

**SAFETY OF MEDICINAL PLANTS: AN IMPORTANT CONCERN****SHAZIA TABASUM<sup>\*1</sup> AND SWATI KHARE<sup>2</sup>**<sup>1</sup>*Department of Botany, Govt. Science and Commerce College Benazeer, Bhopal, M.P, India.*<sup>2</sup>*Department of Botany, Govt. MLB Girls PG Autonomous College, Bhopal, M.P, India.***ABSTRACT**

Medicinal plants are natural sources of drugs used to cure various disorders of mankind. These serve as reliable medicine because of the presence of various biochemical substances. Herbal drugs gained fame in health care all over the world, especially in developing countries as these are locally accessible, economical and are having lesser side effects. But the natural origin may not be a sign of their safety. A limited number of available evidences indicated that adverse effects associated with herbal drugs are fewer. They may cause severe effects on the vital organs of human body chiefly because of self-medication. There is also an inadequate data available for most of the herbal medicines revealing their toxicology, safety and efficacy. Thus, efforts should be taken to ensure the benefits as well as health hazards associated with the herbal remedies.

**KEY WORDS:** Medicinal plants, adverse effects, safety and efficacy**SHAZIA TABASUM**Department of Botany, Govt. Science and Commerce  
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## INTRODUCTION

### *Medicinal plants*

Medicinal plants comprises all those plants that are resources of ingredients used as pioneer for therapeutic purposes, development and synthesis of valuable drugs and medicines suppressing, checking or curing a range of diseases in humans and in their domestic animals too. These plants have also a great contribution in the progress of human civilizations throughout the world<sup>1</sup>. Over 90, 000 plants out of 2, 50,000 higher plant species present on our planet earth have recognized medicinal uses in different cultures and countries, exclusive of having conducted ample research amongst various indigenous and other communities<sup>2</sup>. Plants provide the basic raw materials for all the traditional medicinal preparations in the form of plant parts, crude extracts, mixtures etc. At present a considerable number of drugs are prepared from plants which are used to cure various diseases<sup>3</sup>. Most of these preparations consist of the bioactive chemicals isolated from a particular plant or its part in a modified form. Globally, the estimate of medicinal plant species range from 35, 000 - 50, 000 species and out of this about 4000 - 6000 species have entered the world market of medicinal plants<sup>4</sup>. In the developed countries, 25% of the medical drugs are based on plants and their derivatives and the utilization of medicinal herbs and their preparations is familiar among the indigenous people in rural areas of various developing countries<sup>5</sup>. Demand of medicinal plants is increasing in both developing and developed countries due to growing recognition of natural products, being safe, easily accessible, reasonably priced and sometimes the solitary source of health care available to the poor. The field of medicinal plant has traditionally occupied a vital place in the socio cultural, spiritual and the medicinal sector of rural and tribal lives of developing countries.

### *Traditional use of medicinal plants*

Plants provide a wide variety of biochemical components useful to mankind. These substances can be extracted and used in the preparation of drug, or the plant itself can be used directly as a medication<sup>6</sup>. According to WHO estimates, more than 80% of the world's total population depends on traditional forms of medicine for their principal health care requirements<sup>7</sup>. A huge section of population in developing countries depends on medicinal plants mainly in order to maintain a good health<sup>8</sup>. Moreover, herbal remedies have become much acceptable in these societies for the treatment of various disorders due to rising costs of personal health care requirements<sup>9</sup>. Although modern medicine may exist along with such traditional practice, herbal medicines have regularly uphold their reputation for historical and cultural reasons<sup>10</sup>. Use of traditional medicine is more common in Sri Lanka, Pakistan, India, China, Thailand and Japan<sup>11</sup>. Plants used in traditional medicine have stood up to the test of time and contributed many novel compounds for preventive and curative medicine to modern science. The extensive utilization of traditional herbal medicines and other healthcare preparations has been traced to the occurrence of natural products with great medicinal values as mentioned in ancient texts like the Vedas and

Bible<sup>12</sup>. In spite of such traditional and frequent use of herbal products, it is only since 1978 WHO documented the use of herbal medicines officially for curative, prophylactic, palliative or diagnostic purposes and WHO also recommended the worldwide spreading of knowledge for their proper use<sup>13</sup>. It is because most of these products are often used carelessly with the belief that they are natural and thus free from poisonous and adverse effects<sup>14, 15</sup>.

### *Requirement of safety study of medicinal plants*

Medicinal plant preparations are administered with the hope of promoting health and treating various diseases such as infection, colds, inflammation, GIT disorders, insomnia, depression, heart diseases, diabetes, cancer, acquired immune-deficiency syndrome and liver diseases has increased in recent times<sup>6</sup>. A large section of people particularly in developing countries believe that all medicinal plants being natural are safe and free from harmful effects. However, the belief that traditional use of plants since centuries ascertains their safety does not necessarily hold true<sup>16, 17</sup>. Medicinal plants which are being used on a large scale for the treatment of particular disease are reported to be having serious side effects<sup>6</sup>. Rising interest in medicinal plants has increased scientific scrutiny of their therapeutic efficiency and safety<sup>18</sup>. Scientific studies on efficacy and safety of some medicinal plants indicated that there are many phytochemicals that have toxic effects. All medicinal herbs contain many xenobiotic agents (substances foreign to human body) and the biotransformation products of these substances can be potentially harmful. The effects may arise instantly with obvious signs after the intake or in their prolonged use without any sign or symptom that can be severe and sometimes fatal<sup>13</sup>. Long term use of some well known herbal medicines that resulted in potential geno-toxic effects are also a cause of concern towards their safety study<sup>19</sup>. Lack of basic information regarding the proper utilization of medicinal plants and their products makes them easy targets for self medication<sup>20</sup>. Moreover, the use and prescription of herbal remedies is not regulated that increases the chances of their misadministration particularly those from toxic plants. There are various case reports of severe events that took place after ingestion of herbal medicines and in most of these cases the herbs involved were either self prescribed or obtained from a source other than a registered specialist. Also, as herbal remedies are heterogeneous in nature, they impose several challenges about the quality control and regulatory process. Today, various herbal products are sold in the market without being subjected to the process of drug approval demonstrating their safety, purity and effectiveness. Thus, researches on basic traditional techniques and methodology; isolation of bioactive components and their subsequent modification into new remedies; standardization and validation of already known herbal drugs and other associated fields are required<sup>21</sup>. Toxicity and safety of medicinal plants are currently one of the main topics under consideration as herbal products are globally much popular. There is an inadequate toxicological data available regarding the medicinal plants. Therefore, with the current emphasis on research and development of medicinal plants worldwide, it is prerequisite to have information about

the efficiency and toxicity profile of plants utilized ethnobotanically to treat ailments.

### ORGAN SPECIFIC TOXICITY

The extensive use of plants as medicine has enabled the herbal medicine with some serious and evident toxicity symptoms<sup>16, 17</sup>. Some herbal medicines can damage the internal body organs which have been recognized as a serious toxicological problem. The adverse effects of medicinal plant use arise due to organ toxicity, adulteration, contamination, contents of heavy metals, inherent poisonous photochemical, herb-drug interactions and poor quality control. Many plants showed specific organ toxicity. The photochemical constituents of some medicinal plants are associated with toxicities of heart, liver, blood, kidney and central-nervous system; gastrointestinal disorder such as diarrhoea, and less frequently carcinogenesis<sup>22</sup> and teratogenicity<sup>23</sup>. After all, recent investigations have revealed that many plants used as food or in traditional medicine have mutagenic effects and cyto-toxic and geno-toxic effects in in-vitro and in-vivo assays<sup>24, 25</sup>. Plants rich in pyrrolizidine alkaloids, notably *Crotalaria*, *Heliotropium*, *Aristolochia* and *Senecio* are known to injure the liver in humans giving rise to serious liver damage (hepatic veno-occlusive disease)<sup>26, 27, 28</sup>. Cases of human hepatotoxicity associated with the ingestion of

comfrey have been documented<sup>29, 30</sup>. Doctors in Belgium have discovered recently that a Chinese herb, *Aristolochia fangchi* is not only linked to kidney failure, but may cause cancer as well<sup>31</sup>. Serious liver toxicity has been reported to be associated with the use of some herbal medicines (for example; Kava-Kava, *Piper methysticum*, *Crotalaria*, *Heliotropium* and *Senecio*). Lectins, an active principle found in some plants possess haemagglutinating and potent mitogenic properties. Systemic exposure to poke root has resulted in haematological aberrations. Saponin in some plants causes severe gastrointestinal irritation that involves intense abdominal cramping, haematemesis, hypotension and tachycardia. Many and more of these effects have been associated with unguarded ingestion of herbal medicine. A prospective study shows that 25% of the corneal ulcer in Tanzania and 26% of the childhood blindness in Nigeria and Malawi were associated with the use of traditional eye medicine<sup>32</sup>. A comprehensive investigation of plant extracts as well as identified phytochemical ingredients in relation to their safety and toxicity profile especially in humans can ensure a critical evaluation of their therapeutic potential<sup>33</sup>. Some examples of adverse effects and interactions (herb- drug interactions) associated with the use of common herbs and herbal remedies are summarized below in Table 1 and 2 respectively.

**Table1**  
**Potential toxic effects associated with some common herbs and herbal medicines marketed for different indications.**

S. No.	Drug name	Plant source	Medicinal uses	Toxicological signs	References
1	Aloe	<i>Aloe vera</i> leaves	Wound healing, laxative	Cytogenetic toxicity	34, 35
2	Black Cohosh	<i>Actaea racemosa</i> roots	Alleviating symptoms of menopause and sometimes for weigh loss	Fatigue, abdominal pain, hepatotoxicity	36, 37
3	Chaparral	<i>Larrea tridentata</i> leaves and twigs	Blood thinner, weight loss, mental and physical alertness, antiarthritis, anti-oxidant and anti-cancer	Carcinogenic, nephrotoxicity, hepatotoxicity	38, 39, 40
4	Comferey	<i>Symphytum officinale</i> leaves	Anti-inflammatory, anti-diarrhoeal and treatment of thrombophlebitis	Hepatotoxicity, Carcinogenicity	34, 35
5	Danshen	<i>Salvia miltiorrhiza</i> exterior taperoot	Angina-pectoris, anti-hyperlipidemic, ischemic stroke	Bleeding, anticoagulant effects	35, 41
6	Germander	<i>Teucrium chamaedrys</i>	Weight-loss, general tonic	Hepatotoxicity	42
7	Ginseng	<i>Panax ginseng</i> roots	Relieves stress, promotes mental and physical activity	Central nervous system stimulation, hypertension, skin eruptions	35
8	Ginkgo	<i>Ginkgo biloba</i> leaves, fruits and seeds	Impotence, vertigo, circulatory disorders, improves mental alertness	Gastric irritability, increasing bleeding time, spontaneous haemorrhage, sub dural haematomas	34, 35
9	Hawthorn	<i>Crataegus oxycantha</i> flowers, roots and berries	Mild to moderate congestive heart failure	Cardiac arrhythmias, lowered blood pressure	35
10	Isaphgul	<i>Plantago ovate</i> seeds	Demulcent, laxative	Bronchospasm, asthma, intestinal obstruction. Also causes oesophageal obstruction if swallowed dried	34
11	Kava Kava	<i>Piper methysticum</i> roots	Sedative, anxiolytic	Hepatotoxicity, cytochrome-P450 enzyme inhibitor	35, 43
12	Kelp (Seaweed)	<i>Limnaria digitata</i>	Metabolic tonic, thyroid tonic, anti inflammatory	Arsenic poisoning, hyperthyroidism	35, 44
13	Liquorice	<i>Glycyrrhiza glabra</i> roots	Anti-ulcer, anti-inflammatory, arthritis, chronic depression, demulcent, expectorant	Hypokalemic myopathy, pseudoaldosteronism, thrombocytopenia	34, 45
14	Ma-haug	<i>Ephedra</i>	Promotes weight loss, body building and mood evaluation	Cardiotoxicity, thyrotoxicosis, seizures,	34, 35,

				hepatotoxicity, high blood pressure, restlessness and irritability	
15	Mistletoe	<i>Phoradendron spp., Viscum album</i> leaves and young twigs	Digestive aid, heart tonic, sedative, also used in treating cancer, arthritis and mental disturbances	Hypotension, seizures, hepatitis	35, 46
16	Pennyroyal	<i>Mentha pulegium</i> leaves	Used in aromatherapy, as bath additive and for inducing abortions	Hepatotoxicity, nephrotoxicity, neurotoxicity	37, 47
17	Sassafras	<i>Sassafras officinale</i> root bark	Rheumatism, arthritis, cold and flu	Liver carcinogenicity	34
18	Senna	<i>Senna occidentalis</i> seeds	Laxative, promotes weight loss, treats constipation	Skeletal and cardiac muscle degeneration, hepatotoxicity, neurotoxicity, anaphylactic reactions, grand mal seizures, circulatory failure, hypertension	34, 35
19	Sily marin	<i>Silybum marianum</i> seeds	Liver tonic (hepatoprotective)	Cerebral haemorrhage, Hepatic coma and neuropathy	34
20	Squill	<i>Urginea maritima</i> bulbs	Anti-arthritis, bronchial, expectorant	Symptoms same as digitalis toxicity	35
21	St. John's Wort	<i>Hypericum perforatum</i> aerial parts	Anti-depressant, mood stabilizer	Highly potent cytochrome P450 enzyme inducer which affects drug metabolism, decreases blood concentration. Also causes hepatotoxicity and nephrotoxicity in pregnancy and lactation	34, 35

**Table 2**  
**List of some common herbs involved in drug interaction (herb- drug interaction)**

S. NO	Plant Name	Drug	Results of interaction	Comment	References
1	<i>Areca catechu</i> (Betel nut)	Flupenthixol and Procyclidine	Rigidity, bradykinesia jaw tremor	Betal nut has cholinergic activity due to the presence of an alkaloid arecoline	48, 49
		Fluphenazine	Tremor, stiffness, akathisia		
		Prednisone and salbutamal	Inadequate control of asthma		
2	<i>Peumus boldus</i> (Boldo) (in combination with <i>Trigonella</i> species)	Warfarin	Increased INR	<i>P. boldus</i> constituents have anti-platelet activity.	50
3	<i>Capsicum annuum</i> (Capsicum)	ACE inhibitor	Increased risk of cough	Capsaicin depeletes substance p.	48
		Theophylline	Increased absorption and bioavailability		
4	<i>Matricaria chamomilla</i> (Chamomile)	Warfarin	High INR (7.9), Major bleeding.	Coumarin Constituent of herb resulting in supra therapeutic anti-coagulation.	50
5	<i>Salvia miltorrhiza</i> (Danshen)	Warfarin	Increased INR, prolonged PT/PTT	Danshen decreases the half life period of warfarin.	48
6	<i>Angelica sinensis</i> (Dong quai)	Warfarin	Increased INR and widespread bruising	Dong quai contains couramin derivatives; danshen decreases half life period of warfarin	48,
7	<i>Allium sativum</i> (Garlic)	Warfarin	Increased INR	Garlic has anti-platelet activity.	48, 49
		Saquinavir	Induction of CYP3A4 enzymes.		
8	<i>Zingiber officinale</i> (Ginger)	Phenprocoumon	Decreased anti-coagulant effect	Ginger can inhibit thromboxane synthetase and/or decreases platelet aggregation	49
9	<i>Ginkgo biloba</i> (Ginkgo)	Aspirin	Spontaneous hypHEMA	Ginkgo has anti-platelet activity	48, 50
		Ibuprofen	Fatal intracerebral hemorrhage		
		Nifedipine	Increase in mean plasma level of Nifedipine		

		Tradodone	Seizures	Ginkgo may have GABA-ergic activity	
		Valproic acid	Seizures	Contaminants of leaf/seed that may contain neurotoxins	
10	<i>Panax quinquefolius</i> (Ginseng, American)	Warfarin	Decreased INR	In rats, concomitantly administered ginseng had no significant effect on the Pharmacokinetics or Pharmacodynamics of warfarin.	48
11	<i>Panax ginseng</i> (Ginseng, Asian)	Phenelzine	Headache, sleeplessness and tremor, mania	Patient with mania also ingested bee pollen, and had previously had unipolar depression.	48
12	<i>Eleutherococcus senticosus</i> (Ginseng, Siberian)	Digoxin	elevation of Digoxin concentrations	Herb probably interferred with digoxin assay	48
13	<i>Camellia sinensis</i> (Green tea)	Warfarin	Thickning of blood, Decline in INR from 2-3 to 1.31	Green tea has antagonistic effect due to the presence of vitamin K	50
14	<i>Piper methysticum</i> (Kava)	Alprazolam	Semicomatose state	Additive CNS depressant effect	49
		Levodopa	Reduced efficacy of levodopa	Kava possesses dopaminergic antagonistic Properties	
15	<i>Lycium barbarum</i> (Lycium)	Warfarin	Induction of CYP2C9 by Lycium	-	49
16	<i>Morinda citrifolia</i> (Noni juice)	Warfarin	Decline in INR	Noni juice contains vitamin K	
17	<i>Carica papaya</i> (Papaya)	Warfarin	Increased INR		48
18	<i>Mentha piperata</i> (Peppermint oil)	Nifedipine	Increases oral bioavalibility		49
19	<i>Plantigo</i> species (Psyllium)	Carbamzepine		Psyllium decreases absorption.	49
		Lithium	Decreased plasma lithium concentration	Hydrophilic Psyllium may prevent lithium from ionining.	
20	<i>Glycine max</i> (Soya)	Warfarin	Decreased anticoagulant effect	-	50
21	<i>Pausinystalia yohimbe</i> (Yohimbine)	Tricyclic antidepressants	Hypertension	Yohimbine alone can cause hypertension, but lower doses cause hypertension when combined with tricyclic antidepressants. Effect is stronger in hypertensive than normotensive individuals	48
22	<i>Tamarindus indica</i> (Tamarind)	Aspirin	Increased bioavailability of aspirin	Tamarind is used as a food and a medicine.	48
23	<i>Momordica charantia</i> (Karela)	Chlorpropamide	Less glycosuria	Karela decreases glucose concentrations in blood	48
24	<i>Hypericum perforatum</i> (St.John's Wort)	Cyclosporine	Decreased AUC	Induction of CYP3A4 and modulation of P-glycoprotein	48, 50, 51
		Digoxin	Reduction in serum digoxin level by 18 to 25%	Modulation of P-glycoprotein.	
		General anesthetic agents (fentanyl, propofol, sevoflurane)	Excessive sedation, delayed emergence from anaesthesia	Modulation of P-glycoprotein.	
		Indinavir	A 57% reduction of Indinavir area under-the-curve (AUC)	Induction of CYP3A4	
		Nefazodone	Mild serotonin syndrome	Induction of serotonin syndrome	

Oral contraceptives	Breakthrough bleeding	Induction of CYP3A4 and modulation of P-glycoprotein
Paroxetine	Lethargy, incoherence	Induction of serotonin syndrome
Phenprocoumon	Decreased AUC	Decreased bioavailability
Sertraline	Mild serotonin syndrome	Induction of serotonin syndrome
Simvastatin	Decreased plasma digoxin concentration	Induction of CYP3A4 and P-glycoprotein
Tacrolimus	Lower blood levels of drug	Induction of CYP3A4
Theophylline	Decreased theophylline concentration	Induction of CYP1A2 (only in female subjects)
Trazodone	Mild serotonin syndrome	Induction of serotonin syndrome
Verapamil	Decreased bioavailability of verapamil	Induction of intestinal CYP3A4
Warfarin	Decrease in INR	Induction of CYP2C9

**ACE** (angiotensin-converting enzyme); **INR** (international normalised ratio); **PT**= prothrombin time; **AUC** (area under the concentration/time curve).

## CONCLUSION

Medicinal plants are used by man as medicine science the time immemorial. These have a promising potential and are being increasingly used throughout world as home remedies and as raw material for the pharmaceutical industry. They represent a substantial proportion of the global drug market. Despite the benefits derived from medicinal plants, some of them have some unpleasant side effects which may be related to overdoses, toxic principles, or other factors. Thus, if plants have a therapeutic effect, they are also likely to have side effects, depending on many factors. Certain herbs have become popular over the years, but the general public, and even medical practitioners still

have a poor understanding of safe and effective use of herbal medicine. Various facts and confirmations are emerging on the dangers of indiscriminate use of some of these herbs. These can affect the intact band of organ systems, with some plants having several toxic principles that affect different systems. Thus, medicinal plants must be used with great caution, as their use could be associated with adverse reactions. Scientific evidence of the safety of herbal preparation will help to harness the therapeutic potentials of medicinal plants for further drug development in the future. Medicinal plants as well as the herbal medicines obtained from them thus require an intense inspection in order to recognize their risks, to give them an authorized status, to assess their efficacy and to establish their safety.

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