Chapter 9

Toxic Effects as a Result of Herbal Medicine Intake

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Additional information is available at the end of the chapter

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Abstract

Concurrent use of herbs with therapeutic drugs increases the potential of herb-drug interactions. The clinical importance of herb-drug interactions is associated with the particular herb, drug, and patient profile. Herbs are potentially potent as they affect body functions. The use herbal medicine and supplements can be risky as they are not subject to review by the FDA. In this chapter, we make an attempt to discuss the possible reasons for toxic effects, types of toxicities, some reported cases of toxicities involving the use of herbal medicine alone, and some herb-drug interactions. In addition to this, possible ways to reduce toxic effects of herbal medicines have also been discussed.

Keywords: herbal medicine, toxicity, reported cases, herb-drug interaction

1. Introduction

Herbal medicines are advertised to be free from side effects, which is a myth. A large number of people still rely on herbal medicines, and some people take herbal medicines along with routine allopathic medicines especially in cases of diabetes, hypertension, thyroid disease, etc., where the patient is on long-term or lifelong treatment. Many commercial websites are available on Internet, which insist that herbal medicines have no side effects. In underdeveloped and developing countries, there are no specific laws for herbal practitioners and companies marketing herbal products. People are attracted by such companies and start using herbal medicines pertaining to be free from side effects. In this chapter, we will discuss about possible toxicities of some herbal medicines and their remedies.

2. Possible reasons for toxic effects of herbal medicines

2.1. Self-treatment

Herbal medicines are easily available in market and can be purchased without prescription. These products are advertised on media as a miracle treatment without any side effects to attract people that are fed up with side effects or lost hope for being cured. The patients who like to play safe game are attracted in a manner that they are allowed to continue their regular medicines along with herbal treatment. Even persons caring about their health start herbal treatment to remain healthy proving the proverb "Prevention is better than cure." As a result, a large number of people are attracted towards herbal medicines and they start self-treatment [1].

2.2. Unqualified practitioners

In a large part of the world, unqualified practitioners are prescribing alternative therapies to patients of various diseases, apart from some countries where laws and regulations for herbal practitioners exist and implemented. Medical practitioners are provided vast knowledge about human body, drugs, mechanism of action, pharmacology, case studies, and then allowed to practice. Nowadays, Alternative Medicine Degree Course is available in certain universities with highly qualified and experienced faculty, which is a good source of herbal practitioners, but still 50% of herbal practitioners in the world are unqualified who acquire this profession after their forefathers such as a son of a farmer becomes a farmer, or after reading some books about herbal medicine, conducting 6-month online course about herbal medicine, etc., and start practicing. In underdeveloped countries, people are attracted towards these quacks due to economic reasons and start taking herbal medicine. These unqualified practitioners themselves are not aware of toxic effects of herbal medicines, and if the patient complains, they cannot rectify their mistake.

2.3. Sub-standard product

There are many sub-standard herbal products available in the market. The reason is that these products are not tested accordingly for quality before marketing. Some contain less amount of active ingredient and some do not contain active ingredient at all as a result of incorrect identification of plant by the collector, using adulterant instead of original plant or due to improper storage of plant material, and it loses its efficacy. Sometimes the herbal products contain material not defined on label such as non-herb material, minerals, heavy metals, and addition of particular pharmaceutical product. Occasionally they may contain toxins and pesticides, which is much more dangerous and one of the major reasons of toxic effects after herbal medicine intake [2].

2.4. Improper intake

Allopathic medicines are marketed after extensive testing and trials, and their dose is fixed according to age and weight of the patient. All possible adverse effects are listed in leaflet. But

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no such procedures are followed in case of herbal medicines. Some of herbal medicines are considered as dietary supplements, and proper dose is not mentioned. No measure cup or spoon provided with the medicine as in case of allopathic syrups. Usually, same dose is applied for persons of different age and weight. Companies selling these products misguide people and claim their product totally free from adverse effects. Even there is no period mentioned, some people continue for months or years, which in long term can be harmful for human health [3].

3. Types of toxicities

3.1. Nephrotoxicity

Drug or toxin causing kidney damage upon exposure to a certain level and the kidneys are unable to pass excess urine, and waste product is the condition termed as nephrotoxicity. In this condition, there is an elevation in blood electrolytes such as potassium and magnesium. This condition starts temporarily but, if not detected earlier, could be severe. Nephrotoxicity can be detected by two simple tests of blood urea nitrogen (BUN) and creatinine levels in blood together termed as kidney function tests. Normal range values of BUN and creatinine are 10–25 mg/dl and 0.7–1.4 mg/dl, respectively. These values may increase due to following factors:

a. Dehydration.

b. Blocked blood flow to or from kidney may be due to tumor, stone, or irregular heart rhythms.

c. Nephritis or urinary infection.

d. After effect of disease such as congestive heart failure, diabetic neuropathy, and enlarged prostate gland in man.

e. Gastrointestinal bleeding.

f. Low blood pressure for larger period of time.

g. Increased protein in diet.

h. Radiology procedures in which radiocontrast dye is injected intravenously for a clear picture.

i. Drug toxicity with some chemotherapeutic (carboplatin, carmustine, cisplatin, methotrexate, and mitomycin) and biologic therapeutic agents (interleukin-2 and interferon-alfa), antibiotics (amphotericin B, gentamicin, and vancomycin), NASID's (ibuprofen), diuretics (furosemide), and ACE inhibitors (captopril, benazepril, and enalapril).

j. Nephrotoxicity after herbal medicine intake.

Reason of nephrotoxicity after herbal medicine intake may be addition of toxins during careless preparation, addition of adulterants, heavy metals, and some pharmaceutical products intentionally to reduce cost or increase efficacy [4].

Herbs such as *Tripterygium wilfordii* Hook (thunder god vine) contain diterpenoid epoxide, which induces apoptosis causing kidney damage. *Averrhoa carambola* L. (star fruit) contains oxalate in high quantity, which can cause acute nephropathy. *Guaiacum officinale* L. (rough bark) and *Arctostaphylos uva-ursi* (cranberry) increase stone formation. *Aristolochia fangchi* causes well-known aristolochic acid nephropathy. *Callilepis laureola* DC (Impila) inhibits mitochondrial ATP synthesis. *Uncaria tomentosa* wild DC (Peruvian's Cat Claw) causes acute allergic interstitial nephritis. Studies are being conducted on *Salix alba* L. (willow bark) analgesic nephropathy induction. *Ephedra sinica* Stapf (Chinese ephedra) affects renin-angiotensin-aldosterone system. *Glycyrrhiza glabra* L. (Licorice) and *Harpagophytum procumbens* DC (devil's claw) inhibit renal transport processes [5].

3.2. Hepatotoxicity

Hepatotoxicity, termed after two Greek words *Hepar* and *Toxicon* meaning liver and poison, respectively, may be defined as liver damage due to chemical, drug, herb, or dietary supplement. The damage can be noticed by stomach pain, nausea, vomiting, change in urine and stool color, jaundice, rash, frequent tiredness, weakness, fatigue, and fever. Laboratory tests include some liver function tests, which are conducted on blood samples for the detection of hepatotoxicity. These tests are comprised of alanine transaminase test (normal range 7–55 U/l), aspartate transaminase test (normal range 8–48 U/l), alkaline phosphatase test (normal range 45–115 U/l), albumin test (normal range 3.5–5.0 g/dl), and bilirubin test (normal range 0.1–1.2 mg/dl). Increased levels of ALT, AST, ALP and bilirubin and decreased level of albumin indicate liver damage. In pregnancy, ALP levels are also increased.

Causes of liver damage are both by hepatocellular and by extracellular mechanisms. Some of these mechanisms are mentioned below:

Hepatocyte disruption: When drug binds to intracellular proteins covalently, it may lower ATP level causing actin disruption, which in turn causes bleb and rupture of membrane.

Transport protein disruption: Drugs affecting transport proteins at canalicular membrane may disturb flow of bile juice. This interruption in certain processes and transport prevents bilirubin excretion leading to cholestasis.

T-cell activation: When a drug binds covalently to P-450 enzyme, it acts as immunogen and activates T cells and cytokines resulting in complicated immune response.

Hepatocyte apoptosis: Sometimes apoptotic pathway is activated due to tumor necrosis and α-receptor of F triggering flow of intercellular caspases, which leads to programmed cell death.

Disruption of mitochondria: Some drugs suppress mitochondrial function by effecting on β-oxidation energy production and synthesis of nicotine amide adenine dinucleotide. A second effect is on flavin dinucleotide inhibiting ATP production.

Injury of bile duct: Some toxic metabolites from liver can injure epithelium of bile duct.

Drug toxicity mechanisms: Drugs are major cause of hepatotoxicity. Almost nine hundred drugs, toxins, and herbs are reported for hepatotoxicity. There are two kinds of drug reactions, first

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is reaction directly affecting the liver termed as intrinsic drug reactions, and other is reaction mediating to immune response termed as idiosyncratic drug reactions. In the first category, drug itself or its metabolite produces a dose-related injury, for example, paracetamol and carbon tetrachloride. In second category, hypersensitivity reactions, for example, phenytoin reaction, cause fever, rash, eosinophilia for a short period of time and immunoallergic or metabolic idiosyncratic reaction due to indirect drug reaction. The second type of reactions the response rate is variable, for example, halothane.

Drug interaction mechanisms: Some drugs when taken simultaneously react together and cause liver damage. For example, tylenol can be hepatotoxic in combination with INH, isotamine, laniazid, and nydrazid [6].

Discussing about hepatotoxicity caused by herbal medicine intake, mostly the incident rates are still to be reported. The severity of toxicity is widely variable between mild hepatitis to acute hepatic failure. The scoring system for allopathic medicines can be assessed but is not suitable for herbal medicines and needs validation. Many Ayurvedic and Chinese herbal medicines are reported to cause hepatotoxicity. Major hepatotoxic herbs are *Cimicifuga racemosa* (black cohosh), *Larrea tridentata* (chaparral), *Teucrium chamaedrys* (germander), *Scutellaria lateriflora* (American skullcap), and *Scutellaria baicalensis* (Chinese skullcap), etc.[7].

3.3. Cardiotoxicity

Cardiotoxicity is a term used for damage to heart or altering heart functions. It is a state in which there is alteration in electrophysiological function of heart or cardiac muscle damage, which weakens the heart causing inefficient pumping and circulation of blood. This can be detected by symptoms such as dry, non-productive cough, inflammation of ankles, hand, feet, and neck veins; irregular heartbeat; tachycardia; cardiomegaly; weakness; vertigo, etc.

Some common tests for finding cardiotoxicity include physical examination of heart through stethoscope to check the sounds of heartbeat, chest X-ray to check the size of the heart, echocardiogram imaging test using ultrasound, electrocardiogram (ECG) to measure the electrical activity of heart, multi-gated acquisition scan (MUGA) by injecting a radiotracer into veins to check pumping and function of blood vessels to heart, and troponin blood tests. Troponins are proteins of heart muscles released by dying heart cells into blood stream.

These tests may show results positive for cardiotoxicity due to a number of cardiac events including changes in blood pressure, thrombosis, arrhythmias, inflammation of myocardium, and pericardium leading to cardiac arrest or failure. Cardiotoxic agents include chemotherapeutic drugs of anthracycline class, alkylating agents such as cyclophosphamide, cisplatin, chlormethine, mitomycin, etc. Some other agents such as paclitaxel, etoposide, fluorouracil, asparaginase, tretinoin, pentostatin may cause cardiotoxicity. This may be increased due to cumulative dose, rate, and schedule of administration, history of preexisting cardiovascular problems, and disturbed balance of cardiac electrolytes [8].

Herbal medicines having direct effect on heart include medicine prepared from plants such as *Digitalis purpurea* (digitalis), *Catharanthus roseus* (vinca), *Aconitum napellus* (monk's hood),

Atropa belladonna (deadly nightshade), *Ephedra distachya* (sea grape), *Mandragora officinarum* (mandrake), *Glycyrrhiza glabra* (licorice), etc. [9].

3.4. Neurotoxicity

Neurotoxicity is a term used for a state in which there is a physical brain damage due to exposure to neurotoxin, a substance that disrupts or kills neurons, and in turn alters the activity of nervous system. Signs and symptoms of this type of toxicity are anxiety, depression, limb weakness and numbness, impaired vision, headache, sexual dysfunction and behavioral changes. The reasons may be chemotherapy, radiation therapy, drug abuse, organ transplants, exposure to heavy metals, some food additives, pesticides, cosmetics, cleaning solvents and naturally occurring substances.

The nervous system comprises of central nervous system (CNS) and peripheral nervous system (PNS). CNS consists of brain and spinal cord, and cerebellum is a part of brain primarily affected by neurotoxic substances. Cerebellum is responsible for processing information to conduct muscle activities and maintain body posture. The damaged cerebellum produces altered reflexes, unsteady walk, loss of body control, and confusion. PNS is a network of cranial and spinal nerves emerging from CNS to all parts of body. The system consists of myelinated neurons with layers of Schwann cells, which act as electrical insulator. By the damage of these nerves, the electrical signals are interrupted. Another part of PNS is autonomic nervous system (ANS), which functions without conscious effort. The movements such as cardiovascular, respiratory, gastrointestinal, and endocrine systems are under the control of this system. The toxicity of this system is most dangerous and it results in loss of activities function, retention of urine and stool, impotence, paralysis and impotence [10].

Some common plants used as herbal medicines have potential neurotoxic effects. Among them are *Papaver somniferum* (opium), *Catharanthus roseus* (vinca), *Datura stramonium* (thorn apple), *Atropa belladonna* (deadly nightshade), *Hyoscyamus niger* (henbane), *Cannabis indica* (marijuana), *Conium maculatum* (hemlock), *Coscinium fenestratum* (yellow vine) [11], and *Brugmansia* species (angel's trumpet) [12].

3.5. Skin toxicity

Cutaneous toxicity is a term used for an evident adverse effect such as skin irritation, inflammation, or rashes of epidermal growth factor receptor caused by exposure to a plant, chemical, or environmental factor.

Skin is the largest body organ and a protective barrier comprising of a layer of dead cells and several layers of living cells. When an irritating substance reaches these living cells, these sensitive cells respond by inflammation or dermatitis. Inflammation has four parts, which include redness, pain, heat, and swelling. The skin toxicity is easiest to detect as the reaction is immediately observed.

The most common test for detecting cutaneous toxicity is patch test. In this, the skin is exposed to a small amount of diluted substance in patches and observing the reaction. The most

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common source of skin toxicity is food and cosmetics, and others are medicated lotions, balms, creams, inhalers and essential oils. A variety of herbal material is available in all of the above-mentioned cosmetics and medicated products. Types of skin sensitization reactions include the following:

Primary irritant dermatitis: It is a direct irritation of skin with symptoms such as redness, itching, pain, blusters, peeling, or open wounds. Primary irritant dermatitis may be caused by plants such as *Cannabis sativa* (weed oil), *Dieffenbachia amoena* (dumb canes), *Asclepias syriaca* (milk weed), *Narcissus pseudonarcissus* (daffodils), *Digitalis purpurea* (foxglove), *Ricinus communis* (castor bean), *Tulipa gesneriana* (tulip bulb), *Primula veris* (cowslip), *Hevea brasiliensis* (rubber tree), *Ficus carica* (fig tree sap), *Ranunculus acris* (butter cup), etc. Common foods such as *Pastinaca sativa* (parsnip), *Solanum lycopersicum* (tomatoes), *Daucus carota* (carrot), *Cucumis sativus* (cucumber), *Brassica rapa* (turnip), *Petroselinum crispum* (parsley), *Apium graveolens* (celery) and *Agaricus bisporus* (mushrooms) also can cause primary irritant dermatitis.

Allergic contact dermatitis: It is a true allergic response and is varied from individual to individual. *Toxicodendron diversilobum* (poison oak) and *Toxicodendron rydbergii* (poison ivy) are the most common plants producing allergic contact dermatitis. Others include *Hedera helix* (English ivy), *Toxicodendron vernix* (poison sumac), *Dendranthema grandiflorum* (chrysanthemum), *Narcissus pseudonarcissus* (daffodils), *Tulipa gesneriana* (tulip bulb), *Marchantiophyta species* (liverwort), *Primula vulgaris* (prime rose), *Flavoparmelia caperata* (lichens), *Pinus sabiniana* (pine), *Cedrus deodara* (cedar), *Anacardium occidentale* (cashew), *Apium graveolens* (celery), *Allium cepa* (onions), and *Allium sativum* (garlic).

Photosensitization dermatitis: It is cutaneous toxic response caused by exposure to sunlight when a photosensitizer (compound sensitive to sunlight) is present in body and can be detected by sunburn-like reactions in non-pigmented areas. Plants such as *Tetradymia species* (horse brushes), *Hypericum species* (St John's wort), *Tribulus terrestris* (goats head), *Agave lechuguilla* (lechuguilla), *Bassia scoparia* (kochia), and *Lantana camara* (lantana) cause photosensitization dermatitis.

There is another type of phototoxic photosensitization caused by contact of some plants. When a photoactive chemical produced by plants comes in skin contact, absorbed and activated by sunlight, this type of reaction occurs. The intensity varies depending upon time and amount of exposure. Plants such as *Ficus carica* (figs), *Anethum graveolens* (dill), *Brassica alba* (mustard), *Petroselinum crispum* (parsley), *Citrus aurantifolia* (lime), *Daucus carota* (carrots), *Ranunculus acris* (butter cup), *Hypericum perforatum* (Klamath weed), and *Apium graveolens* (celery) with pink rot are reported to produce contact photosensitization [13].

4. Reported cases of toxicity using herbal medicine solely

Although a large number of herbal toxicity cases are not reported, still there are many reported cases. Some of such cases are listed in **Table 1**.

No.	Herb	Toxicity reported	Indication	Reference
1.	*Stephaniae sinica* *Vernacular* name: Anshu Ling J*in Bu Huan*	Acute hepatitis	Insomnia	[14]
2.	*Larrea tridentata* *Vernacular* name: Chaparral	Hepatic failure Hepatorenal syndrome encephalopathy	Liver detoxification	[14]
3.	*Ephedra sinica* *Vernacular* name: Ma Huang	Tachycardia, difficulty in respiration, insomnia	Nutritional supplement	[15]
4.	*Scutellaria baicalensis* *Vernacular* name: Chinese skull cup; Huang Qin	Acute drug-induced liver injury	Arthritis	[16]
5.	*Panax ginseng* *Vernacular* name: Renshen Yangrong Tang	Chronic renal failure	Anorexia and hypoproteinemia	[17]
6.	*Vaccinium macrocarpon* Common name: Cranberry	Nephrolithiasis	Dietary supplement	[18]
7.	*Salix daphnoides* *Vernacular* name: Willow bark	Renal dysfunction	Analgesic anti-rheumatic	[19]
8.	*Pausinystalia johimbe* *Vernacular* name: johimbe	Progressive renal failure and proteinuria	Male impotence	[20]
9.	*Aconitum napellus* *Vernacular* name: Aconite, monk's hood	Ventricular arrhythmia	Pain	[21]
10.	*Tripterygium wilfordii* Hook F *Vernacular* name: Thunder god vine	Renal and cardiotoxicity	Arthritis	[22]
11.	*Cimicifuga racemosa* *Vernacular* name: Black cohosh	Acute hepatitis	Menopausal symptoms	[23]
12.	*Piper methysticum* *Vernacular* name: Kava kava	Acute liver failure	Tranquillizer	[24]
13.	*Valeriana officinalis Vernacular* name: Valerian	Liver toxicity, neurotoxicity	Sedative	[25]

Table 1. Some of the documented herbal toxicity cases.

5. Herb-drug interactions

Natural products are a mixture of phyto-constituents unlike the conventional drugs. Usually, the quantity and quality of the bioactive substance from the herbs vary depending on the part of the plant used, environmental factors, method of collection and storage conditions. The use of herbs as medicine is getting popular; hence, there is a need to address and review the interaction between the herb and the drug. Certain herbal supplements may cause dangerous side effects when taken with prescription drugs. Furthermore, the complex nature of a natural

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product adds to the complexity of determination of herb-drug interactions. There are no standards for herbal products prescribed/regulated by the FDA [26]. Currently, there are limited reports of adverse herb-drug reactions. The available reports are either individual case reports giving the details of the specific case studied or the suspected interaction or clinical trials, in which the drugs and herbs are combined and are closely monitored. Data concerning the drug-herb interaction are usually unavailable as there is lack of information about nature of the herbal product and their complex reactions. Sometimes the literature available can be confusing due to lack of clarity or even contradictory. This is due to the way these adverse interactions are reported. The data received by experimentation and pharmacodynamics studies may give indications of potential interactions.

Herb-drug interactions can be either pharmacodynamic or pharmacokinetic in nature. When the constituents have synergistic or antagonist activity in relation to the drug, it is termed as pharmacodynamics, which results in concentration-dependent activity, while alteration in ADME of the drug by herbal products results in pharmacokinetic interactions [27].

The Med Watch system is used by the FDA to report adverse reactions for conventional drugs as well as dietary supplements. The complex nature of the herbs creates complications while determining the herb-drug interactions.

A method for the evaluation of herb-drug interactions has been developed for determining the reliability of the case reports on drug-herb interactions. A 10-point scale has been used for detecting the probability of drug-herb interaction. This method consists of ten items and each item being allotted 01 point. The interactions are interpreted as 8–10 points' likely, 4–7 points possible, or 0–3 points unevaluable. A total of 320,860 adverse events were reported to the system in 2002 [28].

The following are the evaluating parameters for determining the probability of herb-drug interactions (1 point is allotted per item) [29] Some herb-drug interactions are listed in (**Table 2**):

a. Adequate patient history.

b. Concurrent diseases, conditions, or other medications associated with adverse event.

c. Concomitant medications are documented.

d. Description of interactors is adequate.

e. Obvious alternate explanations have been excluded.

f. Chronology is complete.

g. Time sequence of drug administration to adverse event is reasonable.

h. Adverse event is adequately described.

i. Event ceases upon stopping drug.

j. Event recurs upon re-challenge.

No.	Herb	Allopathic drug	Indications	Model	Reference
1.	*Hypericum perforatum*	Alprazolam	A twofold decrease in the AUC for alprazolam plasma concentration vs time and a twofold increase in alprazolam clearance. Shortening of alprazolam. elimination half-life.	Clinical study	[30]
2.	*Catha edulis*	Ampicillin	Significantly reduced the bioavailability of orally. administered ampicillin.	Clinical study	[31]
3.	*Piper Methysticum*	Caffeine	Myoglobinuria, rhabdomyolysis, severe muscle pain, dark urine, and elevated creatine kinase.	Case study	[32]
4.	*Ginkgo biloba*	Sodium valproate	3–4 seizures within 2 weeks.	Case study	[33]
5.	*Panax ginseng*	Phenelzine	Headache, insomnia, tremulousness.	Case study	[34]
6.	*Zingiber officinalis*	Metronidazole	Absorption and plasma half-life were significantly increased, significantly decreased the elimination rate constant and clearance of metronidazole.	Animal study	[35]
7.	*Cimicifuga racemosa*	Atorvastatin	It may potently inhibit human cytochrome (CYP) 3A4, which may result in increase of atorvastatin levels, causing an elevation of liver enzymes.	Case study	[36]
8.	*Scutellariae radix*	Losartan	The metabolic activities of losartan were decreased to 71%.	Clinical study	[37]
9.	*Camellia sinensis*	Folic acid	Results in decreased bioavailability of folic acid.	Clinical studies	[38]
10.	*Allium sativum*	Saquinavir	Reduced plasma. saquinavir concentration.	Clinical study	[39]
11.	*Glycyrrhiza glabra*	Anti-hypertensives	Patients with essential HT are more sensitive to the inhibition of beta-HSD by liquorice. Symptoms were more in women than men.	Clinical study	[40]
12.	*Papain*	Warfarin	Skin, urinary, GIT. bleeding.	Case study	[41]
13.	*Betula alba*	Warfarin	GI bleeding and a doubled prothrombin time.	Case study	[42]
14.	*Evolvulus alsinoides*	Phenytoin	Loss of seizure control.	Case study	[43]
15.	*Banisteriopsis caapi*	Fluoxetine	Tremors, shivering, sweating, severe nausea, and vomiting.	Case study	[44]

Table 2. Some of the documented herb-drug interactions.

Although one or two reports may not guarantee an absolute contraindication to combinations of herbal and prescription therapies, certain precautions have to be taken while collecting the medical history of patients during counseling sessions so as to obtain this information regarding the use of drugs and herbs in combination by the patient. Herbal drugs should be prescribed with caution in case of elderly patients, pregnant women, patients suffering from

liver and kidney impairment and patients who have undergone organ transplant. The healthcare professionals can monitor the use of herbal medicines, especially when the patients are taking them along with the prescribed medicine. The patient has to be counseled with enough information about signs and symptoms of herb-drug interactions such that they are able to recognize any adverse reaction whenever it occurs. The patient should be advised to have a gap of 1–2 h or several hours between the intake of herb and drug.

Evidence-based research should be encouraged to document the data regarding the positive and/or negative effects of the use of herb and drugs in combination. Furthermore, it would be of help to if an internationally accessible database documenting the herb-drug interaction would be available.

6. Possible ways to reduce toxic effects of herbal medicines

Natural substances are the best healers, but according to Paracelsus (1493–1541), all substances are poison and that's only the correct dose, which make them a remedy. There are some rules mentioned in the literature, which can be summarized as follows:

a. All herbal medicines should not be considered safe unless prescribed by registered herbalist.

b. Label of herbal product must be checked for seal of regulatory authority and expiry date.

c. If consuming herbal medicine with allopathic medicines, then inform your doctor.

d. Avoid use of herbal products along with drugs having narrow therapeutic index such as warfarin, digoxin, cyclosporine, theophylline.

e. Avoid using herbal products containing heavy metals such as arsenic, lead, mercury.

f. If female user is pregnant or nursing mother, then caution taking herbal medicines such as black cohosh, chamomile, Dong Quai root, feverfew, ginger, kava kava, and St. John's wort.

g. Overuse of herbal medicine intake should be avoided and dosing instructions must be followed.

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