



## MEDICINAL PLANTS: NATURAL BUT NOT INNOCUOUS (PART 1)

**OBJECTIVE** To analyze the evidence about the adverse effects and drug interactions of some of the most consumed medicinal plants. **MATERIAL AND METHODS** Ten of the most consumed medicinal plants were selected. A PubMed search was performed including articles on therapeutic use and safety of the selected plants. We report the results obtained in the data product information of herbal medicines approved by the Spanish Agency for Medicines and Health Products and the public evaluation reports of the European Medicines Agency. Drug interactions were extracted from the Memorial Sloan Kettering Cancer Center website, UpToDate and Stockley's Drug Interactions databases. **RESULTS AND CONCLUSIONS** The use of garlic supplementation in patients receiving antiplatelet or anticoagulation therapy or patients using antiretroviral therapy is not recommended. The intake of aloe vera is not recommended, as it may cause electrolyte alterations and gastrointestinal disorders. Its laxative effects are a consequence of the mucosal irritation. Concomitant use of blueberries and anticoagulant medicines and antiplatelet agents is not recommended. Concomitant use of St John's wort with a large number of medications is contraindicated due to its inducing effect on drug metabolism. Red yeast rice is a homologue of lovastatin without a standardized dose. It can cause the same adverse events and interactions as this drug. The natural origin of these products does not mean that they do not cause any adverse events or drug interactions. Controlled studies evaluating the safety of the use of medicinal plants are necessary. **KEYWORDS** Medicinal plants, interactions, garlic, aloe vera, cranberry, St. John's wort, red yeast rice.

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## INTRODUCTION

Herbs have been used as remedies for a wide range of health problems since ancient times. Indeed, herbal medicines are the origin of modern pharmacology. Phytotherapy has gained popularity in the recent years.

The European Directive 2004/24/CE regulates products that have as their base traditional medicinal plants. This Directive was transposed into Royal Decree 1345/2007 in Spain, which governs the marketing of herbal medicinal products (HMP) in our country. After the entry into force of this Directive, only 12% of the HMPs registered to date in Spain met the quality, efficacy, safety and information standards applicable. The rest of HMPs passed to be marketed in the food sector, which is governed by less strict regulations, or just disappeared.<sup>1</sup>

The use of HMPs has increased in the recent years.<sup>2</sup> A telephone survey on 400 patients performed in a primary care center in Barcelona revealed that 59% of respondents used HMPs.<sup>3</sup> As many as 41% took HMP daily or weekly, and 86% had never disclosed the use of HMPs to their doctor. Disclosure of HMP use to healthcare professionals is crucial, as the risk of drug-herb interaction and adverse reactions is high. Indeed, the Spanish System of Pharmacovigilance has received very few reports of drug-herb interactions and adverse events.<sup>4</sup>

Estimating HMP sales is challenging, as they are dispensed via a multiplicity of channels. Herbal product associations estimate that 35% of HMPs are distributed in pharmacies vs 65% in herbalist's shops and department stores. There are, however, other distribution channels such as dietetics stores, supermarkets, the Internet or street markets.<sup>5</sup>

The perceived advantages of HMP include:

- They are considered harmless and beneficial for their natural components, as opposed to chemical synthesized products.
- HMPs are used as a complement or alternative to prescription drugs, such as benzodiazepines for sleep disorders.

In contrast, their disadvantages include:

- HMPs marketed as food supplements are not required by laws to have proven efficacy or safety as are medicines, which facilitates user's access to these products without having the necessary information.
- The wide range of active ingredients contained in HMPs increases the risk for drug-herb pharmacokinetic and pharmacodynamic interactions.<sup>6</sup>
- Some pharmaceutical forms are formulated as dietary supplements containing significantly higher concentrations than those ingested through food.
- Adherence to medication can be compromised by the use of HMPs, resulting in poor administration or discontinuance of the concomitant medicine.
- There is paucity of scientific-quality data on the pharmacological action, adverse reactions and interactions associated with the concurrent use of medicines and HMPs.

Healthcare professionals should be aware of the widespread use of HMPs in the general population. It is recommended that practitioners ask their patients about the use of other medicines, HMPs, and food supplements.

We performed a review of the most significant drug-herb interactions and adverse events reported for top-selling herbal medicines, namely:<sup>7</sup> garlic (*Allium sativum*), aloe vera (*Aloe vera*), vaccinium berries (*Vaccinium myrtillus*), red cranberry (*Vaccinium macrocarpon*), St John's wort (*Hypericum perforatum*), red-yeast-rice (*Monascus purpureus*), evening primrose (*Oenothera biennis*), licorice (*Glycyrrhiza glabra*), soy (*Glycine max*), green tea (*Camellia sinensis*) and Valerian (*Valeriana officinalis*). In the first part of this study, we focused on five herbs (garlic, aloe vera, vaccinium berries, St John's wort and red-yeast-rice).

Reports of frequent adverse events were obtained from Uptodate® (Lexicomp® drug interactions), Stockley's Drug interactions, data sheets from the Spanish Medicines and Health Devices Agency and the Memorial Sloan Kettering Cancer Center.<sup>8</sup>



## GARLIC

### Scientific name

*Allium sativum*

### Popular uses

No garlic-based products are currently marketed in Spain. Only food supplements are available categorized as healthcare products. Concentrations of garlic or allicin, however, have not been established by laws and regulations. This lack of standardization makes it very difficult to accurately know the dose that a user is taking. Garlic-based preparations are standardized according to their contents of sulfur compounds, more specifically, alliin, or alliin performance. A milligram of alliin equals 0.45 mg of allicin.

Garlic-based supplements are believed to have antihypertensive effects and prevent respiratory infections. Yet, no scientific evidence has been published to date demonstrating these effects.<sup>9,10</sup> The approved indication for popular plant-based products (not marketed in Spain) is "to help reduce slightly-elevated cholesterol and triglyceride levels once the practitioner has ruled out a severe disease, in combination with low-fat diet, exercise and weight loss". The recommended dose for adults is 4 g/day of garlic or 300 mg of garlic powder in capsules (which equals 1.3% of aliin or 0.6% of allicin) twice of three times a day. Yet, no scientific evidence has been published supporting this indication.<sup>11</sup>

### Risks

High-dose garlic-based supplementation (12 g OD)<sup>12</sup> should be suspended at least seven days prior to surgery,<sup>8</sup> as garlic seem to interfere with platelet activation and aggregation.

The safety of garlic supplementation during gestation and breastfeeding (label) has not been established, but its odor and taste are known to pass to the breast milk.<sup>13,14</sup>

Garlic supplementation can cause undesirable gastrointestinal effects such as nausea, vomiting, acute diarrhea, mucosal irritation, feeling of satiety and anorexia.<sup>15</sup>

Cases of allergic reactions (contact dermatitis, severe allergic conjunctivitis, rhinitis, bronchospasm), headache, dizziness, intense sweating and, rarely, bleeding have been reported.<sup>14</sup>

## Herbal medicinal products interact with a large number of medicines.

### Interactions

Garlic supplements can affect coagulation times via the inhibition of platelet aggregation.<sup>16</sup> Garlic supplements should be used with caution in patients receiving oral anticoagulants (it increases warfarin metabolism by inhibiting CYP3A4;<sup>16</sup> heparin or antiplatelet agents.<sup>14,17</sup> A systematic review revealed an increased risk of bleeding in older adults taking concomitantly acetylsalicylic acid and/or warfarin and garlic supplementation.<sup>18</sup>

Co-administration of garlic supplements and isoniazid or inverse transcriptase inhibitors (nevirapine, efavirenz) is not recommended.<sup>14</sup> Garlic can reduce protease inhibitor serum concentrations. Saquinavir has been associated with a 50% reduction in protein inhibitor levels. Therefore, the concurrent use of saquinavir and garlic supplementation (approximate daily dose equaling two garlic cloves of 4g) is not recommended. Garlic can reduce plasma saquinavir concentrations, cause a loss of virologic response, and increase the risk of developing resistance to one or more components of the antiretroviral compound.<sup>19,20,21</sup>

### Conclusions

The use of garlic supplementation in patients receiving antiplatelet or anticoagulation therapy or patients using antiretroviral therapy is not recommended.

## ALOE VERA

### Scientific name

*Aloe vera*, also known as *Aloe barbandensis*

### Popular uses

The juice obtained from aloe vera leaves is used as a topical gel to heal wounds and burns, and orally as a laxative.<sup>8</sup> Below we provide a description of its most popular uses and the scientific evidence available on its potential properties:



## Topic use

### *Treatment of burns and wounds*

A Cochrane's review<sup>22</sup> performed on the effects of aloe vera-based products (dressings and topical gels) for treating severe wounds (lacerations, surgical incisions and burns) and chronic wounds (infected wounds, arterial and venous ulcers) revealed that there is not sufficient scientific evidence supporting the topical use of aloe vera products to treat severe and chronic wounds.

### *Prevention and treatment of radiation dermatitis*

Although topical Aloe vera gels are widely used for the prevention of radiation dermatitis, no evidence has been published to date supporting this indication.<sup>23</sup> The recommendations made by "Choosing Wisely" conclude that aloe vera is not effective in preventing or treating radiation dermatitis.<sup>24</sup>

### *Treatment of phlebitis*

There is no evidence supporting the use of Aloe vera for phlebitis. The studies reviewed were found to be methodologically flawed.<sup>25</sup>

## Oral use

### *Prevention and treatment of radiation mucositis*

A Cochrane's revision<sup>26</sup> of interventions for the prevention of oral mucositis in oncologic patients showed that the evidence available on the beneficial effects of Aloe vera in the prevention of moderate-to-severe mucositis is weak or not reliable.

### *Treatment of ulcerative colitis*

Aloe vera juice has been traditionally used for digestive problems.<sup>27</sup> Aloe vera, however, can cause intestinal irritation, and evidence supporting its use in diseases such as ulcerative colitis or Crohn's disease is weak.<sup>28</sup>

### *Laxative*

Aloe has been widely employed as a laxative in combination with other preparations containing vaccinium berries. Indeed, this combination is available on the market for this indication.<sup>29</sup> According to a monograph carried out by the European Medicines Agency, Aloe Vera should not be used for more than one week. Also, EMA concluded that further methodologically-reliable studies are necessary to determine its efficacy.<sup>30</sup>

## Risks

The topical administration of aloe vera gels is considered to be safe, while its oral use may cause gastrointestinal disorders and electrolyte alterations. Cases of hypokalemia<sup>31</sup> have been reported secondary to a prolonged use or abuse of laxatives. The use of Aloe Vera in patients with cardiovascular disease is not recommended, as it can cause the QT wave prolongation.<sup>32</sup>

The intake of aloe has also been associated with thyroidal dysfunction,<sup>33</sup> perioperative bleeding<sup>34</sup> and acute hepatitis.<sup>35</sup>

Therefore, the FDA does not consider safe using aloe vera as a laxative.<sup>36</sup>

## Interactions

### Oral use:

- Sevoflurane: as sevoflurane inhibits platelet aggregation via the inhibition of thromboxane A<sub>2</sub>, and aloe vera may have antiplatelet effects, their combination may cause hemorrhage.<sup>34,37</sup>
- Insulin: aloe vera taken orally may potentiate the glucose-lowering effect of insulin.<sup>31</sup>
- Warfarin: aloe vera juice contains anthraquinone, which may hinder warfarin absorption.<sup>38</sup>
- Diagnostic studies: the intake of aloe vera can interfere with the Phenolphthalein (PSP) test, as it can alter urine color.<sup>29</sup>

## Conclusions

The intake of aloe vera is not recommended, as it may cause electrolyte alterations and gastrointestinal disorders. Its laxative effects are but irritation caused in the mucosa.

## VACCINIUM BERRIES

### Scientific name

*Vaccinium myrtillus* and *Vaccinium macrocarpon*

Two species of vaccinium berries have been traditionally believed to have medicinal properties.



### *Vaccinium macrocarpon* (American cranberry)

#### Popular uses

The dry extract of American cranberry is indicated for the prevention of recurrent acute non-complicated infections of the lower urinary tract (cystitis), a belief exclusively based on popular tradition. Although it was approved as a medicinal product by the AEMPS, it is not available in the market.<sup>39</sup>

Weak evidence was obtained in a Cochrane's review of studies assessing the efficacy of American cranberry in the prevention of urinary tract infections. The studies identified had serious limitations (lack of relevant data, poor adherence, drop-outs/losses-to-follow-up). Therefore, American cranberry is not recommended for the prevention of urinary tract infections.<sup>40</sup>

American Urology Association guidelines for recurrent uncomplicated urinary tract infections in women do not recommend the prophylactic use of American cranberry for the prevention of urinary tract infections either in juice or pills, without preference for any of these forms.<sup>41</sup>

#### Risks

Concomitant use with anticoagulant agents is contraindicated. This berry is also contraindicated for edema secondary to cardiovascular disease and kidney failure. American cranberry can cause hypersensitivity skin reactions and gastrointestinal disorders such as diarrhea and nausea.<sup>39</sup>

#### Interactions

Concomitant use of anticoagulant therapy and American cranberry concentrates are contraindicated due to the risk of increasing international normalized ratio (INR) and causing hemorrhages as a result of interaction with warfarin, which may also occur with other anticoagulant agents.<sup>8,39</sup>

### *Vaccinium myrtillus* (European blueberry)

#### Popular uses

Dry extract is obtained from fresh blueberry. Blueberry has been traditionally used for the treatment of mild diarrhea and oral mucosa inflammation. These pro-

## **Patients should always be asked about their use of herbal medicinal products**

erties are credited by user experience. Few preclinical pharmacological studies have been published on the effectiveness of blueberry extract in the treatment of diarrhea and peripheral vascular disorders for the modulatory effects of anthocyanins in the activation of capillary microcirculation. Numerous clinical trials have been performed assessing the efficacy of blueberries in improving vascular frailty and eyesight. Yet, the methodological quality of these studies is low.<sup>8,42</sup>

No conclusive evidence was obtained in a systematic review conducted on the beneficial effects of blueberries on eyesight due to variability in eyesight across ages and the lack of data on the place and time of the day at which visual acuity tests were performed. Further studies involving subjects with poor night vision are required to assess its effectiveness.<sup>43</sup>

#### Risks

Studies on their toxicity are very limited. Reproductive toxicity and genotoxicity tests were performed 50 years ago and do not comply with current laws and regulations.<sup>42</sup>

#### Interactions

Blueberries can interact with antiplatelet agents<sup>44</sup> including, but not limited to acetylsalicylic acid and non-steroidal anti-inflammatory drugs.<sup>45</sup>

#### Conclusions

The medicinal properties traditionally attributed to blueberries are not supported by scientific evidence. Concomitant use of blueberries and anticoagulant medicines and antiplatelet agents is not recommended.



## ST JOHN'S WORT

### Scientific name

*Hypericum perforatum*

### Popular uses

St John's wort or hypercium has been traditionally used for depression, anxiety, sleep disorders, colds, and as topical analgesic. However, it can interact with numerous medicines by potentiating their toxicity or reducing their bioavailability.

It is indicated for the treatment of mood disorders causing dejection, loss of interest, fatigue and sleep problems.<sup>46</sup>

Although it is used for depression, scientific evidence on its effectiveness is not conclusive.<sup>8</sup>

Regarding symptoms of menopause, premenstrual syndrome and obsessive-compulsive disorder, the evidence published is not sufficient. Its effectiveness in ADHD, irritable bowel syndrome and smoking cessation has not been conclusively demonstrated.<sup>47</sup>

### Risks

Individuals with clear skin are at a higher risk for photosensitivity induced by St John's wort. Skin reactions similar to skin burns have been described in subjects taking hypercium who were exposed to UV rays for a long time (long sunbathes, UV tanning), especially in clear skin subjects.<sup>46</sup>

The use of St John's wort should be suspended one week before surgery or chemotherapy.<sup>49,46</sup>

St John's wort should not be used concomitantly with antidepressants, with special caution taken in the use of selective serotonin reuptake inhibitors (SSRIs), mono-amino-oxidase (MAO) inhibitors, or triptan medicines.<sup>46</sup> Its use is not recommended in pregnant or breastfeeding women. Co-administration with oral contraceptives is not recommended either, as it may cause bleeding between menstrual periods.<sup>46</sup>

The most common adverse events associated with the use of St John's wort include cephalaea, nausea, dry mouth, sleepiness and gastrointestinal disorders.<sup>8,50</sup>

### Interactions

St John's wort can interact with a large number of medicines, as this berry induces the hepatic cytochrome p450 system and has serotonergic effects.<sup>32,46</sup>

Concomitant use of St John's wort with the following medicines is not recommended:

- Induce hepatic metabolism via the P450 cytochrome.
- Potential serotonergic effects.<sup>37,46</sup>

See tables 1 and 2.

### Conclusions

The evidence provided to date on the effectiveness of hypercium in the treatment of depressive system is not conclusive. Concomitant use of this berry with a large number of medications is contraindicated. Therefore, St John's wort should be taken with caution.



**Table 1.** Drugs that interact with St John's wort.

Therapeutic group	Medicine
Analgesics	Tramadol, tapentadol
Anesthetics	Fentanyl, propofol, midazolam, sevoflurane.
Hormonal antagonists	Exemestane
Antianginal drugs	Ivabradine
Antidysrhythmic drugs	Amiodarone
Anti-asthmatic drugs	Theophylline
Antimicrobial drugs	Erythromycin, clarithromycin Itraconazol, voriconazol Protease inhibitors Non-nucleoside reverse transcriptase inhibitors
Anticoagulants	Warfarin, acenocumarol
Hormonal contraceptives	Oral contraceptives Emergency hormonal contraceptives. Hormonal implants and injections Transdermal patches
Antiepileptics	Carbamazepine, phenobarbital, phenytoin, primidone, sodium valproate
Antiparkinson	Rasagiline
Antipsychotics	Aripiprazol, lithium
Antiemetics	Aprepitant
Calcium-channel blockers	Amlodipine, nifedipine, verapamil, felodipine
Cytotoxics	Irinotecan, dasatinib, erlotinib, imatinib, sorafenib, sunitinib, etoposide, mitotane
Diuretics	Eplerenone
CNS stimulators	Methylphenidate
Cardiac glycosides	Digoxin
Oral antidiabetics	Glicazide
Lipid lowering drugs	Simvastatine, atorvastatin
Thyroidal hormones	Thyroxine
Proton-pump inhibitors	Lansoprazol, omeprazol
Immunosuppressants	Ciclosporin, tacrolimus



**Table 2.** Drugs with serotonergic effects enhanced by St John's wort.<sup>34,43</sup>

Therapeutic group	Medicine
5HT agonists (Tryptans)	Almotriptan, elepriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
Analgesics	Tramadol, tapentadol
Anxiolytics	Buspirone
Antidepressants	Tricyclics (amitriptyline, clomipramine) MAO inhibitors (moclobemide) SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram) Other (duloxetine, venlafaxine)

## CHINESE RED-YEAST RICE

### Scientific name

*Monascus purpureus*

### Popular uses

Chinese red-yeast rice (RYR) is rice fermented with the red mould *Monascus purpureus*. One of its main components is monacolin K, a structural homolog of lovastatin, with inhibitory effects on HMG-CoA reductase and other monacolins, sterols, isoflavones and monounsaturated fatty acids with cholesterol-lowering activity.<sup>51</sup> Co-administration with Coenzyme Q10 seems to reduce LDL cholesterol in subjects with moderate hypercholesterolemia.<sup>52</sup> Its efficacy was evaluated against placebo in patients with hyperlipidemia who had never received any cholesterol medication. Subjects received either a dose of 2.4 g of RYR OD or placebo, and the two groups were recommended to follow a low-fat diet.<sup>53</sup> At eight weeks, total cholesterol levels had decreased in the RYR group, as compared to the placebo group (208 vs 251 mg/dL). LDL cholesterol concentrations also decreased significantly (135 vs 175 mg/dL). In contrast, no changes in HDL concentrations were observed.<sup>53</sup>

The results of this study cannot be generalized to the different preparations and brands available in the market, as several strains exist.<sup>54,55</sup> RYR is available on the market as capsules and tablets.

### Risks

Citrinin is a potentially nephrotoxic mycotoxin that has been found at high concentrations in some preparations.<sup>53</sup>

The most frequent adverse reactions reported are abdominal pain, heartburn, dizziness, abdominal wind, myopathy and hepatotoxicity.<sup>8</sup> Cases of anaphylaxis<sup>56</sup> and rhabdomyolysis<sup>57</sup> in young patients, and hypertransaminasemia<sup>58</sup> and severe hepatitis<sup>59</sup> in adults have been reported.

### Interactions

Monacolin K (lovastatin) has been proven to reduce Q coenzyme levels.<sup>8</sup>

Case reports of rhabdomyolysis and myopathy associated with concomitant use of cyclosporin have been published.<sup>37</sup>

CYP3A4 inhibitors can increase serum concentrations of RYR, thereby increasing the risk of muscular toxicity.<sup>55</sup>

Grapefruit juice potentiates the effects of RYR.<sup>55,60</sup>

### Conclusions

There is evidence supporting that Chinese red-yeast rice reduces cholesterol levels. Yet, the optimal dose of monacolin K is unknown, and further morbidity-mortality studies are needed. Self-administration of this homologue of lovastatin without a standardized dose can result in the occurrence of adverse events and interactions that compromise user's health.

### To know more...

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### Final conclusions

The evidence and information available on plant-based therapies is not sufficient. In many cases, there is not a correlation between dose and indications. Further well-designed clinical studies are required to obtain evidence that supports the recommendation of these products for the treatment of some health disorders.

Easy access to these products favors self-administration and the generalized use of plant-based preparations.

The natural composition of these products does not mean that they do not cause any adverse events or drug interactions.

Concomitant use of medicines should be evaluated before a patient starts on a plant-based therapy.

Practitioners should always ask their patients about the use of medicinal plants to consider potential interactions. For safety reasons, clinicians should determine whether the use of plant-based preparations should be interrupted.

The use of plant-based medicines is not recommended in patients with oncologic or hepatic diseases, patients taking anticoagulants or patients in treatment with antiretroviral medicines due to potential interactions and adverse reactions.



### Summary table

Medicinal plant	Scientific evidence	Adverse reactions	Precautions	Contraindications	Interactions
<b>GARLIC</b>	Lipid-lowering associated with dietetic treatments, exercise and weight lose.	Nausea, vomiting, acute diarrhea, minor GI problems, allergic reactions, headache, dizziness, intense and rarely sweating, bleeding.	Inhibits platelet aggregation. Suspend use seven days before surgery.	–	Antiplatelet agents Anticoagulants Efavirenz Insulin Isoniazide Nevirapine
<b>ALOE VERA</b>	Laxative (occasional constipation).	Oral administration can cause GI disorders and electrolite alterations (hypokalemia).	Not recommended in patients with cardiovascular disease, as it can prolong the QT wave prolongation.	–	Insulin Sevoflurane Phenolphthalein Test Warfarin
<b>VACCINIUM BERRIES</b>	Prevention of recurrent acute non-complicated lower urinary tract infections (cystitis).	Hypersensitivity. Gastrointestinal disorders.	Do not use concomitantly with anticoagulants, anti-platelet drugs and NSAIDs.	Hypersensitivity. Edema secondary to cardiovascular disease and renal impairment.	Warfarin
<b>ST JOHN'S WORT</b>	Symptomatic treatment of mood disorders causing dejection, loss of interest, fatigue and sleep problems.	Headache, nausea, dry mouth, drowsiness. Gastrointestinal disorders.	Higher risk for photosensitivity in clear-skin subjects. Suspend St John's use one week before surgery or chemotherapy.	Hypersensitivity to the extract. Do not use concomitantly with SSRIs, MAO inhibitors. Do not use with oral contraceptives. Pregnant and breastfeeding women.	Anesthetics Calcium antagonists Antianginal drugs Antiarrhythmic drugs Antimicrobial drugs Anticoagulants Oral contraceptives Anticonvulsants Antidepressants Antineoplastic drugs Antiparkinson drugs Antiretroviral drugs Statins Lipid-lowering drugs Immunosuppressants
<b>CHINESE RED-YEAST RICE</b>	Cholesterol-lowering: HMG-CoA reductase inhibition.	Abdominal pain, heartburn, dizziness, abdominal wind, myopathy and hepatotoxicity.	Nephrotoxicity in the presence of citrinin.	–	Ciclosporin Q co-enzyme
<b>ONAGRA</b>	Rheumatoid arthritis (symptoms).	Abdominal pain, nausea, headache, increased blood pressure.	Pregnancy and patients with hormone-sensitive carcinomas.	–	Anticoagulants Antiretroviral drugs Phenothiazines
<b>LICORICE</b>	Anti-ulcer and protector of gastric mucosa. Antitussive. Expectorant.	Hypertension. Hypokalemia. Pseudohyperaldosteronism.	Anticoagulant effect (suspend 2 weeks before surgery).		Antiplatelet agents Anticoagulants Antihypertensive Cytochrome P450 Steroids Loop diuretics Glycoprotein P Cardiac glycosides
<b>SOY</b>	Relief of menopausal symptoms. Antihypertensive. Lipid-lowering.	Intestinal wind. Allergic reactions.	Contraindicated in cases of hypersensitivity.		Cytochrome P450 Strogenic derivatives Glycoprotein P Aromatase inhibitors OATP UGT substrates Tamoxifen
<b>GREEN TEA</b>	Genital warts.	Intestinal winds, insomnia, palpitations, hepatotoxicity.	Pregnancy and breastfeeding: contains caffeine. Peptic ulcer.	Liver failure Peptic ulcer Hyperthyroidism Hypertension Arrhythmias	Antiplatelet agents Anticoagulants Bortezomib Codeine Iron Irinotecan and SN-38 Nadolol Tacrolimus Tamoxifen Verapamil Warfarin
<b>VALERIAN</b>	Relief of mental stress and sleep aid.	Headache, diarrhea, nausea, abdominal cramps, diurnal sedation, altered alertness, depression, pruritus, irritability, dizziness, sweating and bitter taste.  Withdrawal syndrome: cardiac complications and delirium after abrupt discontinuation of high doses taken for a long period of time.	Withdrawal syndrome in patients with tolerance. Dangerous machinery driving.		Benzodiazepines Haloperidol



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