Review

Traditional Phytomedicinal Systems, Scientific Validations and Current Popularity as Nutraceuticals

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Abstract: Medicinal and aromatic plants or botanical herbs are used for their therapeutic, scent, cosmetic or flavor properties. As traditional medicine, many herbs have been used for their claimed health benefits from the dawn of human civilization. Presently, they are sold as fresh or dried plants, teas, extracts, powders, tablets, capsules, forming traditional or commercial natural product therapeutics. The plants, as whole or their parts, e.g. roots, stems, bark, wood, leaves, flowers, fruits and seeds, may have some therapeutic properties. Botanical medicines include the medicinal plants as such and their extracts in processed form. The human populations have developed various uses of medicinal plants for the treatment of the diseases affecting their society. The major traditional systems of medicines which have been in practice for about 5000 years are the Indian system of medicine, called Ayurveda, traditional Chinese medicine, Unani, Siddha, Tibetan system, Egyptian, Greek and Roman. Homeopathy, a relatively newer system, is mainly based on the uses of herbs, therefore a brief description of it has also been included in this review. The current popularity of herbals is mainly based on their uses as nutraceuticals which are taken as the dietary supplements that people take to improve their health. Plant based medicines are believed to have synergistic effects and negligible side effects. However, there are several examples that plant medicines can cause health problem, some of them are not effective and may interact with other drugs being taken, simultaneously. During last decade, enormous volume of information on medicinal plants uses (i) as traditional medicine, (ii)
empowerment of natural products in modern drug development, (iii) scientific validation of biological activities associated with known medicinal and aromatic plants, and (iv) their popularization as nutraceuticals is available. Several reviews have also appeared on these subjects but mostly have dealt with one or more of these points independently. The present review is intended to project detailed information covering all these points at one place, especially, the classical uses of medicinal plants as therapeutic agents in various types of folklore and their increasing demand as nutraceuticals during current era, worldwide. The popularity of folklore medicines versus the necessity of their scientific validations and safety parameters, etc., is also covered.

**Keywords:** medicinal plants; nutraceuticals; traditional systems of medicine; Ayurvedic system; traditional Chinese medicine; functional foods; standards; quality control; safety.

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1. Introduction

As the human population lives longer, age related diseases which are mostly related to dietary habits, continue to attack. For several thousand years, this fact had encouraged the mankind to search and include the plant based medicinal diet to improve the deterioration in health. The use of medicinal plants as an important source of relief from illnesses, can be traced back to five millennia in the form of written documents of the early civilization in China, India and Near East, but undoubtedly it is an art as old as mankind. Even today, plants are not only indispensable in health care but are expected to be ample source for safe future medicines (Anonymous, 1969; Husain et al., 1988 & 1992; Misra et al., 2000; Misra and Kumar, 1997; Tuli et al., 2009; Wagner, 1985). A recently published editorial by A. Schieber, 2012, emphasizes the future scope of phytomedicinal principles in the form of nutraceuticals or functional foods. It was estimated that by 2015, the global nutraceutical market is expected to grow to exceed US $ 243 billion. The main reasons for popularity of phytomedicinal drugs in the form of nutraceutical are (i) increasing cost of health care, (ii) growing trend of self medication, (iii) an increased awareness of the relationship between food and health, and (iv) lifestyle changes in the society.

In spite of the fact that now we have at our command a number of modern drugs, it is still genuinely urgent to discover and develop new therapeutic agents because some diseases cannot yet properly be treated by modern medicine. It has been estimated that the satisfactory therapy by drugs purely from synthetic origin, is available only for limited known symptoms of human ailments. Traditional plant drugs still enjoy important status in the modern day drug industries owing to their
negligible side effects as well as the synergistic and holistic actions of the combination of a variety of compounds. The traditional or folklore medicines, based on the use of plants and plant extracts, are currently termed as herbalism, botanical medicine, medical herbalism, herbal medicine, herbology and phytotherapy (Hamburger and Hostettmann, 1991; Lal, 2007). The scope of herbal medicine is sometimes extended to include bacterial, fungal and bee products, as well as minerals, shells and certain animal parts. During last decade, enormous volume of information on the uses of medicinal plants and their products in traditional medicine, scientific validation by biological activity testings and their popularization as nutraceuticals has been generated. Several reviews have also appeared on these subjects but mostly have dealt with one or the other of these aspects, independently. The present review is intended to project detailed information covering all these points at one place, especially, the classical uses of medicinal plants as therapeutic agents in various types of folklore and their increasing demand as nutraceuticals during current era, worldwide.

Most of the plants synthesize substances that are useful to the maintenance of health in humans and other animals. These include aromatic substances, most of which are phenols or their oxygenated derivatives such as phenyl propanoids and lower terpenoids such as mono- and sesquiterpenoids. Many of the herbs and spices used by humans to yield flavor and fragrance are useful medicinal compounds, also. Many important books have compiled information on the advancement on medicinal plants related research, worth mentioning is one by Wagner et al. (1985) who have published their book on economic and medicinal plants research in several volumes. In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores (Lai and Roy, 2004; Tapsell et al., 2006). People of all constituent have used hundreds to thousands of indigenous plants for treatment of ailments since prehistoric times. Anthropologists theorize that animals evolved a tendency to search bitter plant parts to treat the human illnesses.

Traditional medicine is a culture-bound body of indigenous medical knowledge, belief and practices and has provided the plant-based foundation for many ethnomedical systems which already existed long before the development of modern medicine. While ethnomedicine has been practiced from prehistoric period by virtually all human cultures around the globe, including not only the ‘Great Traditions’ of Hippocratic-Galenic medicine of ancient Greece, the Unani Tibb of Arabia, the Ayurvedic of India and Chinese medicine in Asia, but also the ‘Little Traditions’ in Africa, Europe, Asia and the Americas. It was not until the 16th century that the European expansion brought a wealth of plants, herbs and spices, and related indigenous knowledge from the tropics to Europe.

Since the belief, emotion and intuition on the medicinal properties of plants were not supported by the conditions of scientific parameters, they were belittled and replaced by doubt or distrust. With the passage of time, the modern medical methodology sought to break up complicated phenomena and processes into smaller components which had to be dealt with in isolation, often by distinct sub-
disciplines, as such largely ignoring the principles of synergy and holism. While in diagnosis, the focus was generally laid on the search for a single illness, to be cured ideally by one remedy, in pharmacology the quest was likewise for one active component to be identified and isolated or synthesized. The development and implementation of the scientific methods and techniques in medicine have brought enormous improvements, especially, in all those cases in which material phenomena, including infection, injury, poisoning, nutrition and hygiene, are major factors in the disease etiology. Of course in public health, modern medicine has substantially contributed to the decrease and eradication of some major epidemic diseases such as typhoid, cholera, bacterial infections, parasitic diseases, smallpox and polio.

Although the contribution from the discovery of anti-bacterial agents during post World War II period to the successful fight against infectious and parasitic diseases has been dramatic, recently some problems of bacterial resistance and parasitic immunity to synthetic drugs are creating reason for increased international concern. In degenerative conditions, however, where mental, chronic, allergic, behavioral, emotional and spiritual factors are playing a determining role, the effect of modern medicine are disappointing, and deterioration is becoming rather evident, somewhere. Recent review by Cordell and Colvard (2012) has clearly emphasized on the recent paradigm shifts on the scientific strategies that may enhance the quality, safety and efficacy of traditional medicines and dietary supplements in global health care.

Following the emergence of relatively new, so-far incurable life style diseases such as obesity, diabetes, hypertension and also the HIV/AIDS, rheumatism, the modern medicines which were practically confined to the richer economies of the world and to the urban elites in the developing countries, have failed to show their presence effectively to rest of the world population. The staggering high cost of technologically advanced modern medicine has left little doubt about the today’s focused search for alternative solutions and approaches. In this context, it is not surprising that the worldwide movement of ‘back-to-nature’ among clients, patients and the general public has grown because the industrially produced, sometimes less effective medicines, have shown serious side-effects. In many countries, the age-long persistent reliance on traditional herbal medicine has undergone a revival which is encouraged by integrative strategies from international organizations such as WHO, UNICEF and UNIDO. Now-a-days, the public interest in western countries in knowledge and use of non-western traditional herbal medicines, represented by numerous books, journals, documentaries and exhibitions, has increased tremendously. This has put pressures on drug companies and government to open up their health-care systems to these alternative forms of complementary and alternative medicines. Similarly, parallel developments in the social sciences, notable in the interdisciplinary field of medical anthropology, ethnomedicine and medical ethnobotany, have led to the development of new approaches to identify, document and analyze indigenous medical knowledge and practice, particularly
in the field of medicinal, aromatic and cosmetic plants.

In order to enrich with the scientific basis for the traditional uses of medicinal plants, the random sampling of plant materials is being reconsidered. An improved method in bio-prospecting is being used on the basis of traditional knowledge and practice by traditional healers, birth attendants and their patients. This is known as the ethno-directed sampling of indigenous plant collections. However, despite the advancement in multiple research methods and techniques in the search for new drugs, conventional validation of bioactive components in plant species is still costly and time consuming. One of the factors that lead to such high costs, is the local practice of use of multiple plant mixtures in traditional medicine, posing complex problems to plant screening techniques. Instead of isolating the single plant species in validation, the complete prescription of plant mixtures should also be included in the analysis of the intricate chemical interactions that take place among bioactive components of these plant mixtures. Similarly, preparations of mixtures of plants have shown either to increase the activity of compounds or to reduce the toxicity. It is often argued that such multiple plant mixtures need to be included in the scientific validation process because of the complex chemical interactions among constituents of one single plant or different plants or synthetic drugs taken simultaneously (Butterweck and Darendorf, 2012).

By consequence, the use of traditional botanical knowledge as a promising instrument in bio-prospecting for useful plants for both human and animal medicine has now become more popular, rendering ethnomedical and medical ethnobotanical research methods and techniques contributive to validation and development of new plant-based drugs. Still, this type of research basically focuses on the proper plant species and their assumed bioactive components. It is often discussed that quantitative ethnobotany by further developing a multivariate model of transcultural utilization of medicinal and aromatic plants for health improvement allows the study, analysis and integration of a wider range of active constituents of traditional herbal knowledge, belief and practice into the multiple research process (Slikkerveer, 2006).

Indigenous healers often claim to have learned by observing that the unhealthy animals change their food preferences to nibble at bitter herbs, they would normally reject (Hutchings et al., 2003). It has been found that some birds select nesting material rich in antimicrobial agents who protect their young from harmful bacteria. Sick animals tend to forage plants rich in active metabolites, such as tannins and alkaloids (Huffman, 2003). The self-medication by animals in the wild is done by eating the plants having phytochemicals with antiviral, antifungal antibacterial and antihelmintic properties. It is not only the humans who have understood the medicinal benefit from plants. The plant-animal relationship is many times very attractive. Some animal’s digestive system is especially adapted to cope with certain plant toxins. For example, the koala can live on the aerial parts of the eucalyptus, a plant that is not eaten by most animals. One plant that is harmless to a particular animal may not be
safe for humans to ingest (Huffman, 2003; Hutchings et al., 2003). A reasonable conjecture is that these observations were traditionally made by the practitioners of indigenous tribes, who then passed on safety information and cautions.

The use of herbs and spices in cuisine has developed to counter the threat of food-born pathogens. Studies show that in tropical climates where pathogens are the most abundant, recipes are the mostly spiced. Further, the spices which had potent antimicrobial property tend to be selected (Billing and Sherman, 1998; Sherman and Hash, 2001). Many of the important drugs of the past 50 years, which have revolutionized modern medicinal practice, have been either isolated or derivatized from plants. These chemical ingredients exhibit therapeutic properties of plant drugs. Currently, WHO encourages, recommends and promotes the inclusion of herbal drugs in national health care programs because such drugs are easily available at a price within the reach of the common man and are time tested and thus considered to be quite safe than the modern synthetic drugs. Thus, the investigation of pharmacologically/biologically active agents obtained by screening the plant extracts has led to the discovery of many clinically useful drugs that play a major role in the treatment of chronic diseases. The most important among them are the research work on Catharanthus roseus, Artemisia annua, Lantana camara, Taxus spp., Bacopa spp. etc. Such plants were, earlier, considered as poisonous or useless, but now have been found to contain molecules of high drug values and are now considered as medicinal herbs of great significance. Medicinal plants have proved their significant role in coping with the diseases associated with viral onslaught viz. hepatitis, AIDS, etc (Newman and Cragg, 2012).

During last few decades, a good number of scientifically proven potent drugs and a large number of therapeutic leads and many new pharmacologically active constituents have been developed from herbal drugs. The Industrial scale manufacture of morphine in 1826 marks the beginning of commercialization of plant-derived drugs. Since then a number of plant based drugs or their synthetic analogues are continuously appearing in the market. The introduction of Reserpine, the principal constituent of roots of Indian medicinal plant Rauwolfia serpentina in 1953 is a classical example of plant drugs which have been developed based on Indian system of medicine. Nearly two third of the best selling pharmaceuticals are either from natural products or their derivatives or prototypes (Newman and Cragg, 2012). The plants produce chemical compounds as part of their normal metabolic activities. These are arbitrarily divided into primary metabolites, such as sugars and fats, found in all plants, and secondary metabolites that are not essential for basic function and are found in a smaller range of plants. It has been demonstrated that even common weeds have medicinal properties (Stepp and Moerman, 2001; Stepp, 2004).

The functions of secondary metabolites are varied as some secondary metabolites produce toxins to deter predation, and others yield pheromones to attract insects for pollination. Phytoalexins protect against bacterial and fungal attacks. Allelochemicals are well known to inhibit rival plants that
are competing for soil and light. Plants regulate their biochemical paths in response to the local mix of herbivores, pollinators and microorganisms (Stepp and Moerman, 2001). The chemical profile of a single plant may vary over time as it reacts to changing environmental conditions. It is these secondary metabolites that can have therapeutic actions in humans and can be refined to produce drugs.

Plants synthesize a large variety of phytochemicals but most are derivatives of a few biochemical motifs. Alkaloids contain nitrogen in the ring and they have dramatic effects on the central nervous system. For example, caffeine is an alkaloid that provides a mild lift sometimes causing suppression of sleep but the alkaloids in datura cause severe intoxication which even leads to death. Common examples of old plant drugs are quinine from the cinchona, inulin from the roots of dahlias, morphine and codeine from the poppy, and digoxin from the foxglove. The active compound in willow bark, once prescribed by Hippocrates, is salicin, which is then converted in the body into salicylic acid. The discovery of salicylic acid has eventually led to the development of the acetylated form of salicylic acid, also known as "aspirin", when it was isolated from a plant known as meadowsweet. The word aspirin comes from Genus Spiraea. "Aspirin" is a brand name, and is still a protected trademark in some countries (Anonymous, 2004).

The anthocyanins that give grapes their purple color, the isoflavones, the phytoestrogens from soy and the tannins that give tea its astringency, are phenolics. Similarly, the terpenoids are built up from terpene building blocks. The names monoterpenes, sesquiterpenes, diterpenes and triterpenes are based on the number of isoprene units. For example, the fragrance of many aromatic plants is due to the presence of monoterpenoids. The carotenoids produce the reds, yellows and oranges of pumpkin, corn and tomatoes. Glycosides consist of a glucose moiety attached to an aglycone which is bioactive in its free form but inert until the glycoside bond is broken by water or enzymes. This mechanism allows the plant to defer the availability of the active molecule to an appropriate time which could be explained to a safety lock on a gun. For example, the cyanoglycosides in cherry pits are released as toxins only when bitten by an herbivore.

2. Medicinal Plants as Therapeutic Agents

The use of herbs to treat disease is very popular among non-industrialized nations. At the end of the twentieth century a number of traditions came to dominate the practice of herbal medicine. For example, The Siddha and Ayurvedic medicine systems from Indian sub continent; The herbal medicine system of Greek and Roman; Chinese herbal medicine; Unani- Tibb medicine; Shamanic herbalism from South America, etc. The modern medicinal plant practitioners explain herb actions in respect to their chemical constituents. It is assumed that the specific combinations of secondary metabolites in the plant are responsible for the activity claimed or demonstrated and is supported by the concept of
Herbalists tend to use extracts from parts of plants but not isolate particular phytochemicals. Synthetic medicine is preferred as single ingredient on the ground that dosage can be more easily quantified and is patentable. Herbalists reject the idea of a single active ingredient and support that the different phytochemicals present in many herbs will interact to enhance the therapeutic effects of the herb and dilute toxicity. Furthermore, it is argued that a single ingredient may contribute to multiple effects. It is not plausible that herbal synergism can be duplicated with synthetic drugs. It is believed that phytochemical interactions and trace components may alter the drug response and cannot be replicated with a combination of a few putative active ingredients. Synthetic drug developers recognize the concept of drug synergism but argue for clinical trials to investigate the efficacy of a particular herbal preparation, provided the formulation of that herb is consistent. In some cases the claims of synergy and multifunctionality have been supported by experimental research (Goldman, 2001; Williamson, 2001). Plants are subject to similar selection pressures as humans and therefore they have to develop resistance to environmental threats such as radiation, oxidation and microbial attack in order to survive (Izhaki, 2002). Optimal chemical defenses have been selected by the plant kingdom and have thus developed over millions of years. Human diseases are multifactorial and may be treated by consuming multichemicals present in herbs. For example, bacteria, inflammation, nutrition and reactive oxygen species may together play a role in arterial disease. Herbalists claim a single or combination of herbs may simultaneously address several of these factors (Briskin, 2000; Govindarajan et al., 2005; Grassmann et al., 2002; Mallika et al., 2007; Riddle, 2002). In short herbal drug practitioners believe that it is web of relationships rather than a treatment for single cause and a single cure for a single condition.

In selecting herbal treatments, herbalists may use large base for information because herbs are consumed as vegetables, teas or spices. Therefore large-scale epidemiological studies become feasible and ethnobotanical studies are further source of information (Anonymous, 1969). It is taken as supporting evidence for its efficacy when indigenous peoples from geographically dispersed areas use closely related herbs for the same treatment (Riddle, 2002).

According to the World Health Organization estimate, it is believed that 80 percent of the world's population presently uses herbal medicine for some aspect of primary health care (Anonymous, 2008; Barnes and Ernst, 1998; Casey et al., 2007; Ernst, 2007). Herbal medicines can be grown from seed or gathered from nature for little or no cost and are major components in all traditional medicine systems including Siddha, Ayurvedic, Unani, homeopathic, naturopathic, traditional Chinese medicine, and Native American medicine.

The search for plant based drugs and dietary supplements have accelerated in recent years. Among more than a hundred active compounds currently isolated from the higher plants and widely
used in modern medicine today, 80 percent show a positive correlation between their modern therapeutic use and the traditional use of the plants from which they are derived (Barnes and Ernst, 1998). It is estimated that at least 7,000 medical compounds in the modern pharmacopoeia are derived from plants and about 70% of the world's plant species come from the developing countries (Anonymous, 2008).

The fifteenth, sixteenth, and seventeenth centuries were the great age of herbals, many of them were made available for the first time in English and other languages rather than the old languages, like Sanskrit, Tamil, Latin or Greek. In the twentieth century, the rapid development of chemistry and the other physical sciences, led to the dominance of chemotherapy - chemical medicine - as the popular therapy. Many of the studies conducted refer to animal model investigations or in-vitro assays and therefore cannot provide more than weak supportive evidence.

These days, medical research is very expensive investment. The global spending goes as high as US $ 110 billion but 90% of this spending serves only 10% of the global population. Not only this, WHO has noted that during the past quarter of century, only 1% of the new drugs have been developed to treat the diseases of the poor. True innovation in synthetic drug development is also lacking. It is observed that 75% of the recently approved drugs showed no added therapeutic benefit and the breakthrough drugs constituted to only 5% of the total drugs developed (Newman and Cragg, 2012). On the other hand, the role of natural products in the drug discovery process is being highlighted at various platforms and natural product-likeness scores have been developed for chemical libraries for drug screening. Phytochemicals which are present in food and have been associated to health benefits, mainly, include alkaloids, terpenoids, steroids, phenols, flavonoids, some carbohydrates, glucosinolates, sulphur containing compounds, etc.

There are many herbs which have shown positive scientific results for their traditional uses. Some of the best studied examples are summarized as follows:

_Acorus calamus_ rhizome has shown insecticidal, piscicidal, spasmylytic, hypothermic, CNS active, analgesic activities and the essential oil is anticonvulsant. The major constituents present are flavonoids and terpenoids (Husain et al., 1992). The pod, stem and root of _Albizia lebbek_ have been reported to exhibit anticancer, antiprotozoal, CVS active and hypoglycaemic activities. The major constituents reported from this plant are saponins, triterpenoids and macrocyclic budmunchiamine alkaloids (Husain et al., 1992; Dixit and Misra, 1997; Misra et al., 1995). _Aloe vera_ has traditionally been used for skin improvements and in the healing of burns and wounds (Maenthaisong et al., 2007). A systematic review states that the efficacy of _Aloe vera_ in promoting wound healing is unclear. A review concludes that the cumulative evidence supports the use of _Aloe vera_ for the healing of first to second degree burns (Vogler and Ernst, 1999) while the _Agaricus blazei_ mushrooms prevent some types of cancer (Kimura et al., 2004). _Andrographis paniculata_ has been tested for hepatoprotective,
antidiabetic activities besides the antimicrobial and hypotensive. The andrographolides are responsible for hepatoprotective actions. Some flavones and sterols have also been isolated (Husain et al., 1992).

_Artemisia annua_ is very well known antimalarial plant with artemisinin as potent compound for combating the cerebral malaria (Ahmad and Misra, 1994; Husain et al., 1992; Misra et al., 1993a & b). The aerial part, bark and roots of _Asparagus racemosus_ have been found to be spasmolytic, anticancer, anti bacterial whereas the major constituent shatavarins have been found to be antioxytotic. The Neem tree (_Azadirachta indica_ Syn. _Melia azadirachta_) is very important medicinal plant especially as insecticidal, antibacterial and against pyrrohoea which is effective because of several terpenoidal components. _Bacopa monnieri_, the Brahmi, is established brain tonic and improves learning ability and contains active bacoside saponins along with several alkaloids. The isoquinoline alkaloids from _Berberis aristata_ have also exhibited anti-inflammatory and hypotensive effect. Punarnava (_Boerhavia diffusa_) has shown spasmolytic, antiarrhythmic, anticonvulsant activities because of the presence of alkaloids, sterols and flavonoids in it. Resin from _Boswellia serrata_ is strong antiinflammatory while _Cassia senna_ is very popular laxative. Report of sennosides from this plant is of biological significance. _Centella asiatica_ is also used as brain tonic and is known and active adulterant for _Bacopa monnieri_. Its major biologically active constituents are brahmosides. _Chlorophytum arundinaceum_ is popularly consumed in India for enhancing potency and sexual vigour (Husain et al., 1992).

_Coleus barbatus_ syn. _C. forskohlii_ roots have been biologically proven to be CVS and CNS. The main active constituent is forskolin along with several related diterpenoids. _Commiphora wightii_ syn. _C. mukul_ is a gum yielding shrubby tree which has been proved to be hypocholesteremic due to the presence of guggulsterones (Husain et al., 1992). According to _in vitro_ studies (Gebhardt, 1998) and a clinical study (Bundy et al., 2008), Artichoke (_Cynara cardunculus_) may reduce the cholesterol levels. Blackberry (_Rubus fruticosus_) leaf has been shown to interfere with the metalloproteinases that contribute to skin wrinkling (Herrmann et al., 2007). _Rubus occidentalis_ (Black raspberry) may have a role in preventing oral cancer (Han et al., 2005; Rodrigo et al., 2006; Mallery et al., 2008). Boophone (_Boophone disticha_), a highly toxic plant has been used in South African traditional medicine for treatment of mental illness (Stafford et al., 2008). Research demonstrated its _in vitro_ and _in vivo_ effect against depression (Neergaard et al., 2009; Pederson et al., 2008; Stafford et al., 2008). Calendula (_Calendula officinalis_) has been used for abdominal cramps and constipation. In animal model its flower’s aqueous-ethanol extract was shown to have both spasmolytic and spasmogenic effects (Bashir et al., 2006). There are some reports that calendula cream or ointment is effective in treating radiation dermatitis (Bolderston, 2006; Mcquestions, 2006). Cranberry (_Vaccinium oxycoccos_) may be useful in treating urinary tract infections in women with recurrent symptoms (Jepson and Craig, 2008). _Digitalis purpurea_ yields digitoxins, the known and proven cardiac glycosides (Husain et al., 1992). Echinacea
(Echinacea sp.) extracts may limit the length and severity of rhinovirus colds (Schoop et al., 2006; Shah et al., 2007). Elderberry (Sambucus nigra) is helpful in the recovery from type A and B influenza (Zakay-Rones et al., 2004) but it may be risky in the case of avian influenza because the immunostimulatory effect disturbs the cytokine cascade (Barak et al., 2001). Feverfew (Chrysanthemum parthenium) is useful in the migraine headaches (Diener et al., 2005; Shrivastava et al., 2006; Silberstein, 2005; Pittler and Ernst, 2004). Feverfew is restricted in case of pregnant women as it may be dangerous to the fetus (Modi and Lowder, 2006; Yao et al., 2006).

Garlic (Allium sativum) may lower total cholesterol levels (Ackerman et al., 2001). German Chamomile (Matricaria chamomilla) has shown antispasmodic, anxiolytic, antiinflammatory and some antimutagenic and cholesterol-lowering effects in in vivo tests (Mckay and Blumberg, 2006). In vitro chamomile has demonstrated moderate anticancer, antimicrobial and antioxidant properties and significant antiplatelet activity (Srivastava and Gupta, 2007). Its essential oil was in vitro tested for antiviral agent against herpes simplex virus type 2 (HSV-2) (Koch et al., 2008). Ginger (Zingiber officinale), when orally administered with 250 mg dose for four days, decreased nausea and vomiting of pregnancy in a human clinical trial (Ozgoli et al., 2009). Green tea (Camelia sinensis) components, besides being antioxidant may also inhibit growth of breast cancer cells and may heal scars faster (Belguise et al., 2007; Zhang et al., 2006). Gymnema Sylvester contains sweetening compound known as gymnemic acid. It is also anti-diabetic and insulinotropic (Husain et al., 1992). The extracts of the seeds of Hibiscus sabdariffa may have some antihypertensive, antifungal and antibacterial effect (Ali et al., 2005). Seabuckthorn (Hippophae rhamnoides) is a shrub of high altitude and its fruits are extremely rich in the compounds for cardiac disorders and the essential oil is used in cosmetics. The aqueous extract of lemon grass (Cymbopogon citratus) fresh leaf, lowered total cholesterol and fasting plasma glucose levels in rats. It also increased HDL cholesterol levels but had no effect on triglyceride levels (Adeneye and Agbaje, 2007). Milk thistle (Silybum marianum) is very well recognized for many centuries as liver tonics (Kroll et. al., 2007). Research suggests that milk thistle extracts prevent and repair damage to the liver from toxic chemicals (Szilard et al., 1988).

Mucuna pruriens, locally in Hindi known as Kewatch, is a popularly used for trimmer actions of the body in the Indian system of plant medicine. The scientific evidences have proved that the seeds of M. pruriens contain amino acids and alkaloids, including L-DOPA, which have validated effect against Parkisonism (Misra and Wagner, 2006 & 2007). Nigella sativa (black cumin) has been demonstrated to show analgesic properties in mice. In vitro studies support antibacterial, antifungal, anticancer, anti-inflammatory and immune modulating effects (Ait Mbarek et al., 2007; Al-Ghamdi, 2001; Ali and Blunden, 2003; Hajhashemi et al., 2004; Islam et al., 2004; Kaleem et al., 2006; Khan et al., 2003; Morsi, 2000; Salem, 2005; Salim and Fukushima, 2003). O. sanctum is renowned Indian medicinal plant for its immune-modulating activity. Some phenyl propanoids have been reported to be
the active ingredients of this reputed plant (Noer and Wagner, 1992). Phyllanthus amarus syn. P. niruri is well known and scientifically proven plant for antihepatotoxicity. The lignans, viz. phyllanthin, isolated from this plant are the active constituents (Husain et al., 1992).

Peppermint oil has shown benefits for individuals with irritable bowel syndrome (Cappello et al., 2007; Liu et al., 1997). Picrorhiza kurroa, commonly known as kutki in India is high altitude plant and its bitter principles are well known for hepatoprotection, antimicrobial, muscle relaxant, etc. Piper longum has been known for large number of medicinal properties and many of them have been proven by biological assays, viz. bronchospasm, antiinflammatory, antibacterial, etc. The alkaloids, like piperine, have been responsible for these actions. The seed and husk of Plantago ovata, are strong laxative and is recommended in inflammatory condition of gastrointestinal tract. Podophyllum hexandrum contains lignans, e.g. podophyllotoxin and derivatives which are anticancerous. The heartwood and bark of Pterocarpus marsupium is hypoglycaemic and several flavonoids have been reported from various parts (Husain et al., 1992). Punica granatum (pomegranate) contains the highest percentage of ellagitannins in fruits and is commonly consumed as juice. Ellagitannins have been shown to inhibit cancer cell growth in mice (Heber, 2008; Seeram, 2007).

The roots of Rauwolfia Serpentina are rich in several alkaloids. The major are reserpine and its derivatives which are used extensively in India for sleeplessness, anxiety and high blood pressure (Dev, 1999). Rooibos (Aspalathus linearis) contains a number of phenolic compounds (Krafczyk et al., 2009) and has traditionally been used for skin ailments, allergies, asthma and colic in infants (Joubert et al., 2008). It stimulates insulin secretion in pancreatic beta cells and glucose uptake in muscle tissue (Kawano et al., 2009). The bark of Saraca asoca is used in Indian system of medicine for the gynecological disorders, especially, due to its anti-inflammatory activity. Some phenolic compounds have been reported from this plant but a relationship with the traditional medicinal uses had not been studied. We are currently working on the bioactivity guided extraction and isolation of active components from this tree and have found that the extracts show good antiinflammatory activity. Shiitake (Lentinus edodes) are edible mushrooms that have been reported to be useful in cancer prevention by inhibiting the growth of tumor cells through apoptosis (Fang et al., 2006). Its extracts have demonstrated in vitro antimicrobial activity against pathogenic bacteria and fungi (Hearst et al., 2009; Kuznetsov et al., 2005). Solanum nigrum berries are rich in steroidal alkaloids which possess CVS active, spasmylytic and hypothermic activities. Soy and other plants that contain phytoestrogens have some benefits for treatment of symptoms resulting from menopause (Bai et al., 2007).

St. John's wort (Hypericum perforatum) has yielded promising results for the treatment of depression in clinical trials (Adam et al. 2002; Cole et al., 2008; Davidson, 2002; Fava et al., 2005; Gaster and Holroyd, 2000; Gastpar et al., 2006; Gregory et al., 2009 & 2011; Husain et al., 1988 & 1992; Kasper et al., 2006; Lecrubier et al., 2002; Linde et al., 2005a & b; Newman and Cragg, 2012;
Roeder et al., 2004; Werneke et al., 2004). Stinging nettle (*Urtica dioica*) is effective for benign prostatic hyperplasia (Safarinejad, 2005), the pain associated with osteoarthritis (Randall et al., 2000) and antiinflammatory activity (Riehemann et al., 1999). In a rodent model, it reduced LDL cholesterol and total cholesterol (Daher et al., 2006) and platelet aggregation (Haouari et al., 2006). The *Swertia chirayita*, a plant native to Indian Himalayan region, has been chemically investigated to yield alkaloids and xanthones. It has been tested to show anti-inflammatory and hypoglycaemic activities. The isolation of the diterpenoid, taxol from *Taxus baccata*, as a powerful anticancerous molecule, regenerated the interest and scope of drugs from natural products. Several species of *Terminalia*, viz., *T. alata*, *T. arjuna*, *T. bellerica*, *T. chebula*, *T. paniculata*, etc., are rich sources of medicinal principles and are reported to exhibit various activities, including CVS-CNS active, antispasmodic, semen coagulant, hypoglycaemic, anticancer. *Tinospora cordifolia* is a climber and is used for enhancing the overall immunity system of the body. Biological tests have proved its stem to exhibit antiviral hypoglycaemic, anticancer and spasmyloytic activities, as well (Husain et al., 1992). Ashwagandha (*Withania somnifera*) is a plant rich in a special class of compounds called as withasteroids or withanolides which have large numbers of biological activities including, anticancer, CVS and CNS active. It is well known for antiageing, aphrodisiac, improving vigor, etc. (Chaurasia et al., 2008 & 2009; Husain et al., 1992; Lal et al., 2006; Mandal et al., 2008; Misra et al., 2005, 2008a & b; Sabir et al., 2008a & b; Sangwan et al., 2007 & 2008). Valerian root is reported with validation to be useful in the treatment of insomnia (Husain et al., 1992).

3. Traditional Systems of Medicine

There are numerous kinds of traditional systems of medicines spread worldwide. Many of them are confined to a small group of populations while others are well documented. Efforts have been made to give a brief account of some of the popular documented systems below, as the examples of medicinal plants based therapeutics.

3.1. Ayurvedic System

Turmeric is being used possibly as early as 1900 B.C. in Indian Ayurvedic system of medicine (Aggarwal et al., 2007). During the 1st millennium BC many other herbs and minerals used in Ayurveda were described by ancient Indian herbalists such as Charaka and Sushruta. In the 6th century BC the *Sushruta Samhita* describes 700 medicinal plants, 64 preparations from mineral sources, and 57 preparations based on animal sources (Dwivedi and Dwivedi, 2007). In India, Ayurvedic medicine has quite complex formulas with 30 or more ingredients. This may include a sizable number of ingredients that have undergone alchemical processing and have been described to balance "Vata", "Pitta" or...
"Kapha". Ayurveda, meaning the science of life, is a system of traditional medicine native to the Indian subcontinent (Chopra, 2003) and practiced in other parts of the world as a form of alternative medicine. Ayurveda remains an influential system of medicine in south Asia by evolving throughout its history. The earliest literature of Ayurveda appeared during the Indian Vedic period. The Sushruta Samhita and the Charaka Samhita were influential scripts on traditional medicine during this era. Ayurvedic practitioners also developed a number of medicinal preparations and surgical procedures for curing various ailments and diseases (Dwivedi and Dwivedi, 2007).

According to the Indian heritage and science, "Ayurveda" is an Upaveda or annexure to the four main vedas (knowledge systems). The famous treaties of Ayurveda are Charaka Samhita by Sage Charaka, which includes the prevention and treatment of disease, and Sushruta Samhita of Sage Sushruta, which details the Ayurvedic surgical procedures. In the Ayurvedic system of medicine, it is the prevention of all types of disease which has a prominent place in treatment, including restructuring a patient's lifestyle to align with the course of nature. According to principles of Ayurveda, nothing exists in isolation, that means our diet, interaction with family, work or relationships, has direct effect on our health and well being. One guiding principle of Ayurveda is that mind and body are well connected with each other and that the mind has a profound influence over our health and well-being. The conventional Western medicine is still grounded in the paradigm of mind-body separation but Ayurveda holds that health is more than the absence of disease; it is truly a dynamic state of integrated balance of body, mind, and spirit.

Ayurveda is grounded in a metaphysics of the 'five great Elements' i.e. earth, water, fire, air and ether all of which compose the Universe, including the human body (Chopra, 2003). There are seven primary constituent elements of the body called “Saptadhatu” i.e. Chyle (called Rasa dhatu), blood (called Rakta dhatu), flesh (called Mamsa dhatu), fat (called Medha dhatu), bone (called Asthi dhatu), marrow (called Majja dhatu), and semen or female reproductive tissue (called Shukra dhatu). Ayurveda also gives emphasis on a balance of three Humors or Energies called as “Dosha”, i.e. vata (wind/air), pitta (bile) and kapha (phlegm). These three regulatory principles- Doshas are extremely important for health, because when they are in balanced state, the body is healthy, and when imbalanced, the body has diseases. Ayurveda hold that humans possess a unique combination of Doshas. In Ayurveda, it is also described that the human body perceives attributes of experiences as 20 Guna meaning qualities (Chopra, 2003). Ayurveda is known as the Ashtanga-Ayurveda as this system of medicine has eight distinct branches i.e. (i) general medicine, (ii) surgery, (iii) ear, nose, throat, eye and mouth disease, (iv) psychiatry, (v) midwifery and paediatrics, (vi) toxicology, (vii) rejuvenation and tonics, and (viii) aphrodisiacs.

It emphasizes on the balance with the interpersonal communication and environment. It is based on the principles of microcosmic representations of the entire universe and considers that health
is the natural end of living in harmony with the environment. Disease results from disharmony between the person and the environment, and each case of disease is a manifestation of a unique state in the individual, requiring a unique cure. The practitioner attempts to restore the balance of the *doshas* by applying therapies including diet; herb, color, and sound therapies; aromatherapy including application of medicated oils to the skin and massage and meditation.

It is the only system of medicine which incorporates remedies for both healthy and diseased people. Ayurveda explains that health is not merely the physical well being and just the absence of diseases, it deals with the mental, physical and social well being of an individual, which was recognized by WHO, centuries after. According to Ayurveda every individual is made up of five elements, viz: i) Prithvi (earth), ii) Apa (water), iii) Tejas (fire), iv) Vayu (air), v) Akash (space). The structural aspect of the body consists of these five elements, but the functional aspect of the body is controlled by three biological humors. According to Ayurveda, ether and air combine to form *Vata dosha*. *Vata* is the force which directs nerve impulses, circulation, respiration, and elimination. Fire and water together form the *Pitta dosha*. The *Pitta dosha* governs the transformation or metabolism. Our body’s digestive system is an example of *Pitta* function. *Pitta* is also responsible for metabolism in the organs, tissues and cells. Finally, the water and earth together form the *Kapha dosha*. There are seven types of body systems: mono-types (*vata* or *pitta* or *kapha* predominant), dual types (*vata*-pitta, pitta-*kapha* or *kapha*-vata), and equal types, (*vata*, *pitta* and *kapha* in equal proportions). Every individual has a unique combination of these three *doshas*. To understand the uniqueness of every individual is the very basis of Ayurveda. Following pattern is adopted to study these types as per the status of patients’ mind and body:

**The mind:** Ayurveda distinguishes human temperaments into three basic qualities: *satvic, rajasic* and *tamasic*. *Satvic* qualities depict purity and clarity of perception responsible for goodness and happiness. *Rajas* implies for all movements, and activities leading to the life of sensual enjoyment, pleasure and pain, effort and restlessness. *Tamas* represents darkness, inertia, heaviness and materialistic attitudes. There is a constant interplay of these three *gunas* (qualities) in the individual consciousness. The relative predominance of either *satva* or *rajas* or *tamas* is responsible for psychological constitution.

**The disease process:** Ayurvedic system of medicine describes that health is a state of balance between the body, mind and consciousness. Ayurveda recognizes the three *doshas* (bodily humors) *vata*, *pitta* and *kapha*; seven *dhatus* (tissues), *blood, plasma, fat, muscle, bone, nerve*, and *reproductive*; three *malas* (wastes), *feces, urine* and *sweat*; and *agni*, the energy of metabolism within the body. A condition of disharmony in any of these factors leads to a disease. The root cause of imbalance, or disease, is an aggravation of three *doshas*: *vata, pitta, kapha*. Therefore, Ayurveda can be summarized as the system of medicine which emphasizes to promote health rather than just treat
disease. It is considered that every individual is unique. It is the only system of medicine which takes mental, emotional and spiritual well being into account. All the suggestions and remedies prescribed are totally in conjunction with nature and environment.

**Surgery** and surgical instruments are also the part of Ayurvedic treatment. It is believed that building a healthy metabolic system, attaining good digestion and proper excretion leads to vitality of human organs. Ayurveda also focuses on yoga, meditation, exercise and massages. Thus, body, mind, and spirit/ consciousness need to be addressed (http://www.ayurvedctoronto.com/ayurvedicmed.htm; http://www.tkdl.res.in/tkdl/langdefault/Ayurveda/Ayu_Principles.asp?GL=).

An act was recently passed to standardize the qualifications for Ayurveda and provide accredited institutions for its study and research in India (Kurup, 2003). India supports research and teaching in Ayurveda through many channels (Wujastyk, 2003). The state-sponsored Central Council for Research in Ayurveda and Siddha (CCRAS), NMPB and AYUSH are the apex institution for promotion of traditional medicine in India. The manufacture and marketing of Ayurvedic medicines are commercially done by several pharmaceutical companies (Anonymous, 2002-2005), viz., Dabur, Baidyanath, Zandu, Arya Vaidya Sala, etc. which have maintained the classical range. Even in the United States of America, the NIH NCCAM expends some of its budget on Ayurvedic medicine research. One of the premier institutes had a patent issued to them by United States Patent on the use of turmeric for healing. The patent was contested and won by India on the grounds that traditional Ayurvedic practitioners were already aware of the healing properties of the substance for centuries (Anonymous, 2009). In India, a TKDL (Traditional knowledge & digital library) is now ready which includes codified medicinal information on traditional knowledge existing in the country in languages and format understandable by patent examiners at International Patent Offices (IPOs). This effort is meant to prevent the grant of wrong patents at international level. TKDL thus, acts as a bridge between the traditional knowledge information existing in local languages and the patent examiners at IPOs. About 0.2 million medicinal formulations are available under an agreement between TKDL and patent offices for their access. (http://www.tkdl.res.in/tkdl/langdefault/common/Home.asp?GL=Eng).

3.2. Siddha System

In Tamil Nadu province of India, Tamils have their own herbal medicinal system called as the Siddha medicinal system. The Siddha system is one of the oldest medicinal systems, which is popularly practiced even today, containing roughly 300,000 Tamil verses on all aspects of medicine like anatomy, sex, herbal, mineral and metallic compositions to cure many diseases (http://www.freewebs.com/bethesdacam/principlesofsiddhamed.htm).

3.3. Traditional Chinese Medicine
It is extremely popular in China and throughout the world. With a history of about two to three thousand years, traditional Chinese medicine (TCM) has formed a unique system of diagnosis and curing illnesses. This system of medicine is fundamentally different from that of allopathic medicine. The human body is based on the holistic understanding of the universe as described in Daoism, and the treatment of illness is followed primarily on the diagnosis and differentiation of syndromes. The clinical diagnosis and treatment in TCM are mainly based on the yin-yang and the theory of five elements. These theories apply the phenomena and laws of nature to the study of the physiological actions and pathological changes of the human body and its interrelationships. The TCM approach treats zang-fu organs and tissue which are connected through a network of channels and blood vessels in the body. Qi (or Chi) acts as a carrier of information that is expressed in the form of jingluo system. Pathologically, a dysfunction of the zang-fu organs may be reflected on the body surface through the network thus the diseases of body surface. Tissues may also affect their related zang or fu organs. TCM treatment focuses on the correction of pathological changes through readjusting the functions of the zang-fu organs after a proper diagnosis of the entire system. Therefore, for the same disease two individuals may be treated differently while different diseases may result in the same syndrome and are treated in similar ways. The typical TCM therapies include acupuncture, herbal medicine, and qigong exercises. Herbal medicine is based on zang-fu organs internally, while qigong tries to restore the orderly information flow inside the network through the regulation of Qi. During the Han Dynasty, the first Chinese herbal book, the Shennong Bencao Jing, lists 365 medicinal plants and their uses. It included all major herbs like ma-Huang, the shrub that introduced the drug ephedrine to modern medicine. Succeeding generations augmented on a 7th century Tang Dynasty treatise on herbal medicine: “Treatise on the Nature of Medicinal Herbs” (http://www.amfoundation.org/tcm.htm).

3.4. Unani System of Medicine

The uses of plants for medicine and other purposes by Greek and Roman in the form of writings were preserved by hand copying of manuscripts in monasteries. The monasteries became local centers of medical knowledge, and their herb gardens provided the raw materials for herbal treatments. However, some of the folk medicine in the home and village continues, uninterrupted. During Middle Ages the women who were knowledgeable in herb lore e.g. Hildegard of Bingen, a twelfth century Benedictine nun, who wrote a medical text called Causes and Cures, prescribed herbal remedies often along with spells and enchantments.

During the 9th century in the medieval Islamic world, which was generally more advanced than medieval Europe at the time, the Arabs venerated Greco-Roman culture and learning, and translated tens of thousands of texts into Arabic for further study. The Arab travellers had access to plant material
from distant places such as China and India (Anonymous, 1875). Muslim botanists and physicians expanded on the earlier knowledge of materia medica e.g. the description of more than 637 plant drugs in the 9th century by al-Dinawari (Jacquart, 2008; Krek, 1979). Some experimental scientific methods were introduced into the field of materia medica in the 13th century. The empirical techniques in the testing, description and identification of numerous materia medica were introduced and unverified reports were separated. This facilitated the study of materia medica to evolve into the science of pharmacology (Brater and Daly, 2000; Daly and Brater, 2000).

It was during this era, when the folk medicine continued to thrive. The continuing importance of herbs for the centuries following the Middle Ages is supported by the hundreds of herbal books published after the invention of printing in the fifteenth century. Theophrastus’ Historia Plantarum, Dioscorides’ De Materia Medica, Avicenna's Canon of Medicine and Avenzoar's pharmacopoeia were the books to be made printed (Tschanz, 1997).

3.5. Tibetan System of Medicine

Tibet had religious and cultural influences from the indigenous Bon tradition during the pre-Buddhist era. It is believed that several forms of medical practice existed at that time. However, the precise influence of these practices on the evolution of the Tibetan medical tradition is unclear. During Buddha period the medical text “Vimalagotra” was taught. The documentation of Tibetan medicine was continued, thereafter (http://www.amfoundation.org/tibetanmedicine.htm).

3.6. Homoeopathic System of Medicine

Homeopathy is relatively newer system of medicine and is mainly based on the uses of herbs. Since it is very popular and effective system, a brief description of it has also been included in this review. It is a form of alternative medicine, invented by German physician Samuel Hahnemann in 1796. It treats patients with extremely diluted preparations which are thought to cause effects similar to the symptoms presented on normal concentrations. Homeopathic remedies are prepared by serial dilution with shaking by forceful striking termed as "succussion," after each dilution assuming that this increases the effect of the treatment. Homeopaths call this process "potentization". Dilution is possibly continued until none of the original substance remains. Homeopathy uses many animal, plant, mineral and synthetic substances in its remedies e.g. Arsenicum album (arsenic oxide), Natrum muriaticum (sodium chloride or table salt), Lachesis muta (the venom of the bushmaster snake), opium and Thyroidinum (thyroid hormone). Homeopathic medicines are also prepared from diseased or pathological products such as fecal, urinary, and respiratory discharges, blood, and tissue besides healthy specimens. In the homeopathic system of medicine, mostly the use of various established
medicinal plants and minerals have been described (Bellavite et al., 2005). The Food, Drug, and Cosmetic Act of 1938 recognized homeopathic remedies as drugs. By the 1950s there were only limited numbers of homeopaths practicing in the U.S. (Anonymous, 1956). However, in late 1970s and 80s, homeopathy made a significant comeback and sales of some homeopathic companies increased tenfold worldwide including Brazil, Germany, India (Rader, 1985). During 1990s, the medical profession started to integrate such ideas (Jonas et. al., 2003) and pharma industry recognized the business potential of selling homeopathic remedies (Felix von Reiswitz, 2007).

3.7. Other Systems of Medicine

The Sumerians’ study of herbs dates back to 5,000 years who described well-established medicinal uses for some plants. Ancient Egyptians are known to have used garlic, opium, castor oil, coriander, mint, indigo, and other herbs for medicine during 1000 BC. Ancient Greeks and Romans made medicinal use of plants which has been preserved in the writings of Hippocrates and Galen. Hippocrates advocated the use of a few simple herbal drugs in an environment of fresh air, rest, and proper diet. On the other hand, Galen recommended large doses of drug mixtures - including plant, animal, and mineral ingredients. The Greek physician compiled the first European treatise on the properties and uses of medicinal plants in De Materia Medica. In the first century AD, Dioscorides wrote a compendium of about 500 medicinal plants that remained an authoritative reference into the 17th century. Similarly, the Greek book Historia Plantarum, was written in the fourth century B.C. In America, early settlers relied on local Indian knowledge and plants imported from Europe. According to Cherokee herbalist David Winston the herbs can be divided into foods medicines and toxins and seven plants can be used in the treatment of disease, which is defined with both spiritual and physiological aspects (http://pacs.unica.it/biblio/lesson1.htm). Many traditional African remedies were in practice and have performed well in initial laboratory tests, as well. Gawo, a herb used in traditional treatments, has been tested in rats in Nigeria which passed tests for toxicity and reduced induced fevers, diarrhoea and inflammation (http://www.empowher.com/holistic-health/content/traditional-african-medicine-herbalism-spirituality-and-treating-hivaids?page=0,0).

4. Medicinal Plants as Nutraceuticals-Current Trends

Nutraceutical means food enriched with useful nutrients that are essential to prevent diseases. There are many ways to interpret food. Food provides the energy needed to perform daily functions and maintain normal metabolic processes, therefore food is fuel but the nutraceuticals are more than fuel. The nutrients which are needed to prevent specific diseases have been the major focus of human nutrition research for the past century. Through research it has been determined that significant amount
of each essential nutrient is required to prevent disease in populations of various ages, cultures, and genetic predispositions. The link between diet and health cannot be entirely explained by the absence or presence of the various essential nutrients in our diets. Currently, a multitude of components found in foods are being scientifically investigated to determine what role they play in maintaining health and reducing the risk of disease. Numerous phytochemicals that occur in fruits and vegetables are taking center stage in the researches, as evidences accumulate on their health-promoting properties (Beecher, 1999). Today the advancement in the disease fighting properties of a multitude of phytochemicals present in both food and nonfood plants, have created a renaissance in human health and nutrition research. Therefore, many opportunities for the development of novel dietary products have been developed (Ames et al., 1993).

Dietary Supplement products supply nutrients to the body which include nutritional products, nutraceuticals, nutrition-pharmaceutical products, functional foods, vitamins, minerals etc. With the FDA in United States having given its approval, acceptance of medicinal plants as dietary supplement is gaining popularity. Because of the wide popularity of dietary supplements, in 1994, the United States government passed the Dietary Supplement Health and Education Act. It defines a dietary supplement as any product, except tobacco, that contains a vitamin, mineral, herb, or amino acid and is intended as a supplement to the normal diet. The act requires that the label of a dietary supplement identify it as such and it must state that the claims for the dietary supplement have not been evaluated by the Food and Drug Administration (FDA). It has to list each ingredient by name, quantity, and total weight and must identify the plant parts from which each ingredient is derived.

Nutraceuticals and functional foods are the terms used to describe health promoting foods or their components. Although the exact meaning of these terms is debatable, it is convenient to consider nutraceuticals as healthful products which are formulated and taken in dosage form, for example, capsules, tinctures, or tablets. However, the functional foods are products that are consumed as foods, and not in dosage form. The beneficial role of many nutraceuticals and functional foods may relate to their protective effects against degenerative, cancer and cardiovascular disease. In fact, the active ingredient(s) in the food or supplement is believed to help the body control metabolic processes that lead to degenerative conditions. Therefore, supplementing the diet with beneficial phytonutrients e.g. antioxidants, may reduce the risk of degeneration of tissues during aging.

There is overwhelming evidence to accept that oxygen and its highly reactive by-products are responsible for oxidative damage to biomolecules in our body. It is believed that oxidative damage to cellular DNA is one of the important factors in the initiation of cancer. Similarly, oxidative damage to low-density lipoprotein in the blood is a causal agent in the deposit of atherosclerotic plaque in cardiovascular disease. It has been suggested and supported by various types of evidence that regular intake of antioxidants may provide greater protection against the harmful effects of oxidative damage.
Amongst the phytonutritional principles several groups of polyphenols, viz. anthocyanins, proanthocyanidins, flavonoids, resveratrol, ellagic acid, etc., are currently used in the nutraceutical industry. However, in some cases, the in vitro antioxidant tests are irrelevant in terms of in vivo antioxidant effects. Therefore, it is of utmost importance that bioavailability, metabolism and tissue distribution of these polyphenols in humans are key factors that have to be established for the biological activities of the polyphenol containing nutraceuticals (Espin et al., 2007).

Several groups of phytochemicals e.g. carotenoids, tocopherols, polyphenolics etc. are extremely effective antioxidants; these antioxidants are found in fruits, vegetables, and nonfood plants (Kian, 2007). The field of nutraceuticals and functional foods is new, and many gaps exist in the knowledge base. It is well accepted that the health-promoting properties of foods are not necessarily due to single components, but several active ingredients. This creates a significant shift from the general pharmaceutical model, which is based on the efficacy of single agents. Many of the bioactive phytochemicals have long been ignored, thus methods of proper analysis are lacking. Manufacturers normally make specific claims of health benefits of their products. Therefore, such claims must be based on solid scientific evidence, which is mostly lacking. Government regulatory bodies are trying to control this new category of health products, which lies between foods and drugs. The following definitions should help clarify the difference between dietary supplements and foods (Kian, 2007; Mary, 2000).

4.1. Dietary Supplements

Dietary supplements are defined as any product (except tobacco) that is intended to supplement the diet and contains one or more of the following: herb or other botanical, vitamin, mineral; an amino acid or metabolite; an extract; or any combinations thereof. The U.S. Food and Drug Administration (FDA) regulations clearly notify that a dietary supplement may be marketed in food form if it is not represented as a conventional food and is clearly labeled as a dietary supplement. If adequate scientific substantiation exists for the claim it may be allowed as dietary supplements (Anonymous, 2012; Radimer et al., 2004; http://ods.od.nih.gov/factsheets/list-all; http://abrimed.com/fda-iso-consultants/supplements-alternative-botanicals-nda.html).

4.2. Fortified Foods

Fortified foods are enriched with vitamins and minerals, usually at a range up to 100 percent of the Dietary Reference Intake (DRI) for that nutrient. Often, these foods are called fortified to a level that replaces the total loss of nutrients during processing. For example, vitamins B are added to many baked goods. Breakfast cereals are fortified since the 1940s.
4.3. Functional Foods

Functional foods are any food or food ingredient that may provide a health benefit in addition to the traditional nutrients it contains. The reason is that these are considered essential to the diet and correct a classical nutrient deficiency disease. For example, soy which contains soy protein associated with a reduction in cardiovascular diseases, is a functional food as it is not considered to be essential. Similarly, red grapes and cranberry juice for proanthocyanidins, and oat bran for the fiber content, all with health benefits attributed to non-nutrient compounds as classified by standard agreement of the term, belong to the functional food category (Kian, 2007; Mary, 2000). The super-fortified foods are fortified with more than 100 percent of the DRI and/or foods that have added botanicals or other supplements. They also fall into the category of functional foods. For example, orange juice with echinacea (Echinacea angustifolia or E. purpurea) and salad dressing with omega-3 polyunsaturated fatty acids (PUFAs) are considered as functional foods as they carry health or structure/function claims supported by scientific evidence.

4.4. Medical Foods

Medical foods are referred to a food that is formulated to be consumed or administered internally under the supervision of a physician. If a distinctive nutritional requirement is established by medical evaluation and the food product is prescribed for the specific dietary management of a disease or condition, it is certainly a medical food. Medical foods are generally used to treat lifestyle diseases.

4.5. Nutraceuticals

Nutraceuticals are often defined synonymously with functional foods including dietary supplements, fortified foods enriched with nutrients not natural to the food such as orange juice with added calcium, functional foods and medical foods. Thus, nutraceuticals are generally defined as parts or a whole food having medical or health benefit, including the prevention and treatment of disease. Historically, the FDA has defined any specific foods used for the prevention or treatment of disease as drugs. It legally defines nutraceuticals as a separate regulatory category, to carry specific disease treatment or prevention claims which were previously allowed only for drugs.

5. Regulatory and Perception Issues

Functional foods are regulated either as foods or dietary supplements, depending on how they are labeled. However, following claims are considered:

Health claims include the relationship of diet to a disease, and about a dozen health claims are
approved by FDA. For example, healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord defect. Such health claims normally have been approved based on the concept of significant scientific proof. FDA has defined that a substance, disease relationship exists based on a sound body of scientific evidence and would unlikely be reversed by further studies.

**Structure/Function claims** are statements of health or nutritional benefit permitted on dietary supplement labels without the mention of disease conditions. They must describe the support or maintenance of the normal body functions. Scientific associations, such as the Institute of Food Technologists (IFT), Chicago, Ill., and the American Dietetic Association (ADA) Washington, D.C., support the potential benefits of functional foods only when the claims for them are substantiated by good scientific data. However, the increasing introduction of many functional foods in the marketplace that are high in fat, calories and sodium, it has become a matter of concern, if claims are not adequately substantiated. The evolutionary products, such as orange juice fortified with vitamins C and E, sauces fortified with vitamin E, and beverages with added nutraceutical ingredients, have had great commercial success. A number of food and pharmaceutical companies remain committed to the potential of functional foods and are continuing to pursue the clinical research to substantiate the efficacy of these functional products.

6. **Scientific Substantiation**

During last decade many research groups, including Prof. H. Wagner, Munich, have been advocating the need for investigating the plants for multivalent and multidrug target actions of plant constituents and standardized extracts for rationalizing the therapeutic superiority of many plant extracts over a single isolated pure compound (http://www.arkat-usa.org/get-file/18964/). Although scientific explanations are being given for various traditional systems of medicine (Kurup, 2003), a lot more research experiments are desired to substantiate the claims. Besides the prominent plant drugs acquiring market in pure or mixture forms, there are many examples of functional foods, medical foods and dietary supplements in food which have been introduced into the market with scientific substantiation. Some successful examples in USA and other countries are given below.

**Cranberry Juice:** The women who drank the cranberry juice cocktail were less than half as likely to have bacteria in their urine and only a quarter as likely to have infection in their urine. Cranberry juice cocktail is now popular as a functional food with a structure/function claim regarding support of urinary tract health. It has also been useful to inhibit plaque-forming bacteria in the mouth by the same basic mechanism. The possibility of its applications in products such as toothpaste, dental floss, mouthwash and rinses is also being explored (Avorn et al., 1994; Weiss et al., 1998).
**Cholesterol-lowering margarines and breakfast cereals:** Several companies have marketed breakfast cereals as functional foods by enriching with inulin (an oligosaccharide) or psyllium. By consuming a 50 g serving of a breakfast cereal fortified with 18 percent inulin for four weeks during a study conducted at the University of Milan, Italy, it was found that the plasma total cholesterol was reduced by 7.9 percent and total triglycerides by 21.2 percent in young men (Brighenti et al., 1999). Another study at the University of Sydney, Australia showed that a breakfast cereal containing 50 g of soluble fiber as psyllium, oat and barley significantly reduced total cholesterol and low density lipoprotein (LDL) concentrations in the blood as compared to a wheat bran cereal. Plant sterol-enriched margarines were shown to reduce blood cholesterol levels in mildly hyper-cholesterolemic subjects in a human trial (Hendriks et al., 1999). In another study, it was found that the plant stanol esters, similar to plant sterols were also shown to reduce LDL cholesterol by 10 to 15 percent when consumed in three servings of margarine per day as part of a low-fat diet (Hallikainen and Uusitupa, 1999) reducing the heart disease to 25% (Law, 2000).

**Food Bar for Arterial Disease Prevention:** A medical food bar developed by a pharmaceutical company is available as a soy protein base containing L-arginine and the amounts of vitamins C, E, B6, B12, niacin and folate for those with coronary artery disease. L-arginine is an amino acid which is required for the production of nitric oxide, a potent vasodilator. A clinical study of the food bar among patients with lower limb atherosclerosis, showed that it provided 66 percent improvement in pain-free walking distance and 23 percent in total walking distance who took two bars per day for two weeks vs. placebo (Maxwell et al., 2000).

**Eggs Enriched with PUFAs:** There are currently eggs on the market enriched with PUFAs that function as dietary supplements in food form. In this case the hens were feeded a diet enriched with fish oils, vegetable oils or an algal source of docosahexenoic acid (DHA) providing a more cost-effective way for consumers to obtain omega-3 fatty acids in the diet over servings of cold-water fish. A significant increase in blood omega-3 PUFAs and HDL cholesterol were found in subjects consuming seven enriched eggs per week as compared to controls (Farrell, 1998).

**Probiotic Beverages:** A dietary supplement beverage with clinically proven to fortify the natural defenses, contains *Lactobacillus casei*, *Streptococcus thermophilus* and *Lactobacillus bulgaricus*, *L. casei*. It has been shown in human trials to produce an optimal response to the immune system (Kaila et al., 1992 & 1995; Spanhaak et al., 1998). The food and pharmaceutical companies have demonstrated that a sound scientific base for the efficacy of these products leads to acceptance by consumers for various types of products.

Dietary supplements were defined in a US law passed by Congress in 1994, termed as the Dietary Supplement Health and Education Act (DSHEA). According to DSHEA, a dietary supplement is a product that:
(i) It is intended to supplement the diet, (ii) It contains one or more dietary ingredients including vitamins, minerals, herbs or other botanicals, amino acids etc., (iii) It is intended to be taken by mouth, in forms such as tablet, capsule, powder, softgel, gelcap, or liquid, and (iv) It is labeled as being a dietary supplement.

The herbal supplements are an important dietary supplement. Research has also produced some promising results suggesting that some dietary supplements may be helpful for other health conditions, e.g., omega-3 fatty acids for coronary disease. An American national survey conducted in 2007 found that 17.7 percent of American adults had used natural products, i.e., dietary supplements other than vitamins and minerals in the past 12 months. e.g. fish oil/omega-3/DHA (37.4%), glucosamine (19.9%), echinacea (19.8%), flaxseed oil or pills (15.9%), and ginseng (14.1%). In another survey approximately 52 percent of adult respondents said that they had used common supplements for example, multivitamins/multiminerals, vitamins E and C, calcium and B-complex vitamins. The regulations for dietary supplements are less strict as compared to those for prescribed or over-the-counter sold drugs.

The toxicity tests have also been exempted for dietary supplement, before it is marketed. A manufacturer is permitted to claim that a dietary supplement addresses a nutrient deficiency, supports health, or is linked to a particular body function e.g., immunity. Manufacturers are expected to follow "good manufacturing practices" (GMPs) to ensure that dietary supplements are grown and processed consistently and meet quality standards. GMP requirements went into effect in 2008 for large manufacturers and are being made effective to small manufacturers in 2010. But once a dietary supplement is on the market, the FDA monitors safety and if it is unsafe, it can take action against the manufacturer and/or distributor. Similarly, it monitors product information, label claims and package inserts. The Federal Trade Commission (FTC) is strictly regulating product advertising, if it is truthful and not misleading (Anonymous, 2004; Barnes et al., 2004).

7. Establishing Standards and Quality Control

The increasing popularity of herbal care or nutraceuticals invites attention to establish the standards and quality control for their applications. On several occasion the adulteration in plant material has been reported. Methods are being developed to have fingerprints of the extracts of the known plant drugs. The book by Wagner and Bladt is one of the most important reference and popular books useful in confirming the authenticity of the plant by their known chemical constituents through thin layer chromatography (Wagner and Bladt, 2001). Because dietary supplements have history of safety, they are not regulated as drugs by the FDA. The need to evaluate supplements in humans has been recognized only recently and much of the available information has not been gathered.
systematically or scientifically which generates difficulty to evaluate them. The evidence supporting the effectiveness of supplements varies greatly. In some supplements, evidence supporting their effectiveness is convincing, but for many, scientific studies have not been designed well enough to provide clear, reliable answers. Herbal remedies are quite popular in Europe. In Germany, herbal medications are sold by drug stores. Prescription drugs are sold alongside essential oils, herbal extracts, or herbal teas as the herbal remedies and are believed to be preferred to chemical compounds which have been industrially produced. The exact composition of a herbal product may be influenced by the method of extraction. A polar compound will be rich in polar solvent while oil, on the other hand, is a non-polar solvent and it will absorb non-polar compounds. Alcohol lies somewhere in the middle. There are many forms in which herbs can be extracted:

- **Tinctures** - Alcoholic extracts of herbs are usually obtained by combining pure ethanol, or a mixture of ethanol with water with the herb. A tincture has an ethanol content of at least 40-60%, sometimes up to 90%.

- **Herbal wine and elixirs** are alcoholic extract of herbs; usually containing 12-38% of ethanol. Herbal wine is a maceration of herbs in wine, while an elixir is a maceration of herbs in spirits.

- **Tisanes** represent hot water extracts of herb, such as chamomile.

- **Decoctions** - Long-term boiled extract of normally roots or bark.

- **Macerates** - Cold infusion of plants with high mucilage-content as sage, thyme, etc. are chopped and added to cold water. They are then left to stand for 7 to 12 hours.

- **Vinegars** are the acetic acid extracts of herbs.

- **Essential oils** - Application of essential oil extracts are followed usually by diluting in a carrier oil e.g. olive oil, because many essential oils can react with the skin.

- **Salves, oils, balms, creams and lotions** - Most topical applications are oil extracts that are available in the form of salves, oils, balms, creams and lotions. Soaking herbs in food grade oil from weeks to months allows non-polar phytochemicals to be extracted into the oil. This oil are then made into salves, creams, lotions, or simply used as oil for topical application. Most of the massage oils, antibacterial salves and wound healing compounds are made this way.

- **Poultices and compresses** are made by using whole herb or a part of the plant by crushing or drying and re-hydrating with a small amount of water and then applied directly in a bandage, cloth as such.

- **Whole herb consumption** can be done either as dried herbal powder or fresh juice etc.

- **Syrups** are the extracts of herbs made from syrup or honey. Sugar is mostly mixed with water and herb, then boiled and macerated for three weeks.

- **Extracts** include (i) liquid extracts, (ii) dry extracts, and (iii) nebulisates. Liquid extracts are liquids with a lesser ethanol content than tinctures and are usually made by vacuum distilling tinctures.
Dry extracts are extracts of plant material which are distilled to a dry mass for further use as a capsule or tablet. Dry extracts are also created by freeze-drying. Nebulisation is the breaking down of a liquid into very small droplets, which in the case of medication can be inhaled, thus deposited right into the problem area in the lungs.

**Inhalation as in aromatherapy** can be used as a mood happiness treatment (Herz, 2009) to fight a sinus infection or cough, or to improve the skin on a deeper level. It is getting popular these days among elite class as through this, the plant volatile oils are very effective in physical and psychological treatment when they are used correctly and safely.

**Purity and Standardization:** The most important area of concern is the purity and standardization of dietary supplements. Usually, they are not regulated to ensure that they contain the amount of active ingredients, they have been claimed. As a result, the supplement may contain dangerous substances such as heavy metals. The percentage of active ingredient in a dose of a supplement may vary, especially when whole herbs are ground or made into extracts to produce a tablet, capsule, or solution. We may face risk of getting less, more, or none of the active ingredient in a supplement. Standardization requires that each individual dosage form of the product contains a precise amount of its active ingredients. However, most herbal products are mixtures of several substances, and the active ingredient is not always known. Therefore, standardization of active components is sometimes difficult. Some supplements have been standardized and may include a description of standardization on the label. In 2007, the FDA created current good manufacturing practices (GMPs) to standardize the manufacturing, packaging, labeling, and storing of dietary supplements. These GMPs intend to ensure the quality of dietary supplements and help protect the public health.

**8. Medicinal Plants Supplement-Drug Interactions**

These days, it is quite common among patients to take more than one medications simultaneously. There are numerous potential, often unpredictable, drug interactions with more than one medication. The synergistic effects of various components of herbal preparation are very well known. Prof. Wagner, Munich, Germany, advocates this phenomenon well, stating that “The longstanding, successful use of herbal drug combinations in traditional medicine makes it necessary to find a rationale for the pharmacological and therapeutic superiority of many of them in comparison to isolated single constituents. Synergistic effects can be produced if the constituents of an extract affect different targets or interact with one another in order to improve the solubility and thereby enhance the bioavailability of one or several substances of an extract”. A special synergy effect can occur when antibiotics are combined with an agent that antagonizes bacterial resistance mechanisms. The
verification of real synergy effects can be achieved through detailed pharmacological investigations and by means of controlled clinical studies performed in comparison with synthetic reference drugs. All the new ongoing projects aim at the development of a new generation of phytopharmaceuticals which can be used alone or in combination with synthetic drugs or antibiotics. This new generation of phytopharmaceuticals could lend phytotherapy a new legitimacy and enable their uses to treat diseases which have hitherto been treated using synthetic drugs alone (Wagner and Ulrich-Merzenich, 2009; Williamson, 2001). However, in some cases, this scenario gets more complex when drugs are co-treated with phytomedicines.

The lack of information on interaction potential of herbal drugs with concurrently used drugs undoubtedly poses serious challenge to the society. This problem has been taken up by the journal Planta Medica by bringing out a special issue on this subject, recently. The papers in this issue have covered various aspects related to this important problem (Butterweck and Darendorf, 2012). For example, emphasis is now given for the studies on pharmacokinetics and pharmacodynamics of such interactions (Vieira and Huang, 2012). Only recently the plant secondary metabolites have been observed as modulators of human drug disposition. These interactions may affect the pharmacokinetics of concomitantly administered drugs whereas in some cases these interactions show beneficial effects like cancer prevention. It has been found that botanicals phytomedicinal principles act as mechanism based inhibitors of cytochrome P450 enzyme activity or act as ligands for orphan nuclear receptors (Gurley, 2012; Gurley et al., 2012). It is also under discussion to provide scientifically proven information on such interactions in the package leaflets of the phytomedicinal preparations (Steinhoff, 2012).

9. Extinction of Medicinal Plants

It is estimated that more than 90% Ayurvedic plants are under the threat of their extinction. The main reason is that about 95% of these plants for commercial use are collected from wild and majority of them through destructive means (Platt, 2010). Belinda Hawkins, author of the “Plants for Life: Medicinal Plant Conservation and Botanic Gardens,” states that “Many medicinal plants are being destroyed at an unprecedented rate and are threatened with extinction. The destruction of plant species is occurring at a rate unmatched in geological history. Current extinction rates are at least 100 to 1,000 times higher than natural background rates, with a quarter of the world's coniferous trees in jeopardy, and as many as 15,000 medicinal plants threatened,” (Brower, 2008). The Botanic Gardens Conservation International represented botanic gardens of 120 countries in a meeting on January 18, 2008, stated that "400 medicinal plants are at risk of extinction, from over-collection and deforestation, threatening the discovery of future cures for disease." The list is even higher and many plants from
Himalayan regions are under extinction and unnoticed. The world wide concern is on many important drug yielding plants. These included mainly (i) Yew trees (the bark is used for cancer drugs, paclitaxel); (ii) Hoodia (from Namibia, source of weight loss drugs); (iii) Magnolias (Chinese medicine for cancer, dementia and heart disease); and (iv) Autumn crocus (for gout), etc. It is mentioned that 5 billion people benefit from traditional plant-based medicine for health care (http://www.docstoc.com/docs/111711947/Botanic_Gardens_Conservation_International#).

10. Safety Concerns

Despite the increased popularity of herbal treatments, the safety and effectiveness of alternative medicines have, unfortunately, not been scientifically validated. A number of herbs may possibly cause adverse effects. Additionally, the adulteration, inappropriate formulation, or lack of understanding of plant and drug interactions may lead to adverse reactions that are sometimes life threatening or lethal (Elvin-Lewis, 2001). The common names of herbs might group together different plant species with different effects. For example, in Belgium 1993, the medical practitioners created a formula including some Traditional Chinese medicine (TCM) herbs for weight loss. In that formula Stephania tetrandra was used for Aristolochia fangchi whose name in Chinese was extremely similar but which contained higher levels of a renal toxin, aristolochic acid. It was inferred that this mistake resulted in 105 cases of kidney damage (Vanherweghem, 1998). In Chinese medicine these herbs are prescribed for certain forms of acute arthritis and edema (Vanhaelen et al., 1994; Vanherweghem et al., 1993). To be sure, the standard double-blind clinical trials are recommended to determine the safety and efficacy of each plant for medical use (Pinn, 2001). Besides possible toxic effects of its own, the herbal medicines may interact with synthetic drugs taken simultaneously causing toxicity to the patient and may have contamination leading to safety concerns.

The issue of regulation is an area of continuing controversy worldwide. At one end of the spectrum, most of the herbalists maintain that traditional remedies have a long history of use, and do not require the level of safety testing as xenobiotics or single ingredients in an artificially concentrated form but others are in favor of legally enforced quality standards, safety testing and prescription by a qualified practitioner. Some professional herbal companies have favoured a category of regulation for herbal products but others agree with the need for more quality testing without government intervention. In the EU, herbal medicines are now regulated under the “European Directive” on Traditional Herbal Medicinal Products which was established to provide a regulatory approval process for herbal medicines in the European Union (EU), and came into force on 30 April 2004. Before this, there was no formal EU authorization procedure, therefore each EU member state regulated these types of products at the national level.
After promulgation of this regulation, all herbal medicinal products are required to obtain an approval to market within the EU. Those products which have been marketed before this legislation came into force could continue to market their product until 30 April 2011, under the transitional measures defined in the Traditional Herbal Medicinal Products Directive. Now that this time limit has expired, all herbal medicinal products must have prior authorization before they can be marketed in the EU. For those herbal medicinal products that were not on the market before 30 April 2004, an authorization must be obtained prior to bringing into the market. The only herbal medicines that are exempted from the regulations of the Traditional Herbal Medicinal Products Directive are those unlicensed remedies that made up for a patient following a consultation directly with an herbalist.

Herbal medicines must be now manufactured under Good Manufacturing Practice (GMP) to ensure the quality of the finished product and also demonstrate traditional safety. Although the manufacturers of products in the United States of America falling into this category, are not required to prove the safety or efficacy of their product, but the FDA may withdraw a product from sale should it prove harmful (Anonymous, 2007; Goldman, 2001). From 2002, the National Nutritional Foods Association, the industry's largest trade association, has run a program examining the products and factory conditions of member companies, giving them the right to display the Good Manufacturing Practices (GMP) seal of approval on their products (Anonymous, 1999-2009).

Since 2004, the sale of ephedra as a dietary supplement is prohibited in the USA by the Food and Drug Administration. Similarly in the UK, herbal remedies that are bought over the counter are regulated as supplements, as in the US. However, the herbal remedies when prescribed and dispensed by a qualified Medical Herbalist, after consultation, are regulated as medicines. Covered by Schedule III of the Medicines Act, a Medical Herbalist can prescribe some herbs which are not available over the counter. Further changes to laws regulating herbal products in the UK, are intended to ensure the quality of herbal products. Some herbs, e.g. cannabis, are out rightly banned in most countries.

Standardization of purity and dosage is not mandated in most of the countries, but even products made to the same specification may differ as a result of environmentally influenced biochemical variations in plant. Since the plants have chemical defense mechanisms against predators, they can have adverse or lethal effects on humans. Some of the examples of highly toxic herbs include poison hemlock and nightshade (Mueller, 1998). They are not marketed to the public as herbs, because the risks are well known, partly due to a long history (Lee, 2006) although the adverse reactions have not frequently been reported for herbs, in most of the use (Pinn, 2001). A case of potassium depletion chronic licorice ingestion has been reported (Lin et al., 2003; Meltem et al., 2009). Black cohosh has been attributed for the liver failure (Lynch et al., 2006). One study on the safety of herbs for pregnant women has revealed that use of complementary and alternative medicines are associated with a 30% lower pregnancy and live birth rate for fertility treatment (Boivin and Schmidt, 2009; Born and Barron,
2005). Some of the examples of herbal treatments with adverse events have been found in aconite, Ayurvedic remedies, broom, chaparral, Chinese herb mixtures, comfrey, flavonoids, germander, guar gum, liquorice root, and pennyroyal (Ernst, 1998). When some herbs were taken on long term, adverse effects have been observed in cases of ginseng, goldenseal, milk thistle, senna, aloe vera juice, buckthorn bark and berry, cascara sagrada bark, saw palmetto, valerian, kava, St. John's wort, khat, betel nut, ephedra, and guarana. Numerous herbs are known to have interactions with drugs (Elvin-Lewis, 2001).

When a physician is consulted, usage of herbal remedies should be clarified, as some herbal remedies have the potential to cause adverse drug interactions when used in combination with various prescription and over-the-counter pharmaceuticals. For example, low blood pressure may result from the combination of a herbal remedy lowering blood pressure along with the prescribed drug that has the same effect. Some herbs may enhance the effects of anticoagulants (Spolarich and Andrews, 2007).

In a study on 230 products, toxic heavy metals such as lead, mercury and arsenic have been found in 20% of Ayurvedic preparations from South Asia. It was concluded that excess consumption of these improperly cultivated products could cause health risks. Further studies have shown about 20% of remedies purchased over the internet from both US and Indian suppliers showed a contamination of lead, mercury or arsenic (Saper et al., 2004). However, more recently an Indian group has developed a chemometric method by which the relationship among the elements in the herbal drugs can be established. They were able to use this method on several commercial herbal drugs to determine the safety, quality and efficacy of such samples. What is of more significance is that these tested samples showed the presence of Cd, Pb and Ni but were under the permissible limits as prescribed by WHO (Armugam et al., 2012).

Traditionally the toxicity of Ayurvedic medicines are believed to be reduced through processes such as samskaras or shodhanas (for metals), which is similar to the Chinese pao zhi. While planning to have surgery, it is important to consider that certain dietary supplements may increase the risk of bleeding or affect the response to anesthesia, especially to a pregnant or nursing a baby or feeding a child with dietary supplements. It has to be noted that many of the dietary supplements have not been tested in pregnant women, nursing mothers, or children.

Reading the label instructions is necessary while taking a dietary supplement. If a consumer experiences any side effects, he may stop taking the dietary supplement, contact health care provider and share it with organizations like the FDA's MedWatch program.

It must be kept in mind that although many dietary supplements and some herbal drugs come from natural sources but natural does not always means safe. For example, the herbs comfrey and kava can cause serious harm to the liver. One must understand that a herbal supplement may contain compounds in hundreds and its active ingredients may not be known. Research is being carried out on
many of these products to identify active ingredients and understand their effects in the body. Also, it must be considered that the label may not be the same as inside the bottle. Sometimes, analyses of dietary supplements find differences between labeled and actual ingredients. Some of the points of consideration are given as below:

(i) A herbal supplement may not contain the correct plant species. (ii) The amount of the active ingredient as stated in the label. This will change the dose amount in the dietary supplement. (iii) Contamination with other herbs, pesticides, or metals, or even adulterated with unlabeled ingredients.

For the safety of particular dietary supplements, the "Dietary Supplements: Warnings and Safety Information" section of the FDA Web site at www.fda.gov/Food/DietarySupplements/Alerts/default.htm or the "Alerts and Advisories" section of the NCCAM Web site at nccam.nih.gov/news/alerts. NCCAM, which is part of the National Institutes of Health (NIH), may be checked. A wide array of research is sponsored to see how dietary supplements might affect the body and their use in clinical trials is tested. Recently, NCCAM has supported more than 200 research projects studying dietary supplements, including herbs and botanicals. In order to strengthen knowledge by supporting and evaluating research, disseminating results, and educating the public, the Office of Dietary Supplements of NIH, USA focuses specifically on dietary supplements. To fund dietary supplement research centers focused on botanicals is taken care by NCCAM and ODS which is collectively known as the NIH Botanical Research Centers Program. These centers are advancing the scientific base of knowledge about botanicals, to evaluate their safety and effectiveness. NCCAM also sponsors a number of centers of excellence for research on CAM, including the studying of: (i) antioxidant therapies, (ii) botanicals for autoimmune and inflammatory diseases, (iii) grape-derived polyphenols for Alzheimer's disease, and (iv) for pancreatic diseases and colorectal cancer.

Office of Dietary Supplements (ODS) seeks to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, supporting research, sharing research results, and educating the public. The publications fact sheets on a variety of specific supplement ingredients and the International Bibliographic Information on Dietary Supplements (IBIDS) database are the typical resources of this office (www.ods.od.nih.gov).

U.S. Food and Drug Administration (FDA) oversees the safety of many products, such as foods, medicines, dietary supplements, medical devices, and cosmetics (www.fda.gov).

Center for Food Safety and Applied Nutrition (CFSAN) oversees the safety and labeling of supplements, foods, and cosmetics (www.fda.gov/AboutFDA/CentersOffices/CFSAN/).

MedWatch is the FDA's safety information and adverse event reporting program and allows consumers and health care providers file reports on serious problems suspected with dietary supplements. (www.fda.gov/Safety/MedWatch/HowToReport/ucm053074.htm).

Federal Trade Commission (FTC) is the Federal agency entrusted to protect the public
against unfair and deceptive business practices and regulates the advertising (ftc.gov).

**PubMed®** is a service of the National Library of Medicine (NLM). It contains published information and brief summaries of articles from scientific journals. CAM on PubMed, developed jointly by NCCAM and NLM, is a subsection of the PubMed system and focusing on the topic of CAM. ([www.ncbi.nlm.nih.gov/sites/entrez; nccam.nih.gov/research/camonpubmed/]).

**MedlinePlus and Dietary Supplements Labels Database** provides resources that help answer health questions ([www.medlineplus.gov]). They provide information about ingredients in more than 2,000 selected brands of dietary supplements ([dietarysupplements.nlm.nih.gov/dietary]).

Sometimes, the cases of supplement products being subpotent or had contamination problems are noticed which could have been averted if controlled by cGMP. The cGMPs are designed to assure that product quality is, as it should be, and that the product is made fresh and first time, every time. The cGMP regulations specify required procedures with regard to packaging, including inspection of containers and labeling as well as the documents. The packaging and labeling has to be treated at par with other factors essential for dietary supplements. The regulations have been made for written procedures and other records on components, packaging, and labeling. The rule has been phased in most of the countries to comply with the directives by 2010.

In comparison to foods, drug and medical products have long followed more extensive cGMP. But it was in 1994 when the law was changed: (i) to define supplements as foods, and (ii) to give supplements the ability to make drug-like claims of health benefits. In western countries especially in USA, it was then recognized to have the FDA imposed regulations controlling their manufacture to assure the quality and safety. This was an important step since the products would be reviewed and approved by the FDA before floating into the market. These meaningful regulations have been promulgated to dietary supplement manufacturers and packagers to control the claims about effects on the structure or function of the body for which supplements are designed. If cGMPs do their job right and cGMPs are properly followed to make it free of contaminants and are packaged and labeled correctly then the dietary supplement products should be perfect. According to the European legislation, the authorized (well established medicinal use) or registered (traditional use) herbal medicinal products are desired to prove their quality, safety and efficacy or tradition (Steinhoff, 2012).

11. Future Scope and Conclusions

If the standard for pharmaceutical testing is properly followed, the plant products or pharmaceutical drugs derived from them will be incorporated into medicine. Normally, to recoup the considerable costs of testing to the regulatory standards, the substances are first patented, then marketed by pharmaceutical companies. It has been observed that many herbs have shown positive
results in-vitro, animal model or small-scale clinical tests (Srinivasan, 2005). A few studies on herbal treatments have also found negative results (Pittler et al., 2000). The quality of the trials on herbal remedies is not consistent and many trials of herbal treatments are of sub-standard, with many trials lacking an intention to treat with proper analysis (Linde et al., 2001). Some of the double-blind tests are sometimes questioned on methodological grounds or interpretation. The studies published in peer-reviewed medical journals receive more reading than those published in specialized herbal journals. It is because high impact factor mainstream medical journals published good number of trials with positive and negative results. Interestingly in high impact journals, trials finding positive results were also found to have lower citations than the finding of negative results (Pittler et al., 2000). But the matter of fact is that some clinical studies of herbal medicines were not inferior to similar medical studies (Nartey et al., 2007).

Herbalists are of the view that the mainstream studies make insufficient use of historical usage, which has been shown useful in drug discovery and development. They maintain that traditional knowledge guides well the selection of factors such as optimal dose, species, time of harvesting and target population. Dosage is a real issue for herbal treatments. While most of the medicines are properly tested to determine the most effective and safest dosages, there are fewer dose related tests for various herbal treatments on the market. Furthermore, the plant medicines taken in whole form cannot guarantee a consistent dosage as certain samples may contain more or less amount of active ingredients (Fabricant and Farnsworth, 2001). Several methods of standardization may be applied to herbal products preparations. However, the real difficulty is that different specimens of even the same plant species may vary in chemical constituents. The only possibility is the standardization on major compounds. Several countries including the USA have started government funding on clinical trials into the effectiveness of herbal medicine (Fabricant and Farnsworth, 2001).

While preparing this review, full care has been taken to collect information from important original papers from scientific journals. However, several popular links (given at the end of References) on herbs have also helped prepare this review exhaustively. Thus after studying all these data, a conclusion could be drawn that the medicinal plant research requires a multidisciplinary approach. The quality of research can only be as good as the co-operation between botanists, phytochemists and pharmacologists. A good collaboration between botanists and phytochemists has developed over the years, as numerous joint publications testify. The collaboration with pharmacologists is, in general, a recent development and needs to be intensified. There is definitely a requirement for more appropriate assays to be used in plant screening. All plant extracts and pure compounds isolated in the phytochemical laboratories should be submitted to a wide range of bioassay tests, as detailed as possible. Numerous plant extracts and isolates have to be tested and there are certainly many interesting activities yet to be discovered.
Epidemiological studies show a link between the consumption of plant-derived foods and the health benefits. These benefits have certainly close association to some of the active phytochemical constituents. In the last few years, nutraceuticals or diet supplements have appeared in the market. These are sometimes in pharmaceutical forms (pills, powders, capsules, vials, etc.) containing food bioactive compounds as active principles. The bioactive phytochemicals are undoubtedly very significant source for nutraceutical ingredients. Scientific research supports the biological activity of many of these phytochemicals, but the health claims attributed to the final nutraceutical products have sometimes doubtful scientific foundation. This is due to the fact that a lot of the scientific evidence is derived from animal testing and in vitro assays. The human clinical trials are rare and many times inconclusive. Some key issues such as bioavailability, metabolism, dose response and toxicity of these food bioactive compounds or the nutraceuticals themselves have not been well established yet and deserve proper attention of researchers. Toxicity points are no doubt an important issue but if the herbal/ traditional or dietary supplements are carefully manufactured and prescribed, there need not be extra ordinary concern about the negative effects on human while under the plant drug treatment.

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