

## REVIEW ARTICLE

# Possible Herbal-Drug Interactions An Evidenced Base Review

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### ABSTRACT

**Background** • The use of herbal/ herbal products has increased from more than a decade. Other than increasing the safety and efficacy of these products, the public needs to be aware of the possible interactions that could occur when combined with conventional drug therapy. Despite the lack of sufficient information on the safety of herbal products, their use as an alternative and complementary medicine is globally widespread. Herbal medicines are now mainly used in active pharmaceutical ingredients. Concurrent usage of natural and prescription medicines is of significant concern. The most significant therapeutic consequence of this approach is the herbal-drug interface (HDI). The proof of HDI is of various degrees of clinical significance utilizing a formal assessment method. Pharmacodynamics HDIs are also recognized for the inherent pharmacological effects of phytochemicals.

**Objective** • The main concern is to mainly highlight the most common Herb-Drug interaction concerning most common herbal-drug interaction.

**Method** • The current review mainly focused on the literature available for the drug-drug interaction in case of most commonly used herbal drugs. Some of the evidence has been compiled through extensive literature survey on different database platforms like Pubmed, Embase and google scholar supporting our review in every aspect of

drug-drug interactions reported in these ten years, our team has also tried of including some previous studies by researchers.

**Result** • The data reliability of such data can be questionable in terms of authenticity, but due to availability of some documented case reports, the risk for HDI will be evaluated in a not-clinical health evaluation step of the product development cycle for the increasing number of plant-based pharmacological activities. The primary concern which was seen to be worried was the self-medication of many herbal drugs which are readily available OTC for the consumers. Available evidence on HDIs is inadequate for therapeutic uses; thus, it may need further clinical studies. This is valid from in vitro trials, and clinical research tested for herbal-drugs interactions.

**Conclusion** • The purpose of this article was to gather data to cater an evidence-based discussion and information for providing complete knowledge to existing patients and consumers regarding herbal drug-drug interactions, would also help them a brief knowledge that what can go wrong in case of herbal-drug interaction, in conclusion, we also found that there is still no basic guideline defining the drug-drug interactions. (*Altern Ther Health Med*. 2022;28(2):70-77).

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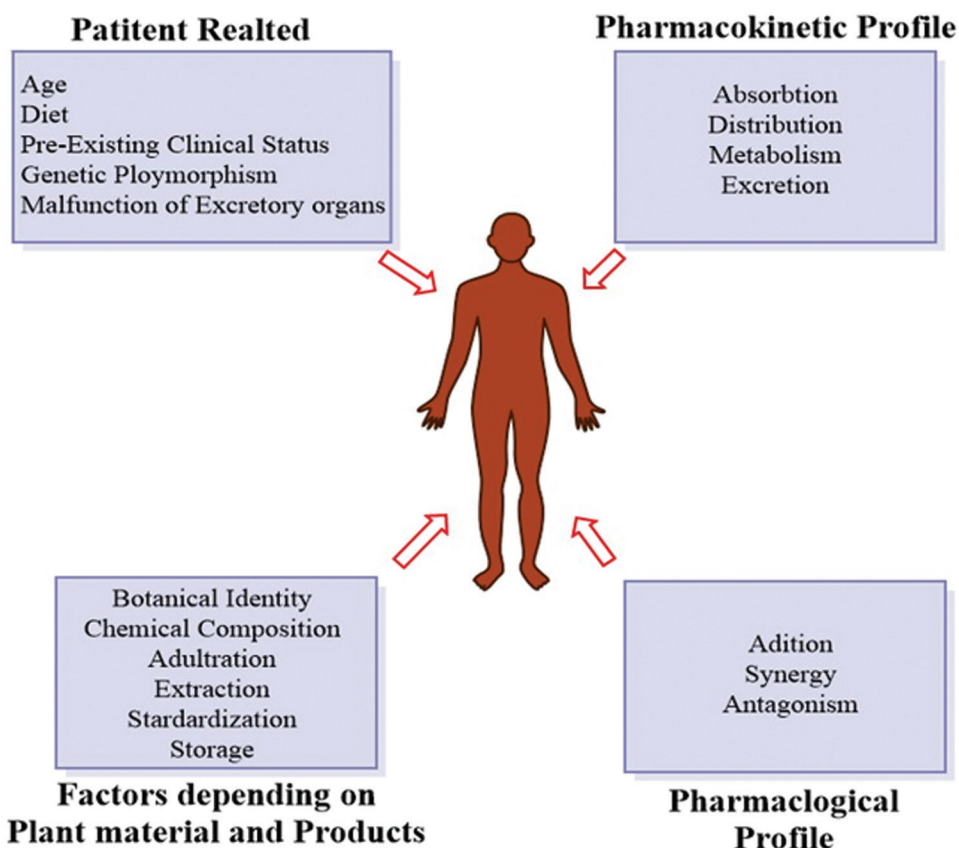
### INTRODUCTION

Nearly 80% of the human population around the globe depend upon herbal medicines for their primary health care. The data for 2008 stated the global market trend of about USD 83 billion, currently, which is about USD 100 billion.<sup>1</sup> In 2013, the medicinal industry of China had an output of USD 80 billion from Chinese patent medicines. Herbal medicines are nascent and are most widely preferred from ancient times for various medicinal marketed purposes. These medications were believed to be safe and reliable methods to treat a particular disease. Their availability was entirely influenced by the environmental factors, which also helped in

determining the shelf life of these drugs. Their administration was quite versatile depending upon the type of plant or plant part intended to be administered, i.e. leaves, roots, rhizomes, flowers, etc.<sup>2</sup>

In concomitant use of medicines and pharmaceutical medications, HDI is among the most significant health problems. The requirement for polypharmacy to manage specific diseases raises HDI patients' risk further. The potential of C.Y.P.s in the intestines, as well as hepatitis to metabolize various structurally different substances is responsible for many recorded drug-drug reactions, as well as the low oral bioavailability of other medications which is the primary concern.<sup>3</sup> A considerable amount of the population is initially dependent upon the herbal drugs. As the new age industry is growing at a high pace, but it could not replace herbal from its position. Taking their toxicity into concern, there is a misconception that "herbal drugs have least side effects", and however with the changing era, the propositions of herbals and their toxicities has been changed to a great extent as the researchers have managed to get various developed forms of products, as a result of which various toxicity charts are also framed out from these developed forms. These toxicity charts will eventually alter the efficiency. The usage of medicinal plant species in treating common diseases has documented significant side effects, on a full scale.<sup>4</sup> Most medications are extracted from bioactive plant chemicals and are related to their particular therapeutic applications by multiple active chemicals. The most significant distinction between having a medicinal plant versus a pharmaceutical medication is that doctors with classical experience in plants, which is very important to the average man, have not been adequately educated. Synthetic drugs usually consist of a straightforward chemical, whereas a complicated combination of 400 or more chemicals can be present in medicinal plants. However, it is difficult for scientists to track the complicated interactions and synergies between all chemicals in plants or the pure commodity extract comprising all of these traditional compounds, but this is not necessary to track every component responsible for the HDI, the studies could involve taking the interaction holistically.<sup>5</sup>

**Figure 1.** Important risk Factors involved in Occurrence of Herbal-Drug interactions.



## METHODOLOGY

The current review mainly focused on the literature available for the drug-drug interaction in case of most commonly used herbal drugs. Some of the evidence has been compiled through extensive literature survey on different database platforms like Pubmed, Embase and google scholar supporting our review in every aspect of drug-drug interactions reported in these ten years, our team has also tried of including some previous studies by researchers. Libraries were looked into original researches, and case reports on HDI using the following search terms or combinations thereof: "drug-herb", "herb-drug", "interaction", "plant", "extract", "herbal and orthodox medicines".

## Possible Classification of Herb-Drug Interactions

The probable or potential pharmacological or in-vitro evidence form the foundation of medication interactions. These interactions may take place in any organ or at the target site. The dose of a drug plays an essential role in these interactions as some drugs are active at one dose and can be toxic at other. While warfarin typically interacts with many herbs, only a few herbs have been reported in actuality. Some of the possible risk factors in case of Herbal- Drug interactions are well described in Figure 1.

The best example know to us is St. John's Wort is the most commonly researched medicinal, medicinal and displays the most considerable potential contact. Herbal

medicines used in conjunction with other herbal medicines may contribute to toxicity that is noticeable in finished or medium-sized items.<sup>6</sup>

The findings of adverse clinical studies, medicinal product toxicity and medication reactions may be classified as<sup>7</sup>:

- A. Abnormal check findings (medication concentration) attributed to herbal products 'adverse impact.
- B. Unanticipated medical dosage levels are attributable to experiences with natural drugs.
- C. Unforeseen existence of a drug in a patient that never took it.

To order to make better choices, Pharmaceutical practitioners and other health personnel are taking an active role in the herbal and other drug additive research. Patients should be questioned regarding their usage of herbs.<sup>8</sup> It is essential. Therefore, the F.D.A.'s adverse incident monitoring system will track alleged herbal medication exposures. In brief, the overwhelming majority of medicinal herbs are safe for usage, but following smooth. Still, responsive self-treatment recommendations will be advisable: (1) for trusted herbal texts, we can use only herbs approved. (2) It is essential to prevent experimental or unproven remedies (3) The herb intake will be stopped if, after a prolonged period, no advantages or outcomes have taken place or negative consequences arise. (4) In specific conditions lacking expertise, nurses or physicians may not indulge in substance usage. (5) Substance reactions and contraindications must be treated separately into account. (6) During breastfeeding, you should stop herbal remedies.<sup>6</sup> While medicinal plants, in general, are commonly used and believed to be healthy, they may be poisonous. Where toxicity of medicinal plants is reported, the plants are typically misidentified as marketed or poorly handled and treated by inadequately qualified workers. Below are descriptions of side effects/effects and reactions with popular herbal medical items used commonly in traditional medicine for centuries.<sup>9</sup>

### Herb-Drug Interactions A Major Concern

Current reports report that 50% of adult Americans are on at least one prescribed medication and 7% of adult Americans use five or more prescription medications. 16 percent do use herbal supplements in prescription drug users; nevertheless, there is an acknowledgement of the incidence of clinically relevant herbal-medication encounters.<sup>10,11</sup> Another aspect that may be blamed for the scarcity of evidence on the actual occurrence of herbal product interactions is that knowledge is frequently scarce to assess if an incident happened attributable to:

1. A lack of information concerning the "contents" of the herbal product
2. Incomplete or inaccurate product information
3. Multiple ingredients.

### Herbal-Drug Interactions

Food and drug reactions in nature are usually triggered by encounters with prescription drugs, certain nutritional products, or occasionally even from the most common allergic reactions to botanical drugs.<sup>11</sup> Blood sugar prescriptions interfere with anticoagulant Induce results of Barbiturate Interacting with heart glycosides Improves results of Barbiturate Change effects of blood sugar Drug interacts with anticoagulant Interacts with a botanical/pharmaceutical relationship that may be the most severe or life-threatening contact with medicines and drugs: consequences of drug absorption.<sup>12</sup>

Like traditional pharmaceutical products, most natural goods are a complex chemical blend. This is also unclear whether the bioactive compounds in a medicinal component are fully defined. Besides it differs depending on the region of the plant used (bark, branches, leaves, roots, rhizomes), atmosphere, growing conditions, processing conditions and storage conditions for the chemicals compound of natural products.<sup>13</sup> Further complicating matters are blended goods made of different natural ingredients. The nature of a natural commodity allows the assessment of herbal medicines associations more complicated, as does the manufacturing process (e.g., drying process and extraction methods) Relates to difficulty overall. As stated earlier, there are no requirements for herbal products, as the F.D.A does not control herbal products. Besides, it has observed that herbal products are misidentified or mistaken with certain natural products or undesirable substances or adulterated with such drugs.<sup>14</sup>

It is the following herbal collection involves Aconite, Alfa alfa, Aloe vera, Borage, Calamus, Chaparral, Coltsfoot, Comfrey, Ephedra, Ginkgo biloba, Ginseng, Glycyrrhiza glabra (Licorice) Isapgul, Sassafras, Senna Silybum Mariánum, St. John's name etc. Its selection is also accessible in portion. All of the following are discussed briefly further.<sup>15</sup>

**Aconite.** Aconite alkaloids found inside the root stages of Aconitum family plants have been approved for the treatment of rheumatism, neuralgia and heart disorders with an analgesic and anti-inflammatory activity in many conventional medicine schemes. They are now commonly prescribed.<sup>16</sup>

**Alfa Alfa.** The plant widely used in homoeopathy is usually composed of A, C, E and K vitamins, calcium, potassium, phosphorus and magnesium. Nevertheless, it has been reported that this herb is a treatment for Systemic Lupus Erythematosus (S.L.E.) in individuals predisposed to this disease.<sup>17</sup>

**Aloe Vera.** The seventh most popular herb used for hundreds of years to treat mild wounds and has been used recently for internal use in foods. Long-term usage of aloe latex could contribute to a deficiency of potassium such that a risk of electrolyte imbalances might result from laxatives containing anthraquinone glycosides not consistently used for longer than 1 to 2 weeks. Certain medications can interact positively or negatively with the glycosides contained in the drug.<sup>18</sup>

**Comfrey.** The herb was used in the first century by Greek doctors to aid the breaking of fractured bones in the shape of a poultice. By the end of 1970 scientists also discovered that it produces hepatotoxic pyrrolizidine alkaloids, together with impaired blood flow through the liver, which may contribute, in addition to the possibility of cancer, to hepatotoxic reactions.<sup>19</sup>

**Ephedra.** Since ancient times the herb was used for the diagnosis of respiratory illness in traditional Chinese medicine. The medicine has been released for weight control, company construction, and mood adjustment as a potentially healthy, natural medication. Recently, the medication became very contentious because of its use in the slimming of formulas and products which appear to be legally high and pose significant health risks. Ephedra has numerous adverse effects, including calming, irritability, blood pressure and cardiovascular conditions. Ephedra's alkaloid ephedrine may cause severe toxic reactions, from liver damage to extreme hypertension or heart failure.<sup>20</sup>

**Ginkgo Biloba.** Over millions of years, ginkgo fruit and seeds are being used extensively to improve social perception and associated cognitive disorders. Extreme pill activation is an effective inhibitor, and long-term use has been related to accelerated bleeding, uncontrolled hemorrhage and subdural hematomas.<sup>21</sup> Ginseng: the 4th largest medicinal plant in China since time immemorial for treating various diseases, Ginseng is used as a general tonic and appears to boost body stress-resistance and produce general strength, aside from treating hypertension, diabetes, depression.<sup>22</sup> Lately, the herb has been reported to cause hypertension and mastalgia as documented side effects. Taking Ginseng may keep blood thinners from working correctly, resulting in problems with blood clotting.<sup>23</sup>

**Isabgol.** Isabgol, deemed the best and most used since centuries for its Antidiarrheal and laxative properties, has a harmful effect, like bronchospasm, asthma and intestinal obstruction. This may induce oesophageal obstruction when swallowed dry.<sup>24</sup>

**Liquorice (Glycyrrhiza Glabra).** Asthma, stomach and duodenal ulcers, persons (the origin of infection of Herpes),

diabetes, persistent depression, etc., have historically been treated by the root of liquorice. This has demulcent properties and expectorant properties (soothing to stressed membranes) as well as activated mucous trachea secretions.<sup>25</sup> Other behaviours have significant anti-inflammatory, anti-allergic and anti-toxic impacts on the liver. Recent work has shown that the excretion of hormones through the surface cortex is induced by glycyrrhizinate. Liquorice toxicity is attributed to the mineralocorticoid and glucocorticoid effects of glycyrrhizinate. Recently it has been found that glycyrrhizinic acid is an active ingredient that may facilitate the accumulation of sodium and oxygen, as well as the loss of potassium in large concentrations which is dangerous for those suffering from blood pressure or kidney or heart disease. Oedema and hypertension related to prolonged usage are potential adverse consequences.<sup>26</sup> Claydon. If you collect medicine with A.C.E., morphine, digoxin, corticosteroids, leptin and laxatives, you will not take liquorice. Drug-drug of Interactions of liquorice is given below in Table 1.

**Sassafras.** For the prevention of rheumatism, asthma, colds and flu, the grass has been used in herbal medicine for decades in North America. The root bark is small if ingested in significant amounts or over an extended time, as a potent liver carcinogen.<sup>27</sup>

**Senna.** Senna, another so-called weight-loss herbal drug used traditionally for constipation, can have adverse effects on the heart because regular consumption is reported to deplete the body of potassium, causing fatalities. Other adverse reactions include grand mal seizures, circulatory failure, hypertension and anaphylactic reaction.<sup>28</sup>

**Silybum Marianum.** Silymarin derived as a liver tonic and commonly marketed from Silybum marianum herb has been linked with brain leakage, hepatic paralysis and neuropathy.<sup>29</sup>

**St. John's Wort.** A nutritional replacement and an opioid have a business opportunity in Europe and America. In research performed by NIH in the U.S.A., an essential drug association was identified between the Wort of St. John's and the protease Indinavir inhibitor of infection. Depending on these results, blood production of the herb (FDA

**Table 1.** Brief description of the Herb-drug interaction relating to liquorice (Wang et al., 2013).<sup>25</sup>

Drug	Effect
Warfarin (major interaction)	Liquorice increases the breakdown of warfarin which leads to decreased efficacy, it also increase blood clotting
Digoxin	Liquorice decreases the potassium level
Estrogens	Liquorice changes the hormone levels. It may also decrease the effectiveness of estrogen pills.
Ethacrynic acid	Interaction between ethacrynic acid might decrease the potassium levels in the body.
Furosemide	This interaction may also lead to decrease in potassium levels.
Antihypertensive drugs (losartan, captopril, etc)	This interaction may decrease the effectiveness of antihypertensives, leading to elevated blood pressures.
Anti-inflammatory drugs (hydrocortisone, prednisolone, etc.)	This interaction may report huge fall in potassium levels.
Water pills (diuretics)	Decreased potassium levels in the body.



guidelines) is predicted to decrease dramatically. The plant nevertheless does not seem to be a significant danger to animals since one of *Hypericum*'s early signs includes lack of appetite, which prevents the production of the photodynamic pigment, hypericin.<sup>30</sup> The drug hypericin is consumed from the stomach and concentrates next to the skin in the event of *Hypericum* toxicity. St. John's words have proven that the cytochrome enzyme P450 CYP3A4 and even CYP2C9 induce several therapeutic associations. This contributes to an improved metabolism which increases the volume which therapeutic impact of such medications.<sup>31</sup> Hyperforin and amentoflavone are significant components known to be responsible for the usage of P-glycoprotein (P-GP). The efflux transporter has also shown the effect of St. John's Wort on drug reactions. Proper P-GP development contributes to lower absorption and improved clearance and reduces the therapeutic response of the effective treatment of these drugs. St John's Wort, in conjunction with other pharmaceuticals that may raise the central nervous (C.N.S.) 5-HT (serotonin) level, can also contribute to serotonin syndrome,<sup>32</sup> which is a possible life-threatening adverse reaction. Some of the significant interactions of S.T. John's Wort is listed briefly in Table 2.

**Cannabis.** It's acknowledged that Cannabis 'psychoactive properties are biphasic in fact. The critical psychoactive symptoms include euphoria from the central psychoactive drug, tetrahydrocannabinol and, to a smaller degree, relaxation. Secondary psychoactive symptoms, such as a metaphysical thought facility; an anxiety and fear introspection and metacognition have been identified. Finally, the tertiary psychoactive effects of cannabis that involve a rise in heart and malnutrition, which is expected to result in a psychotic metabolite T.H.C. produced in the liver, 11-Hydroxy-THC.<sup>33</sup> Using smoking pipes, bongs or vaporizers, natural consciousness should be returned in around three hours at higher doses. However, the symptoms may linger for longer if a substantial dose were ingested orally. Over the 24 hours, based on dosage, duration and resistance to the drug, minuscule psychoactive symptoms will be experienced. There are various varieties of cannabis products, including derivatives such as hashish and hash oil, which are more vulnerable to adulterants and left unchecked due to their presence. The Cannabis sativa plant is considered to induce more appetite and a more comically or energy-oriented mood. Inverse, it is often recognized that the Marijuana indica plant induces more "stony" or contemplation owing to a higher CBD to T.H.C. ratio.<sup>34</sup> This attenuating or diminishing cannabidiol (CBD), by itself, may not have psychotropic symptoms, even though often it has minor stimulants, including caffeine. The higher THC-induced fear rates.<sup>35</sup>

**Cinchona.** Some who believe industrial drugs are superior to natural medicines can shock with their equivalence of medicinal efficacy, but the usefulness of Cinchona compared to Quinine has proven itself. Of one study, rats were injecting an infectious malaria agent and subsequently either feeding (or injected) quinine or feeding cinchona

extract. Animals were restored in all categories as soon as an appropriate medication dosage had been obtained.<sup>36</sup> Quinine is a cell and protoplasm toxin of general intent that prevents several enzyme processes by complexing with D.N.A. and preventing nucleic acid synthesis. The antipyretic activity of Quinine is the product of oxidative inhibition.

Furthermore, Quinine prolongs the refractory process of the smooth muscles and reduces the contractibility of the heart. The membrane-stabilizing agent contains quinidine and adverse inotropic action. For general fatigue, with anorexia and contraindicated in breastfeeding, Cinchona is suggested.<sup>37</sup> This plant is mixed with camomile, lemon bables, the root of marshmallows, root of angelic, and hops for the diagnosis of anorexia, nerves, yarrow and mint. Neonatal jaundice may cause side effects or an association of the oxytocic-like effect of this herb that will conflict with the test outcome for serum bilirubin. Increases the impact of anticoagulants when delivered at the same time. This diuretic is more likely to cause hypokalemia in combination with ACTH or corticoids. The half-life of anticoagulants was tentatively improved by allopurinol.<sup>38</sup> Some of them are explained in brief with the help of Table 3.

### Toxicity Possibilities Of The Drug-Herbal Interaction

Different drugs listed briefly about all possible toxicity reactions which can happen in the body concerning the herbal drug with their uses and biological sources; it can be seen in Table 4.

### CONCLUSION

The possible association between herbal medicines is important for health practitioners as well as patients. The drawbacks of the pre-marketing process of product production at specific risk of new drugs are recognized to certain patients and to some degree physicians. The goal is to make the patient conscious of potential risks connected with herbal medicines and for healthy usage. The most significant adverse effects arise from overuse or abuse of drugs like this. Regulatory authority requires for herbal pharmaceutical items. If the manufacture and selling of these goods are essentially uncontrolled and even unchecked, the risk of side-effects is enhanced and the customer is not properly informed of their appropriate use. The main focus is on environmental monitoring of genotoxic and carcinogenic substances produced by humans. This contradicts research on the potential safety hazards or adverse consequences of natural agents that people are subjected to regularly in their everyday lives. This group of compounds contains basic phenolics. These are toxic to animals, these are used as dietary additives and they are consumed in milligrams every day. D.N.A. ruptures, D.N.A. adducts, defects and chromosome aberration are often known to cause in a large number of test systems. Nevertheless, both in vitro and in vivo, experiments have demonstrated that genotoxic actions can be disrupted by such carcinogenic substances. Similar herbs must be closely examined for evidence of toxicity or tolerance,

**Table 2.** Brief description about the Herb-drug interaction of ST.jonh's wort.<sup>31</sup>

Drug	Effect
Aminoevulinic acid	Increase skin sensitivity
Amitriptyline	Decrease efficacy by enhancing the elimination of drug
Contraceptive pills	Decreased efficacy of drug
Cyclosporine	Decreased efficacy of drug
Digoxin	Decreased absorption
Fenfluramine	Combination may increase the serotonin level in brain which leads to anxiety, heart problems and headache.
Imanitib	Increases elimination rate of drug
Irinotecan	Decreased efficacy
Anti-depressants (Flouxetine, Amytriptiline, etc)	Increased level of serotonin which leads to heart problem, anxiety and shivering.
Narcotic Drugs	Increases side effects of narcotic drugs
Photosensitizing drugs	Increases skin sensivity
Meperidine	Combination may increase the serotonin level in brain which leads to anxiety, heart problems and headache
Nefazodone; Paroxetine; Pentazocine; Sertraline	Combination may increase the serotonin level in brain which leads to anxiety, heart problems and headache
Nortriptyline; Phenobarbital; Phenprocoumon; Phenytoin; Tacrolimus; Warfarin	Increases elimination rate of drug
Reserpine	Decreased efficacy
Clopidogrel; Simvastatin; Theophylline	Decreased efficacy and increased elimination rate
Dextromethorphan	Combination may increase the serotonin level in brain which leads to anxiety, heart problems and headache
Fexofenadine	Increased side effects

**Table 3.** Drug interaction of cinchona.<sup>37</sup>

Drugs	Interactions
Anticoagulants or Antiplatelet drugs	When this drug is taken along with cinchona, the duo might increase the chances of bleeding as the rate of clotting is slow.
Quinidine; quinine; phenobarbital	The combination might of two might increase the effects and the side effects of the drug
Carbamazepine	The effect of carbamazepine is decreased as the elimination rate is enhanced
Antacids	Cinchona might decrease the effects of antacids

**Table 4.** Overview of Herb-drugs interaction and their toxicity potential.<sup>51,52</sup>

	Herbal Name	Biological Source	Use	Toxicity profile for the Interactions	References
1	Aconite	Aconitum napellus, Ranunculaceae	Analgesic, anti-inflammatory	Actonite Poisoning	Majumder et al., 2018 <sup>39</sup>
2	Alfaalfa	Medicago sativa, fabaceae		Systemic lupus	Ghimire et al., 2019 <sup>40</sup>
3	Aloevera	Aloe sinenses, liliaceae	Minor bruises	Potassium deficiency, electrolyte imbalance	Izzo et al., 2016 <sup>41</sup>
4	Comferey	Symphyton officinale, Boraginaceae	Wound healing, to help knit broken bones	Hepatotoxic, carcinogenic	Izzo et al., 2016 <sup>41</sup>
5	Ephedra	Ephedra sinica, ephedraceae	Respiratory ailments	Restlessness, irritation, increased B.P., arrhythmia,	Izzo et al., 2016 <sup>41</sup>
6	Ginkgo biloba	Gingkg biloba, ginkgoaceae	Improvement of mental alertness and memory related problems	Increase in bleeding time, spontaneous hemorrhage and sub-duralhaematomas	Mei et al., 2017 <sup>42</sup>
7	Licorice	Glycyrrhizaglabra, Leguminosae	Asthma, stomach and duodenal ulcers, arthritis, chronic depression	Promotes sodium and water retention, potassium depletion, edema and hypertension	Nazari et al., 2017 <sup>43</sup>
8	Sassafras	Sassafras albidum, Lauraceae	Rheumatism, arthritis, cold and flu	Carcinogenic	Gross et al., 2017 <sup>44</sup>
9	Senna	Cassia acutifolia, leguminosae	Constipation, cytochromeoxidase negative fibers.	Grand mal seizures, circulatory failure, hypertension and anaphylactic reactions	Ulbricht et al., 2011 <sup>45</sup>

**Table 4.** (continued)

10	Silybummarianum	Silybum marianum, asteraceae	Liver tonic	Cerebral haemorrhage, hepatic coma and neuropathy	Fanoudi et al., 2020 <sup>46</sup>
11	St. John's wart	Hypericum perforatum, Hypericaceae	Anti-depressant	Decrease blood concentration	Izzo et al., 2016 <sup>41</sup>
12	Garlic	Allium sativum, Liliaceae	Anti-diabetic, antifungal	Halitosis	Gebreyohannes et al., 2013 <sup>47</sup>
13	Digitalis	Digitalis purpurea, Scrophulariaceae	CHF	Nausea, vomiting, diarrhea, abdominal pain, mild hallucination, headache	Whayne et al., 2018 <sup>48</sup>
14	Cannabis	Cannabis sativa, Cannabinaceae	Sedative, analgesic and psychotropic	Primary and secondary psychoactive effects	Wong et al., 2018 <sup>49</sup>
15	Cinchona	Cinchona calisaya, Ruyiaceae	Antiviral, antimalarial, antipyretic	Anorexia, pregnancy complications	Gurung et al., 2017 <sup>50</sup>
16	Ginseng	Panax ginseng, araliaceae	Increase body's resistance to stress, hypertension, Diabetes, depression	Hypertension, mastalgia	Izzo et al., 2016 <sup>41</sup>
17	Isapgghul	Plantago ovate, plantaginaceae	Demulscant and laxative	Bronchospasm, asthma and intestinal obstruction	Izzo et al., 2016 <sup>41</sup>

provided that many herbs are used in formulations, more than one herbal treatment has been used and herbal medication might have been used in combination with prescription medicines in several of the cases investigated. This can be important, however, for a single herbal treatment to be assigned toxicity and potential medication reactions to be taken into account. However, use of herbs known or discovered to be potentially toxic should be prohibited, not just the specific preparation implicated. Phenolic have been found to be effective carcinogenesis inhibitors. Further studies may validate the degree to which a health threat or beneficial impact of complex food mixtures is induced by the phenolic material. Moreover, these different, often conflicting roles of single phenolics render it challenging to consider their usage as chemical preventive agents.<sup>53</sup>

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#### CONFLICT OF INTEREST

There is no conflict of interest.

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