Can plants growing in diverse hostile environments provide a vital source of anticancer drugs?

Review Article

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Summary

The therapeutic use of plants against critical human illnesses predates recorded history and represents the most significant direct antecedent to modern medicine. With the advances of various in-silico technologies, the introduction of plant derived bioactive agents into the cancer armamentarium has changed the natural history of many types of human cancer. In spite of numerous advances in the field of cancer research, the world still continues to be in the grip of this dreadful disease and there is an urgent need to design well tolerated anti-cancer therapeutic agents. Numerous plants have the potential of anticancer activity but are still to be investigated. However, existing flora is so vast that it is humanly impossible to investigate each and every plant for anti-cancer activity. Increasing global warming, malnutrition and various environmental insults continue to increase the incidences of cancer. “Cancer is hostile to human body and hostile environment is cancerous to plants”. Accordingly, those plants which are able to comfortably survive under multiple but diverse hostile environments may act as a vital source of anti-cancer agents. Moreover, these anticancer agents are likely to be safe by virtue of being of natural origin. Various plants reported/studied for anticancer activity till date have been briefly reviewed in the present article. An urgent need for screening plants surviving in diverse hostile environments for anticancer activity has been emphasized so as to accelerate development of effective but safe anticancer drugs.

I. Introduction

Despite numerous technological advances in the understanding and management of neoplastic diseases during past few decades, cancer still remains amongst the leading causes of illness and death internationally (Timar et al., 2001; Dal Lago et al., 2008). Cancer is a dreadful human disease, increasing with changing life style, nutrition and global warming. Deaths from cancer worldwide are projected to rise continuously and reach an alarming figure of about 13 million in 2030 (Rebecca et al., 2012). This high mortality rate among cancer patients is an indication of the limited efficacy of the current therapies including radiotherapy, chemotherapy and surgery (Talib, 2011).

The surgical treatment cannot be applied once cancer has spread. Radiotherapy and chemotherapy do not distinguish normal cells from cancer cells and can induce serious side effects. Therefore, these anticancer therapies have significant limitations and cannot cope up with the increasing cancer incidence (Wang et al., 2006). The rapid clearance of small molecules coupled with increased hydrostatic pressure in solid tumors further decreases the tumor-specific activity of chemotherapy. In contrast, monoclonal antibodies (mAbs), are relatively large molecules (150 kDa). mAbs are retained for a considerable period up to several weeks in the vasculature and slowly diffuse into perivascular tissues (Oldham and Dillman, 2008; Grever, 2013). The use of drugs offer the only approach to treat cases where the cancer has spread (metastasised).
through the body (http://nzic.org.nz). Until recently, almost all the cancer drugs were cytotoxic agents (cell-killing) that disrupts the cell cycle in order to change the cellular makeup so that the cell cannot divide, or damage the cellular makeup enough to cause the cell to die. Moreover, many cytotoxic drugs are not specific to cancer cells and can also damage healthy cells, especially those with rapid turnover, such as gastrointestinal and immune cells (de Melo et al., 2011).

In order to circumvent this obstacle in drug development, introduction of targeted therapeutics such as noncanonical antibodies including Antibody–Drug Conjugates (ADCs), bispecific antibodies, engineered antibodies and Peptide Drug Conjugates (PDC) for cancer during past two decades provides a new opportunity for significantly improving therapeutic index and the future of cytotoxic therapy (Reichert and Dhimolea, 2012; Panowski et al., 2014). An ADC provides the possibility of selectively ablating cancer cells by combining the specificity of a mAb for a target antigen to deliver highly toxic drugs to cancer cells (Sievers and Senter, 2013). Only 2 ADCs have been approved by FDA for cancer therapy till date (Senter and Sievers, 2012; Lewis Phillips et al., 2008). In addition, more than 30 molecules are undergoing clinical trials (Firer and Gellerman, 2012; Panowski et al., 2014). Recently Tian and colleagues (Tian et al., 2014) reported a new approach for generating site specific drug conjugates (termed as NDCs) in order to control the site and stoichiometry of drug conjugation to the mAb (Flemming, 2014). Each of aforementioned targeted therapies has its own advantages and limitations and a better interplay of these will allow a more rational selection of mono- or even combination therapies (Firer and Gellerman, 2012).

As a result of the innate complexities of the disease, no single or even combination of drugs, works for all cancers and drugs are normally targeted to specific cancers based on certain characteristics called validated targets that are often upregulated in cancer cells to allow their unchecked growth (Shaikh et al., 2012). The limited progress achieved in cancer therapy during the last three decades has led scientists to explore alternate therapies. The introduction of active agents derived from nature into the cancer armamentarium has changed the natural history of many types of human cancer. The plant derived active principles are offering a great opportunity to evaluate not only totally new chemical classes of anticancer agents but also novel and potentially relevant mechanisms of action (da Rocha et al., 2001). Plants continue to be the subject of extensive biological screening worldwide, in an attempt to discover more effective anticancer drugs (Bachrach, 2012). Much of the world’s population (about 70-80%) still rely on plant-derived medicines for the health care. This is especially true in developing countries (Rivera et al., 2013). Use of herbal remedies is also widespread in many industrialized nations and numerous pharmaceuticals are either based on or derived from plant sources (Mans, 2013). The World Health Organisation (WHO) estimates that the global market for use of herbal medicines is approximately US $83 billion annually (Robinson and Zhang, 2011; Rivera et al., 2013). An important analysis of the anticancer drug market in 2006 revealed that 47% of a total of 155 clinically approved anticancer drugs were either unmodified natural products or their semi-synthetic derivatives, or synthesized molecules based on natural compound pharmacophores (Newman and Cragg, 2007). Since then numerous types of bioactive compounds have been isolated from plant sources. Several of them are currently in clinical trials or preclinical trials or undergoing further investigation (Corson and Crews, 2007; Butler, 2008; Harvey, 2008; Saklani and Kutty, 2008; Sashidhara et al., 2009, Pan et al., 2010; Pan et al., 2013).

II. Carcinogenesis

Cancer is nowadays used as a generic term applied to a group of about 120 diverse malignant diseases that may affect any part of the human body. It is characterized by abnormal growth and proliferation of cells which may mass together to form a growth or tumour, or proliferate throughout the body, initiating abnormal growth at other sites (Yarbro et al., 2005). Patients with this frightful disease, suffer from pain, disfigurement and loss of many physiological processes. It is caused by a complex, poorly understood interplay of genetic and environmental factors (Pandey and Madhuri, 2009). Increasing global warming, malnutrition, and various environmental insults continue to increase the incidence of cancer (Boopathy and Kathiresan, 2010). The group of chemicals that cause cancer in human and animals are collectively referred to as carcinogens (Bhattacharya, 2012). The principal carcinogenic agents are exogenous or metabolically generated electrophiles and reactive oxygen species (ROS) generated as by-product from normal cellular metabolic activities and from the environment (Talalay and Fahey, 2001; Bhattacharyya et al., 2014). The increased levels of these reactive species initiate and promote various types of tumours and may ultimately lead to carcinogenesis (Yang and Liu, 2009). Factors affecting carcinogenesis include environmental factors [pollution, industrial effluents/waste containing chemical carcinogens such as polycyclic aromatic hydrocarbons, aromatic amines, aminoazo dyes and natural carcinogens (aflatoxin [I and asbesitos]) (Luch, 2005; Belpomme et al., 2007), unhealthy lifestyle habits (inhalation of tobacco and related products, improper diet, alcohol consumption, obesity, sedentary life) (Seitz et al., 2001; Thuin et al., 2002; Anand et al., 2008), occupational factors (e.g. synthesis, dyes, fumes) (Siemiatycki et al., 2004) and other factors (excessive exposure to sunlight, radiation, viruses, etc) (Pohansish, 2011). These causal factors may either act together or in a sequence to initiate or promote the development of cancer (Goyal, 2012).
Carcinogens include chemicals or non-chemical agents which under certain conditions are able to induce cancer. Carcinogens may be of chemical, physical or biological origin (Latosińska and Latosińska, 2013). Carcinogens may increase the risk of cancer by altering cellular metabolism or damaging DNA directly in cells or interfering in biological processes leading to the uncontrolled and malignant division with ultimate formation of tumours (Dholakia et al., 2011).

It is difficult to assign an exclusive role to a single process alone in carcinogenesis. A single carcinogen can have multiple effects and hence may be perceived as operating through several mechanisms. An important part of the cancer etiology lies in stepwise accumulation of genetic changes induced by chemical carcinogens including gene mutations, gene amplifications (Bishop, 1987; Sadikovic et al., 2008), chromosomal rearrangement and neoplastic aneuploidy (Duesberg et al., 2001; Ricke and van Deursen, 2013). A number of carcinogens and their metabolites can directly initiate the carcinogenesis by yielding highly reactive species that bind covalently to cellular DNA resulting in a substrate-DNA adduct (Weinstein, 1985; Klaunig et al., 2010). The term genotoxic agent is thus assigned to physicochemical carcinogens that directly damage DNA and possess mutagenic properties (Klaunig et al., 2010). Indirect-acting chemical carcinogens (also termed as precarcinogens) require metabolic activation to induce mutations to cellular DNA. The indirect action is realized through the mechanisms that generate chemical species (free radicals, reactive oxygen species, carcinogenic metabolites) which are capable of entering the nucleus of the cell (Latosińska and Latosińska, 2013). In contrast to direct-acting carcinogens, precarcinogens are generally stable in the environment and represent an appreciable hazard to the general population (Weisburger, 1994).

Since the carcinogens are involved in the initiation and promotion of cancer, the significance of novel bioactive phytochemicals in counteracting these carcinogenic effects is now gaining credence. Such chemicals that reduce the frequency or rate of spontaneous or induced carcinogenesis caused by physical and chemical carcinogens are referred to as antitumor or carcinopreventive agents (Mitscher et al., 1986; Stagos et al., 2005). Prevention of cancer and other related diseases can be pursued by avoiding exposure to recognized carcinogens, by favouring the intake of protective agents and by fortifying physiological defence mechanisms (Bhattacharya, 2012).

III. Plants as a source of anti-cancer agents

The role of natural products, especially those from plant kingdom, as a source for remedies has been the mainstay of cancer chemotherapy since ancient times (Farnsworth et al., 1985; Mann, 2002; Mondal et al., 2012). For a long time, plants have been used as an important therapeutic source for the treatment of cancer either as herbal teas or juices, as crude extracts, or as standard enriched fractions in pharmaceutical preparations such as tinctures, fluid extracts, powders, tablets and capsules (Karacas and Fakim, 2006; Mondal et al., 2012). This strategy would not only enhance the chances of success in terms of providing effective and safe drugs, but also is considered to minimize the risk of post-marketing withdrawals (Katiyar et al., 2012). Herbal medicines as a source of new chemical entity are going to become a global trend in the pharmaceutical world (Pan et al., 2013). The pioneering work involving active phytoconstituents of Podophyllum peltatum L. (Berberidaceae) by the late Dr. Jonathan Hartwell (1969) and isolation of anti-lukemic agents - vinblastine and vincristine from Catharanthus roseus by late Dr. Gordon Svoboda (1975) provided valuable evidence that plants can serve as a potential source of novel anticancer agents (Roja and Rao, 2000). United States National Cancer Institute (NCI) initiated a program for the collection and screening of plants for antitumor activity in 1960. This led to the discovery of many novel chemotypes showing a range of cytotoxic activities (Cassady and Douros, 1980). During the period 1986 - 2004, the Natural Products Branch of the Developmental Therapeutics Program (DTP) at NCI organized the collection of about 60,000 higher plant samples in various targeted tropical and sub-tropical regions of the world. Extracts of these plant samples were pre-screened initially against a 60-cell line tumour panel derived from nine cancer types, followed by further in vivo evaluation when merited (Pan et al., 2010; Cragg et al., 1999; 2006). These screening programs played significant role in the development of the most exciting plant-derived anticancer drug - taxol now named as Paclitaxel. This was originally isolated from the bark of the relatively rare Pacific Yew, Taxus brevifolia Nutt. (Taxaceae) (Wani et al., 1971). The discovery of pharmacological action of taxol was a key milestone in the tedious development process, and it was finally introduced in the U.S. market for clinical use in early 1990s (Wall and Wani, 1996; Balunas and Kinghorn, 2005). Isolation and characterization of pharmacologically active compounds from plants continues unabated.
Half of the existing pharmaceuticals today are inspired by natural products (Li and Vederas, 2009). Plants with promising anticancer properties have been enlisted in Table 1. Some herbs protect the body from cancer by enhancing detoxification functions of the body while other herbs reduce the toxic side effects of chemotherapy and radiotherapy. Scientists all over the world are concentrating on the herbal medicines to boost immune cells of the body against cancer. However, the lack of detailed evaluation of potential plants to validate their use may cause serious side effects (Souza et al., 2004). Accordingly, there is an overwhelming need to discover new chemoprotective agents that are not only effective but also safe. By understanding the complex synergistic interaction of various anticancer plant metabolites, the new chemoprotective agents can be developed that can kill cancerous cells or render them benign without causing any damage to normal cells (Saxe, 1987; Sporn and Liby, 2005; Prakash et al., 2013; Khazir et al., 2014).

IV. Plants growing in hostile environment: Untapped potential

Life has thrived on earth since long. However, extremes of nature can threaten the survival of individuals, communities and even species on earth (Huppert and Sparks, 2006). Tectonic and climatic changes repeatedly generated large territories that were virtually devoid of life and exhibited harsh environmental conditions (Krämer, 2010). Hostile environment poses a significant stress on the plant kingdom. Plant growth can be significantly influenced by the habitat and the environment in which it grows. Diverse environments hostile to plant life include drought, high salinity, acid rains, extremes of temperature, hypoxia (restricted oxygen supply in waterlogged and compacted soil), mineral/nutrient deficiency, heavy metal toxicity, pollutants, reduced microbial activity (essential for soil and plant health), excessive exposure to radiation and high light intensity, earthquake and volcano eruptions (Smirnoff, 2001; Chaves et al., 2003; Sax, 1955; de Micco, 2011; Cheng, 2003; Memon and Schröder, 2003; Ort, 2001; Mahajan and Tuteja, 2005). Besides natural calamities, human activity is producing changes in the environment on an unprecedented scale at global level. Soil and environment are under tremendous pressure due to large scale industrialization and discharge of effluents - a globally important issue (Islam et al., 2006). The properties of soil are generally dependent on the combined effects of climate, biological activity, topography and the mineralogical composition of the parent rock (Whitfield and Claxton, 2004). The adverse effects on the plants can be attributed to the presence of contaminants in soils. Industrial wastes are a major source of soil pollution that originate from coal and mineral mining industries, chemical industries, metal processing industries and the like. These wastes include diverse chemicals ranging from heavy metals to synthetic compounds that may accentuate the effects of salinity on the growth of planted vegetation (Dueck et al., 1987; Ho et al., 2012). The apparent innocuous discharges of effluent and sewage sludge on agricultural land has become a common practice in the world as a result of which, these toxic metals can be transferred and concentrated into the plant tissues from the soil (Ho et al., 2012; Ghani, 2010). They can cause adverse toxic effects on the plants growing in the affected area leading to a decrease in agricultural productivity. The heavy metals exceeding certain concentrations are considered to be cytotoxic, mutagenic and carcinogenic. Radioactive material from atmospheric fall out (nuclear explosions) and from radioactive waste (produced by nuclear testing laboratories and industries) remained a major factor in soil contamination. Despite this, some plants grow well in industrial areas where effluents are continuously contaminating the soil. Similarly, in areas where volcanoes erupt, the immediate effect on plant life is destructive and deadly. As lava, heat, and ash cover the landscape, trees and other plants are burned, buried and destroyed. Besides these hostile environments, a great variety of plants can survive around volcano and aid in the recovery of the ecosystem after a volcanic event. Scientists were surprised to see that how quickly the areas impacted by the eruption were recolonized, even in places where nothing had survived the blast (www.livescience.com/6450-mount-st-helens-recovering-30-years.html). In many plants various genes get upregulated in response to diverse stresses resulting in altered metabolic functions, which can mitigate the effect of stress and lead to plant adaptation (Babich and Stotzky, 1980). During the last couple of decades a number of second messengers and hormones that are altered in response to stresses have been identified (Tuteja and Sopory, 2008). The ability of such plant species to survive in such a harsh environment is of paramount ecological and pharmacological importance because such plants may offer more beneficial nutrient products than those grown under seemingly ideal conditions (Krämer, 2010).

It is natural to expect such plants to have developed unique mechanisms to respond to environmental stresses, both in terms of growth/development and tolerance mechanisms. Moreover, plants that grow around stressed environments are instrumental in re-establishing ecosystem. The surface of these unique natural resources has barely been scratched (Ferguson, 2004). A better understanding of the plant resistance towards environmental stress is required in order to facilitate the identification of phyto-constituents responsible for plant’s natural defence. Literature revealed the production of a high concentration of health-promoting substances (like flavonoids and phenolics) by plants in response to environmental stresses (Asami et al., 2003; Hooper et al., 2010). It is hypothesized that such plants adapting well in the harsh/hostile environment may have better protective properties than conventionally grown plants in combating diseases like cancer in human beings.
In view of above authors opine that plants growing well in hostile environment may be a real choice for being investigated for the discovery of anticancer agents. There are numerous medicinal plants available in nature; which have anticancer properties and the majority of them are still to be explored. Out of the 250,000-500,000 plant species on earth, probably less than 20% of the known plants on earth have ever been investigated phytochemically. Moreover, only a small fraction of plant species have been studied for possible anticancer activity (Cragg et al., 2009; Pan et al., 2010). Even with the advances in combinatorial chemistry and High Throughput Screening (HTS), it would be a huge task to screen all plant species in the planet to identify curare for tumor cells. It is this ‘knowledge in advance’ that makes reverse pharmacology so enticing. (Mohamed et al., 2012).

The corresponding author visited the Old Faithful, Yellowstone National Park in the United States. It is also called the most predictable geographical feature on Earth erupting almost every 45-90 minutes. Yellowstone is sitting on a large volcanic field that, millions of years ago, had some of the world’s largest known eruptions. Author observed that many plants have adapted well to such a hostile ecosystem. Many exotic, colourful flowers were found growing particularly well in the volcanic soil. He photographed many plants surviving comfortably in multiple but diverse hostile environments (including extremes of temperatures due to volcanic eruptions as well as normal freezing temperature, continuous exposure to acids and other toxic chemicals) (See Figures 1-9). Later, the corresponding author also visited Watsonville, California, USA and observed some of these plants also growing comfortably in entirely different hostile environment (salinity and sandy) in a beach in Watsonville, California, USA.

Despite so many important contributions from the plant kingdom in the past, numerous plant species have never been described and remain unknown to science till date. Thus, it is reasonable to expect that new plant sources of valuable and pharmaceutical interesting materials remain to be discovered and developed.

V. Conclusion

Natural flora offers a vast potential for providing safe and effective drugs for the treatment of cancer. However, existing flora (250,000-500,000 plant species) is so vast that it is humanly impossible to investigate each and every plant for anti-cancer activity. It will be highly worthwhile to shortlist plant species to a very few through the leads provided by the nature. Accordingly, plants growing in multiple but diverse hostile environments can easily provide valuable leads with regard to anticancer activity. Increasing global warming, malnutrition and various environmental insults continue to increase the incidences of cancer. “Cancer is hostile to human body and hostile environment is cancerous to plants”. Accordingly, few plants which are able to comfortably survive under stressed conditions in highly hostile environment may act as a vital source of anti-cancer agents. Such plants may produce bioactive constituents that can prove hostile to mammalian cancerous cells with minimal adverse effects.

As an initiative towards war on cancer, plant species with a capacity of defending themselves in multiple but diverse hostile environments can be easily shortlisted and subjected to systematic phytochemical and biological screening with main emphasis on anticancer activity. Moreover, these anticancer agents are likely to be safe by virtue of being of natural origin.

There is an urgent need to conduct a systematic survey of plants growing in diverse hostile environments in order to accelerate discovery of anticancer drugs from the plant kingdom. Those plants which are able to survive comfortably in multiple but diverse hostile environments should be first shortlisted and subjected to systematic phytochemical and biological screening with main emphasis on anticancer activity. Such an approach is most likely to result in discovery of numerous anticancer drugs for treatment of various types of cancer.
Figure 1. A photograph showing few plants surviving comfortably in highly acidic environment due to volcanic eruptions in Yellowstone National Park, USA. Moreover, these plants are also subjected to extremes of temperatures due to exposure to both snow and steam (being liberated during volcanic eruption).

Figure 2. A photograph showing damage to vegetation in background due to simultaneous exposure to both steam and acidic gases emanating from volcanic eruptions in Yellowstone National Park, USA.
Figure 3. Another photograph showing barren land with damaged trees in the background due to simultaneous exposure to steam and acidic gases emanating from volcanic eruptions in Yellowstone National Park, USA.

Figure 4. A photograph showing plants growing well in highly hostile environment involving acids and exposure to extremes of temperature in Yellowstone National Park, USA.
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Figure 5. A photograph showing plants growing in hostile environment due to high salinity, nutritional deficiency and extremes of temperature at a Pacific beach, Watsonville, California, USA.

Figure 6. A photograph of a plant growing comfortably in sandy but saline environment in a Pacific beach at Watsonville, California. The same plant was also observed to survive comfortably in another hostile environment involving acids and extremes of temperature due to volcanic eruptions in Yellowstone National Park, USA.
Figure 7. A photograph showing lack of vegetation in the vicinity of a pool of acid (resulting from volcanic eruptions) at Economic Geyser, Faithful Inn, Yellowstone National Park, USA.

Figure 8. A photograph of another plant growing comfortably in saline environment along Pacific beach at Watsonville, California. The same plant was also observed to survive comfortably in another hostile environment involving acids and extremes of temperature due to volcanic eruptions in Yellowstone National Park, USA.
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**Figure 9.** A photograph showing a rare plant growing in a hostile environment involving acids and extremes of temperatures
Table 1: Plants with anticancer activity

<table>
<thead>
<tr>
<th>Family</th>
<th>Name of Plants</th>
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<tbody>
<tr>
<td>Actinidiaceae</td>
<td>Actinidia chinensis (Zhu et al., 2003)</td>
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<tr>
<td>Agaricaceae</td>
<td>Lentinus edodes (Chihara et al., 1970)</td>
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<tr>
<td>Amaranthaceae</td>
<td>Iresine herbstii (Dipankar et al., 2011)</td>
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<tr>
<td>Anacardiaceae</td>
<td>Anacardium occidentale (Kubo et al., 1993), Myracrodruon urundeuva (Ferreira et al., 2011)</td>
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<tr>
<td>Annonaceae</td>
<td>Annona glabra (Cochrane et al., 2008)</td>
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<tr>
<td>Apiceae</td>
<td>Anethum graveolens (Zheng et al., 1992), Angelica sinesis (Zhu et al., 2012; Cao et al., 2010)</td>
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<tr>
<td>Apocynaceae</td>
<td>Hancornia speciosa (Endringer et al., 2009), Bleekeria vitensis (Cragg and Suffness, 1988; Paolotti et al., 1980), Catharanthus roseus (Carter and Livingstone, 1976; El-Sayed and Cordell, 1981; El-Sayed et al., 1983), Ervatamia coronaria (Hullatti et al., 2013), Forsteronia refracta (Xu et al., 2006), Himatanthus articulates (Rebouças Sde et al., 2011), Himatanthus succuaba (Persinos and Blomster, 1978), Ochrosia borbonica (Svoboda et al., 1968), Ochrosia elliptica (Kuo et al., 2005)</td>
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<tr>
<td>Araceae</td>
<td>Arisaema tortuosum (Dhuna et al., 2005)</td>
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<tr>
<td>Araliaceae</td>
<td>Aralia nudicaulis (Wang et al., 2006; Huang et al., 2006), Acanthopanax gracilistylus (Shan et al., 1999; Xie, 1989), Panax ginseng (Chang et al., 2003)</td>
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<tr>
<td>Areceaceae</td>
<td>Orbignya phalerata (Remó et al., 2008)</td>
</tr>
<tr>
<td>Asclepiadaceae</td>
<td>Marsdenia tenocissima (Zhang et al., 2010)</td>
</tr>
<tr>
<td>Asteraceae</td>
<td>Acanthospermum hispidum (Rajendran and Deepa, 2007), Aster squamatus (Bibi et al., 2011), Calendula officinalis (Ukiya et al., 2006), Centaurea montana (Shoeb, 2006), Centaurea jacea (Forgo, 2012), Centaurea schischkinii (Shoeb et al., 2006), Echinacea angustifolia (Huntimer et al., 2006), Eupatorium formosanum (Lee et al. 1972), Eupatorium perforatum (Habtemariam and Macpherson, 2000), Silybum marianum (Tyagi et al., 2002), Tanacetum parthenium (Parada-Turska et al., 2007), Elephantopus mollis (Ooi et al., 2011)</td>
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<tr>
<td>Berberidaceae</td>
<td>Berberis amurensis (Xie et al., 2009; Xu et al., 2006), Berberis amurensis (Park et al., 2009; Duan et al., 2010), Podophyllum emodi, P. peltatum (Stähelin, 1973; Damayanthi and Lown, 1998)</td>
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<tr>
<td>Betulaceae</td>
<td>Betula alba (Fulda, 2008), Betula utilis (Patočka, 2003)</td>
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<tr>
<td>Bignoniaceae</td>
<td>Tabebuia avellanedae (Rao et al., 1968; Hussain et al., 2007; Epifano et al., 2014)</td>
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<td>Boraginaceae</td>
<td>Symphytum officinale (Roman et al., 2008)</td>
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<td>Brassicaceae</td>
<td>Brassica oleracea (Devi and Thangam, 2012)</td>
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<td>Bromeliaceae</td>
<td>Ananas comosus (Chobotova et al., 2010)</td>
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<tr>
<td>Cannabaceae</td>
<td>Cannabis sativa (Munson et al., 1975; Casanova, 2003; Kerbel and Folkman, 2002)</td>
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<td>Caricaceae</td>
<td>Carica papaya (Alessiani et al., 2008; Breemen and Pajkovic, 2008)</td>
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<td>Casealpiniaceae</td>
<td>Deionix regia (El-Sayed et al., 2011)</td>
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<tr>
<td>Celastraceae</td>
<td>Maytenus ilicifolia, Tripterygium wilfordii (Costa et al., 2008; Shirotai et al., 1994) (Wong et al., 2012)</td>
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<tr>
<td>Cephalotaxaceae</td>
<td>Cephalotaxus harringtonia (Powell et al., 1970; Ohmuma and Holland, 1985; Beranova et al., 2013)</td>
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<tr>
<td>Chenopodiaceae</td>
<td>Chenopodium ambrosioides (Nascimento et al., 2006; Effert et al., 2002)</td>
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<tr>
<td>Chinese recipe</td>
<td>Danggui Longhui Wan (Hoessel et al., 1999)</td>
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<td>Family</td>
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<td>Chlorellaceae</td>
<td><em>Chlorella pyrenoidosa</em> (Sheng et al., 2007)</td>
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<td></td>
<td><em>Parinari curatellifolia</em> (Lee et al., 1996)</td>
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<tr>
<td>Colchicaceae</td>
<td><em>Colchicum autumnale</em> (Lindholm et al., 2002; Bhattacharyya et al., 2008)</td>
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<td>Combretaceae</td>
<td><em>Combretum caffrum</em> (Dorr et al., 1996)</td>
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<td>Compositae</td>
<td><em>Arctium lappa</em>, <em>Artemisia argyi</em> (Machado et al., 2012)</td>
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<td><em>Seco et al., 2003</em>)</td>
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<tr>
<td>Convolvulaceae</td>
<td><em>Ipomoea batatas</em> (Christian et al., 1989; da Rocha et al., 2001)</td>
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<tr>
<td>Cucurbitaceae</td>
<td><em>Cucurbita andreana</em> (Jayaprakasam et al., 2003; Bernard and Olayinka, 2010)</td>
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<tr>
<td>Dioscoreaceae</td>
<td><em>Dioscorea colletii var. hypoglaucia</em>, <em>Dioscorea zingiberensis</em> (Hu and Yao, 2003) (Tong et al., 2012)</td>
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<td>Erythroxylaceae</td>
<td><em>Erythroxylum Pervillei</em> (Mi et al., 2001; 2002; 2003)</td>
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<tr>
<td>Fabaceae</td>
<td><em>Anadenanthera Colubrine</em> (Moreto et al., 2004), <em>Arachis hypogea</em> (Huang et al., 2010; Ku et al., 2005), <em>Bauhinia forficata</em> (Lim et al., 2006), <em>Copaifera langsdorffii</em> (Costa-Lotufo et al., 2002), <em>Copaifera multijuga</em> (Gomes et al., 2008; Lima et al., 2003), <em>Glycyrrhiza glabra</em> (Rathi et al., 2009; Honga et al., 2009), <em>Psoralea corylifolia</em> (Ryu et al., 1992; Wang et al., 2011), <em>Senecio occidentalis</em> (Calderón et al., 2006)</td>
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<tr>
<td>Fucaceae</td>
<td><em>Ascoephylllum nodosum</em> (Religa et al., 2000)</td>
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<td>Ganodermataceae</td>
<td><em>Ganoderma Lucidum</em> (Sliva et al., 2012)</td>
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<tr>
<td>Guttiferae</td>
<td><em>Hypericum perforatum</em>, <em>H. adenotrichum</em> (Vacek et al., 2007; Ozmen et al., 2007)</td>
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<tr>
<td>Gyroforaceae</td>
<td><em>Gyrofora esculenta</em> (Sone et al., 1996)</td>
</tr>
<tr>
<td>Juglandaceae</td>
<td><em>Juglas mandshurica Maxim</em> (Zhang et al., 2012; Yao et al., 2012)</td>
</tr>
<tr>
<td>Labitae</td>
<td><em>Salvia prionitis</em> (Zhang et al., 1999; Meng et al., 2007)</td>
</tr>
<tr>
<td>Lamiaceae</td>
<td><em>Menih piperita</em>, <em>Scutellaria Indica</em>, <em>Ocimum sanctum</em> (Kumar et al., 2004) (Bonham et al., 2005) (Karthisayan et al., 1999; Prakash and Gupta, 2000)</td>
</tr>
<tr>
<td>Lecythidaceae</td>
<td><em>Couroupita guianensis</em> (Premanathan et al., 2012)</td>
</tr>
<tr>
<td>Leguminosae</td>
<td><em>Astragalus membranaceus</em> (Auyeung et al., 2009), <em>Vicia faba</em> (Wang et al., 2002; Ravindranath et al., 2004)</td>
</tr>
<tr>
<td>Liliaceae</td>
<td><em>Allium sativum</em> (Ejaz et al., 2003), <em>Aloe arborescens</em> (Lissoni et al., 2009; Furukawa et al., 2002; Jin et al., 2005), <em>Aloe vera</em> (Patel et al., 2012; El-Shemy et al., 2010; Lin et al., 2006; Pecere et al., 2000)</td>
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<td>Linaceae</td>
<td><em>Linum usitatissimum</em> (Toure and Xueming, 2010)</td>
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<tr>
<td>Lygodiaceae</td>
<td><em>Lygodium flexuosum</em> (Wills and Asha, 2009)</td>
</tr>
<tr>
<td>Malvaceae</td>
<td><em>Hibiscus mutabilis</em> (Lam and Ng, 2009)</td>
</tr>
<tr>
<td>Meliaceae</td>
<td><em>Amorpha rohituka</em> (Rabi et al., 2013), <em>Azadirachata indica</em> (Gogate, 1991), <em>Dysoxylum binectariferum</em> (Mohana Kumar et al., 2012)</td>
</tr>
<tr>
<td>Mimosaceae</td>
<td><em>Mimosa pudica</em> L (Hullatti et al., 2013)</td>
</tr>
<tr>
<td>Family</td>
<td>Name of Plants</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Moraceae</td>
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<tr>
<td>Myrtaceae</td>
<td>Maclura pomifera (Son et al., 2007)</td>
</tr>
<tr>
<td>Myrtaceae</td>
<td>Rapanea guianensis (Cordero et al., 2004)</td>
</tr>
<tr>
<td>Nyctaginaceae</td>
<td>Boerhavia diffusa (Manu and Kuttan, 2009; Leyon et al., 2005; Ahmed-Belkacem et al., 2007)</td>
</tr>
<tr>
<td>Nyssaceae</td>
<td>Campsotroca acuminata (Wall et al., 1966)</td>
</tr>
<tr>
<td>Oleaceae</td>
<td>Forsythia corea (Moon et al., 1985)</td>
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<tr>
<td>Oscillatoriaceae</td>
<td>Lyngbya majuscula (Caret, 1996), Symplaca spp. (Taori et al., 2008)</td>
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<td>Papaveraceae</td>
<td>Chelidonium majus (Staniszewski et al., 1992), Papaver somniferum (Ye et al., 1998; Li et al., 2012; Sueoka et al., 1996)</td>
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<td>Plantaginaceae</td>
<td>Plantago major (Galvez et al., 2003; Velasco-Lezama et al., 2006)</td>
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<td>Pleurotaceae</td>
<td>Pleurotus citrinopileatus (Li et al., 2008)</td>
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<tr>
<td>Plumbaginaceae</td>
<td>Plumbago scandens (Nguyen et al., 2004; Lin et al., 2003), Plumbago zeylanica (Sand et al., 2012)</td>
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<tr>
<td>Polygonaceae</td>
<td>Fagopyrum esculentum (Liu et al., 2001), Polygonum barbatum (Abdul Mazid et al., 2011), Rheum palmatum (Shoemaker et al., 2005; Chun-Guang et al., 2010)</td>
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<td>Polyperaceae</td>
<td>Anrodia cinnamomea (Lin and Chiang, 2011; Chiang et al., 2010; Chen et al., 2012), Anrodia camphorata (Lin and Chiang, 2011; Chiang et al., 2010), Coriolus versicolor (Cui and Chisti, 2003)</td>
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<td>Primulaceae</td>
<td>Rrapanea guianensis (Cordero et al., 2004)</td>
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<td>Ranunculaceae</td>
<td>Hydrastis Canadensis (Sun et al., 2009), Nigella sativa (Gali-Muhtasib et al., 2006)</td>
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<td>Rhizophoraceae</td>
<td>Caulerpa spp (Fischel et al., 1995; Parent-Massin et al., 1996; Barbier et al., 2001), Bruguiera sexangula (Loder, and Russell, 1969)</td>
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<tr>
<td>Rhodolclaceae</td>
<td>Chondria spp (Palermo et al., 1992)</td>
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<tr>
<td>Rosaceae</td>
<td>Dachesna chrysanth (Lee and Yang, 1994), Prunus dulcis (Laughton et al., 1991; Soliman and Mazzio, 1998)</td>
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<tr>
<td>Rubiacceae</td>
<td>Psychotria ipecacuanha (Larsson et al., 2009), Trailliaedoxa gracilis (Svejda et al., 2010)</td>
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<tr>
<td>Rutaceae</td>
<td>Citrus limon (Miller et al., 2004; Manthey, and Guthrie, 2002)</td>
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<td>Scrophulariaceae</td>
<td>Picrorrhiza kurroa (Rajkumar et al., 2011)</td>
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<td>Scelaginellaceae</td>
<td>Selaginella moellendorffii (Sun et al., 1997)</td>
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<td>Simaroubaceae</td>
<td>Brucea antidysenterica (Cuendet, M. and Pezzuto, 2004)</td>
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<td>Solaraceae</td>
<td>Capsicum frutescens (Maoka et al., 2001; Jun et al., 2007), Fabiana imbricate (Reyes et al., 2005), Solanum lycocarpum (Munari et al., 2014), Solanum nigrum (Li et al., 2009; Lee et al., 2004)</td>
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<td>Taxaceae</td>
<td>Taxus brevifolia, Taxus Canadensis (Wani et al., 1971; Schiff et al., 1979), Taxus baccata (Malik et al., 2011), Taxus canadensis (Gunawardana et al., 1992)</td>
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<td>Theaceae</td>
<td>Camellia sinensis (Katiyar et al., 1992)</td>
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<td>Thymelaceae</td>
<td>Wikstroemia indica (Lu et al., 2011; Diogo et al., 2009)</td>
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<td>Violaceae</td>
<td>Viola odorata (Perwaiz and Sultana, 1998; Lindholm et al., 2002)</td>
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<td>Vitaceae</td>
<td>Vitis vinifera (Manna et al., 2000)</td>
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<td>Zingiberaceae</td>
<td>Curcuma longa (Hatcher et al., 2008; Jiao et al., 2008)</td>
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<tr>
<td>Dictyocaulaceae</td>
<td>Stypodium spp (Gerwick et al., 1981)</td>
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</table>
References:


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