactive substances have promoted the growing interest of pharmaceutical, food and cosmetic industries as well as of individual consumers in the quality of herbal products. The oxidative deterioration of lipids is of great concern in the shelf life of foods. Lipid peroxidation leads to development of undesirable off-flavors and decreases the acceptability of foods. In addition, lipid oxidation decreases food safety and nutritional quality by the formation of potentially toxic products and secondary oxidation products during cooking or processing. To prevent and retard lipid oxidation, synthetic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and propyl gallate (PG) have been added to lipid-containing foods.

However, potential health hazards of synthetic antioxidants in foods, including possible carcinogens, have been reported several times. Antioxidants are compounds that can delay, inhibit, or prevent the oxidation of oxidizable matters by scavenging free radicals and diminishing oxidative stress. Plants contain a wide variety of antioxidant phytochemicals or bioactive molecules, which can neutralize the free radicals and thus retard the progress of many chronic diseases associated with oxidative stress and reactive oxygen species (ROS). The intake of natural antioxidants has been associated with reduced risk of cancer, cardiovascular disease, diabetes and diseases associated with ageing. Studies on dietary free radical scavenging molecules have attracted the attention to characterize phenolic compounds and other naturally occurring phytochemicals as antioxidants. [34, Rank 3]

English Ivy

Bio-inspiration for novel adhesive development has drawn increasing interest in recent years with the discovery of the nanoscale morphology of the gecko footpad and mussel adhesive proteins. Similar to these animal systems, it was discovered that English ivy (*Hedera helix* L.) secretes a high strength adhesive containing uniform nanoparticles. Recent studies have demonstrated that the ivy nanoparticles not only contribute to the high strength of this adhesive, but also have ultraviolet (UV) protective abilities, making them

ideal for sunscreen and cosmetic fillers, and may be used as nanocarriers for drug delivery. To make these applications a reality, the chemical nature of the ivy nanoparticles must be elucidated.

Recent studies showed that the root hairs from the adventitious roots of English ivy (*Hedera helix* L.) secrete a nanocomposite adhesive composed of nanoparticles and a liquid polymer matrix. The naturally secreted nanoparticles are highly uniform with a diameter of 50–80 nm, as measured by atomic force microscopy (AFM), and were hypothesized to contribute to the high adhesive strength of English ivy. Force spectroscopy conducted on the freshly secreted adhesive found that the strength of the ivy adhesive was much greater than similar bioadhesives.

In order to determine the potential contribution of the ivy nanoparticles to the generation of the measured adhesive force, a contact fracture mechanics model was developed to predict the attachment strength of the nanoparticles. Based on the model, it was discovered that van der Waals forces between the nanoparticles alone were not strong enough to generate the attachment strength observed experimentally. The data led to the hypothesis that the interaction between the nanoparticles and the polymer matrix generates cross-linking reactions that lead to an increased strength of adhesion. This hypothesis is consistent with the mechanism of other bioadhesives, such as those of marine mussels and barnacles, where adhesive proteins interact with divalent cations and polysaccharides to generate a stable water-resistant adhesive. [23, Rank 4]

Andrographis

Andrographis paniculata (Burm. f.) Wall. ex Nees (AP) is an important medicinal plant and widely used around the world. It belongs to the family Acanthaceae. AP is used as a traditional herbal medicine in Bangladesh, China, Hong Kong, India, Pakistan, Philippines, Malaysia, Indonesia, and Thailand and is ethnobotanically used for the treatment of snake bite, bug bite, diabetes, dysentery, fever, and malaria. In the Unani and Ayurvedic medicines, AP is one of the mostly used medicinal plants. In recent times, commercial preparations of this plant extracts are also used in certain countries. However, the preparations yet need to be standardized for their better efficacy. The aerial part of AP is most commonly used; its extracts contain diterpenoids, diterpene glycosides, lactones, flavonoids, and flavonoid glycosides.

Whole plant leaves and roots are also used as a folklore remedy for different diseases in Asia and Europe. AP has been reported to have a broad range of pharmacological effects including anticancer, antidiarrheal, antihepatitis, anti-HIV, antihyperglycemic, anti-inflammatory, antimicrobial, antimalarial, antioxidant, cardiovascular, cytotoxic, hepatoprotective, immunostimulatory and sexual dysfunctions.

As aboriginal sources of medications, medicinal plants are used from the ancient times. *Andrographis paniculata* is one of the highly used potential medicinal plants in the

world. This plant is traditionally used for the treatment of common cold, diarrhoea, fever due to several infective cause, jaundice, as a health tonic for the liver and cardiovascular health, and as an antioxidant. It is also used to improve sexual dysfunctions and serve as a contraceptive. All parts of this plant are used to extract the active phytochemicals, but the compositions of phytoconstituents widely differ from one part to another and with place, season, and time of harvest.

The demand of AP is greatly increased in the past few years for its overwhelming therapeutic potentials. Available data on AP also clearly expresses a broad spectrum of pharmacological properties of this plant. Due to possessing extensive pharmacological activities, the AP can be safely regarded as one of the modern catholicons. However, the investigated pharmacological activities of AP need validation through the clinical study. Though several clinical studies were successfully completed without adverse effects or fatalities, most of them only investigated upper respiratory tract infections for a variety of conditions. Verification of the efficacy of other biological activities of AP including antidiabetic, anticancer, anti-inflammatory, and hepatoprotective activities, on human study subjects would bring a lot of benefits for the largest population of the globe. [117, Rank 4]

Conclusion

The global acceptance and use of herbal medicines and related products continue to assume exponential increase. Issues relating to adverse reactions in recent times are also becoming more vivid, increasing in prevalence and no longer debatable because of previous misconception of regarding or categorizing herbal medicinal products as “safe” because they are derived from “natural” source. The reality is that “safety” and “natural” are not synonymous. Therefore, regulatory policies on herbal medicines need to be standardized and strengthened on a global scale. Relevant regulatory authorities in different countries of the world need to be proactive and continue to put in place appropriate measures to protect public health by ensuring that all herbal medicines approved for sale are safe and of suitable quality.

Providers of medicines, such as physicians, nurses, and pharmacists, often have little training in and understanding of how herbal medicines affect the health of their patients. Many of them are also poorly informed about these products and how they are being used. Adequate training is now very essential since most patients are almost often on other types of prescription or non-prescription medicines. In spite of the fact that the active involvement of orthodox healthcare professionals is continuously solicited and huge responsibility lies with them in terms of their valuable contributions to safety monitoring of medicinal products, it is also very important that all providers of herbal medicines are sufficiently empowered to play a role in monitoring safety of herbal medicines. This, however, should be in collaboration with the orthodox healthcare professionals. For this to be effective, it would be essential to create an atmosphere of trust to facilitate adequate sharing of knowledge about the use and safety of herbal medicines. In fact, the education of

healthcare professionals, providers of herbal medicines, and patients/consumers is vital for the prevention of potentially serious risks from misuse of herbal medicines.

Of crucial importance also is an appropriate knowledge base relevant to diagnostic and treatment decision-making. Furthermore, individual healthcare provider should also show sufficient commitment toward understanding the use of herbal medicines. This can be by asking relevant questions about the use of these herbal remedies among others whenever they encounter patients who are taking these medications. Health professionals who work in poisons centers and health information services also need to be informed about herbal medicines. Finally, as with other medicines for human use, it has become mandatory that herbal medicines are covered in every country of the world by a drug regulatory framework to ensure that they conform with required standards of safety, quality, and efficacy. [65, Rank 5]

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