



HERBAL DRUG INTERACTION: AN OVERVIEW

*Ranjeet Kumar Bhargav and Rehana Parveen

BBS Institute of Pharmaceutical and Allied Sciences, Greater Noida.

*Corresponding Author: Ranjeet Kumar Bhargav

BBS Institute of Pharmaceutical and Allied Sciences, Greater Noida.

Article Received on 10/03/2020

Article Revised on 30/03/2020

Article Accepted on 20/04/2020

ABSTRACT

People use herbal treatments along with prescription and nonprescription medications. Although considered natural, many of these herbal therapies can interact with other medications, causing either potentially harmful side effects and / or reduced activity of medicines. Currently, there is very little information published on herb-drug interactions whilst the use of herbs is progressively growing across the world. The increasing use of herbal medicinal products in the community where people are also receiving prescription medicines suggests that adverse herb-drug interactions may be of significant public health consequence. The aim of this literature^[1] review is to provide critical insight and commentary into the issues that need to be considered in applying evidence based principles to assess clinically important herb-drug interactions. Herb-drug interactions are a stark reality today. Hence, proper reporting of cases, careful vigilance, evidence-based appraisal and constantly updated reviews of such herb-drug interactions are very important to promote systematic research.

KEYWORDS: Drug Interaction, Herbal medicine, pharmacodynamic, pharmacokinetic.

INTRODUCTION

Drug interaction is a reaction between two or more drugs, between drugs and food or beverage or supplement inside the body. Millions of people today use herbal therapies along with prescription and nonprescription medications. Although considered natural, many of these herbal therapies can interact with other medications, causing either potentially dangerous side effects and / or reduced benefits from the medications. Currently, there is very little information published on herb-drug interactions whilst the use of herbs is progressively growing across the world. India is very rich in natural resources and the knowledge of traditional medicine and the use of plants as a source of medicine is an innate and very important component of the healthcare system. The Indian system of medicine has identified 1,500 medicinal plants of which 500 are commonly used. It is estimated estimated that there are over 7800 medicinal drugmanufacturing units in India, which are estimated to consume about 2000 tons of herbs annually.^[5] According to a recent estimate of the World Health Organization (WHO), 70-80% of the world population especially in developing countries, relies on traditional medicine, mostly plant drugs for their primary healthcare needs.^[2,3]

All herbs are derived from natural materials i.e. herbs are plant or plant derivatives. Some issues are arising today about interactions of herbs or herbal drugs. The Indian

Medicine System has the main aim to preserve normal health and to cure the disease one. Drug safety is a very basic and fundamental concept in medical practice. The current issue is with respect to alternative medicine and Ayurveda is increasing reports of adverse drug reactions (ADR) related to herbal medicine.

Herbal Drug: An herb^[5] is a plant or plant part used for its scent, flavor, or therapeutic properties. Herbal medicines are one type of dietary supplement. They are sold as tablets, capsules, powders, teas, extracts, and fresh or dried plants. People use herbal medicines to try to maintain or improve their health.

Many people believe that products labeled "natural" are always safe and good for them. This is not necessarily true. Herbal medicines do not have to go through the testing that drugs do. Some herbs, such as comfrey and ephedra, can cause serious harm. Some herbs can interact with prescription or over-the-counter medicines. If you are thinking about using an herbal medicine, first get information on it from reliable sources. Make sure to tell your health care provider about any herbal medicines you are taking.

Drug Interaction: Drug interaction is a reaction between two or more drugs, between drugs and food or beverage or supplement inside the body. When herbal medicine is interact with food-beverages/other drug

present in human body, greater chance of herbal drugs interaction with each other. One factor may increase activity of other drug or inhibit its activity or may cause side effects. There are more opportunities today than ever before to learn about your health and to take better care of yourself. It is also more important than ever to know about the medicines you take. If you take several different medicines, see more than one doctor or have certain health conditions, you and your doctors need to be aware of all the medicines you take to avoid potential problems, such as drug interactions.

The Drug interaction.^[4] may be classified as per mentioned in Ayurveda:

1. HERB-HERB INTERACTION: This type of interaction is also known as Drug-Drug interaction. These are common type of drug interaction. When more herbal medicine are administered together, greater chance of herbal drugs interaction with each other. One drug may increase activity of other drug or inhibit its activity or may cause side effects. Eg: Vicodin ^[6] is a pain killer when taken with sedating antihistamin medicaments, Benadryl produce an additive effect of drowsiness.

2. HERB-FOOD INTERACTION: It is also known as food-drug interaction. In this type of interaction drugs interact with food/beverages present in the stomach and may cause various side effects. Eg: combination of mils preparation and Mantha (gruel) is contraindicated, grape juice reduces enzyme activity in liver which are responsible for metabolism of drugs. it may cause side effects or may produce toxic effects.

3. HERB-DISEASE INTERACTION: It is also known as drug-disease interaction. In some few cases drug also interact with disease where disease alter drug activity. It may occur when an existing medical condition makes certain drugs potentially harmful. For example, if you have high blood pressure you could experience an unwanted reaction if you take a nasal decongestant. Oral decongestant like phenylephrine may increase blood pressure and can be dangerous pro patient having hypertension.

Factors Affecting Drug Interaction

Mainly two types of factor ^[7] affecting drug interaction, which are:

1) Drug-Related Factors

- Low bioavailability
- Drug formulation (presence of interacting excipients)
- Drug stereochemical and physiochemical properties
- Drug potency
- Steep dose–response curve
- Duration of therapy (acute vs chronic administration)

- Drug dosage (a higher dose yields a more significant interaction)
- Drug concentration in blood and tissue
- Timing and sequence of administration of interacting
- Route of administration
- Baseline blood concentration of interacting drug and its therapeutic index
- Narrow therapeutic range

2) Patient-Related Factors

- Body weight, composition, and size
- Quantity and activity of specific drug-metabolizing enzymes)
- Age
- Gender
- Race
- Tobacco use
- Alcohol use (acute or chronic)
- Diet
- Underlying disease states and their severity (acute, chronic, unstable)
- Malfunction and disease of organs of drug elimination (e.g., liver, kidney)
- Polypharmacy (particularly with enzyme inhibitors or inducers)

Mechanism Of Drug Interaction

Drug interaction can occur in different ways starting from its absorption to its elimination from the body. Following two types ^[9] of mechanism of drug interaction which are:

1. Pharmacodynamic interaction:

The term “pharmacodynamic ^[8] interactions” refers to interactions in which drugs influence each other’s effects directly. It occurs when two or more drugs administered together which act at the similar receptor site leading increase or decrease effects. As a rule, for example, sedatives can potentiate each other. The same is true of alcohol, which can potentiate the sedative effects of many drugs.

Eg: chlorpromazine given to prevent nausea and vomiting, when interact with antipsychotic drugs like haloperidol and produce serious and possible fatal irregular cardiac rhythm.

In pharmacodynamic interactions, it is not possible to demonstrate a simple systematics as it is in pharmacokinetic interactions; instead, they require a careful weighing up of which drug groups cause desired and which undesired effects.^[10] which can in turn either potentiate or weaken each other (*Table 1 & 2*).

Table 1:

Additive interaction		
Substance I	Substance II	Possible Effect
Quinolones	Citalopram	QT-interval prolongation,
ACE inhibitors	Amiloride	Hyperkalemia
NSAIDs	SSRI, Phenprocoumon	Increased risk of bleeding
NSAIDs	Glucocorticoids	Increased risk of gastric bleeding
SSRIs	Tryptans	Serotonin syndrome
Tricyclic antidepressant	Low-Potency Neuroleptics	Increased anticholinergic effects

Table 2:

Antagonistic interaction		
Substance I	Substance II	Possible Effect
Phenprocoumon	Vitamin K	Reduced effects
ACE inhibitors	NSAIDs	Reduced effects
Levodopa	Classical neuroleptics	Reduced effects
Acetylsalicylic acid	Ibuprofen	Reduced effects

2. Pharmacokinetic interaction

Pharmacokinetic interactions occur during the process of ADME & alter the absorption, distribution, metabolism, excretion or transport of a drug. Corresponding or independent changes in pharmacological response or therapeutic outcome may or may not occur.^[11,12,13,14] Bioavailability can be affected by physicochemical factors such as complexation and nonspecific adsorption of the drug and by physiological factors such as gastrointestinal motility, gastrointestinal pH, presence of gastrointestinal disease, gastric emptying time, intestinal blood flow, intestinal metabolism, and inhibition /induction of transport proteins. In infectious diseases, changes in extent are more clinically important than changes in rate of absorption. As safety and effectiveness are concerns in pharmacokinetic interaction studies, the use of *exposure* rather than *rate and extent of absorption* concepts is encouraged, because the term exposure expresses more clinical relevance and focuses on the shape of the drug concentration– time profile^[15].

Pharmacokinetic interaction classified in four classes.^[16]

- Absorption interaction
- Distribution interaction
- Metabolism interaction
- Excretion interaction

a. Absorption interaction: When one drug alter the absorption of another drug or effect the absorption process, this type of interaction called Absorption interaction.

Eg: calcium can bind with some drugs like tetracycline and HIV drug dolutegravir and block its absorption; hence such drugs should not be taken with milk and antacids.

b. Distribution interaction: When one or more than one drug compete with each other for plasma protein binding sites resulting in displacement of one drug thereby increasing its blood level and toxicity.

Eg: when warfarin and fenofibric acid administered together, compete for protein binding sites leading to

displacement and increased blood levels of warfarin thus resulting in bleeding.

c. Metabolism interaction: Enzymes present in liver are responsible for metabolism of drugs and eliminating them from the body. When drugs may alter the enzyme activity or influence its level, resulting serious liver and muscles side effects.

Eg: Diltiazem (antihypertensive) inhibit the cytochrome enzyme which is responsible metabolizing simvastatin (hypochlestremic) and increase its blood level resulting serious liver and muscles side effects.

d. Excretion interaction: When drugs influence the excretion process, this type of interaction is called excretion interaction.

Eg: NSAIDs like indomethacin may lower the kidney function and reduce the excretion of lithium, a drug used for bipolar disorder. In this type of situation dose adjustment is required.

Study of Some Common Herbs And Their Interaction

1. Hypericum: It is also known as St. John,s Wort. It is obtained from aerial parts of herb known as *Hypericum perforatum*. Belonging family Hypericaceae. All members of the genus may be referred to as *St. John's wort*, and some are known as *goatweed*.The white or pink flowered marsh St. John's worts of North American and eastern Asia are now separated into the genus *Triadenum*. It contain many pharmacologically active ingredients including naphodianthrone, phloroglucinols derivatives, and flavonoids. Such extract are used to treat mild to moderate depression & anxiety.

Side effects: Dry mouth, GI symptoms, allergic reactions, fatigue, trouble sleeping, vivid dreams, nervousness, skin allergy etc.

Interactions^[17]

- Hypericum along with alprazolam might decrease the effectiveness of alprazolam.

- Hypericum might decrease the affect of amitriptyline by increasing breakdown of amitriptyline in the body.
- Hypericum with birth control pills might decrease effect of control pill.
- St. John's wort might reduce effect of digitoxin & digoxin.
- St. John's wort with cyclosporin decrease effect of cyclosporine.
- St. John's wort along with medicines for depression might increase serotonin too much and cause serious side effects including heart problems, shivering and anxiety.

2. Kava: Kava kava is an extract obtained from herb *Piper methysticum*, belonging to family Piperaceae. Mainly it is found in Pacific islands.^[19] The name kava comes from the Polynesian word "awa" which means bitter. The root of the plant is used to produce a drink which has sedative, anesthetic and euphoriant properties. Its active ingredients are known as kavalactones.^[20] It is generally taken by mouth to calm enxiety, stress and restlessness. It is also used to treat epilepsy, psychosis, migraines and for Attention deficit-hyperactivity disorder.

Side effects: Kava^[21] can cause liver damage. Its extract produces sedation do do not take kava before driving. Early symptoms of liver damage are yellowed eyes and skin (jaundice), fatigue, and dark urine.

Interactions

1. Kava should not be taken with drugs which act on nervous system such as barbiturates, antidepressant, antipsychotic, and alcohol.
2. It is reported that concomitant use of kava with central nervous system depressants can increase the risk of drowsiness and motor reflex depression.
3. Using with alcohol, muscle relaxant or other sedative can result in high additive effect including coma.
4. Using with acetaminophen may injure the liver.
5. Kava has also reported to produce hepatotoxicity when taken with some drugs.
6. Kava may also interact with anti-cancer and birth control drugs.

3. Ginkgo: It is obtained from herb *Ginkgo biloba*^[22] belonging to family Ginkgoaceae. Commonly known as ginkgo or gingko^[24]. It is also known as the maidenhair tree^[23] is the only living species in the division Ginkgophyta, all others being extinct. It is found in fossils dating back 270 million years. Native to China^[25]. The tree is widely cultivated, and was cultivated early in human history. It has various uses in traditional medicine and as a source of food. It contain high levels of flavonoids and terpenoids, antioxidants that provide protection against oxidative cell damage from harmful free radicals. It reduces the chance of cancer. Extract of *Ginkgo biloba* leaf used as dietary supplements. Ginkgo

extract is also used in Alzheimer's disease and high blood pressure.

Side effects: It produces minor side effect like dtomach upset, headache, dizziness, constipation, allergic reactions. Leaf extract may increase the risk of cancer. The use of *Ginkgo biloba* leaf extracts may have undesirable effects, especially for individuals with blood circulation disorders and those taking anticoagulants, such as aspirin or warfarin.

Interactions

1. Ginkgo should avoided with other herbal/health supplements that can affect blood clotting.
2. It includes garlic, clove, capsicum, panax ginseng, turmeric, red clover etc.
3. With warfarin, ginkgo affect activity of warfarin.
4. Ginkgo should not be taken with NSAIDs.
5. Ginkgo should not be taken with Narcotic medicines.
6. Ginkgo should not be taken with insulin or other diabetic medicine.
7. Ginkgo should not be taken in following conditions: any type infection, in depression, in high BP condition, migraine, rheumatoid arthritis, autoimmune disorders.

4. Ginseng: It is obtained from root of herb *Panax ginseng*^[26] belonging to family Araliaceae, also known as Korean ginseng, South China ginseng (*P. notoginseng*), and American ginseng (*P. quinquefolius*), typically characterized by the presence of ginsenosides and gintonin. It is used to improve body's resistance to stress, boost the immune system & improve the sense of well being and stamina. Ginseng may be included in energy drinks or herbal teas in small amounts or sold as a dietary supplement.^[29] Generally taken by mouth to improve thinking, concentration, memory, Alzheimer, work efficiency, and to prevent muscle damage from exercise. It is also used in depression, anxiety, general fatigue, multiple sclerosis and for boosting the immune system.

One of the first written texts covering the use of ginseng as a medicinal herb was the *Shen-Nung Pharmacopoeia*, written in China in 196 AD. In his *Compendium of Materia Medica* herbal of 1596, Li Shizhen described ginseng as a "superior tonic". However, the herb was not used as a "cure-all" medicine, but more specifically as a tonic for patients with chronic illnesses and those who were convalescing.^[27]

Control over ginseng fields in China and Korea became an issue in the 16th century.^[28]

Side effects: The most common side effect is to trouble sleeping (insomnia). Others are menstrual problems, breast pain, increased heart rate, BP problrm, headache, itching, rash, mood changes, vaginal bleeding etc.

Interactions

- a) When administered with warfarin it reduces activity of warfarin (blood thinner). And increase risk of blood clotting. So it should be avoided to take with anticoagulants.
- b) It is also affect the activity of anti diabetic drugs, Ginseng lower blood sugar levels, increasing risk of Hypoglycemia. Hence it should be avoided in such cases.
- c) It is also reported that ginseng decrease effectiveness of antihypertensive drugs, resulting high blood pressure.
- d) Ginseng may make the effect of caffeine stronger, possibly causing nervousness, sweating, insomnia, or irregular heart beat.
- e) Ginseng may interact with Angiotensin converting enzymes (ACE) inhibitors like: Captopril, Benazepril, enalapril etc.
- f) Asian ginseng make heart medication, including calcium channel blocker, to work differently than proposed. These medication include: Diltazem, Nifedipine etc.
- g) Ginseng may interact with drugs taken to treat autoimmune disease or drugs taken after organ transplant. Hence it should be avoided in such cases.
- h) Ginseng may increase the stimulant effect of some drugs used for Deficit Hyperactivity Disorder.
- i) When ginseng taken with morphine, it reduces pain relieving activity of morphine. Hence it should be avoided in such cases.
- j) When taken with monoamine oxidase inhibitors (MAOIs), ginseng may increase the risk of Mania. It's a kind of antidepressant.

5. Garlic: Biological source of garlic is bulb of herb known as *Allium sativum*, belonging to family **Amaryllidaceae**. Fresh or crushed garlic yields the sulfur-containing compounds alliin, ajoene, diallyl polysulfides, vinylthiols, S-allylcysteine, and enzymes, saponins, flavonoids, and Maillard reaction products, which are not sulfur-containing compounds. A large number of sulfur compounds contribute to the smell and taste of garlic [30]. Allicin has been found to be the compound most responsible for the "hot" sensation of raw garlic.

It is used in various conditions like to lower blood sugar level, reduce menstrual pain, lower cholesterol level & decrease BP. Mainly it is used as flavoring agent. Garlic is mainly taken by mouth.

Side effects: Redness, redness, blistering when applied to the skin, bleeding, unpleasant breath, heart burn, burning in our mouth.

Interactions

- a) Garlic is reported to reduce the efficacy of drugs whose distribution is dependent on efflux transporter mechanism.

- b) It is also reported to effect the blood clotting hence should be avoided in patients taking blood thinning agents like aspirin and warfarin.
- c) Garlic supplement has decreased the blood levels of HIV protease when used together.
- d) It is advisable that following drugs should be avoided with garlic:

Acetaminophen
Birth control pills
Chlorzoxazone
Cyclosporine
Warfarin
Theophyllin
HIV or AIDS medicine
NSAIDs

6. Ephedra: It is obtained from the herb *Ephedra*^[17] *sinica*, belonging to family Ephedraceae. It has been used in traditional medicine for more than 2000 years. Its branched and flowering tops are used in medicinal preparation. Basically it is used for weight loss, obesity and to maintain performance. Ephedra is used to treat allergies, high fever, and respiratory tract conditions like bronchospasm, asthma, and bronchitis.

7.

Ephedra contains ephedrine which is a potent drug and stimulate heart, lungs and nervous system.

Side effects: Ephedra is not safe for adult^[17] and children. It can cause severe life threatening or disabling conditions. Dietary supplements containing ephedra alkaloids have been found to be unsafe, with reports of serious side effects and ephedra-related deaths.^[31,32,33,34] In response to accumulating evidence of adverse effects and deaths related to ephedra, the U.S. Food and Drug Administration (FDA) banned the sale of supplements containing ephedrine alkaloids in 2004.^[35] The ban was challenged in court by ephedra manufacturers, but ultimately upheld in 2006 by the U.S. Court of Appeals for the Tenth Circuit. Ephedra extracts not containing ephedrine have not been banned by the FDA and are still sold legally.

Interactions

- a) Ephedra may reduce the effect of antihypertensive and could rise the blood pressure.
- b) Ephedra should not be mixed with other CNS stimulants such as amphetamine, and its derivatives as it may enhance hyperactivity and can produce serious problems.
- c) It should be avoided with blood thinning drugs such as aspirin and warfarin. It may increase bleeding.
- d) Ephedra should be avoided in people suffering from seizures, as it may worsen the onset of seizures.
- e) Ant diabetic drugs interact with ephedra. Diabetes medicines are used to lower blood sugar. By increasing blood sugar, ephedra might decrease effect of anti diabetic drugs.

8. Pepper: It is obtained from herb *Piper nigrum* belonging to the family Piperaceae. Cultivated fruit are known as a peppercorn, which is usually dried and used as a spice and seasoning. When fresh and fully mature, the fruit is about 5 mm (0.20 in) in diameter and dark red, and contains a single seed, like all drupes. Peppercorns and the ground pepper derived from them may be described simply as pepper, or more precisely as black pepper^[36] (cooked and dried unripe fruit), green pepper (dried unripe fruit), or white pepper (ripe fruit seeds). Black pepper contains piperine as active constituents. It is used to treat arthritis, asthma, stomach upset, and sinus infections.

Side effects: It is safe when taken by mouth in fixed amount. It may cause heart burn, large amount can affect your lungs. It should be avoided in following conditions:
Pregnancy
Breast feeding
Bleeding conditions
Diabetes
Surgery

Interactions

1. Black and white pepper interact with Lithium. Pepper might decrease metabolism and excretion of lithium.
2. P-Glycoproteins substrates interact with pepper this may cause more side effect from same medication.
3. Phenytoin interact with pepper and might increase absorption of phenytoin in the body.
4. It should be avoided with blood thinning drugs such as aspirin and warfarin. It may increase bleeding.
5. Black pepper may increase the blood level of cefotaxime and cyclosporine, resulting high effect of drugs with side effects.
6. Pepper is reported to inhibit various cytochrome enzymes, resulting in increased blood level of certain drugs like carbamazepine, midazolam, diclofenac, phenytoin, and warfarin.

CONCLUSION

This review has provided an overview of the issues that herbal drugs are safe when ingredients are pure and prescribed physician. Life-threatening events reported from them are rare, compared to pharmaceutical products. However, there are always risks when appropriate regulations do not mandate the appropriate formulation of the remedies, or when self-medication fosters abuse. Using examples from four commonly used herbal medicines, we have demonstrated that conclusive evidence of herb-drug interactions is often lacking, and where clinical observations have been made or studies conducted. This review has provided an overview of the issues that contribute to the difficulty in assessing the significance of herb-drug interactions. It is clear that.

Patients receiving drugs with a narrow safety margin and those who are most at risk of serious drug interactions

should be closely monitored to avoid the possible adverse consequences of herb-drug interactions.

REFERENCE

1. P.D. Coxeter et al., Herb-Drug Interactions: An Evidence Based Approach, Current Medicinal Chemistry, 2004; 11, 1513-1525.
2. Agrawal OP, Raju PS. In: Abdin MZ, Abroi YP, editors. Global market of herbal products: Opportunities for India. Traditional system of medicine. Narosa Publishing House: New Delhi, India, 2006; 5-10.
3. WHO Traditional Medicine Strategy 2002-2005, Document WHO/EDM/TRM/2002.1, WHO: Geneva, 2002; 11.
4. Dr. Zeeshan Afsar, Text book of "essential of herbal drug technology", PV publication, 41.
5. <https://medlineplus.gov/herbalmedicine.html>.
6. <https://www.standardprocess.com/MediHerb-Documents/Library/Catalog-Files/herb-drug-interaction-chart.pdf>.
7. Infectious Disease: Drug Interactions in Infectious Diseases, Second Edition Edited by: S. C. Piscitelli and K. A. Rodvold © Humana Press Inc., Totowa, NJ.
8. Ingolf Cascorbi, Drug Interactions-Principles, Examples and Clinical Consequences Reply, Deutsches Ärzteblatt International, August 2012.
9. Dr. Zeeshan Afsar, Text book of "essential of herbal drug technology", PV publication, 42.
10. Deutsches Ärzteblatt International | Dtsch Arztebl Int, 2012; 109(33-34): 546-56.
11. Therapeutic Products Programme Guidance Document. Drug-drug interactions: studies in vitro and in vivo (September 21, 2000). Therapeutics Products Directorate, Health Canada.
12. Fuhr U. Drug interactions with grapefruit juice: extent, probable mechanism and clinical relevance. Drug Safety, 1998; 18: 251-272.
13. Hansten P. Drug interactions. In: Applied Therapeutics: The Clinical Use of Drugs. Vancouver, WA: Applied Therapeutics, 1995; 2-10.
14. Gibaldi M. Drug interactions: part II. Ann Pharmacother, 1992; 26: 829-834.
15. Tozer TN, Bois FY, Hauck WW, Chen M-L, Williams RL. Absorption rate vs exposure which is more useful for bioequivalence testing? Pharm Res., 1996; 13: 453-456.
16. Dr. Zeeshan Afsar, Text book of "essential of herbal drug technology", PV publication, 42.
17. Dr. Zeeshan Afsar, Herb/food-drug interaction, Text book of "herbal drug technology", PV publication, 87.
18. "Hypericum perforatum (St John's wort)". CABI. 27 September 2018. Retrieved, 22 February 2019.
19. "Kava". Merriam-Webster Online Dictionary, 2018.
20. Wang, J; Qu, W; Bittenbender, H. C; Li, Q. X. "Kavalactone content and chemotype of kava beverages prepared from roots and rhizomes of *Isa* and *Mahakea* varieties and extraction efficiency of

- kavalactones using different solvents". *Journal of Food Science and Technology* 2013; 52(2): 1164–1169. doi:10.1007/s13197-013-1047-2. PMC 4325077. PMID 25694734.
21. Clough, Alan R.; Bailie, Ross S.; Currie, Bart (1 January). "Liver Function Test Abnormalities in Users of Aqueous Kava Extracts". *Journal of Toxicology: Clinical Toxicology*, 2003; 41(6): 821–829. doi:10.1081/CLT-120025347. ISSN 07313810. PMID 14677792.
 22. https://en.wikipedia.org/wiki/Ginkgo_biloba.
 23. "Ginkgo biloba". *Natural Resources Conservation Service PLANTS Database*. USDA. Retrieved 19 January.
 24. Company, Houghton Mifflin Harcourt Publishing. "The American Heritage Dictionary entry: ginkgo". www.ahdictionary.com, 2016.
 25. "The IUCN Red List of Threatened Species". *IUCN Red List of Threatened Species*. January 1998. Retrieved 24 October 2018.
 26. "Ginseng". *Cambridge Dictionaries Online*. Retrieved, 2011-06-04.
 27. Mahady, Gail B.; Fong, Harry H.S.; Farnsworth, N.R. *Botanical Dietary Supplements*. CRC Press, 2001; 207–215. ISBN 978-90-265-1855-3.
 28. Kim, Seonmin "Ginseng and Border Trespassing Between Qing China and Choson Korea". *Late Imperial China*, 2007; 28(1): 33–61. doi:10.1353/late.2007.0009.
 29. "Ginseng". *Drugs.com*. 2019. Retrieved 1 April, 2019.
 30. Zohary, Daniel; Hopf, Maria (2000). *Domestication of Plants in the Old World* (3rd ed.). Oxford University Press (published January 11, 2001; 197. ISBN 978-0-19-850357-6.
 31. Haller C, Benowitz N "Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids". *N Engl J Med*, 2000; 343 (25): 1833–38. Doi:10.1056/NEJM200012213432502. PMID 11117974.
 32. Jump up to:^{a b} Bent S, Tiedt T, Odden M, Shlipak M "The relative safety of ephedra compared with other herbal products". *Ann Intern Med*, 2003; 138(6): 468–71. doi:10.7326/0003-4819-138-6-200303180-00010. PMID 12639079.
 33. "National Center for Complementary and Alternative Medicine Consumer Advisory on ephedra". 2004-10-01. Retrieved, 2007-02-13.
 34. "Food and Drug Administration summary of actions regarding sale of ephedra supplements". Archived from the original on 2007-02-10. Retrieved, 2007-02-13.
 35. FDA Final Rule Banning Dietary Supplements With Ephedrine Alkaloids Becomes Effective". *U.S. Food and Drug Administration*. Retrieved 7 February, 2007.
 36. https://en.wikipedia.org/wiki/Black_pepper.