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GENERAL AWARENESS TO COMMON MEDICINAL HERBS, "THE NATURAL, DOESN'T MEANS SAFE" - A REVIEW

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ABSTRACT: The term "Naturals are the safer" is quite trendy, but the incomplete knowledge of the natural herbs interaction may result in several allergies and unwanted effects that may even take life and sometimes be critical to a life-threatening extent. The responsibility of the FDA is to ensure that the safety and efficacy of the drug consumed by humans and veterinary should be worthful and should cause no harm to their life. FDA also plays a vital role in the protection of public health by ensuring the effectiveness of the biological product and medical devices. Still, FDA does not show the same concern and guidelines for the efficacy and safety studies used for the common prescribed herbal drugs, dietary supplements, and marketing in the public domain. AS the favorability and likeliness of patients are inclining towards herbal remedies, there is increased production of such products. While manufacturing these products, the producers cannot submit the proof of safety and efficacy laid by the USFDA guidelines to the FDA before marketing. This is the major reason for the adverse drug effects and drug interactions associated with the herbal remedies; also, their effects are largely unknown in the public domain. This article summarizes the adverse drug event and side effects of various herbs and herbal medicines. Some herbs and herbal drugs are discussed in this article about their life-threatening side effects, excessive use, contraindications, drug interactions, etc.

INTRODUCTION: The term "Naturals are the safer" is quite trendy, but the incomplete knowledge of the natural herbs interaction may result in the number of allergies and unwanted effects. The medicinal herbs used in several natural products may interact with each other.

The naturopathy treatment in today's being well-being mark in divergence to the synthetic products and medicines that are regarded as unsafe to an individual and society. Herbs may be used to treat the primary condition or to reduce the side effects of conventional treatment¹. Herb, like chamomile, echinacea, aloe vera, garlic, etc., are reported to have a wide curing ability^{2, 5}.

It may interact with other herbs, fibers, excipients, bases, or other food materials in the products. FDA's role is to compile all the efficacy and safety documented proof for all the medical equipment and the drugs products which are to be consumed

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by humans and animals. They also have to ensure that our country's food supply, cosmetics and other products like radioactive are safe and cause less harm or may show no harmful effects. Still, these all precautions are concerning the drugs used in allopathy and not with regards to naturopathy⁶. But FDA Does not apply the equivalent efforts for safety profiling studies used for prescribed herbal drugs, dietary supplements. Herbal supplements are not under investigation studies and review or any clinical trials by the FDA authority. The use of such herbal treatments may be harmful and life-threatening. However, one should need to know that though the label may indicate "natural", these products may or may not be always safe and are being used by us without consulting our

physician and seeking their opinion and knowing about their side effects. Even though herbal supplements are made from plants and herbs the active constituents from that are Very potent, which might cause severe effects or can damage the human system when they interact with the other medicines or food which is part of our daily diet. When these potent ingredients are combined or interact with, there may be a chance of synergistic or antagonistic activity, which may harm our body deeply. The majority of the people use herbs in an uncontrolled and traditional manner. There have been several cases of injury and even death resulting from misuse, contamination, and/or adulteration of medicinal herbs^{7,8}.

Commonly Used Medicinal Herbs In Herbal Drugs:

TABLE 1: COMMONLY USED HERBAL DRUGS WITH THEIR USE AND ADVERSE SIDE EFFECT

Scientific Names	Common Names	Family	Active Constituents	Uses	Serious ADR	References
<i>Valeriana officinalis</i>	Garden heliotrope, common valerian	<i>Caprifoliaceae</i>	Valerenic acid, valerane, beta-sitosterol, ursolic acid, caryophyllene acid,	Insomnia promote relaxation	Delirium	¹³
<i>Ginkgo biloba</i>	Maidenhar tree	<i>Ginkgoaceae</i>	Myricetin, kaempferol, isorhamnetin, quercetin	Blood disorders, memory problems, cardiovascular function, eye health.	Bleeding	¹⁴
<i>Hypericum perforatum</i>	St John's wort	<i>Hypericaceae</i>	Hyperforin, hypericin, adhyperforin	Nervousness, tiredness, poor appetite, trouble sleeping	Photosensitivity	¹⁴
<i>Ephedra sinica</i>	Joint-pine, jointfir, ma-huang	<i>Ephedraceae</i>	Ephedrine, methylephedrine, cathine	Allergies, hay fever, bronchitis	Myocardial infarction, kidney stones	¹⁴
<i>Piper methysticum</i>	Kava	<i>Piperaceae</i>	Kavain, methysticin, dihydromethysticin	Respiratory tract infections, musculoskeletal pain, epilepsy	Exacerbation of Parkinson's disease	¹⁴
<i>Panax ginseng</i>	Ginseng, Korean ginseng	<i>Araliaceae</i>	Ginsenosides, Panaxosides, Demerol.	Boost energy, lower blood sugar, manage sexual dysfunction in men	Cardiac shock	¹⁵
<i>Aconitum carmichaelii</i>	Chinese aconite, Carmichael's monkshood	<i>Ranunculaceae</i>	Aconitine, mesaconitine, hypaconitine	Treat fear, acute sudden fever, influenza, tinting	Cardiac and neurological toxicity	¹⁵
<i>Datura stramonium</i>	Thorn-apple, daturas, devil's weed	<i>Solanaceae</i>	Scopolamine, hyoscyamine, and atropine	Hydrophobia, epilepsy, breast, smallpox, mumps, and leprosy	Dilated pupils, urinary retention	¹⁵
<i>Podophyllum emodi</i>	Himalayan Mayapple,	<i>Berberidaceae</i>	Podophyllin, podophyllotoxin	Hepatic stimulant, purgative,	Neuropathy and encephalopathy	¹⁵

<i>Salvia miltiorrhiza</i>	Devil's apple, Duck's foot Red sage, danshen	<i>Lamiaceae</i>	podophyllic acid, and picropodophyllin Salvianolic acid dihydrotanshinone, tanshinone I, tanshinone IIA and Tanshinone IIA	alterative, anthelmintic, antirheumatic Cirrhosis, venous thromboembolism,	Excessive bleeding	15
<i>Aristolochia fangchi</i>	Birthwort, pip evine	<i>Aristolochiaceae</i>	Aristolochic acids I, II and IIIa, allantoin, aristolactam, β -sitosterol, and magnoflorine	Eczema, increase sexual desire, intestinal pain, gallbladder pain	Urothelial carcinoma	15
<i>Angelica sinensis</i>	Dong quai,	<i>Apiaceae</i>	Polysaccharides, ligustilide, ferulate, butylphthalide, Phytosterols, cnidilide, isoenidilide, p-cymene	Promote blood circulation, menstrual disorders, menstrual cramps	Breast cancer	12
<i>Larrea tridentate</i>	Creosote bush, greasewood	<i>Zygophyllaceae</i>	Nordihydroguaiaretic acid, apigenin, nordihydroguaiaretic acid	Arthritis, bowel cramps, urinary tract infections, and upper respiratory tract infections.	Toxic hepatitis	13
<i>Glycyrrhiza glabra L</i>	Liquorice, Kzyl Miya	<i>Fabaceae</i>	Glycyrrhizin, liquiritic acid, and glycyrrhetol	Skin inflammation and infection, Hepatitis-C, Sore throat	Fanconi syndrome	13
<i>Areca catechu</i>	Betel nut	<i>Arecaceae</i>	Arecoline, arecaine, guvacine, arecolidine.	Anthelmintic	Known carcinogen contributing to cancer of the mouth, pharynx, esophagus, and stomach	16

In India, from very ancient times, drugs of herbal origin have been used, which are evolved from systems of medicines such as Unani and Ayurveda⁹. The systems of medicines such as Ayurveda & Unani include approximately 700 species, Siddha & Amchi has near about 600 and³⁰. More than 8,000 herbal remedies are collected in Ayurveda. In Rigveda, 67 medicinal plants and Yajurveda has 81 species under their records, Atharvaveda has around 290 species, Charak Samhita and Sushrut Samhita have all together uses of 1100 and 1270 species respectively, in intensifying of traditional medicine and the use is unmovable being continued¹⁰. According to the studies for primary health care, herbal medicines are still the focused choice of near about 75-80% of the worldwide population, mainly in developing countries that use the traditional medicines. Most of the ceremonial drugs evolved from the natural

herbal plant sources: most of the effective or potent drugs were plant-originated, which include are Aspirin from willow bark, Digoxin from foxglove, quinine from cinchona bark, and Morphine from the opium poppy^{11, 12}. Some of the commonly used herbal drugs with their active constituents, and possible serious adverse drug reactions are discussed in **Table 1**.

RESULT AND DISCUSSION

Valnerian Officinalis: The species Valeriana belongs to the family Valerianaceae and consists of 250 various species. *Valeriana officinalis* L *Valeriana wallichii* DC and *Valeriana edulis* are of specific importance due to their herbal medicine used as a mild sedative. The most well-liked, epoxy iridoids, which are important amalgams, which are also known as valepotriates, their break down products, are in the form of ballerinas and the

nonvolatile terpenoids known as valerenic acid¹⁷. Women's use Valerian during Menopausal symptoms. Various more uses of these medicinal herbs are reported with Insufficient Evidence for Premenstrual disorders (PMS), restlessness, stress. These are also used to treat many disorders such as Attention-deficit hyperactivity disorder (ADHD), Convulsions, Epilepsy, Chronic fatigue syndrome (CFS), Headache, Menopausal symptoms with hot flashes, and Mild tremors, Muscle and joint pain, dyspepsia, and indigestion¹⁸.

There are many side effects related to the use of Valeriana. Still, the serious and major side effects Are observed in embryonic growth, which ultimately ends up showing physical and cognitive adaptation and which comes with the side effects of VPA treatment on young patients, which causes the increase in sleep duration and also cause the changes in the secretion levels of cholesterol, serum triglycerides and fast glucose. Still, these effects are slight as per studies. Dermatological repercussions of Valproic acid are related to stomatitis,¹⁹ other cases of cutaneous leukocytic vasculitis and the psoriasiform eruption were evidenced at the time of the study, these also show the Valproic acid-induced alopecia, which is caused due to the telogen shedding that starts appears within three months of the initiation of the treatment. Which ultimately induces transient alopecia and results in thinning of the hair, hair color changes, hair texture changes and rare rashes. Stevens-Johnson syndrome and toxic epidermal necrolysis²⁰ are VPA concerning side effects. VPA also encounters Effects on Fertility, Pregnancy and Fetus when used in pregnancy. VPA has great stability to induce Parkinsonian symptoms as they have direct neurological side effects. It also causes hepatotoxicity induced by VPA in children undergoing various treatments at the same time²¹.

Ginkgo biloba: *Ginkgo biloba* is a derivative of the leaves of the maidenhair tree and is a largely demanded herbal remedy species in the U.S. It is used for cognition, memory and they also show its effectiveness in treating cerebrovascular disease and peripheral vascular disease, most effective in treating sexual dysfunction, multiple sclerosis, and eye disorder²² i.e retinal disorders and deafness²³. They also show their good medicinal properties in treating Free radical scavenging, antiplatelet

actions, anti-inflammatory actions, and vasodilation effectively and also decreased blood viscosity which is the most important characteristic of ginkgo, and its constituent helps to improve vascular health. Ginkgo contains flavonoids and terpenoids.

Endorsement of 120 to 240 mg extract two to three times daily will be effective for cerebral insufficiency. Most of the common side effects are nausea, dyspepsia, headache, and allergic skin reactions. Induced spontaneous subdural hematomas, intracerebral hemorrhage, and hyphema are the most serious adverse effects, as well as warfarin and trazodone interactions, are studied²⁴. The evidence showed that the use of *Ginkgo biloba* extract causes spontaneous hemorrhages and also causes immediate bleeding from the iris into the anterior chamber of the eye when they are taken orally. *Ginkgo biloba* extract shows the antiplatelet effects even if used for the short term²⁵. There are a sufficient amount of toxin traces, which, when consumed, may result in convulsions and unconsciousness and may also cause life-threatening effects. There is also evidence of hemorrhage in the parietal lobe of the brain in the woman who had been stable for over a while on anticoagulant drugs such as warfarin and has initiated to consume the potent extract of Ginkgo for two months before the event. There is also evidence and study reports that show that consuming the extract of Ginkgo for over a chronic period may show Bilateral subdural hematoma, and protracted bleeding time was established which was eventually resolved by suspending the consumption of the extract²⁶. A neuraxial blockade causes an increased risk of epidural hematoma²⁷.

Hypericum Perforatum: *Hypericum perforatum*, also known as St. John's wort (SJW), which is the most abundant herbal preparation used widely, has been showing implicated in drug-drug interactions, which is the result of the persuaded countenance from cytochrome P450 CYP3A4 isoform. There are many pharmacological activities, which include CNS-related activity and Antiviral effects²⁸, which are supported by evidence for the traditional uses. The pharmacological activities are due to the attribution of flavonoid constituents²⁹ and the hypericin is also reported to be liable, which undergo the photosensitivity reactions. It also

shows the properties such as sedation and astringency used to treat excitability, neuralgia, fibrositis, menopausal neurosis, anxiety attacks, depression, and wound healing effects. With the effects, there are also many side effects related to St. John's wort which include dryness of mouth, vertigo, and confusion.

Few phototoxicity effects are manifested by utilization of St. John's wort includes erythematous lesions and itching. In a case study report, a 35-year-old woman was self-medicating herself with consuming the ground St. John's wort but after four weeks, she experienced developing stinging pain in the areas which was exposed to the sun. Her pain was worsened by other symptoms such as cold, minimal stimuli. But once is discounted the treatment of the extract she experienced symptom recovery over a couple of months. This was due to the effect of demyelination of cutaneous axons caused by photo-activated hypericin. Sensitivity to rays of sunlight followed by the assimilation of hypericin or hypericin which is also known as hypericium. Hypericin is the photo sensitizing agent which is present in St. John's wort; also St. John's wort is reported for delayed hypersensitivity or photodermatitis³⁰.

Ephedra Sinica: Ephedra, also known as Ma Huang, is the main component in herbal weight-loss products referred to as "herbal fen-phen." Ephedrine products are used as decongestants, bronchodilators³¹, and stimulants. Other uses include augmentation of the athletic act and body-building efforts. Ephedra alkaloids containing herbs can drain out sympathetic neurotransmitters, predisposing them to peri-operative hypotension³². Ephedra-containing products may cause seizures, subarachnoid hemorrhage, ischemic attacks, etc. The various adverse reactions included insomnia, nervousness, tremor, headaches, hypertension, seizures, arrhythmias, heart attack, stroke, and death, comparatively young age group in which serious cardiovascular events have occurred is of concern. These products have also been reported to develop kidney stones³³.

Sympathomimetic agents sensitive patients, including those with hypertension, hyperthyroidism, diabetes mellitus, psychiatric conditions, glaucoma, prostate enlargement, seizure

disorders, and cardiovascular disease, are advised not to use ephedra-containing products. Ephedra has many side effects, including restlessness, irritability, increased blood pressure, and cardiac rhythm disorders. *Ephedra herbs* can cause serious toxic reactions, including liver damage, severe high blood pressure, and heart problems when taken with MAO and also with ergot alkaloid derivatives or oxytocin, cardiac glycosides, halothane, guanethidine. Ephedra herbs are advised not to be taken with any MAO-inhibitors (monoamine oxidase inhibitors, such as those in some antidepressants) or heart or blood pressure medications. It induces uterine contractions; thus, should be avoided by pregnant women. Ephedra products have been associated with adverse events, including deaths due to myocardial infarction and cerebrovascular accidents.

Piper Methysticum: *Piper methysticum*, also known as Kava or kava-kava is a Pacific Islands crop. The name kava is derived from Tongan and Marquesan, which means bitter. The root of the plant is used to produce a drink with sedative, anesthetic³⁴ and euphoriant properties. It contains active ingredient as kavalactones. Kavalactones are more effective than a placebo at treating short-term anxiety³⁵. In a series involving four patients, a study shows that kava was associated with drug-induced movement disorder at dosages of 100 to 450 mg per day. For the patient with a single dose of 100 mg, symptoms occurred 90 min later, four hours after one patient took a single 100-mg dose, four days after one patient started with 150 mg three times daily, and 10 days after one patient began taking 150 mg two-dose daily. The extrapyramidal drug-induced movement disorder included oral and lingual movement disorder, torticollis and painful Dystonia, oculogyric crisis, and exacerbation of Parkinson's disease. Kava is also reported to maximize the effects of central nervous system depressant drugs. A patient who was taking alprazolam, cimetidine, and terazosin became sluggish and disoriented after consuming kava. Some drugs, including benzodiazepines, antipsychotics, barbiturates, and alcohol, are advised to refuse to take with kava. Also, patients with a neurodegenerative disorder like Parkinson's disease should discontinue using products having kava. Being lipophilic, it was hypothesized that

kava may concentrate in sebaceous oils and trigger an immune response, resulting in various drug reactions.

Panax Ginseng: *Panax ginseng* species is the most frequently used and furthestmost highly researched species of ginseng. The most active and important constituent in *Panax ginseng* is ginsenosides³⁶, which are having the highest medicinal property and come under the triterpene saponins class. Various side effects are observed by the long-term use of these medicinal herbs; some symptoms are elevation of mood and anxiety related to the neurological systems; this is due to the abusive use of ginseng, which is caused by the presence of dammarenetriol glycoside in ginseng.

It is the most likely medicinal herb used for the treatment of various medical conditions; there are various uses of ginseng which have the efficacy to treat medicinal conditions ginseng is used in the tonic, which increases the body's immunity and also helps in stress management and is also used in treating the diabetic, besides which hypertension and mastalgia are the side effects reported to the use of Ginseng. Ginseng shows its anticoagulant property, which would be the side effects with blood clotting for the patients. Ginseng shows its interference with warfarin and digoxin. Digoxin poisoning is reported when the two drugs Ginseng and Digoxin are taken together; this shows the synergetic effects, which increase Digoxin levels in the blood serum. If the two drugs that are ginseng and antidiabetic drugs³⁷ are taken together, which leads to decrease blood sugar levels which makes the anxiety and discomfort are experienced. Ginseng also interacts with many drugs, which have steroids, antidepressants, estrogen. Excess use of Ginseng causes insomnia and raised blood pressure³⁸.

Aconitum Carmichaelii: Aconites are perennials stirring that mainly grow in the moderate climate regions of Eurasia, usually in the hilly areas. Most of the species grow in the cool and humid atmosphere, preferable for their good conditioning and to get the best medicinal properties. They are grown in the form of tubers, which get enlarged at the bottom of the stem. They have poisonous property, due to which they were used to kill human beings and animals. The toxic

effect is posed due to the presence of the diester diterpene alkaloids, which also involve aconitine, mesaconitine, hypaconitine³⁹. The monoester alkaloids are two thousand times more toxic than the diester alkaloids when they get breakdown when they are subjected to humidity. These poisoning symptoms are seen very quickly with few hours of the intake of the extract, and the main cause of death is cardiac arrest with neurotoxicity⁴⁰. The various other species of the *Aconitum* are used, which is in the form of the dried root; some of them are *carmichaelii* A. and *kusnezoffii* A., which are most probably used to treat anti-inflammation or to show analgesic effects.

The main constituents of the species *aconitum* are aconitine and diterpenoid esters, which cause the triggering of sodium channels in vivo, which results in dose-dependent cardiac and neurological toxicity. The most common signs are parasthesia of the mouth, tongue, extremities, Hypotension, and arrhythmias like atrial flutter or fibrillation can occur, and also with ventricular fibrillation and cardiovascular collapse is caused due to the intake of higher doses than the lethal window. There is a way to decrease the toxic effects of the extract if the herbs are boiled in the water; this process converts the toxic aconitine into less toxic benzoyllecgonine.

Datura Stramonium: The wild-growing herbal plant belonging to the family Solanaceae. *Datura stramonium* L, is broadly scattered and readily available. They contain a large variety of alkaloids that show toxic side effects, one of which is tropane alkaloids which consist of atropine, hyoscyamine, scopolamine⁴¹. In the Ayurvedic system of medicines, these species of *Datura* showed widespread treating/ curing properties in humans such as ulcers, inflammation, rheumatism and gout, sciatica; they also have the healing properties for bruises and swellings, elevated temperatures, asthma, and bronchitis it also is used in treating the tooth problems⁴².

There are many cases of unknowing poisoning caused by the intake of the decoction prepared for the herbal products. Some of the symptoms seen when there is such poisoning include delirium, seizures, mydriasis, blurred vision, dry mouth, thirst, tachycardia, nausea and vomiting, difficulty

swallowing, hyperthermia, hypertension, and coma^{43, 44}. The study stated that 100 mg/kg of *D. stramonium* can cause acute toxicity, which may cause decreases in the weight of the liver, spleen, and brain, which directly affects the functioning and also affects the composition of blood; this effect causes substantial surges in the echelons of red blood cells, hematocrit, hemoglobin, and white blood cells and dose above 10 mg for adults and 4 mg for children may cause the serious side effects and also may be fatal. One can get poisoned with 20 seeds, and the lethal dose is more than 10 mg of atropine and 2 mg to 4mg for scopolamine⁴⁵.

Podophyllum Emodi: *Podophyllum emodi* roots have medicinal properties which are applied to the skin to treat warts and condylomata. *Podophyllum emodi* shows the resemblance to *Gentiana* registers and *Clematis*, if mistakenly ingested, they may cause side effects such as nausea and vomiting, and there is a severe risk of neuropathy and encephalopathy. This is due to the inhibition of the cellular protein synthesis, and hence the enzyme and neurotransmitters cause mitosis in the brain, liver and pancreas, which causes excess cell growth. They also show some serious side effects while they are orally taken, and this is due to the presence of alkaloids in them, which results in Bloody diarrhea, stomach discomfort, also shows effects such as hallucinations, muscular paralysis, kidney failure, breathing discomfort, neurologic manifestations and some side effects are seen on the skin involves irritation on to the applied area. These plants show very potent effects and are highly poisonous for ingestion, so they should be used under supervision only, and they are banned for prescribing in the case of pregnant ladies⁴⁶.

Salvia Miltiorrhiza: *Salvia miltiorrhiza* is also called red sage; they are also known as tan shen or danshen. They are a perennial plant of *Salvia* species are having high importance from the roots, which shows the medicinal property. These are indigenous to China and Japan region; the specific epithet *miltiorrhiza* means "red ochre root. The Chemical compounds isolated from *Salvia miltiorrhiza* include salvianolic acid, dihydrotanshinone, tanshinone I, and tanshinone IIA47; these are the constituents due to which they show their activity. Tanshinone IIA is one of the

most abundant and important constituents which are extracted from the root of *Salvia miltiorrhiza*. This herb shows promising results in the treatment of COPD and improving the symptoms of the same. It also proves its efficacy in treating various cardiovascular and cerebrovascular diseases⁴⁸. Side effects of *Salvia miltiorrhiza* containing products, such as abdominal discomfort, decreased appetite, convulsions, dystonia syndrome, and allergy, have been reported. However, these side effects are relieved once stopped the use of SM products⁴⁹. There were some common side effects such as itching, stomach problems, and appetite loss when they were administered by IV. The study has also shown that the danshen causes the risk of hemorrhage hence one with any serological disorder, and it also causes slow blood clotting during surgery therefore it is advised to stop the danshen intake before surgery for a couple of weeks, should not be consumed. Ingestion of danshen may also cause a decrease in blood pressure⁵⁰.

Aristolochia Fangchi: *Aristolochia* is a species of well-known perennial lianas and herbaceous evergreens. They have smooth stems which are in erect form and the arrangements of leaves are somewhat alternate and cordate; they show somewhat membranous properties; they have no stipules, so leaves grow on the stalks. The studies and evidence have stated that the constant use of powder form of *Aristolochia* species may cause an increase in the risk of urothelial cancer⁵¹. Another risk that was seen while intake of the extract was end-stage renal disorder which was allied with the weight loss; the *Stephania tetrandra* was being replaced with *Aristolochia fangchi*.

The cases of nephropathy were identified by the consumption of this preparation,⁵² which resulted in the transplantation of the kidney or the patients were put on dialysis. *Aristolochia* is reported as a strong carcinogen, and a potent kidney toxin and many studies of Epidemiology and laboratory prove this. Urothelial cancer is caused due to the aristolochic acid Linked to *Aristolochia*; they are potent carcinogens. They cause the somatic mutation of DNA. They adduct on the transcribed DNA strand within genes are detected, and they get removed by transcription, and the non-transcribed strand remains, resulting in the defected DNA

replication. Henceforth, these newly formed nucleotide metabolites appear to choose CAG and TAG sequence formation⁵³. A higher intake of these mixtures induces tubular necrosis in humans.

Radix Angelica Sinensis: *Radix Angelica Sinensis* (RAS), is also called Danggui in Chinese,⁵⁴ is the root of *Angelica Sinensis* (Oliv.) Diels (Apiaceae). These were used to rejuvenate blood cells and blood, revitalize blood, and moisten the intestines, it was also called “female ginseng”. It is also most known for treating various gynecological conditions which are generally not easy to treat with conventional medicines, which involve menstrual disorders, amenorrhea, and dysmenorrhea⁵⁵. It is also used in getting the conditions better in menorrhagia and rheumatologic. It is used as a tonic, hematopoietic and anti-inflammatory agent for a very long time in the Chinese system of treatment. These herbal medicinal plants exhibit various pharmacological effects such as Radioprotective effect, Memory amelioration, Anti-cancer effect, Neuroprotective effect, Immunoregulatory activity, Hematopoietic activity, Antioxidant activity, etc. *A. Sinensis* extract measured when given I.V administration of the essential oil shows a decrease in blood pressure and depression of respiration. They show various side effects and are contraindicated so they are avoided, particularly in pregnancy this is caused due to uterine stimulation and relaxant effects⁵⁶. Extract of *Angelica* cause a laxative effect and also evoke strong menstrual bleeding. This is because the plant's root contains substances called psoralens which may cause hypersensitiveness to the sun⁵⁷. Due to a high dose of *angelica* oils, poisoning has been reported, Skin allergies has been reported, and a sensitivity to light is possible when the extract is consumed⁵⁸.

Larrea Tridentata: *Larrea tridentata* is also recognized as creosote bush, also known as chaparral, and also as a medicinal herb. There are various uses and medicinal properties of chaparral, including Arthritis, Bladder infection, Carcinoma, Chickenpox, Diabetes, Respiratory infection, and dermal infection problems, including acne, STDs Snake-bite, abdominal spasm, and Tuberculosis. Chaparral plants produce a constituent known as nordihydroguaiaretic acid (NDGA)⁵⁹, which shows antioxidant properties. The extract of Chaparral

is likely unsafe. This extract shows the poisoning effects such as acute hepatitis and kidney and liver damage, resulting in kidney and liver failure or dysfunction. Chaparral also shows some common side effects such as can stomach pain, nausea, diarrhea, weight loss, and fever. It has not been observed any dermatological effects when applied to the skin. It is seen and reported unsafe for Pregnant and lactating mothers. With serious effects on the kidney (Nephrotic cells) and liver (Hepatic cells). Chaparral might make liver disease worse if used in a higher amount. Hepatotoxicity is the major side effect related to the ingestion with chaparral⁶⁰. Low doses of chaparral-containing products are considered safe. However, a large amount dose will cause kidney failure and cancer⁶¹.

Glycyrrhiza Glabra L: *Glycyrrhiza glabra*, also known as Liquorice, is the most abundantly used medicinal plant from ancient times. These belong to the Family: *Fabaceae* (*Leguminosae*) and Genus: *Glycyrrhiza*. These are perennial herb inhabitants of the Mediterranean region, central and south western Asia these are also cultured in subtropical regions⁶². *Glycyrrhiza* extract is extracted from the dried roots and stolon of the plants and shrubs. Liquorice is used in foods as a natural flavoring agent and used as spices. There are various useful properties such as soothing, anti-inflammatory, and antitussive properties; they are also used to treat infection of respiratory and gastric diseases and also use to treat primary adrenocortical insufficiency. The most important and abundant chemical constituent found in liquorice is Triterpene saponins⁶³. Acquired apparent mineralocorticoid excess syndrome is the side effect which is caused by ingestion of liquorice, which shows other effects such as retention of sodium and fluids, depletion of potassium, cardiac irregularities, and followed by cramps. Excessive or long-term intake has resulted in symptoms like hypertension, hypoglycemia,⁶⁴ and gains in weight, hypokalemia, but also the low level of plasma renin activity, aldosterone, and plasma renin activity, aldosterone, and antidiuretic hormone.

Consumption of liquorice 10-45 g/day causes increases blood pressure, together with a blocked aldosterone/rennin axis and electrocardiogram

activity change⁶⁵. The synergetic effect of liquorice and thiazide diuretics caused a high risk of hypokalemia and antagonized the effectiveness of the diuretic^{66, 67}. The synergetic effects of liquorice with corticosteroids result in increased and extended effects due to inhibition of their metabolism. Blood pressure and fluid retention risk are elevated due to the use of liquorice. Hence, licorice consumption is high risk in patients with hypertension, cardiovascular disease, bile tract system, kidney, or adrenal gland. It is also unsafe in hyperaldosteronism, during pregnancy, and in diabetic patients. (*Glycyrrhiza glabra* L.), which contains glycyrrhizin, is associated with Fanconi syndrome.

Areca Nut: *Areca nut* is also called betel nut it is a seed of *Areca catechu*, and they grow in much of the humid climate of Pacific Asia and some parts of East Africa. They are chopped wrapped inside the betel leaves (paan) or with tobacco (betel quid). *Areca* is the most obsessive addictive substance used worldwide after nicotine, ethanol, and caffeine and is used up by around 10% of the world's population. *Areca nut* shows the major evidence for causing the carcinogenetic effects⁶⁸ in cancers of the mouth and esophagus; they also have the Evidence in causing the cancer of the liver and biliary tracts and the uterus⁶⁹. The brain, heart, lungs, gastrointestinal tract, and reproductive organs are the human organs that get majorly affected by the ingestion of the *Areca* extract. The use of extract causes the aggravation of physical conditions such as neuronal injury, myocardial infarction, cardiac arrest (arrhythmia), hepatotoxicity, asthma and obesity, and type II diabetes, hyperlipidemia, and metabolic syndrome. Researchers have stated that the risk of coronary artery disease gets associated with the intake of *Areca nuts* in men and women⁷⁰.

Increased palpitation, sudden aggravation in blood pressure, unstable body temperature regulation, hot flushing, and sweating within minutes of consumption are some of the side effects of the *Areca nut*. Some serious effects are caused due to the intake of extract, which causes a significant decrease in sperm motility, sperm count, sperm abnormalities, these are problems related to the reproduction system, and the activity of antioxidant enzymes are also altered and decreased in the

females habitual of chewing *areca nut*, the level of female hormones i.e., progesterone and estradiol remain unchanged. The levels of serum calcitriol get abridged by using *Areca nut*; it also shows the effects of Vitamin D deficiency^{71, 72}.

CONCLUSION: This systematic review suggests that herbal medicines and their preparations play a vital role in maintaining and treating the general healthcare and lifestyle systems of many countries worldwide. AS the herbal preparations are readily available over the OTC. There is no necessity to produce prescriptions to purchase them, but medical expert supervision and guidance are very necessary as they may have serious side effects and may interact with the potential of a drug interaction. With dietary supplements as part of our diet, the physician needs to ask about the preparation and its content as the medication history to avoid synergetic or antagonistic effects. Physicians should discuss or advise patients concerning using the natural product about the Adverse reaction effects, side effects, such as allergy, drug-food interactions, poisonings, reactions to adulterants or contaminants, and toxicities, which can be serious to the patients' health. When these problems arise, a rational approach to supportive care can be helpful.

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