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MEDICINAL HERBS: NATURAL BUT NO INNOCUOUS (PART 2)

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 evening primrose oil is not recommended during gestation. Licorice's use is not recommended in patients with high blood pressure, cardiovascular disease or receiving steroid, anticoagulant, antiplatelet or digoxin therapy due to their mineralocorticoid effects. The consumption of soy in women with hormone-dependent tumors is not considered safe. The use of green tea is associated with severe adverse events such as liver and cardiovascular diseases. Valerian supplements should be avoided in patients with liver or pancreatic disease, as well as concomitant use with other sedatives. 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, evening primrose, licorice, soy, green tea, valerian.

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Introduction

Herbs have been the primary source of remedies for a range of diseases since the ancient times. Indeed, herbal medicines are the origin of modern pharmacology. Phytotherapy has gained popularity in the recent years.[1]

The perceived advantages of HMP include:

- They have been traditionally considered harmless and beneficial for their natural origin, 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 of safety, as are medicines, which facilitates user's access to these products without the necessary information.
- The wide range of active ingredients of HMPs increases the risk for drug-herb pharmacokinetic and pharmacodynamic interactions.[2]
- Some pharmaceutical forms are formulated as dietary supplements containing significantly higher concentrations than those ingested by dietary intake.
- 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 concurrent use of medicines and HMPs.

Healthcare professionals should be aware of the frequent use of HMPs in the general population. Therefore, it is recommended that apart form other medicines, they also ask their patients about the use of HMPs, dietary supplements or herbal medicinal products.

We performed a review of the most significant drug-herb interactions and adverse events associated with top-selling herbal medicines, namely:[7] garlic *(Allium sativum)*, aloe vera *(Aloe vera)*, blueberry *(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 this Part 2, we will focus on five medicinal herbs: evening primrose, licorice, soy, green tea and valerian.

The most frequently reported adverse events were obtained from Uptodate®,[4] Stockley´s Drug interactions, data sheets from the Spanish Medicines and Health Devices Agency and Memorial Sloan Kettering Cancer Center.[5]

EVENING PRIMROSE

Scientific name

Oenothera biennis

Popular uses

The Spanish Medicines and Health Devices Agency has not approved any evening primrose-containing product as a prescription medicine for any health problem. However, it is widely used for a variety of disorders:

Itching secondary to skin dryness

In 2018, the HMPC (Committee on Herbal Medicinal Products) of the European Medicines Agency (EMA) recommended short- and long-term use of evening primrose oil to relief itching symptoms secondary to skin dryness both in the.[6]

Rheumatoid arthritis

A Cochrane's review revealed that gamma linolenic acid-rich oils (GLA) such as evening primrose oil could help improve symptoms of rheumatoid arthritis. Thus, GLA-containing oils were found to reduce pain (difference: -32.8 points (95%CI -56.3 to -9.4)) and improve disability (difference -15.8% (95%CI -27.1 TO -4.4%). However, significant differences were not found at 12 weeks in the only trial that included evening primrose oil.[7]

Dermatitis

Evening primrose oil is used orally for treating dermatitis, although evidence supporting this use is limited.[8]

Breast pain

The daily use of evening primrose taken orally was associated with pain relief in a randomized clinical trial. Yet, the small sample size and heterogeneity across groups limit the generalization of results.[9]

Risks

The use of evening primrose is not recommended in pregnant women,[10,11] as it is associated with an increased risk for gestation and labor complications. Reports of petechia and ecchymosis in neonates have also been documented.[12,13]

In addition, patients with hormone-sensitive cancer should use it with caution, as some forms may contain phytoestrogens.[5]

The potential adverse events of evening primrose oil include abdominal pain, nausea, hypersensitivity or cephalea.[10,11] Long-term safety of evening primrose oil has not yet been studied.[11]

The use of evening primrose oil has proven to increase systolic arterial pressure significantly (125.4 mmHg vs 130.1 mmHg; p<0.001),[14] although this effect does not seem to be clinically relevant.

Interactions

- Blood thinners: the use of primrose evening oil in patients receiving anticoagulation therapy may increase the risk of bleeding.[11,15,16]

- Antiretrovirals: there is a case report of a patient on lopinavir therapy whose concentrations increased significantly with the concomitant use of evening primrose oil.[17] The mechanism of action associated with this interaction is based on the inhibition of isoenzymes 3A4 and 2D6 of the cytochro9me P450. Considering this mechanism, evening primrose oil may interact with other antiretrovirals by increasing their effects.[18]

- Phenothiazines: Some cases of epilepsy have been reported in patients treated with Phenothiazines (chlorpromazine, levomepromazine, fluphenazine, perphenazine) using evening primrose oil concomitantly.[19] This mechanism of action is not clear.

Herbal medicines are not innocuous

Conclusion

Evening primrose oil has not been demonstrated to be effective in the treatment of the health problems it is generally used for. Additionally, it may interact with concomitant therapies by increasing the risk for their associated adverse events. The use of evening primrose oil is not recommended during gestation.

LICORICE

Scientific name

Glycyrrhiza glabra, Glycyrrhiza uralensis

Popular uses

Licorice has healing, antiinflammatory, anticoagulant, antiulcer, anti-cough and expectorant properties.[20] Licorice is available in forms such as root, powders and extract.[5] Its most popular uses and scientific evidence supporting them include:

Anti-ulcer and gastric protector.

Carbenoxolone, a component of licorice, has been reported to relief pain and gastric acidity and accelerate healing in patients with peptic ulcer. Yet, its use is associated with adverse effects such as liquid retention, hypokalemia and arterial hypertension.[21] Further studies are needed to confirm these results.

Carbenoxolone has also been used as gel or mouthwash to relief symptoms of oral ulcer.[22] This component is marketed in Spain as an oral ointment at a concentration of 20 mg/g for the treatment of oral ulcers.[23]

Weight loss

A meta-analysis of 26 clinical trials including a total of 985 patients revealed an association between the use of licorice and weight loss (mean weight difference -0.4 kg; 95%CI: -0.7 to -0.2) and, as a consequence, body mass index (BMI) of patients (mean BMI difference): -0.2 kg/m2; 95%CI: -0.2 to -0.06).[24] However, its use was linked to an increase in diastolic arterial pressure (DAP) (mean DAP difference: 1.7 mm Hg; 95%CI: 0.8 to 2.6) associated with hypernatremia. The authors concluded that patients with high blood pressure should avoid the use of licorice. The duration of these studies was 4 to 12 weeks.

Cough

Roots and underground stems of *Glycyrrhiza glabra* have been historically used for cought. Licorice contains mucilage, which forms a protective film over the oral and throat mucosa thereby facilitating the clearance of bronchial secretions in patients with upper airway problems.[21]

Relief of menopausal symptoms

Licorice roots have been traditionally used for the treatment of menopausal symptoms. However, no scientific data have been published that support the safety and effectiveness of this use.[21]

Treatment of skin rash and other skin disorders

Licorice is used for skin rash including dermatitis, eczema, pruritus and cysts,[21] but further studies are needed to confirm its effectiveness for these indications.

Risks

The most frequent adverse events associated with licorice include hypertension and hypokalemia[25] secondary to the effects of cortisol mineralocorticoids.[24] It is not recommended to exceed a daily dose of glycyrrhizin of 100 mg,[26] as it may cause pseudohyperaldosteronism secondary to depression of the renin-angiotensin-aldosterone system. This effect may reduce diuresis and induce sodium, chlorine and water retention and increase the clearance of potassium and the risk for hypertension, nephropathy, nephropathy, hypertensive retinopathy, complex arrhythmias and thrombocytopenia.[27]

Therefore, the use of licorice is not recommended in patients with hypokalemia, hypertension, kidney or cardiovascular disease.[20]

Patients undergoing general or dental surgery or other invasive interventions must discontinue licorice use two weeks before the intervention due to its effects on coagulation.[4]

Pregnancy and breastfeeding

A Finnish study suggested that excessive intake of licorice (≥ 500mg/week) during pregnancy could cause reasoning, behavior and attention deficit in children. Fifty-five children with high maternal exposure to glycyrrhizin scored 7 points below in intelligence tests (95%CI: 3.1 to 11.2), their memory was poorer (p< 0,04) and were more likely to have attention deficit/hyperactivity disorder (95% CI (1.4 to 7.7) as compared to 327 children of mothers who took small amounts of licorice (≤ 249 mg/weeks) or did not use it at all.[28] Further studies are needed to confirm these results.

Interactions

- Anticoagulant and antiplatelet drugs: Licorice may potentiate the effect of these drugs if used concomitantly. The occurrence of adverse events such as bleeding or bruising should be monitored in patients taking licorice concomitantly with these drugs.[4]
- Antihypertensive drugs: Licorice may reduce the effects of these drugs. Blood pressure should be monitored.[23]
- Cardiac glycosides: The risk for digital toxicity increases in the presence of hypokalemia. Several cases of severe hypokalemia associated with the use of licorice have been reported. The amount required to induce hypokalemia is unknown. Yet, it is recommended to monitor serum potassium levels and watch for the appearance of signs and symptoms of digoxin toxicity.[29,30]
- Diuretics: Licorice when administered concomitantly with loop diuretics may induce an exacerbation of hypokalemia.[26]
- Corticosteroids: The administration of licorice and Corticosteroids may cause hypokalemia.[30] It can also delay prednisolone and hydrocortisone clearance thereby increased tissue cortisol concentrations.[31]
- Cytochrome p450 substrate drugs: Licorice is a P450 enzyme inducer and it may interact with drugs which metabolism is mediated by this pathway.[20,32]

Conclusions

Although it is a popular sweetener widely used in beverages and food, its use is not recommended in patients with high blood pressure, cardiovascular disease or receiving steroid, anticoagulant, antiplatelet or digoxin therapy. There is no evidence supporting its medicinal use.

SOY

Scientific name

Glycine max

Popular uses

Soy is a plant in the pee family that has been used in Asian diets for thousands of years. Soy is also present in modern Western diets as a food and food ingredient.

In addition to its food uses, soy is available in dietary supplements, in forms such as tablets or capsules.[5]

Soy is indicated for the relief of menopausal symptoms as a result of estrogen deprivation.[33]

Epidemiological data suggest that women who take high doses of phytoestrogens in the form of soy isoflavone supplements are less likely to develop cardiovascular diseases, breast and uterine cancer and exhibit menopausal symptoms, as compared to those who follow a Western diet. Yet, there is no conclusive evidence proving these effects.[34]

Soy is rich in phytoestrogens, being isoflavones the most common and widely studied, whereas Genistein and daidzein are the most active. Soy has a selective estrogenic activity. Thus, whereas it has proestrogenic effects in some tissues, it acts as an estrogen inhibitor in other tissues. As compared to estradiol, soy demonstrates an affinity that is 100 and 1000 times lower, respectively, with weak estrogenic activity.[35,36]

Cardiovascular effects

Preclinical and clinical studies have revealed that isoflavones and phytosterols may exert lipid-lowering effects. Therefore, soy is associated with reduced levels of total cholesterol, LDL and triglycerides.[37] Soy was also associated with lower blood pressure in a study performed in 302 *naïve* patients (systolic pressure (130-159 mmHg, diastolic pressure 80-99 mmHg) who were randomized to receive either 40 g of soy protein supplements daily or carbohydrate complexes for 12 weeks. Net changes in the reduction of systolic and diastolic pressure were -7.9 mmHg (95%CI: -4.7 to -11.1 mmHg) and -5.3 mmHg (95%CI: -3.0 to -7.5 mmHg) respectively in hypertensive patients, although differences among hypertensive patients were not significant.[38]

Herbal medicinal products can interact with a large number of medicines

Menopause

The effect of isoflavones on menopausal symptoms cannot be clearly explained, as they do not seem to be related. The efficacy of isoflavones in the treatment of menopausal symptoms has been examined in several studies. No evidence has been obtained that isoflavones exert any beneficial effect on or reduces the frequency of hot flashes, as only a very slight reduction was observed as compared to placebo.[39] In addition, neurotransmitters such as noradrenaline and serotonin, as well as ß-endorphins are also involved in hot flashes.[11]

A Cochrane's review of 33 controlled trials involving perimenopausal or menopausal women experiencing hot flashes returned no evidence supporting the effectiveness of soy in reducing the frequency and severity of hot flashes.[40] Therefore, there are no sufficient clinical data on the role of isoflavones in the relief of menopausal symptoms, and its medicinal use is not well established.[39]

Risks

The main adverse effects of soy include flatulence and allergic reactions.[5]

The use of soy is not recommended in women with a history of hormone-dependent tumors or endometrial hyperplasia, as cases of abnormal uterine bleeding associated with the use of soy have been reported in women with endometrial disorders.[41]

Pregnancy and breastfeeding

It is not recommended .[33]

Interactions

- Levothyroxine: soy-containing products can impair the absorption of this drug thereby requiring a dose adjustment.[42]
- Tamoxifen: genistein can counter the effect of tamoxifen, which is used for estrogen-dependent breast cancer (MCF-7).[43,44]
- Estrogen derivatives: concomitant use may cause signs and symptoms of estrogen overdose.[5]
- Aromatase inhibitors: genistein induces the growth of tumor cells (MCF-7).[5]
- Cytochrome P450 and P glycoprotein: Soy induces the two metabolic pathways and may alter blood concentration of some drugs.[5,45]

Conclusion

Further studies are required to conform the potential medicinal uses of soy and establish the dose needed to achieve therapeutic effects. The use of soy in women with hormone-dependent tumors is not considered safe and it can interact with a large variety of drugs.

GREEN TEA

Scientific name

Camellia sinensis

Popular uses

Green tea extract has been marketed as a dietary supplement for a wide range of health problems. However, there is not sufficient evidence to recommend its use and its benefits are associated with its polyphenolic catechin content.[1] It has been traditionally used for a diversity of purposes:

Weight loss

Green tea is marketed as a herbal medicinal product in Spain as a dietary supplement in the form of capsules containing 300 mg of frozen leaves with the indication of weight loss.[46] A systematic Cochrane's review was performed to explore the effects of green tea on weight loss. The evidence obtained did not show that green tea has clinically relevant effects on weight loss or weight maintenance.[47,48]

Cancer

A systematic review of studies intended to demonstrate that green tea has preventive effects against cancer revealed that there is not sufficient evidence supporting this indication.[49]

Cardiovascular disease

LDL cholesterol,[4,50] total cholesterol and systolic blood pressure[50] have been reported to decrease with the use of catechin-containing green tea. Blood triglyceride concentrations, however, increased significantly.[4] In all cases, reductions were statistically significant, although they were not clinically relevant.

Genital warts

Green tea is marketed in Spain a green tea extract medicinal product for topical administration (Veregen® 100 mg/g). It is indicated for the treatment of external and perianal genital warts (Condylomata acuminata).[51] A randomized clinical trial where sinecatechins were used at 10% and 15% revealed that the two doses were effective and well-tolerated for the treatment of anogenital warts.[52]

Risks

The label of the medicine as approved in Spain mentions liver failure as a contraindication.[46] The EMA added peptic ulcer, hypertension, Arrhythmias and Hyperthyroidism to the list of contraindications.[48]

Its use has been associated with hepatotoxicity.[48,53] Lesions usually exhibit a hepatocellular pattern, although cases of cholestasic or mixed lesions have been reported too. These adverse events usually occur within the first months of use and resolve after green tea therapy is discontinued.[4] Some factors contributing to the hepatotoxicity of green tea include genetic predisposition, female sex and fasting.[4]

Other less severe adverse reactions associated with the high intake of green tea include flatulence, insomnia or palpitations, which are probably caused by its caffeine content. Caffeine content is hard to control, as caffeine concentrations vary across the different forms available, ranging from 10 to 50 mg per cup, reaching 10% in green tea extracts.[1]

Pregnancy and breastfeeding

The use of green tea should be limited in pregnant or nursing mothers, as it can be excreted into breast milk and cause iron metabolism disorders and microcytic anemia. Its use is not recommended either in children or adolescents.[48]

Interactions

According to the label, no drug-interaction studies have been performed in relation to the use of green tea.[46]

Yet, several studies report an association between green tea or green tea extract could interfere with the absorption, bioavailability or activity of a range of drugs.[1]

- Bortezomib: polyphenol contents of green tea may inhibit the effect of bortezomib and other proteasome inhibitors. Therefore, their concomitant use is not recommended.[4,5]
- Iron, codeine and warfarin: tannins in green tea extract have been associated with an impaired absorption of iron, codein and warfarin.[1,5,54-56] It is recommended to administer green tea two hours before or four hours after the intake of iron supplements to prevent interactions.[5]
- Tacrolimus: green tea catechins may increase tacrolimus levels by its inhibitory effects on CYP3A4 and P glycoprotein (56). Tacrolimus concentrations have been reported to have doubled in a patient taking this supplement (57).
- Nadolol: green tea extract has been demonstrated to inhibit OATP1A2 and OATP2B1 transporters, which may alter the absorption of OATP2B1-containing drugs, such as nadolol[4,5] or rosuvastatin.[56]
- Irinotecan: irinotecan has been found to inhibit the transportation of irinotecan and its metabolite for bile clearance, thereby extending its half-life and increasing its toxicity.[58]
- P glycoprotein inhibition: This effect increases the bioavailability of drugs such as tamoxifen and its metabolite 4-hydroxy tamoxifen,[59] or verapamil.[60] Yet, this activity has not been sufficiently investigated in humans and further studies are required.
- Antiplatelet and anticoagulants: Concomitant use of green tea with these drugs is not recommended for the risk for bleeding.[4] The mechanism of interactions seems to be based on the antagonism between the anticoagulant effects of green tea exerted by its vitamin K content.[5]

Patients should always be asked whether they take herbal medicinal products

Conclusions

The use of green tea is associated with severe adverse events such as liver and cardiovascular disease. In addition, green tea can interact with some drugs thereby increasing their toxicity and reducing their effects.

VALERIAN

Scientific name

Valeriana officinalis

Popular uses

The root of *Valeriana officinalis* has been traditionally used as a tranquilizer, sedative and to improve sleep quality.[61]

The active substance of the plant are valepotriates. Valepotriates are highly instable compounds that are only found on the fresh plant or when it has been dried at temperatures below 40º. Valerian also contains alkaloids, flavonoids, gamma-amino butyric acid, glutamine and arginine.[62]

Valerian is available in the form of hydroalcoholic cryogenized herbal extract of the root of Valerian or as teas with a characteristic odor.

According to the label of this traditional medicine, it is indicated for the "relief of mild symptoms of mental stress and as a sleep aid" in adults, adolescents and children older than 12 years.[61]

The recommended doses of hydroalcoholic dry extract of the roof of valerian are:

- For the relief of mild symptoms of mental stress: 400 to 600 mg up to three times a day.
- For the treatment of sleep disorders: 400 to 600 mg half an hour or an hour before going to bed. An additional dose can be taken in the evening, if needed.

The maximum daily dose of dry hydroalcoholic extract is 2,400 mg, and the recommended duration of the treatment is 2-4 weeks.[61]

Anxiolytic effect

A literature review revealed that there is not sufficient evidence on the anxiolytic effect of valerian.[63]

Sedative effect

Evidence has been published that valerian slightly improves sleep quality[64,65] but not sleep induction.[5]

Other studies have shown that valerian may improve sleep and anxiety in HIV patients receiving antiretroviral therapy,[66] facilitate progressive withdrawal of benzodiacepines[67] and attenuate obsessive-compulsive disorder.[68]

Risks

The adverse effects associated with the use of valerian root include headache, diarrhea, nausea, abdominal cramps, daily sleepiness, alertness alterations, depression, pruritus, irritability, dizziness, sweating and bitter taste.[69]

Sudden withdrawal in patients with good tolerance (high-dose long-term therapy) can cause a withdrawal syndrome similar to that of benzodiazepines.[5,70,71]

It is not recommended to drive or operate heavy machinery after having taken valerian root, as it can reduce alertness for one or two hours after administration.[69] In addition, the use of Valerian supplements is not recommended in patients with liver of pancreatic disease, as cases of hepatotoxicity and acute pancreatitis have been reported.[5]

Pregnancy and breastfeeding

No safety studies have been conducted on the use of valerian root during pregnancy. No sufficient data have been published either as to valerian excretion into human milk and its effects on the newborn. Therefore, the use of Valerian root is not recommended in pregnant or nursing mothers.[69]

Interactions

Concomitant use with other sedatives is not recommended:[69,72,73]

- Benzodiazepines: valerian can exert synergic effects.[74,75]
- Haloperidol: valerian can have additive effects causing liver damage.[76]

Conclusions

The use of valerian supplements should be avoided in patients with liver or pancreatic disease, as well as concomitant use with other sedatives.

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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 dosage 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 nt mean that they do not cause 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 herbal medicines 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

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