Unexplored Medicinal Plants of Potential Therapeutic Importance: A Review

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ABSTRACT

Herbalism is the old concept employing plants as medicinal agents. Herbology or Herbal Medicine refers to the use of plants for medicinal purposes and study of such uses. Since prehistoric era, the use of plants as medicine has been documented in indigenous traditional knowledge systems around the world. Following the perspective of ethnopharmacology, many plants have been taken into consideration for the prevention and cure of the various ailments of the current era. Many medicinal plants like Curcuma longa, Panax Ginseng, Commiphora wightii, Zingiber officinale have been investigated intensely for their therapeutic properties and have been recognised well for their beneficial effects. However, the vast databases of medicinal plant are still unexplored and needs attention. The current review discusses some chosen unexplored medicinal plants of therapeutic importance which could attract the attention of researchers in the field of herbal medicine to investigate and explore their clinical efficacy and medicinal potential as new therapeutic agents in disease prevention.

Keywords: Medicinal plants, Disease prevention, Phytomedicine, Ethnopharmacology.

Introduction

A plant is considered to be medicinal if any part or product of the plant is used in order to relieve, prevent or cure a disease or to alter the physiological and pathological process, or employed as a source of drug or their precursors.1 Since prehistoric era every civilization of the world has deciphered plants ability in treating human disease. Evidence exists that traditional medical systems such as Unani, Ayurveda, Chinese, European and Mediterranean cultures systematically and officially used these medicinal plants/herbs for over 4000 years as medicine.2 Ancient Unani manuscripts,3 Ayurvedic doctrines,4 Egyptian papyrus,5-6 and Chinese writings7 extensively described the uses of herbs. As per the data available, over three-quarters of the world population relies mainly on plants and plant extracts for their health care needs.8 About 80% of the population in developing countries use traditional medicines since they cannot afford the high cost of western pharmaceuticals and health care, the other reason for relying on traditional medicines corresponds to its acceptance from a cultural and spiritual perspective.9 Another major advantage of relying on the traditional sources of healthcare is the belief that natural products exerts minimal or no side effects during treatment. The involvement of herbal medicines and plant products serving as drug precursors is obvious from the fact that more than 30% of the entire plant species, at one time or the other was used for medicinal purposes. Examples of important drugs obtained from plants are cardioactive drugs (Digitoxin and Digoxin from Digitalis purpurea L.),9,10 antimalaria and antiarrhythmic drug (Quinine and Quinidine from Cinchona spp.),9,10 antinociceptive and cough suppressant drugs (Morphine and Codeine, respectively from Papaver somniferum),11 the anti-inflammatory drug (Aescin from Aesculus hippocastanum L.),9 antitumour agent (Etoposide from Podophyllum peltatum), muscle relaxants (Atropine from Atropa belladonna),12 chemotherapeutic drug (Vincristine and Vinblastine from Catharanthus roseus),13,14 antancer drugs (Paclitaxel and Abraxane from Taxus brevifolia) and dermatitis curing drug (Allertretinoid from Daucus carota),9,11,12 Anti-tumour and anti-infectious drugs accounts for the major percentage among the total plant derived drugs.9 Moreover, some plants products are considered as an important source of nutrition and as a result of that, they are recommended for their therapeutic values e.g. Green tea, Walnuts, Safed Musli, Cranberry, Raspberry, Pepper, etc.12 Over the past three decades there has been tremendous increase in the phytomedicine and nutraceutical research; however, there is still an insignificant research data in this field. Ethnopharmacology provides us with the clue of beneficial properties of medicinal plant15,16 and most plants selected on the virtue of traditional knowledge have been validated scientifically and their pharmacological attributes of the plant drugs are now confirmed; however, many plant species having very strong ethnopharmacological values are often overlooked, thus creating a redundancy in the exploration of medicinal plants, having the potential to cure specific diseases. In this regard, since 1999, WHO has published three volumes of the WHO monographs on selected medicinal plants to accelerate evidence based research in phytomedicine.15-17 The current review intends to highlight some medicinal plants which have not been explored much, despite having strong ethnomedical leads.

Methodology

For this review, the referencing materials have been collected from electronic databases sources i.e. Google Scholar, Web of Science, PubMed, directory of open access journals (DOAJ) and websites like www.thepplantlist.org, www.effloraindia.nic.in, www.medicinalplants.in. The search was performed by using combinations of the following keywords and or their equivalents; phytomedicine, ethnopharmacology, drug discovery, therapeutic medicinal plants, plant based modern drugs, unexplored medicinal plants, cancer and plants. Ethical issues (including plagiarism and double publication) have been completely observed by the authors.

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**Therapeutic medicinal plants: An Indian perspective**

Ayurveda is an ancient health care system which evolved in India, it dates back to about 5000 years ago. It was practiced during Vedic period of India. About 700 plants were described in Charaka Samhita and Sushruta Samhita during the 1st millennium BC.1, 2 Ayurvedic System of India aims to promote, prevent and sustain good health and prevent diseases through healthy lifestyle practices. The literal meaning of Ayurveda is the “Science of life”. It is estimated that about 7,500 plants are used in local health traditions in most rural and tribal villages in India. Herbal treatments are the most popular form of Traditional Medical System in such regions.3

Considering the emerging challenges in the healthcare system, there is need to integrate Ayurveda into the medical system for the management and treatment of lifestyle-related diseases. Ayurveda can offer Drug-free solutions by curing and managing the diseases and improving the quality of life. In order to augment the traditional system of medicine, Government of India has set up a National Level Policy for growth, promote and development of the Traditional System of Indian Medicine. The Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) has created separate departments for Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy collectively known as AYUSH. Figures 1 and 2 show the different school of thoughts exploring and employing the use of medicinal plants in the prevention and cure of diseases and their respective percentages.

**Bioactive constituents from medicinal plants**

Phytochemicals (from the Greek word phyto, meaning plant) are biologically active, naturally occurring chemical compounds found in plants, which provide health benefits for humans other than those attributed to macronutrients and micronutrients.20 These specific compounds are synthesized by primary or rather secondary metabolism of living organisms with an aim to provide defense against environmental factors and infectious agents in plants.21 The biological activity of secondary metabolites is not only restricted to plant defense system but have also been used to cure various human diseases. Secondary metabolites present in plants as organic compounds provide definite physiological action on the human body. Plant active bioconstituents are known to have a vast range of therapeutic activity ranging from antibacterial, antiviral, immunomodulatory, anti-inflammatory to most extensive anticancer activity. These bioactive substances include tannins, alkaloids, carbohydrates, terpenoids, steroids and flavonoids.20 These can be derived from barks, leaves, flowers, roots, fruits or seeds.22

The major active components present in medicinal plants are broadly classified as under:

**Phenolics**

Phenolics comprise the largest group of secondary metabolites with wide distribution and a myriad of characteristics. Phenols have a distinctive ability to form non-covalent, intermolecular complexes with each other and with both large and small molecules. Phenolics have an aromatic ring bearing one or more hydroxyl groups and their structures may range from that of a simple phenolic molecule to that of a complex high molecular weight polymer. Phenolics are derived from pentose phosphate, shikimate, and phenylpropanoid pathways in plants.23 The major characteristics of polyphenols are radical-scavenging capacity, which is involved in antioxidant properties (key factor involved in the chemical defense of plants against pathogens and predators and in plant-plant interferences), and the ability to interact with proteins.22 Phenolic compounds as functional food render their effects via anti-oxidation and relief from oxidative stress and its consequences. The anti-oxidative effect of phenolic in functional foods is due to the direct free radical scavenging activity, reducing activity and an indirect effect arising from chelation of pro-oxidant metal ions.20 The chelation of metal ions generally requires ortho-dihydroxylation on the phenyl ring in phenolic acids and flavonoids or the presence of a 3- or 5-hydroxyl group of flavonoids.27 Dietary polyphenols from food industry are the good source of antioxidants and are one of the main composition of the nutraceutical products available in the market. The most important dietary phenolics are the phenolic acids (including hydroxybenzoic and hydroxycinnamic acids), polyphenol (hydroxylizable and condensed tannins) and flavonoids, the latter being the most primitively studied group.28

**Terpenoids (terpenes)**

The terpenes, also known as isoprenoids, are the largest class of phytounitrients in green plants, soy plants and grains.29 The importance of terpenes to plants relates to their necessity to fix carbon through photosynthetic reactions using photosensitizing pigments. Terpenes have a unique antioxidant activity in their interaction with free radicals. Terpenes react with free radicals by partitioning themselves into fatty membranes by their long carbon side chain.20 Perhaps the most studied of the terpene antioxidants are the tocotrienols and tocopherols. The biological relevance of terpenoids is well established.31 The use of γ-tocotrienols, a mixed isoprenoid, and β-ionone, a pure isoprenoid, to suppress the growth of diverse tumour cell lines via initiation of apoptosis and concomitant arrest of cells in the G1 phase of the cell cycle have been reported.32

**Alkaloids and other nitrogen-containing metabolites**

Alkaloids are natural products that contains heterocyclic nitrogen atoms that are basic in character. Alkaloids are naturally synthesized by large numbers of organisms, including animals, plants, bacteria and fungi. Alkaloids are significant for the protection and survival of plant because they ensure their survival against micro-organisms (antibacterial and antifungal activities), insects and herbivores (feeding deterrents).33 and also against other plants by means of allopathically active chemicals.34 Alkaloids derived from higher plants exhibited marked pharmacological activity.34 Functional foods with alkaloids have numerous pharmacological activities including anti hypertensive effects, antiarrhythmic effect, antimalarial activity, antiviral and anticancer actions.34

**Saponins**

Saponins glycosides widely distributed in the plant kingdom, include a diverse group of compounds characterized by their structure containing a steroidal or triterpenoid aglycone with one or more sugar chains.35 Their structural diversity is reflected in their physicochemical and biological

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**Figure 1:** Percentage of plant species utilization under different medicinal set up (Source: NMPB, 2008).

**Figure 2:** Canopy of Various School of Medicine in India.
properties, which are exploited in a number of traditional (as soaps, fish poison, and molluscicides) and industrial applications, saponins in foods have traditionally been considered as “anti-nutritional factors” and in some cases have limited their use due to their bitter taste. Therefore, most of the earlier research on processing of saponins targeted their removal to facilitate human consumption. However, recent research has shown that saponins have come into renewed focus in recent years due to increasing evidence of their health benefits such as cholesterol lowering and anticancer properties. The proposed mechanism of anti-carcinogenic properties of saponins includes direct cytotoxicity, immune-modulatory effects, bile acid binding and normalization of carcinogen-induced cell proliferation.

Recent research has established saponins as the active components in many herbal medicines and highlighted their contributions to the health benefits of foods such as soybeans and garlic. Saponins are often used to permeabilize membranes in order to make intracellular compartments accessible for antibodies.

Unexplored Medicinal Plants of Therapeutic Importance

1. *Faujasiopsis flexuosa* (Lam.) C. Jeffrey (*Asteraceae*), *Faujasiopsis flexuosa* (Lam.) C. Jeffrey belonging to the family Compositae, is an indigenous medicinal plant covering the habitat of Mascarene Island in Mauritius. This plant has been used for the cure of dysentery and diarrhea in the local practice of the region, and has been recognised as an important traditional medicine to be used in many formulations. Recent studies indicate its therapeutic potential as an antioxidant, antimicrobial and immunomodulatory agents. It has also been shown to possess anti-diabetic effects in vitro thereby indicating its ethnopharmacological value. Phytochemical evaluation reveals alkaloids as the active constituent of the plant. Recently, fourteen pyrrolizidine alkaloids have been isolated from the crude leaves and stem extracts of *Faujasiopsis flexuosa*, however, some toxic alkaloids have also been reported from the species. Despite evidence from in vitro studies, no in vivo documentation for its therapeutic potential has been recorded so far.

2. *Elephantorrhiza elephantina* (*Elephantorrhiza elephantina*) is one of the nine species belonging to the genus *Elephantorrhiza*. The shrub has a peculiar morphological characteristic of having large underground stem of up to 8 m long which confers to it a title as ‘Elephant Root’. Its habitat ranges from hot and patchy dry areas of grasslands to open acacia cobremb tum gregarious scrub. Many species belonging to this genus are highly regarded as medicinal plants in Southern Africa. *Elephantorrhiza elephantina* has a vast ethnopharmacological evidence and has been used in curing several ailments all over the world where it is considered indigenous. A detailed information on region based ethnopharmacological uses of *Elephantorrhiza elephantina* has been given in a review by Maroyi Alfred. The major disorders treated with this shrub are gastrointestinal problems where it has been found very effective in the treatment of bloody diarrhoea and dysentery, it is also used to treat skin diseases like acne, sexual disorders like erectile dysfunction, syphilis, herpes, HIV/AIDS. It is also sold as herbal medicines in the local markets under different vernacular names and is consumed in the form of root decoction. It is also utilized as fodder for animals in South Africa and have been considered as a veterinary medicine. A wide range of phytochemicals such as anthocyanidins, anthraquinones, esters, fatty acids, phenolic compounds, flavonoids, glycosides, polysterols, saponins, sugars, tannins, and triterpenoids have been isolated from rhizome extracts of *E. elephantina*. The rhizome or root extract contains a variety of bioactive compounds like isoprenylated flavonoids, saponins, tannins, and triterpenoids. Studies have shown that the crude leaves and stem extracts of *E. elephantina* have led to the isolation of bioactive compounds like isoprenylated phnols which was found to have therapeutic effects against cancer and liver damage. Echinatin, a potent NRF2 activator isolated from *Glycyrrhiza uralensis* attenuated CCL4-induced liver damage in mice indicating its hepatoprotective potential. Recent research conducted by Jo and colleagues was treated with different concentrations of *G. paraguayense* root extract or ethyl acetate extract activated Nrf2 transcript indicating its hepatoprotective potential, however not much attention has been paid to *Glycyrrhiza uralensis* which shows some differences in its chemical composition from *Glycyrrhiza glabra*. Biological studies have revealed the presence of phenolic compounds, flavonoid glycosides and saponins from *G. paraguayense*, and recent investigations have shown that these compounds have led to the isolation of bioactive compounds like isoprenylated phnols which was found to have therapeutic effects against cancer and liver damage. A detailed information on region based ethnopharmacological uses of *G. paraguayense* has been given in a review by Maroyi Alfred.

3. *Tithonia diversifolia* (Hems) A. Grey, commonly known as Mexican sunflower is an aggressive invading weed which originally belongs to North and Central America, having been introduced into other regions of the world such as Africa, Asia and Australia. In folklore medicine around the world, it is used for the treatment of myriad of ailments, ranging from abscesses, hematomas, muscle cramps, skin infections to diseases of major concern like malaria, and liver damage. Sesquiterpenes are the major constituent of the plant. Recent studies on *Tithonia diversifolia* isolated anti-inflammatory and antitumor activities and regulation of the pro-inflammatory cytokines IL-6, IL-8 and TNF-α. In a study conducted by Lu et al. induction of apoptosis by ethyl acetate extracts of *T. diversifolia* leaves in human hepatoma (HepG2) cells was observed, indicating its potential role in cancer cure. Furthermore, saponins derived from *T. diversifolia* induces significant reduction in the level of triglycerides, low density lipoprotein (LDL), cholesterol, creatinine, urea, lactate dehydrogenase (LDH), , packed cell volume (PCV) and hemoglobin with a concomitant increase in high density lipoprotein (HDL), white blood cell and lymphocyte in normal rats when 20-100 mg/kg of saponins rich extract was administered, suggesting its anti-inflammatory and cholesterol lowering potential.

4. *Glycyrrhiza uralensis* (*Glycyrrhiza uralensis*) popularly known as Chinese Licorice/Gancao is cultivated originally in North China, Mongolia and Siberia. Licorice is a genus of the *Glycyrrhiza* family is a well-known herbal medicine in Chinese system of Medicine and have been documented in the Chinese Pharmacopeia. Traditionally, Gancao, is used as a flavouring agent and sweetening agent in tobaccos, chewing gums, candies, and toothpaste. *Glycyrrhiza glabra* a well-known species form the same genus have been found to contain compounds like glycyrrhizin, liciritrin, liciritrinigen, and isolaricinogen havengrown health benefits. It is cultivated originally in Mexico. It possesses several health benefits. It is used for the treatment of myriad of ailments including, high blood pressure, skin disorders, various respiratory problems where it has been found very effective in the treatment of bloody diarrhoea and dysentery, it is also used to treat skin diseases like acne, sexual disorders like erectile dysfunction, syphilis, herpes, HIV/AIDS. It is also sold as herbal medicines in the local markets under different vernacular names and is consumed in the form of root decoction. It is also utilized as fodder for animals in South Africa and have been considered as a veterinary medicine. A wide range of phytochemicals such as anthocyanidins, anthraquinones, esters, fatty acids, phenolic compounds, flavonoids, glycosides, polysterols, saponins, sugars, tannins, and triterpenoids have been isolated from rhizome extracts of *E. elephantina*. The rhizome or root extract contains a variety of bioactive compounds like isoprenylated flavonoids, saponins, tannins, and triterpenoids. Studies have shown that the crude leaves and stem extracts of *E. elephantina* have led to the isolation of bioactive compounds like isoprenylated phnols which was found to have therapeutic effects against cancer and liver damage. Echinatin, a potent NRF2 activator isolated from *Glycyrrhiza uralensis* attenuated CCL4-induced liver damage in mice indicating its hepatoprotective potential. Recent research conducted by Jo and colleagues was treated with different concentrations of *G. paraguayense* root extract or ethyl acetate extract activated Nrf2 transcription was measured as significant compared to the aqueous extract rich in flavonoid glycosides and saponins from *G. paraguayense*. A study conducted by Thanh et al. demonstrated the ability to scavenge free radicals and exh...
liver disorders including Hepatitis, Cirrhosis, Fibrosis, and Hepatocellular carcinoma reoccurrence episodes post-surgery/chemotherapy.

6. Acer saccharum and Acer rubrum
Among the maple (Acer) species that are native to North America, the sugar (Acer saccharum Marsh) and red (A. rubrum L.) maples are well known for yielding maple syrup, a natural sweetener that is obtained by concentrating the sap of these trees. There has been considerable interest in the identification of compounds from both maple sap and syrup. There has been considerable interest in the identification of compounds from both maple sap and syrup.

Furthermore, phenolic-enriched extracts of maple sap and syrup have been reported to show antiproliferative effects against a panel of human tumour cell lines. The antiproliferative effects of maple syrup in colon cancer cells were also seen without any apoptosis induction indicating potential anti-colon cancer effects by cell cycle arrest mechanism.

7. Crocus sativus
Saffron is the dried stigma of Crocus sativus and has been used for centuries in traditional medicine mainly for its aroma and food colouring properties, as well as for the treatment of various pathological conditions. The phytochemistry and pharmacological experiments have indicated that crocin and safranal, the major active ingredients of saffron, exert important actions, such as antioxidant, anti-inflammatory and anti-atherosclerotic activities. It has been suggested that the cytotoxic effect of saffron is associated with the interaction of carotenoids with topoisomerase II, an enzyme regulating cellular DNA and proteins synthesis. The antiproliferative effects of saffron are also seen without any apoptosis induction indicating potential anti-colon cancer effects by cell cycle arrest mechanism.

Table 1: Summarized List of Unexplored Medicinal Plants and Their Therapeutic Activities

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Plant Name</th>
<th>Vernacular Name</th>
<th>Family</th>
<th>Habitat/ Origin</th>
<th>Part Used</th>
<th>Traditional Uses</th>
<th>Pharmacological Potential</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Faujasiospis flexuosa (Lam.) C. Jeffrey</td>
<td>Zigzag, Liane Zig-Zag</td>
<td>Compositae</td>
<td>Mauritius</td>
<td>Leaves Stem</td>
<td>Dysentery, Diabetes</td>
<td>Antioxidant, Antimicrobial, Antidiabetic, Immunomodulatory</td>
<td>50,51, 52, 53, 54, 52</td>
</tr>
<tr>
<td>2.</td>
<td>Elephantorrhiza elephantina</td>
<td>Elephant's Foot, Eland's Bean</td>
<td>Fabaceae</td>
<td>South Africa</td>
<td>Rhizome Roots</td>
<td>Dermatitis Gastrointestinal Disorders Sexual disorders Bloody Diarrhoea Veterinary Medicine Cytoxic Antimicrobial Antidiarrheal Antiviral</td>
<td>72, 62, 64, 65, 66</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Tithonia diversifolia (HemsI) A.Grey.</td>
<td>Mexican Sunflower, Tree Marigold</td>
<td>Asteraceae</td>
<td>North and Central America</td>
<td>Leaves</td>
<td>Abscesses Hematomas Skin Infection Menstrual muscle cramps</td>
<td>Antimalarial, Anti-tumor, Anti-inflammatory, Anticancer</td>
<td>76,77,78, 85, 82, 84, 85</td>
</tr>
<tr>
<td>5.</td>
<td>Graptoptetalum paraguayense</td>
<td>Ghost Plant, Mother of Pearl Plant</td>
<td>Crussulaceae</td>
<td>Mexico</td>
<td></td>
<td>Diuretic, Hepatic Disorders, Blood Pressure Lowering</td>
<td>Antioxidant Anticancer (Hepatocellular carcinoma), Neuroprotective</td>
<td>102, 107, 105</td>
</tr>
<tr>
<td>7.</td>
<td>Crocus sativus</td>
<td>Zafran Saffron</td>
<td>Iridaceae</td>
<td>Mediterranea European, Western Asia</td>
<td>Stigma</td>
<td>Aphrodisias Antipoison Dysentery Measles Wound healing, Abscesses</td>
<td>Anti-carcinogenic Immunomodulatory</td>
<td>114,115</td>
</tr>
</tbody>
</table>

References
Platyphylline (1)  Senocionine (2)  Epigallocatechin (3)  Palmitic Acid (4)

Tagitinins A (5)  Neoglycyrol (6)  Licochalcone A (7)

Glycyrrhizin (8)  Gallic Acid (9)  Daidzein (10)  Genistein (11)

Salicin (12)  Picein (13)  Crocetin (14)
Figure 3: Molecular structures of the chemical constituents present in the unexplored medicinal plants: 1 and 2 - from Faujasiosis flexuosa, 3 and 4 - from Elefantorrhiza elephantina, 5 - from Tithonia diversifolia, 6, 7 and 8 – from Glycyrrhiza uralensis, 9, 10 and 11 - from Graptotepalum paraguayense, 12 and 13 - from Aecer Saccharum, 14, 15 and 16 - from Crocus Sativus.

Conclusion

The available literature explores the therapeutic usefulness for those plants which have not come under the scrutiny of clinical research for the development of novel plant based drugs. So far, only a minute percentage of medicinal plants have been identified and characterized for their beneficiary effects and studied at pre-clinical and clinical trial levels. However, with the huge availability of millions of plant species on the earth there is always a possibility for the exploration of plants with tremendous beneficial effects. In the present review, few examples of such unpopular plants have been discussed, which is backed by ethnomedical lead along with pharmacological and therapeutic information and still there are hundreds of unexplored medicinal plants that need much detailed survey. The isolation, identification of active principles and pharmacological studies of the active phytoconstituents of the discussed plants may be considered and studied elaborately in order to be employed in the treatment of various diseases.

Conflict of interest

The authors declare no conflict of interest.

Authors’ Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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