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Review Article

Herbal and Dietary Supplement–Drug Interactions in Patients Taking Digoxin

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Abstract

Many people who use prescription medication also take complementary and alternative medicines such as a vitamin, minerals, herbal products, or other botanical drugs. The mechanisms of interaction can be based on the following methods: affecting the absorption, metabolism, and disposition of other drugs. Pharmacological effects of digoxin include the increased force of myocardial contraction, decreased heart rate and the activity of the sympathetic nervous system. Digoxin is characterized by a narrow therapeutic index and is the potential drug for interacting with other drugs, herbs, and supplements. Since these interactions can cause fatal and dangerous complications; with regard to these properties, we decided to review the evidence about the interaction between herbal-dietary supplements and digoxin. We searched several sources, including MEDLINE (PubMed), Embase, CINAHL, the Cochrane Library, CISCOM databases from 1970 to 2018. Our keyboards for the search were digoxin interactions, digoxin-drug interaction, digoxin-supplement interaction, and herb-drug interaction. We reviewed the following types of articles for writing this review article: case reports, case series, original articles, and review articles. Taking together, 210 articles were obtained from databases. However, only seventy-one related articles were chosen for the preparation of this review article. We found fifty herbal products that could interact via a different mechanism with digoxin. St. John's wort has the most documented interactions with digoxin. Some of the information on these reviews resulted from in vitro and animal studies with no clinical evidence, and others resulted from clinical evidence. Therefore, our confirmation of them in the body is incomplete. We recommend that the use of these herbs with digoxin be avoided.

Keywords: Digoxin, Herb-drug interaction, Food-drug interactions

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Introduction

Many people who use prescription medications also take complementary and alternative medicines such as vitamins, minerals, herbal products, or other botanical drugs. These supplements have physiological and pharmacological properties that can interact with prescription medications. The mechanisms of

interaction can be based on the following methods: affecting the absorption, metabolism, and disposition of other drugs. The possibility of herb-drug interaction is highly likely because drugs contain single affective entities, while herbal products contain blends of pharmacologically active components. Digoxin is prescribed for the treatment of heart failure and atrial fibrillation. The pharmacological effects of digoxin include the increased force of myocardial contraction, decreased heart rate and the activity of the sympathetic nervous system. For treatment efficacy without potential toxic impacts of digoxin, it is recommended that the serum digoxin level be less than 1.0 ng/ml. Dioxin has various drug-drug, drug-herb, and drug-dietary supplement interactions due to its narrow therapeutic index. The use of herbal medicines is increasing. For instance, about 40% of patients with cardiovascular disease use herbal products. Hence, the study of herb-drug interactions is an important issue. Some herbal medicines with different mechanisms are interfering with digoxin, e.g. by decreasing or inhibiting the effects of digoxin or with digoxin-like effects and increasing its effects. Licorice (*Glycyrrhiza glabra*), hawthorn (*Crataegus oxyacantha*), St. John's wort (*Hypericum perforatum*), Siberian ginseng (*Eleutherococcus senticosus*), and *Ginkgo biloba* are examples of these herbal medicines. This review focuses on the interactions that exist between herbal and dietary supplements with digoxin. This systematic review aims to evaluate these interactions (1-3).

Methods

Digoxin has a narrow therapeutic index and is the potential drug for interacting with other drugs, herbs and supplements. These interactions can cause fatal and dangerous complications. Hence, with regard to these properties, we decided to review the evidence about the interaction between herbal-dietary supplements and digoxin. We searched several sources, including MEDLINE (PubMed), Embase, CINAHL, the Cochrane Library, and CISCOM databases from 1970 to 2018. Our keywords for the search were digoxin interactions, digoxin-drug interaction, digoxin-supplement interaction, and herb-drug interaction. We reviewed the following types of articles for writing this article review: case reports, case series, original articles, and review articles. Taking together, 210 articles were obtained from databases, but only seventy-one related articles were chosen for the preparation of this review article.

Results and Discussion

Digoxin is a cardiac glycoside that works by affecting sodium and potassium levels inside heart cells. It is used in the treatment of HF and AF. Digoxin can regulate heart rhythm and help the heart maintain the rate in a normal range. The half-life of digoxin is long (about 36 hours) and its usual dosing is 125-µg or 250-µg doses per day. Renal excretion is the main elimination route for the clearance of digoxin from the body. P-glycoprotein is responsible to exert digoxin into the kidney and the gut.Ttherefore, drugs and herbs affect this protein action leading to significant clinical interactions with digoxin.

Evidence of Interactions between Herbs and Supplements with Digoxin:

Eleuthero (Eleutherococcus Senticosus)

Eleuthero or Siberian ginseng is the herb from the Araliaceae family. Some effects of Eleuthero are decreasing at the time of fatigue or increasing capacity for work and concentration. The result of an in vitro study showed that ginseng has a digoxin-like immunoreactive substance that interacts with digoxin in the assessment with fluorescence polarization (FPIA) method. These interactions cause false results in serum digoxin levels. There exist similar results from other studies. In a case report study, a man who consumed digoxin and ginseng had an elevated serum digoxin level without a symptom of toxicity. After stopping using ginseng, digoxin level returned to the normal level. It has been shown in several studies that ginseng (Siberian ginseng), eleuthero (Eleutherococcus senticosis), and American ginseng (Panax quinquefolius) have similar effects on the serum levels of digoxin (4-8).

African Mistletoe, Bitter Leaf

African mistletoe (*Tapinanthus sessilifolius Blume* (ML)) from family Loranthaceae, is a herbal medicine which is used to treat malaria in Africa. Bitter leaf (*Vernonia amygdalina*) is a green leafy vegetable that contains iron, calcium, phosphorous, fiber, and vitamins such as A, B1, B2, B3, C, K. In an in-vitro

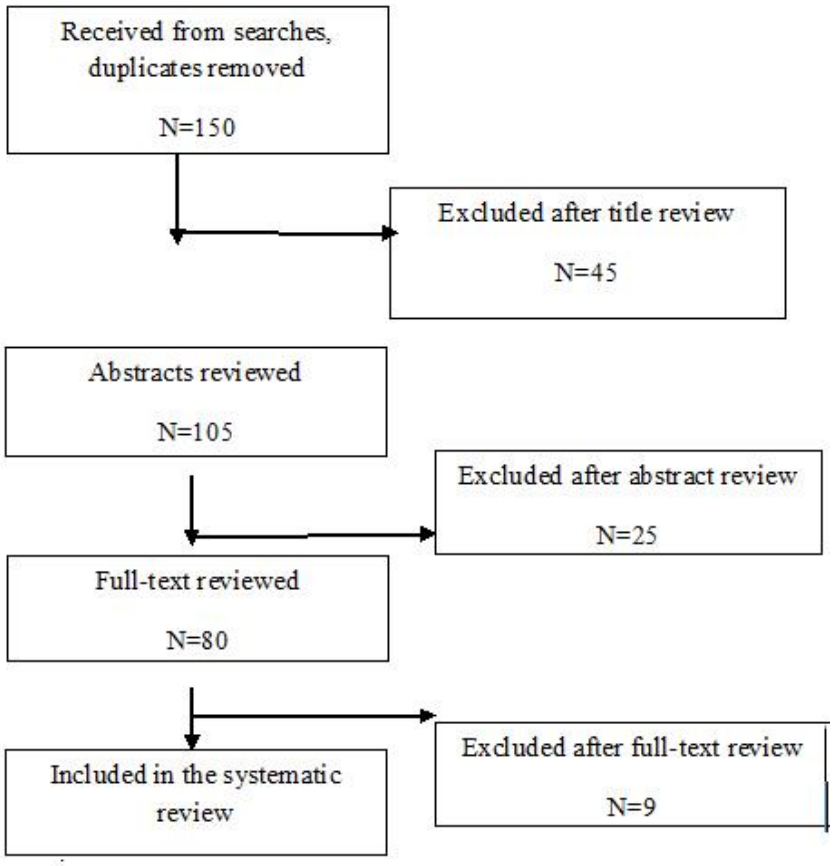

Figure 1. Methodology of article.

study, the effect of this herb on p-glycoprotein was examined. This study showed that the extract of ML could significantly inhibit p-GP and potentially increase the serum level of digoxin. (9)

Garlic Clove (Allium sativum)

The usage of garlic is the treatment of hypercholesterolemia, and prevention of arteriosclerosis. Garlic powder contains alliin, diallylsulphides, and essential oil. The effect of garlic on CYP enzymes was examined in a research in which it was suggested that garlic oil could inhibit CYP2E1. In an in vitro study, the results showed that the garlic extract could express intestinal of P-glycoprotein. Moreover, garlic extract could increase the serum level digoxin with increased absorption of digoxin from P-glycoprotein channels (10).

Ginger Rhizome (Zingiber officinale)

The therapeutic effects of ginger are related to its ability to decrease nausea and vomiting. This plant has an antiplatelet effect and can increase INR. In a study, the results showed that this plant could increase the serum levels of digoxin. Based on the FDA reports, this interaction occurred in 9 patients who consumed digoxin along with ginger (11).

Brimstone Tree (Morinda Lucida), Pawpaw (Carica Papaya)

This plant is rich in anthraquinones and is used for the treatment of diabetes in Africa. Pawpaw contains carpaine, alkaloids, terpenes, and flavanols. Pawpaw is a plant with antimalarial effects and is used to prevent cancer, treat diabetes, and prevent the recurrence of human papillomavirus (HPV). In an in-vitro study, the effect of these herbs on p-glycoprotein was examined.

Table 1: The List of Herbs and Supplements that Can Interact with Digoxin

Name of herb	Effect of interaction
Ginseng *(Siberian ginseng)*	It raised digoxin level (60-64).
Eleuthero *(Eleutherococcus senticosis)*	It raised digoxin level (62).
American ginseng *(Panax quinquefolius)*	It raised digoxin level (62).
African mistletoe *(Tapinanthus sessilifolius)*	It raised digoxin level (4).
Bitter leaf *(Vernonia amygdalina)*	It raised digoxin level (4).
Garlic clove *(Allium sativum)*	It raised digoxin level (5).
Ginger rhizome *(Zingiber officinale)*	It raised digoxin level (6).
Brimstone tree *(morinda lucida)*	It raised digoxin level (7).
Pawpaw (*Carica papaya)*	It raised digoxin level (7).
Ginkgo *(Ginkgo biloba)*	It raised digoxin level (8-10).
Black pepper *(Piper nigrum)*	It raised digoxin level (14, 15).
Grapefruit	It raised digoxin level (12).
Tangerine *(Citrus reticulate)*	It raised digoxin level (13).
Turmeric *(Curcuma longa)*	It raised digoxin level (11).
Capsicum *(Capsicum specie)*	It decreased digoxin level (20).
Horse chestnut *(Aesculus hippocastanum L.)*	It raised digoxin level (9, 19).
Peppermint *(Mentha piperita L.)*	The augmented risk of toxicity (65).
Digitalis, foxglove *(Digitalis purpurea)*	The augmented risk of toxicity (11).
Kyushin	The augmented risk of toxicity and interference with digoxin assay (47-49).
Hawthorn *(Crataegus sp.)*	The augmented risk of toxicity and interference with digoxin assay (50-53).
Senna *(Cassia senna, Cassia angustifolia)*	It can cause digoxin toxicity (38, 54).
Aloes	It can cause digoxin toxicity (57).
Squill *(Urginea maritima)*	It can lead to digoxin-type toxicity (58).
Lily of the valley *(Convallaria majalis)*	It can cause digoxin-like toxicity (58).

Kushen ***(Radix Sophorae Flavescentis)***	It can cause digoxin-like toxicity (40).
Milkweed ***(Asclepias syriaca)***	It can cause digoxin-like toxicity (45).
Black Hellebore***(Helleborus niger)***	It can cause drug toxicity (36).
Oleander ***(Nerium oleander)***	It can predispose patients to digoxin toxicity (66).
Licorice ***(Glycyrrhiza glabra)***	It can lead to digoxin toxicity by potassium depletion (55, 67).
Black Indian Hemp ***(Apocynum cannabinu L.)***	It can cause drug toxicity (36).
The summer pheasant's-eye ***(Adonis aestivalis L)***	It has additive effects with digoxin (36).
Wheat bran	It decreases absorption of digoxin (35).
Rhubarb ***(Rheum officinale, Rheum palmatum)***	It can cause digoxin toxicity (28, 38).
Horsetail ***(Equisetum arvense)***	It causes digoxin toxicity (9, 59).
St. John's wort ***(Hypericum perforatum. L.)***	It reduces serum digoxin levels and therapeutic effect (43-55)(21-32).
Psyllium ***(Plantago spp.)***	It decreases the rate of absorption of digoxin (28, 38).
Konjac ***(Amorphophallus rivieri)***	It decreases the rate of absorption of digoxin (28, 38)
Gum guar***(Cyamopsis tetragonolobus)***	It decreases the rate of absorption of digoxin (68).
Danshen ***(Saliva miltiorrhiza)***	It interferes with digoxin evaluation and can cause drug toxicity (16, 17, 69-72).
Ashwagandha ***(Withania somnifera)***	It interferes with digoxin evaluation (42, 43).
Buckthorn ***(Rhamnus cathartica)***	It interferes with evaluation and the pharmacodynamic activity of digoxin (44).
Golden seal ***(Hydrastis Canadensis)***	It increases serum digoxin concentration (10, 18)
Alfalfa ***(Medicago sativa)***	It might increase digoxin levels (11).
Kudzu ***(Pueraria Montana)***	It might increase digoxin levels (40).
Milk thistle ***(Silybum marianum)***	It reduces the AUC of digoxin (33, 34).
Shatavari (***Asparagus racemosus Willd)***	It decreases the absorption of digoxin (39).
Magnesium	It might impair the absorption of the drug (58).
Cluster bean ***(Cyamopsis tetragonoloba)***	It decreases digoxin concentration (36).
Wallflower ***(Erysimum)***	It has digoxin-like properties (36).

This study indicated that the extract of ML could significantly inhibit p-GP and potentially increase the serum level of digoxin (9-12).

Ginkgo (Ginkgo biloba)

Ginkgo extract has therapeutic properties, including recovering cognitive impairments and dementia. The effect of ginkgo on various CYP enzymes and P-glycoprotein and the results show that this plant has a minor effect on their levels. In an in vitro study, the results indicated that ginkgo could inhibit CYP2C8

and potentially increase the digoxin (13, 14,15).

Black Pepper (Piper nigrum)

Piperine is the main constituent of Black piper whose ability to inhibit several cytochrome P450-mediated pathways has been shown. It has been reported in in vitro studies that piperine is able to increase the serum levels of theophylline, phenytoin, rifampin, and propranolol. Certain human studies have showed that it can increase plasma concentrations of rifampin, phenytoin, propranolol, and theophylline. In an in vitro study, Rajinder *et al*. indicated that the piperine could inhibit P-glycoprotein-mediated, polarized transport of digoxin, and potentially increase the serum level of digoxin (16, 17).

Grapefruit

Grapefruit juice contains vitamins A and C, natural fat and glucose. Different studies showed that it could inhibit the activity of both cytochrome P-450 3A4 (CYP4503A4) and P-glycoprotein, and potentially increase the plasma level of digoxin. In an open-randomized study, the results showed that grapefruit juice could significantly increase the AUC of digoxin during the first 24 h digoxin ingestion (18).

Tangerine (Citrus reticulate), Turmeric (Curcuma longa)

Mandarin orange (Citrus reticulata) is a citrus tree whose juice contains disomin that can inhibit p-glycoprotein CYP3A4 and CYP1A2 in vitro. Therefore, it can potentially increase the serum level of digoxin. (19) Turmeric (Curcuma Longa) contains curcumin and curcumas. The results of an in vitro study showed that curcumas could increase the expressions of P-gp. Furthermore, it was indicated that curcumin could inhibit the activity of P-gp, and turmeric could influence the plasma levels of digoxin (20).

Capsicum (Capsicum specie)

Capsaicinoids are the main components in chili peppers. These components can induce acute pain, cough, and long-term analgesia. A study showed that the intensive use of capsaicin could inhibit P-glycoprotein, while long-term exposure resulted in P-glycoprotein. Hence, capsaicin can influence the serum level of digoxin. In the co-administration of capsaicin and digoxin, initially, digoxin levels raise and then decrease (21).

Horse Chestnut (Aesculus hippocastanum L.)

Horse chestnut has long been consumed by people as a natural remedy to cure joint pain, bladder and digestive issues, fever, and leg cramps. Consumption of horse chestnut is advantageous for several reasons, most notably due to its ability to figt chronic venous insufficiency (a vascular condition), hemorrhoids, and swelling after surgery. In an in vitro study, the esults revealed that the horse chestnut could inhibit CYP and potentially increase the level of digoxin (14, 22).

Peppermint (Mentha piperita L.)

Peppermint (Mentha piperita) is used for treating digestive disorders and decreasing the symptoms in irritable bowel syndrome (IBS) patients. Peppermint contains about 30 micrograms of digoxin equivalents per cup. Drinking 5 cups of peppermint tea per day has a cardiac effect similar to a therapeutic daily dose of digoxin. Peppermint has potentially the risk of digital-like toxicity, particularly, when it is used along with digoxin (23).

Digitalis, Foxglove (Digitalis purpurea)

Digitalis purpurea and *Digitalis lanata* belong to *Digitalis* species. These plants have traditionally been used to treat heart conditions, fevers, wounds, swelling or inflammation, sores, ulcers, cancer, edema, and infections. Since these plants contain cardiac glycosides, their concomitant use with digoxin can potentially induce cardiac toxicity (11).

Kyushin

Kyushin is a Chinese medicine that has a cardiac effect. The results of an in vitro study showed that it could crossreact with digoxin assays and have digoxin-like immunoreactivity. Moreover, it contains a component digoxin-like effect. Then, it can augment the risk of digoxin toxicity and interfere with digoxin assay (24-26)**.**

Hawthorn (Crataegus sp.)

Hawthorn is a plant that has traditionally been used in the treatment of heart disease, hypertension, hyperlipidemia, and congestive heart failure. This plant contains alkaloid flavonoids, i.e., epicatechin, chlorogenic acid, isoquercitin, and hyperoside. These components have digoxin-like effects. The result of an in-vitro study indicated that the alkaloids of hawthorn are structurally similar to digoxin and interfere with serum digoxin measurement using immunoassays. In a

randomized crossover trial conducted on 8 healthy volunteers, the results showed that the consumption of digoxin and hawthorn may be safe, though hawthorn has an effect on P-glycoprotein activity. The use of hawthorn is associated with digoxin augmentation, risk of toxicity, and interference with digoxin assay (27-30).

Senna (Cassia senna, Cassia angustifolia)

Sennoside or senna is a herbal medicine used to treat constipation. Hypokalemia induced by sennoside theoretically can cause digoxin toxicity. In an in-vitro study, the impact of anthraquinones of senna on the absorption of digoxin was examined. The results showed that this component could decrease digoxin (31, 32).

Aloes

Aloes is a plant that has traditionally been used to treat diabetes, hepatitis, inflammatory bowel diseases, osteoarthritis, stomach ulcers, asthma, radiation-related skin sores, fever, itching, and inflammation. Moreover, it has the laxative effect and theoretically can cause hypokalemia. Therefore, it increases the risk of digoxin toxicity (33).

Squill (Urginea maritima)

Squill is a plant used in the treatment of cardiac diseases such as mild heart failure, irregular heartbeat, "nervous" heart complaints, and certain vein problems. It has digoxin-like effects because of containing steroidal cardioactive glycosides, including scillaren A, glucoscillaren A, scillaridin A, and scilliroside. Hence, theoretically, it can lead to digoxin-type toxicity (34).

Lily of the Valley (Convallaria majalis)

This medication contains cardiac glycosides similar to those in digitalis and is used to treat heart palpitations, arrhythmia, congestive heart failure (CHF), cardiac edema, cardiac asthma, kidney and bladder stones, and urinary tract infection. It theoretically can cause digoxin-like toxicity (35, 36).

Milkweed (Asclepias syriaca)

The product from this plant is used in the treatment of venereal disease, edema, and kidney stones. The main components of this plant include pregnane and cardiac glycosides, as well as glycosylated flavonoids that can cause digoxin-like toxicity (35).

Black Hellebore (Helleborus niger)

The traditional usage of this plant includes the treatment of nausea, worms, kidney infections, colds, and constipation. Since this plant contains components similar to digoxin, its simultaneous use along with digoxin can cause drug toxicity (37).

Oleander (Nerium oleander)

Oleander is a poisonous plant which issometimes used to treat skin problems, asthma, epilepsy, cancer, painful menstrual periods, leprosy, malaria, ringworm, indigestion, and venereal diseases. This plant has the cardiac effect. Therefore, its simultaneous use along with digoxin can predispose patients to digoxin toxicity (38).

Licorice (Glycyrrhiza glabra)

The herbal product of licorice is used in the treatment of peptic ulcer and catarrhs of the upper respiratory tract**.** The main components of this plant are glycyrrhizin and glycyrrhetic acid that can inhibit CYP3A4. It theoretically can lead to digoxin toxicity by potassium depletion (39, 40).

Black Indian Hemp (Apocynum cannabinu L.)

This plant is used for preparing laxative tea and treating hair loss. It contains the cardiac glycoside. Hemce, it can cause heart toxicity, particularly along with digoxin (37).

The Summer Pheasant's-eye (Adonis aestivalis L)

This plant contains cardenolides and can cause acute myocardial necrosis and endocardial hemorrhage. It has additive effects along with digoxin (37).

Wheat Bran

The medical uses of wheat bran include preventing colon diseases (including cancer), stomach cancer, breast cancer, gallbladder disease, hemorrhoids and hiatal hernia. Moreover, it is used in the treatment of constipation, irritable bowel syndrome (IBS), high cholesterol, high blood pressure, and type 2 diabetes. It has been shown in pharmacokinetic studies (one study was conducted on 16 healthy volunteers and another was performed on 30 elderly patients) that it can reduce the serum level of digoxin because it contains high levels of fiber. Fiber can reduce the absorption of digoxin in the gut (41).

Rhubarb (Rheum officinale, Rheum palmatum)

Medical uses of rhubarb include constipation, diarrhea, heartburn, stomach pain, and gastrointestinal (GI) bleeding. It theoretically can cause digoxin toxicity by potassium depletion (31, 32).

Horsetail (Equisetum arvense)

Medical uses of horsetail include stopping bleeding, healing ulcers and wounds, and treating tuberculosis and kidney problems. It theoretically can cause digoxin toxicity by potassium depletion (14, 42).

St. John's Wort (Hypericum perforatum. L.)

The main medical use of St. John's Wort (Hypericum perforatum) is the treatment of mild to moderate forms of depression. The most components of St. John's Wort are the naphthodianthrone hypericin and the phloroglucinol hyperforin. It is primarily involved in both pharmacokinetic and pharmacodynamic interactions. It has been shown in several pharmacokinetic and clinical trials that it can induce P-glycoprotein. Hence, it can reduce serum digoxin levels and has therapeutic effect. According to the results of a single-blind, placebo-controlled parallel study, this plant has a time-dependent effect on digoxin pharmacokinetics. In a randomized, placebo-controlled, parallel-group study that was conducted on 96 healthy volunteers in 3 study parts, the results showed that the concomitant use of a high dose of hyperforin with digoxin cause dose-dependent reduction in serum digoxin level. In another randomized trial that was performed on healthy volunteers, the results showed that this plant could increase the expression of p-glycoprotein (43-55).

Gum Guar (Cyamopsis tetragonolobus)

This herbal product is used for different commercial products. In a study, the interaction of digoxin with gum guar was examined in 10 healthy volunteers. The results of this study showed that this product can reduce serum digoxin level during the early absorption period because it contains high fibe (31, 32)r.

Psyllium (Plantago spp.)

Psyllium is used for its laxative effects. Theoretically, it decreases the rate of absorption of digoxin because of containing high levels of mucilage (31, 32).

Konjac (Amorphophallus rivieri)

Konjac contains high levels of fiber; hence, decreases the rate of dioxin absorption (31, 32).

Danshen (Saliva miltiorrhiza)

This Chinese medicinal plant has traditionally been used to treat acute ischemic stroke and myocardial infarction. Danshen can inhibit digoxin efflux by P-gp. Therefore, it can cause drug toxicity. The effect of danshen on the serum level of digoxin that was measured by different methods has been examined in some in-vitro studies. The results of these studies showed no interference of danshen in either EMIT, Randox, or ECLIA assays (enzyme-linked chemiluminescent immunosorbent (ECLIA) digoxin assay) but interference with the FPIA assay was (57-62).

Ashwagandha (Withania somnifera)

Ashwagandha is used to treat arthritis, anxiety, bipolar disorder, attention deficit hyperactivity disorder (ADHD), balance, obsessive-compulsive disorder (OCD), trouble sleeping (insomnia), tumors, tuberculosis, asthma, white patchiness (Leukoderma), bronchitis, backache, fibromyalgia, menstrual problems, hiccups, Parkinson's disease, and chronic liver disease. The results of two in-vitro studies showed that its extract can interfere with measurements using immunoassays digoxin (63, 64).

Goldenseal (Hydrastis canadensis)

The historical use of goldenseal includes the treatment of gastrointestinal disturbances, urinary disorders, skin ailments, and various infections. A clinical trial performed on twenty healthy volunteers showed that it does not affect the disposition of digoxin. The results of an in-vitro study indicated that it can interfere with the evaluation and pharmacodynamics activity of digoxin (65).

Shatavari (Asparagus racemosus Willd)

Asparagus racemosus (Shatavari) is used in the treatment of dyspepsia (amlapitta). This plant reduces gastric emptying time similar to metoclopramide. Therefore, theoretically it decreases the absorption of digoxin (69).

Magnesium

It might impair drug absorption (34).

Cluster bean *(Cyamopsis tetragonoloba)*

It decreases digoxin concentration (37).

Wallflower (Erysimum)

The traditional use of wallflower includes treating heart problems, constipation, liver disease, and gallbladder disease. Due to the effect of wallflower on the heart, taking it along with digoxin can cause heart toxicity (37).

Milk Thistle *(Silybum marianum)*

Milk thistle product has a therapeutic effect on liver diseases. Its extract has minor effects on the CYP enzymes or P-glycoprotein. In a clinical trial, the impact of milk thistle on the pharmacokinetics of digoxin was examined and the results showed that milk thistle administration had no statistically significant effects on digoxin pharmacokinetics (67, 68).

Pharmacodynamic and pharmacokinetic interactions are types of interaction mechanisms between drugs and herb-dietary supplements. Pharmacodynamic interactions are defined as the intrinsic actions interacting with herb-dietary supplements that augment or antagonize the activity of another drug. Pharmacokinetic interactions are defined as the result of alterations in metabolism, excretion, absorption, or protein binding of the active ingredient of the herb-dietary supplement or the drug (70). Furthermore, interactions between digoxin and herb-supplements are categorized as pharmacodynamic and pharmacokinetic interactions. The pharmacokinetics of digoxin is variable, and the concomitant consumption herbs and dietary supplements can affect digoxin pharmacokinetics. Some herbs or supplements can reduce digoxin absorption. Digoxin is mostly eliminated via the kidneys and a high-affinity substrate for the multidrug efflux transporter P-glycoprotein. The components that affect P-gp activity can increase or decrease serum levels of digoxin (1-3). African mistletoe, bitter leaf (9), garlic clove (10), ginger rhizome (11), brimstone tree, pawpaw (12), ginkgo (13-15), turmeric (20), grapefruit (18), tangerine (19), black pepper (16,17), danshen (57, 62), goldenseal (15,66) and horse chestnut (14, 22) can potentially raise digoxin level by inhibiting P-Glycoprotein drug efflux that ultimately results in digoxin toxicity. Capsicum (21), St. John's wort (43-55), and milk thistle (67, 68) decreased digoxin level by the induction (or stimulation) of the activity P-glycoprotein drug efflux. (21) The supplement contains high fiber such as wheat bran (41) and cluster bean (37) can reduce the absorption and decrease the effectiveness of digoxin. Psyllium, konjac (31, 32), and gum guar can delay gastric emptying and then decrease the rate of digoxin absorption. Shatavari (69) increases the gastric emptying rate and then decreases digoxin absorption. Herbal products contain isoflavones such as alfalfa (11), kudzu (36) and red clover (71) that can increase digoxin levels.

Other herbs containing constituents structurally similar to digoxin, including ashwagandha (63, 64), danshen, ginseng (4-8), and buckthorn (65) interfere with digoxin immunoassay.

Examples of Pharmacodynamic Interactions: Some herbal products have glycoside or other components named digoxin-like substances and have similar effects. They include wallflower (37), lily of the valley (35), kushen (36), milkweed black hellebore (35), oleander(38), black Indian hemp, the summer pheasant's-eye (37), peppermint (23), digitalis, foxglove (11), kyushin (24-26) and hawthorn (27-30). This substance has additive effects with digoxin that can potentially cause digoxin-like toxicity. In a situation such as hypokalemia, or low potassium, digoxin can more easily bind to the ATPase pump and then result in digoxin toxicity. Numerous herbs such as senna (31, 32), licorice, (39, 40), aloes (33), squill (34), rhubarb (31, 32), and horsetail (14, 42) cause diarrhea or potassium depletion and predispose to digoxin toxicity. The summary of these results has been presented in Table 1.

Conclusion

We found fifty herbal products that can interact by a different mechanism with digoxin, and St. John's wort has the most documented interactions with digoxin. Some of the information on these reviews result from in vitro and animal studies with no clinical evidence, while others result from clinical evidence. Hence, our acknowledgment about them in the body is incomplete. We recommend that the use of these herbs with digoxin be avoided. The purpose of this article is to provide a comprehensive and functional source about the interactions of herbs and foods with digoxin for the user-patient and the person prescribing this drug.

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None.

Conflict of Interest

The authors declare that they have no conflict of interest.

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