

## Review Article

# Herbal and Dietary Supplement–Drug Interactions in Patients Taking Digoxin

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Received: 13.01.2020; Accepted: 28.01.2021

## 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, CISCOP 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 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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**Please cite this article as:** Ahmadpour F, Ahmadpour F. Herbal and Dietary Supplement–Drug Interactions in Patients Taking Digoxin. *Herb. Med. J.* 2021; in press.

## 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. Digoxin 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, 2, 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 CISCOP 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- $\mu$ g or 250- $\mu$ g 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. Therefore, 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 senticosus), and American ginseng (*Panax quinquefolius*) have similar effects on the serum levels of digoxin. (4,5,6,7,8)

#### *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

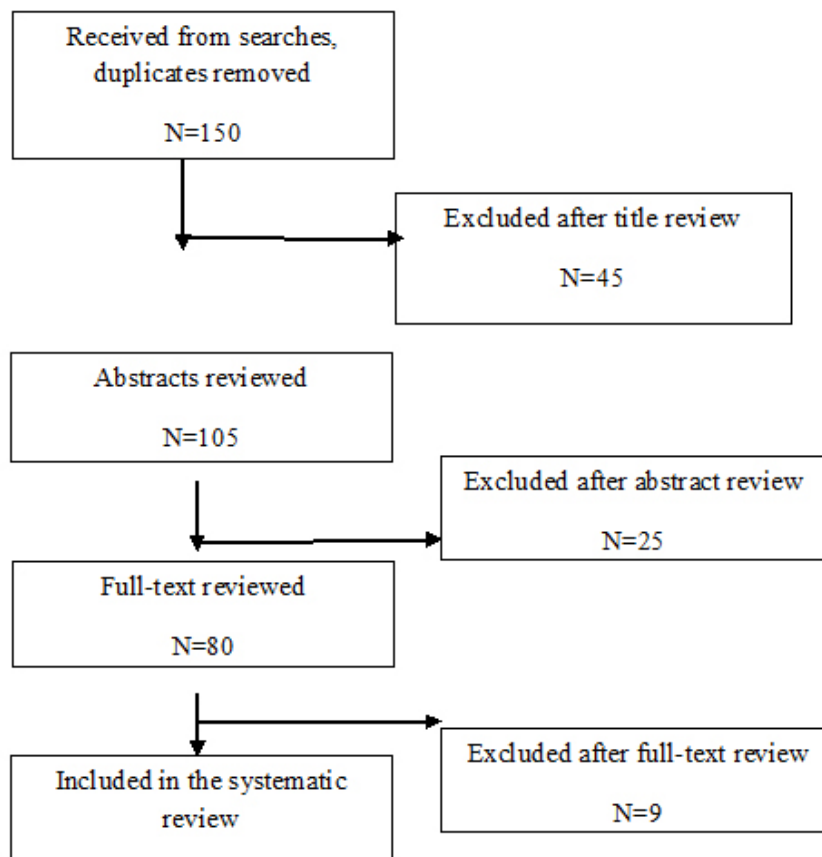


Figure 1. Methodology of article.

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

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

<b>Kushen (<i>Radix Sophorae Flavescentis</i>)</b>	It can cause digoxin-like toxicity (40).
<b>Milkweed (<i>Asclepias syriaca</i>)</b>	It can cause digoxin-like toxicity (45).
<b>Black Hellebore(<i>Helleborus niger</i>)</b>	It can cause drug toxicity (36).
<b>Oleander (<i>Nerium oleander</i>)</b>	It can predispose patients to digoxin toxicity (66).
<b>Licorice (<i>Glycyrrhiza glabra</i>)</b>	It can lead to digoxin toxicity by potassium depletion (55, 67).
<b>Black Indian Hemp (<i>Apocynum cannabinu L.</i>)</b>	It can cause drug toxicity (36).
<b>The summer pheasant's-eye (<i>Adonis aestivalis L</i>)</b>	It has additive effects with digoxin (36).
<b>Wheat bran</b>	It decreases absorption of digoxin (35).
<b>Rhubarb (<i>Rheum officinale, Rheum palmatum</i>)</b>	It can cause digoxin toxicity (28, 38).
<b>Horsetail (<i>Equisetum arvense</i>)</b>	It causes digoxin toxicity (9, 59).
<b>St. John's wort (<i>Hypericum perforatum. L.</i>)</b>	It reduces serum digoxin levels and therapeutic effect (43-55)(21-32).
<b>Psyllium (<i>Plantago spp.</i>)</b>	It decreases the rate of absorption of digoxin (28, 38).
<b>Konjac (<i>Amorphophallus rivieri</i>)</b>	It decreases the rate of absorption of digoxin (28, 38)
<b>Gum guar(<i>Cyamopsis tetragonolobus</i>)</b>	It decreases the rate of absorption of digoxin (68).
<b>Danshen (<i>Saliva miltiorrhiza</i>)</b>	It interferes with digoxin evaluation and can cause drug toxicity (16, 17, 69-72).
<b>Ashwagandha (<i>Withania somnifera</i>)</b>	It interferes with digoxin evaluation (42, 43).
<b>Buckthorn (<i>Rhamnus cathartica</i>)</b>	It interferes with evaluation and the pharmacodynamic activity of digoxin (44).
<b>Golden seal (<i>Hydrastis Canadensis</i>)</b>	It increases serum digoxin concentration (10, 18)
<b>Alfalfa (<i>Medicago sativa</i>)</b>	It might increase digoxin levels (11).
<b>Kudzu (<i>Pueraria Montana</i>)</b>	It might increase digoxin levels (40).
<b>Milk thistle (<i>Silybum marianum</i>)</b>	It reduces the AUC of digoxin (33, 34).
<b>Shatavari (<i>Asparagus racemosus Willd</i>)</b>	It decreases the absorption of digoxin (39).
<b>Magnesium</b>	It might impair the absorption of the drug (58).
<b>Cluster bean (<i>Cyamopsis tetragonoloba</i>)</b>	It decreases digoxin concentration (36).
<b>Wallflower (<i>Erysimum</i>)</b>	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 reticulata*), 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 fight chronic venous insufficiency (a vascular condition), hemorrhoids, and swelling after surgery. In an in vitro study, the results 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, 25, 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, isoquercetin, 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, 28, 29, 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, glucoscallaren 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 is sometimes 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. Hence, 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 fiber. (31, 32)

***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. (1,2,3) African mistletoe, bitter leaf (9), garlic clove (10), ginger rhizome (11), brimstone tree, pawpaw (12), ginkgo (13,14,15), 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.

## Acknowledgements

None.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## References

- Gardiner P, Phillips RS, Shaughnessy AF. Herbal and dietary supplement-drug interactions in patients with chronic illnesses. *American family physician*. 2008;77(1):73-8.
- Fugh-Berman A, Ernst E. Herb-drug interactions: review and assessment of report reliability. *British journal of clinical pharmacology*. 2001;52(5):587-95.
- Ting LS, Shalansky SJ, Neall E, Ensom MH. Use of dietary supplements by patients taking digoxin. *The Canadian Journal of Hospital Pharmacy*. 2008;61(1).
- Dasgupta A, Wu S, Actor J, Olsen M, Wells A, Datta P. Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays: significant variation in digoxin-like immunoreactivity among commercial ginsengs. *American journal of clinical pathology*. 2003;119(2):298-303.
- McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. *CMAJ: Canadian Medical Association Journal*. 1996;155(3):293.
- Dasgupta A, Reyes MA. Effect of Brazilian, Indian, Siberian, Asian, and North American ginseng on serum digoxin measurement by immunoassays and binding of digoxin-like immunoreactive components of ginseng with Fab fragment of antidigoxin antibody (Digibind). *American journal of clinical pathology*. 2005;124(2):229-36.
- Chow L, Johnson M, Wells A, Dasgupta A. Effect of the traditional chinese medicines Chan Su, Lu-Shen-Wan, Dan Shen, and Asian Ginseng on Serum Digoxin measurement by Tinaquant (Roche) and Synchron LX system (Beckman) digoxin immunoassays. *Journal of clinical laboratory analysis*. 2003;17(1):22-7.
- Awang DV. Siberian ginseng toxicity may be case of mistaken identity. *CMAJ: Canadian Medical Association Journal*. 1996;155(9):1237.
- Oga EF, Sekine S, Shitara Y, Horie T. P-glycoprotein mediated efflux in Caco-2 cell monolayers: the influence of herbals on digoxin transport. *Journal of ethnopharmacology*. 2012;144(3):612-7.
- Berginc K, Žakelj S, Kristl A. In vitro interactions between aged garlic extract and drugs used for the treatment of cardiovascular and diabetic patients. *European journal of nutrition*. 2010;49(6):373-84.
- Ondieki G, Nyagblordzro M, Kikete S, Liang R, Wang L, He X. Cytochrome P450 and P-glycoprotein-mediated interactions involving African herbs indicated for common noncommunicable diseases. *Evidence-Based Complementary and Alternative Medicine*. 2017;2017.
- Mauro VF, Mauro LS, Kleshinski JF, Khuder SA, Wang Y, Erhardt PW. Impact of Ginkgo biloba on the pharmacokinetics of digoxin. *American journal of therapeutics*. 2003;10(4):247-51.
- Hellum BH, Nilsen OG. In vitro inhibition of CYP3A4 metabolism and P-glycoprotein-mediated transport by trade herbal products. *Basic & clinical pharmacology & toxicology*. 2008;102(5):466-75.
- Etheridge AS, Black SR, Patel PR, So J, Mathews JM. An in vitro evaluation of cytochrome P450 inhibition and P-glycoprotein interaction with goldenseal, Ginkgo biloba, grape seed, milk thistle, and ginseng extracts and their constituents. *Planta medica*. 2007;73(8):731.
- Bhardwaj RK, Glaeser H, Becquemont L, Klotz U, Gupta SK, Fromm MF. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. *Journal of Pharmacology and Experimental Therapeutics*. 2002;302(2):645-50.
- Han Y, Tan TM, Lim LY. In vitro and in vivo evaluation of the effects of piperine on P-gp function and expression. *Toxicology and applied pharmacology*. 2008;230(3):283-9.
- Lim GE, Li T, Buttar HS. Interactions of grapefruit juice and cardiovascular medications: a potential risk of toxicity. *Experimental & Clinical Cardiology*. 2003;8(2):99.
- Mallhi TH, Sarriff A, Adnan AS, Khan YH, Qadir MI, Hamzah AA, et al. Effect of fruit/vegetable-drug interactions on CYP450, OATP and p-glycoprotein: A systematic review. *Tropical Journal of Pharmaceutical Research*. 2015;14(10):1927-35.
- Hou XL, Takahashi K, Tanaka K, Tougou K, Qiu F, Komatsu K, et al. Curcuma drugs and curcumin regulate the expression and function of P-gp in Caco-2 cells in completely opposite ways. *International Journal of Pharmaceutics*. 2008;358(1-2):224-9.
- Reilly CA, Yost GS. Metabolism of capsaicinoids by P450 enzymes: a review of recent findings on reaction mechanisms, bio-activation, and detoxification processes. *Drug metabolism reviews*. 2006;38(4):685-706.
- Hellum BH, Hu Z, Nilsen OG. The induction of CYP1A2, CYP2D6 and CYP3A4 by six trade herbal products in cultured primary human hepatocytes. *Basic & clinical pharmacology & toxicology*. 2007;100(1):23-30.
- Longerich L, Johnson E, Gault MH. Digoxin-like factors in herbal teas. *Clinical and investigative medicine. Medecine clinique et experimentale*. 1993;16(3):210-8.
- Fushimi R, Tachi J, Amino N, Miyai K. Chinese medicine interfering with digoxin immunoassays. *The Lancet*. 1989;333(8633):339.
- Cheng TO. Herbal interactions with cardiac drugs. *Archives of Internal Medicine*. 2000;160(6):870-1.
- Xie S, Spelmink L, Codemo M, Subramanian K, Pütsep K, Henriques-Normark B, et al. Cinobufagin modulates human innate immune responses and triggers antibacterial activity. *PLoS One*. 2016;11(8):e0160734.
- Dasgupta A, Kidd L, Poindexter BJ, Bick RJ. Interference of hawthorn on serum digoxin measurements by immunoassays and pharmacodynamic interaction with digoxin. *Archives of pathology & laboratory medicine*. 2010;134(8):1188-92.
- Tanknow R, Tamer HR, Streetman DS, Smith SG, Welton JL, Annesley T, et al. Interaction study between digoxin and a preparation of hawthorn (*Crataegus oxyacantha*). *The Journal of Clinical Pharmacology*. 2003;43(6):637-42.
- Chang Q, Zuo Z, Harrison F, Chow MS. Hawthorn. *The Journal of Clinical Pharmacology*. 2002;42(6):605-12.
- Davidson P, Hancock K, Leung D, Ang E, Chang E, Thompson DR, et al. Traditional Chinese Medicine and heart disease: what does Western medicine and nursing science know about it. *European Journal of Cardiovascular Nursing*. 2003;2(3):171-81.
- Newall CA, Anderson LA, Phillipson JD. Herbal medicines. A guide for health-care professionals. The pharmaceutical press; 1996.
- Laitinen L, Takala E, Vuorela H, Vuorela P, Kaukonen AM, Marvola M. Anthranoid laxatives influence the absorption of poorly permeable drugs in human intestinal cell culture model (Caco-2). *European Journal of Pharmaceutics and Biopharmaceutics*. 2007;66(1):135-45.
- Boudreau MD, Beland FA. An evaluation of the biological and toxicological properties of Aloe barbadensis (miller), Aloe vera. *Journal of Environmental Science and Health Part C*. 2006;24(1):103-54.
- Mehralian HA, Moghaddasi J, Rafiei H. The prevalence of potentially beneficial and harmful drug-drug interactions in intensive care units. *Drug metabolism and personalized therapy*. 2019;34(1).
- Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Archives of internal medicine*. 1998;158(20):2200-11.
- Huang KC. The pharmacology of Chinese herbs. CRC press. 1998.

37. Mashour NH, Lin GI, Frishman WH. Herbal medicine for the treatment of cardiovascular disease: clinical considerations. *Archives of internal medicine*. 1998;158(20):2225-34.
38. Eddleston M, Ariaratnam CA, Sjöström L, Jayalath S, Rajakanthan K, Rajapakse S, et al. Acute yellow oleander (*Thevetia peruviana*) poisoning: cardiac arrhythmias, electrolyte disturbances, and serum cardiac glycoside concentrations on presentation to hospital. *Heart*. 2000;83(3):301-6.
39. Li HY, Xu W, Su J, Zhang X, Hu LW, Zhang WD. In vitro and in vivo inhibitory effects of glycyrrhetic acid on cytochrome P450 3A activity. *Pharmacology*. 2010;86(5-6):287-92.
40. Ernst E. *Professional's Handbook of Complementary and Alternative Medicines. Focus on Alternative and Complementary Therapies*. 2000;5(1):56-59.
41. Nordström M, Melander A, Robertsson E, Steen B. Influence of wheat bran and of a bulk-forming ispaghula cathartic on the bioavailability of digoxin in geriatric in-patients. *Drug-nutrient interactions*. 1987;5(2):67-9.
42. Brinker FJ. *Herb contraindications and drug interactions: with appendices addressing specific conditions and medicines*. Eclectic medical publications 1998.
43. Dresser GK, Schwarz UI, Wilkinson GR, Kim RB. Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. *Clinical Pharmacology & Therapeutics*. 2003;73(1):41-50.
44. Fugh-Berman A. Herb-drug interactions. *The Lancet*. 2000;355(9198):134-8.
- 45- Hu Z, Yang X, Ho PC, Chan SY, Heng PW, Chan E, et al. Herb-drug interactions. *Drugs*. 2005 1;65(9):1239-82.
46. John A, Brockmüller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clinical Pharmacology & Therapeutics*. 1999;66(4):338-45.
47. John A, Brockmüller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clinical Pharmacology & Therapeutics*. 1999;66(4):338-45.
48. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *British journal of clinical pharmacology*. 2002;54(4):349-56.
49. Mueller SC, Uehleke B, Woehling H, Petzsch M, Majcher-Peszynska J, Hehl EM, et al. Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin. *Clinical Pharmacology & Therapeutics*. 2004;75(6):546-57.
50. Croom EM. *Herbal Medicines: A Guide for Healthcare Professionals*. *Economic Botany*. 2005;59(3):306.
51. Hennessy M, Kelleher D, Spiers JP, Barry M, Kavanagh P, Back D, et al. St John's wort increases expression of P-glycoprotein: implications for drug interactions. *British journal of clinical pharmacology*. 2002;53(1):75-82.
52. Dürr D, Stieger B, Kullak-Ublick GA, Rentsch KM, Steinert HC, et al. St John's Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clinical Pharmacology & Therapeutics*. 2000;68(6):598-604.
53. Arold G, Donath F, Maurer A, Diefenbach K, Bauer S, Henneicke-von Zepelin HH, et al. No relevant interaction with alprazolam, caffeine, tolbutamide, and digoxin by treatment with a low-hyperforin St John's wort extract. *Planta medica*. 2005;71(04):331-7.
54. Gurley BJ, Swain A, Hubbard MA, Williams DK, Barone G, Hartsfield F, et al. Clinical assessment of CYP2D6-mediated herb-drug interactions in humans: Effects of milk thistle, black cohosh, goldenseal, kava kava, St. John's wort, and Echinacea. *Molecular nutrition & food research*. 2008;52(7):755-63.
55. Huupponen R, Seppälä P, Iisalo E. Effect of guar gum, a fibre preparation, on digoxin and penicillin absorption in man. *European journal of clinical pharmacology*. 1984;26(2):279-81.
56. Wahed A, Dasgupta A. Positive and negative in vitro interference of Chinese medicine Dan Shen in serum digoxin measurement: elimination of interference by monitoring free digoxin concentration. *American journal of clinical pathology*. 2001;116(3):403-8.
57. Yu XY, Lin SG, Zhou ZW, Chen X, Liang J, Liu PQ, et al. Role of P-glycoprotein in the intestinal absorption of tanshinone IIA, a major active ingredient in the root of *Salvia miltiorrhiza* Bunge. *Current drug metabolism*. 2007;8(4):325-40.
58. Yu XY, Zhou ZW, Lin SG, Chen X, Yu XQ, Liang J, et al. Role of ATP-binding cassette drug transporters in the intestinal absorption of tanshinone IIB, one of the major active diterpenoids from the root of *Salvia miltiorrhiza*. *Xenobiotica*. 2007;37(4):375-415.
59. Dasgupta A, Actor JK, Olsen M, Wells A, Datta P. In vivo digoxin-like immunoreactivity in mice and interference of Chinese medicine Danshen in serum digoxin measurement: elimination of interference by using a chemiluminescent assay. *Clinica chimica acta*. 2002;317(1-2):231-4.
60. Dasgupta A, Kang E, Olsen M, Actor JK, Datta P. New enzyme-linked chemiluminescent immunosorbent digoxin assay is free from interference of Chinese medicine DanShen. *Therapeutic drug monitoring*. 2006;28(6):775-8.
61. Datta P, Dasgupta A. Effect of Chinese medicines Chan Su and Danshen on EMIT 2000 and Randox digoxin immunoassays: wide variation in digoxin-like immunoreactivity and magnitude of interference in digoxin measurement by different brands of the same product. *Therapeutic drug monitoring*. 2002;24(5):637-44.
62. Dasgupta A, Peterson A, Wells A, Actor JK. Effect of Indian Ayurvedic medicine Ashwagandha on measurement of serum digoxin and 11 commonly monitored drugs using immunoassays: study of protein binding and interaction with Digibind. *Archives of pathology & laboratory medicine*. 2007;131(8):1298-303.
63. Dasgupta A, Kang E, Olsen M, Actor JK, Datta P. Interference of Asian, American, and Indian (*Ashwagandha*) ginsengs in serum digoxin measurements by a fluorescence polarization immunoassay can be minimized by using a new enzyme-linked chemiluminescent immunosorbent or turbidimetric assay. *Archives of pathology & laboratory medicine*. 2007;131(4):619-21.
64. Kuhn MA. *Herbal remedies: drug-herb interactions*. *Critical care nurse*. 2002;22(2):22-32.
65. Gurley BJ, Swain A, Barone GW, Williams DK, Breen P, Yates CR, et al. Effect of goldenseal (*Hydrastis canadensis*) and kava kava (*Piper methysticum*) supplementation on digoxin pharmacokinetics in humans. *Drug metabolism and disposition*. 2007;35(2):240-5.
66. Salphati L. Metabolism of digoxin and digoxigenin digitoxosides in rat liver microsomes: involvement of cytochrome P4503A. *Xenobiotica*. 1999;29(2):171-85.
67. Gurley BJ, Barone GW, Williams DK, Carrier J, Breen P, Yates CR, et al. Effect of milk thistle (*Silybum marianum*) and black cohosh (*Cimicifuga racemosa*) supplementation on digoxin pharmacokinetics in humans. *Drug metabolism and disposition*. 2006;34(1):69-74.
68. Dalvi SS, Nadkarni PM, Gupta KC. Effect of *Asparagus racemosus* (Shatavari) on gastric emptying time in normal healthy volunteers. *Journal of Postgraduate Medicine*. 1990;36(2):91.
69. Gardiner P, Phillips RS, Shaughnessy AF. Herbal and dietary supplement-drug interactions in patients with chronic illnesses. *American family physician*. 2008;77(1):73-8.
70. Peng SX, Ritchie DM, Cousineau M, Danser E, DeWire R, Floden J. Altered oral bioavailability and pharmacokinetics of P-glycoprotein substrates by coadministration of biochanin A. *Journal of pharmaceutical sciences*. 2006;95(9):1984-93.

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