Chapter 4

Interactions with Drugs and Dietary Supplements Used For Weight Loss

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Additional information is available at the end of the chapter

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1. Introduction

Obesity and overweight have increasingly become major global health issues. Data from the World Health Organization (WHO) reports a near doubling of the prevalence of obesity worldwide from 1998 to 2008 [1]. In the European Region, an average of over 50% of adults are overweight and nearly 23% obese, with the prevalence of overweight and obesity being highest in Finland (67.1%), Germany (67.2%), the United Kingdom (67.8%), Malta (73.3%), and Greece (77.5%) [2]. Similar alarming trends are seen in the United States NHANES data where 68% of adults have a body mass index (BMI) greater than 25 (overweight or obese) and nearly 37% of the population is considered obese [3-7]. A large burden of health care costs can be attributed to overweight and obesity since multiple disease states such as diabetes, cancer, heart disease can be linked overweight and obesity [8-10]. The WHO estimates that up to 6% of health care expenditures in the European Region, while estimates for the United States have been estimated at 5.7% of the National Health Expenditure [8-11]. Most major organizations, like the WHO, and governmental agencies such as the U.S. Department of Agriculture Center for Nutrition Policy and Promotion have a major focus on the treatment of the obesity epidemic through promotion of proper healthy lifestyle changes [11, 12]. Although multiple anti-obesity agents have progressed through the development process, few drug products have made it through the approval process due to safety or lack of efficacy concerns. Several products, such as amphetamine, fenfluramine and sibutramine, have had their approval removed and/or have been removed from the market following reports linking the drugs to cardiovascular side effects (e.g. hypertension and myocardial infarction), addiction, and death [13-15]. As an alternative, overweight or obese patients may turn to less regulated dietary supplements as a means to assist in weight loss. Multiple herbal products are available that are indicated, often without significant scientific basis, for the treatment of overweight and obesity. The safety and

efficacy of herbal products is often unknown, especially given the presence of multiple chemical compounds, lack of known active constituents or lack of standardization of known compounds [16-19].This chapter presents a review of the chemistry and pharmacology of approved anti-obesity drug products, the proposed mechanism of action for common dietary supplements used in the management of weight loss, and potential drug-drug or herb-drug interactions.

2. Drugs used in weight LOcSS

2.1. Sympathomiometic agents

2.1.1. Diethylpropion hydrochloride (Tenuate®; Tenuate® Dospan®; Durad®)

Diethylpropion HCl (amfepramone, Figure 1a) is a sympathomimetic aminoketone agent with some similarity both chemically and pharmacologically to amphetamines and other related stimulant drugs. Similarly to amphetamine, diethylpropion stimulates release while inhibiting reuptake of dopamine, norepinephrine, and 5-hydroxytryptamine [20, 21]. The increase in norepinephrine and dopamine levels along with inhibition of their reuptake is proposed as the mechanism of diethylpropion anorectic effects [22]. Diethylpropion is indicated for short term management of obesity in patients with a body mass index (BMI) of > 30 kg/m^2 who have not responded to diet and exercise alone [23]. Because of its similarity to amphetamine, some patients become psychologically dependent on diethylpropion with an increased risk of self-medicating at higher dosages, increasing potential for drug interactions.

Diethylpropion is a monoamine and therefore can interact with monoamine oxidase inhibitors (MAOI), resulting in hypertension [23]. The manufacturer recommends avoiding use of diethylpropion during or within 14 days of discontinuation of MAOI administration. There is also one reported case of diethylpropion -induced psychosis in a 26 year old female patient taking phenelzine [24]. The authors hypothesized that chronic diethylpropion use led to an increased sensitivity to MAOI psychosis-inducing effects. Although the additive effects of diethylpropion in combination with other anorectic agents has not been studied, combined use of these agents is contraindicated due to the potential increased risk of cardiovascular issues [23]. In an early study of diethylpropion in 32 obese hypertensive patients, a drop in blood pressure was observed [25]. However, it was unclear if the drop in blood pressure in these subjects was due to weight loss or the additive effect of additional hypertensive agents that the patients were taking. The manufacturer also recommends potential modification of insulin dosing, although no strong evidence to support this statement can be found. In one study done in the rat, it was determined that anorectic drugs acting via the dopaminergic system antagonize hyperphagia induced by 2-deoxy-D-glucose, although the authors did not find any modifications to insulin-induced hypoglycemia [26]. There are no reported cases of drug-herb interactions with diethylpropion. However, theoretically herbal products with CNS stimulant properties (e.g. ephedra, caffeine, bitter orange), potential for interaction with sympathomimetic agents (e.g. Indian snakeroot), or MAOI activity (e.g. yohimbe) should be

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avoided due to an increased risk of hypertension, cardiovascular effects, and changes in blood pressure [27].

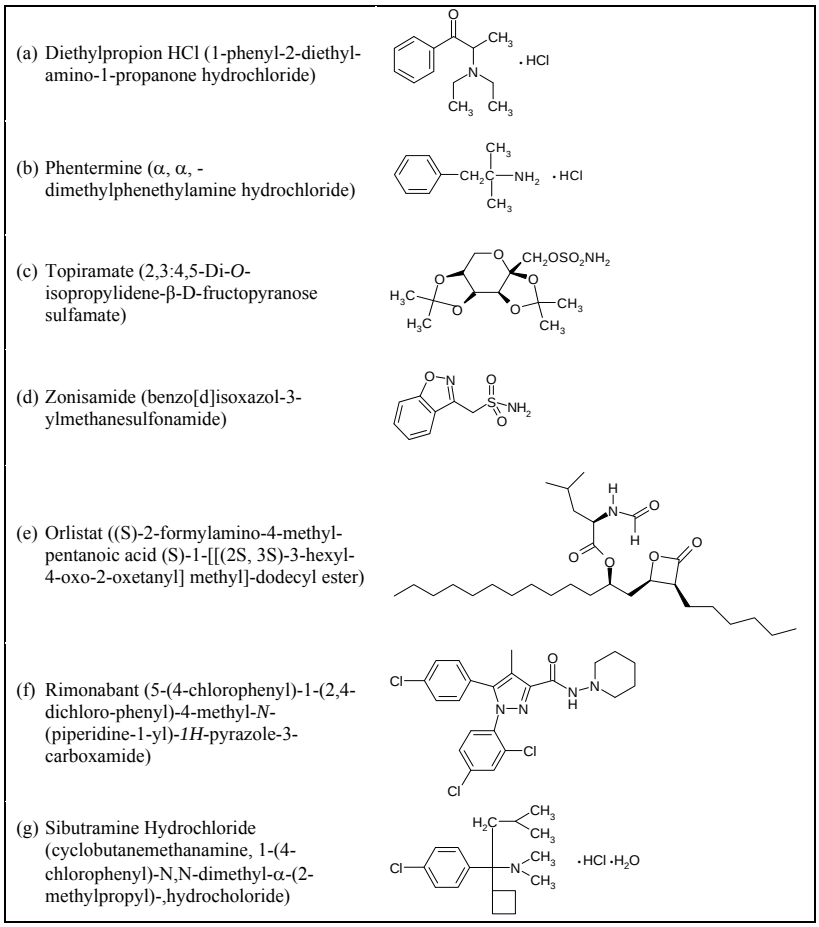

Figure 1. Molecular structures of anorectic drugs.

2.1.2. Phentermine / Phentermine hydrochloride (Fastin®, Ionamin®, Adipex-P®, Suprenza®)

Phentermine (Figure 1b), a member of the β-phenylethylamine family of compounds, exerts anorectic activity centrally through appetite suppression and is indicated in the short term treatment of obesity in patients with a BMI ≥ 30 kg/m^2 [28]. A meta-analysis of six randomized controlled trials of phentermine cumulatively show an added 3.6 kg weight loss over 2 to 24 weeks compared to control groups [29]. Phentermine acts by increasing the release of and inhibiting the reuptake of norepinephrine or dopamine [22]. Although one of the oldest

approved anti-obesity drugs, the safety of monotherapy of phentermine is relatively scarce due to the long history of combination products, most notably phentermine/fenfluramine (Phen-Fen), which was removed from the market due to serious and potentially fatal cardiovascular effects [30, 31]. More recently a combination product containing phentermine and topiramate has been investigated (see *Topiramate* below) and is currently under review by the US Food and Drug Administration (FDA).

Because of the similarity in activity and mechanism of action, drug interactions with phentermine are similar to those for diethylpropion (see *Diethylpropion* above) including avoidance of alcohol, potential changes to antidiabetic agent therapy, and avoidance of coadministration of MAOIs [28]. There is one case report of a female patient experiencing two penropative hypertensive crises, which were attributed to an interaction between phentermine and anesthetic agents [32].

2.2. Antiepileptic agents

Several antiepileptic agents are known to have an effect on weight gain [33]. However, two newer antiepileptic agents, topiramate and zonisamide, have shown an associated decrease in weight in patients taking these medications [34]. Therefore, these two drugs are being looked at as potential anorectic agents.

2.2.1. Topiramate (Topamax®)

Topiramate is a carbonic anhydrase inhibitor (Figure 1c) that is typically used in the treatment of migraines and as an anticonvulsant [35]. Topiramate is proposed to exert its antiepileptic activity via gamma-aminobutyric acid (GABA)-A-mediated inhibition via a benzodiazepine insensitive pathway, although the drug also blocks voltage dependent sodium channels [35-37]. Weight loss has been a commonly reported adverse effect of topiramate; therefore, the drug has recently come into focus as a potential anorectic agent [38-42]. Topiramate has shown promise as a combination low-dose therapy with phentermine (Qsymia(R) (originally Qnexa(R), Vivus Pharmaceuticals, Mountain View, CA, USA) for long term treatment of obesity [43-46]. Despite, safety concerns related to teratogenicity and cardiovascular effects, the product has recently been approved by the U.S. Food and Drug Administration."

Drug interactions with topiramate include coadministration with other antiepileptic agents. Although no changes in carbamazepine or phenytoin levels were seen, topiramate levels decreased by 40% or 48%, respectively [35]. However, there have been two case reports of antiepileptic drug intoxications in patients initiated on topiramate who were already taking the maximum carbamazepine dose [47]. Decrease in carbamazepine dosage resolved the interaction. Hyperammonemia, hypothermia and potentially encephalopathy can result from a synergistic interaction between topiramate, valproic acid, and phenobarbital, although the exact mechanism of this interaction is unknown [35, 48-50]. Levels of ethinyl estradiol can be significantly decreased in patients taking topiramate as an adjunctive therapy with valproic acid [35]. As a carbonic anhydrase inhibitor, topiramate can cause metabolic acidosis, and therefore is contraindicated in patients taking metformin, while patients taking other carbonic

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anhydrase inhibitors should be monitored due to the potential additive effects when coadministered with topiramate [51-55]. High doses of topiramate (600 mg/day) can increase systemic exposure to lithium. However, since topiramate dosage proposed to anorectic effects is low, this interaction may not be a significant concern when used as anti-obesity treatment [56]. No clinical studies or case studies are available for interactions with CNS depressants (e.g alcohol), although combined use is contraindicated by the manufacturer due to combined CNS depression [35]. No data supporting herb-drug interactions are available specifically related to use of topiramate at low doses as an anorectic agent [27].

2.2.2. Zonisamide (Zonegran®)

Zonisamide (Figure 1d), a methanesulfonamide, is an antiepileptic agent which has broad spectrum activity and has proven to be useful in patients not responding to other antiepileptic treatments [57]. The drug blocks sustained and repetitive neuronal firing by blocking voltage sensitive sodium channels and decreasing voltage sensitive T-type calcium channels [58, 59]. Additionally, it was found that zonisamide has dopaminergic and serotonergic activity, which contributes to the anorectic effects of the drug [60, 61]. In one randomized placebo-controlled trial, 30 subjects were administered zonisamide 100 mg daily along with a low calorie diet (500 kcal/day) for a period of 16 weeks. Dosage was increased to up to 600 mg/day for patients not losing >5% of their initial body weight within the first 12 weeks. The zonisamide group lost significantly more body weight at the end of the trial compared to the placebo group (approx. 6% loss vs. 1% loss) [62].

Zonisamide is metabolized by the cytochrome P450 3A4 system and therefore can potentially interact with other drugs metabolized via this route. In one study, the half-life of zonisamide ($t_{½}$ = 60 h) was decreased in patients receiving both zonisamide and phenytoin ($t_{½}$ = 27 h), carbamazepine ($t_{½}$ = 38 h, and sodium valproate ($t_{½}$ = 46 h) [57, 63]. Another study in the dog demonstrated decreased plasma levels of zonisamide during administration of phenobarbital [64]. However, any associated decrease in levels of other antiepileptic drugs was not found to be clinically significant [65, 66]. Cigarette smoking may alter the pharmacokinetics of zonisamide. Coadministration of carbonic anhydrase inhibitors may increase risk of metabolic acidosis and kidney stone formation, therefore monitoring is recommended in this patient population [66]. One study on the effects of cigarette smoke on zonisamide concentrations in rats suggests that cigarette smoke may decrease plasma levels of the drug due to decreased oral absorption [67]. Brain, but not plasma levels of zonisamide may be affected by chronic ethanol consumption. In one study inbred EL mice were administered zonisamide 75 mg/kg for 1 – 4 weeks along with 10% ethanol *ad libidum*. In groups with 4 week coadministration, representing chronic use of alcohol, a decrease in zonisamide brain concentrations, but not serum concentration were observed [68].

2.3. Orlistat (Xenical®, Alli®)

Orlistat (Figure 1e) is a gastrointestinal lipase inhibitor approved both as a prescription (Xenical®) and over-the-counter (Alli®) weight loss aid in the long term treatment of obesity [69]. The drug exhibits antiobesity activity by inhibiting the absorption of dietary fat from the

lumen of the stomach and small intestine through covalent binding with gastric and pancreatic lipase active serine residues [70]. Multiple randomized controlled trials have reported significant weight loss in patients taking orlistat compared to placebo controlled groups. One meta-analysis cites mean weight loss compared to control of -2.59 kg [95%CI, -3.46 to -1.74] or -2.9 kg [95%CI, -3.2 to -2.5] over 6 or 12 months, respectively, with a corresponding decrease in waist circumference, blood pressure, and blood glucose and lipid profiles [71-73].

A large number of preclinical and clinical studies and case reports related to potential drug interactions with orlistat have been published. There have been several cases of orlistat interaction with cyclosporine [74-79]. In all cases, significant decreases in plasma cyclosporine levels were observed following adjunct treatment with orlistat for cyclosporine-associated weight gain. Although one proposed mechanism for the reduction in plasma cyclosporine is a decrease in drug absorption, decreased levels may be due to rapid gastrointestinal transit time resulting from contraindicated high fat diets rather than a true drug-drug interaction [80]. Because orlistat is designed to inhibit gastrointestinal lipases, theoretically absorption of lipophilic molecules would also be inhibited [81-83]. In one open-label, placebo-controlled randomized two-way crossover study, orlistat (120 mg) was administered to 12 healthy subjects three times daily for 9 days followed by administration of Vitamin A (25,000 IU) or Vitamin E (400 IU) [82]. Although no effect was seen on Vitamin A levels, a significant reduction in C_{max} (approx. 43%) and AUC (approx. 60%) were observed for Vitamin E, suggesting impaired absorption of Vitamin E by orlistat. In another study, approximately a 30% reduction in beta-carotene levels was observed after administration of orlistat (120 mg) for four days followed by administration of 0 – 120 mg of beta-carotene three times a day for six days [83]. Absorption of lipophilic drugs such as the CNS agent lamotrigene can also be affected by orlistat. In one report, increased frequency of seizures was reported in an 18 year old female taking lamotrigene following initiation of an orlistat regimen [84]. One case of hypothyroidism in thyroid carcinoma was reported, presumably due to decreased absorption of thyroxine [85]. Although orlistat was not found to alter warfarin kinetics *per se*, but the drug may alter absorption of the fat soluble vitamin K which can have an effect warfarin levels and therefore these patients should be monitored for changes in coagulation parameters [86].

2.4. Rimonabant (Acomplia®, Zumulti®)

Rimonabant (Figure 1f) is a cannabanoid receptor antagonist that suppresses appetite by preventing activation of CB_1 receptors by the endogenous cannabanoids anandamide and 2-arachidonoyl-glycerol [87]. In clinical trials the drug resulted in improvement of multiple endpoints associated with obesity and metabolic syndrome compared to control groups including significant weight loss, reduction in waist circumference, decreased triglycerides, blood glucose, fasting insulin, and leptin levels with increased HDL cholesterol and adiponectin levels [88-96]. Although rimonabant proved a potentially successful drug in the treatment of obesity, especially given lack of cardiovascular risks compared to other weight loss drugs (see *Sibutramine* below), the drug has not been approved by the U.S. Food and Drug Administration (FDA). Additionally, although the drug was initially approved in 2006 by the European Medicines Agency (EMEA), later studies indicating serious neuropsychiatric

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adverse events, especially related to increased risk of suicide, caused the Agency to rescind the approval in 2009. Although rimonabant is not available in most major markets, ongoing investigations surrounding the development of the drug continue, while the drug has been approved in other markets [97-100]. Additionally, the drug appears to be available readily via online pharmacy services and has been identified as an adulterant in dietary supplements marketed for weight loss (see *Adulteration of Dietary Supplements* below) [101-103].

Given the limited and short-lived approval status of rimonabant, there is little information regarding potential drug-drug and herb-drug interactions available. According to package insert data submitted to the EMEA, rimonabant is known to be eliminated hepatically and into the bile by amidohydrolase and CYP3A4, with a 104% increase in rimonabant AUC (95% CI 40 – 197%) upon coadministration of ketoconazole [92, 96, 104, 105]. Therefore, the manufacturer indicated potential interactions with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir, telithromycin, clarithromycin, and nefazodone) and inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, and St. John's Wort). Because rimonabant can decrease levels of fasting insulin and blood sugar, use of rimonabant in diabetic patients taking anti-diabetic agents is cautioned [92, 96, 104, 105].

2.5. Sibutramine (Meridia®, Reductil®)

Sibutramine hydrocholoride (Figure 1g), and its active primary (M_1) and secondary (M_2) metabolites, is a selective serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake inhibitor [106-110]. Clinical data supported the efficacy of sibutramine as a weight loss agent, reporting significant weight loss compared to placebo for patients taking at least 10 mg/day for up to one year [107, 110-114]. The drug was approved as an anti-obesity agent in 1997 by the U.S. FDA and in 2002 by the EMEA, despite evidence of increased risk of hypertension and tachycardia, with a requirement that additional post-marketing safety data be collected relative to cardiotoxicity. As a result, the SCOUT (Sibutramine Cardiovascular OUTcomes) trial was implemented, which enrolled 10,000 overweight or obese patients aged 55 and older with coexisting diabetes and/or heart disease in a randomized controlled trial with a 6-month lead in period [115-118]. At the end of the six year study period, data showed a significant decrease in body weight compared to placebo but increased cardiovascular morbidity in the randomized sibutramine group [115-118]. Following publication of the SCOUT trial results in 2010, the EMEA and most other major markets pulled sibutramine while the United States and Australia required stricter labeling. By 2011 sibutramine was pulled from all major markets globally. However, as with the case of rimonabant (see above), sibutramine is of note since it is the primary contaminant found in dietary weight loss supplements (see *Adulteration of Dietary Supplements* below).

Sibutramine is known to be metabolized by CYP 3A4 into two active metabolites (M_1 and M_2). Data reported by the manufacturer in limited clinical trials (n = 12 – 27 patients) suggest potential pharmacokinetic changes in AUC and C_{max} for sibutramine when taken in combination with CYP 3A4 inhibitors such as cimetidine, ketoconazole, erythromycin, simvastatin, and omeprazole; while sibutramine does not generally have a significant impact on the levels of these drugs in return [106]. Because of the role of CYP 3A4 in sibutramine elimination, use of

the drug with other CYP 3A4 substrates, including coadministration with grapefruit juice, is contraindicated [111]. One case report describes a possible interaction between sibutramine and citalopram in a 43 year old female patient who experienced hypomanic symptoms shortly after adding 10 mg sibutramine to her current citalopram and fluoxetine regimen [119]. Symptoms ceased within one day of discontinuing sibutramine. Although the exact mechanism of the interaction is unknown, the author hypothesized a possible amphetamine-like hypomania or serotonin syndrome due to increased brain serotonin levels via the combination of a serotonin reuptake inhibitor and serotonin-norepinephrine reuptake inhibitor. Another case report notes a possible interaction between sibutramine and cyclosporine in a 26 year old transplant patient resulting in significant increases in cyclosporine trough plasma levels, likely due to inhibition of CYP 3A4 metabolism [120]. Coadministration of α_2 adrenergic blockers, such as the herb yohimbine, with sibutramine has been recognized as potentially life threatening due to potential sympathetic side effects resulting in hypertension and tachycardia [121]. Due to the potential risk of bleeding caused by sibutramine, the drug should be used with caution in patients taking warfarin and other anticoagulants [106].

3. Herbs and dietary supplements used in weight loss

3.1. Açaí (*Euterpe oleracea*)

The açaí berry is harvested from the palm species *Euterpe oleracea* and is used mainly for dietary consumption as whole fruit, juice, or as a flavoring and coloring agent [27]. The fruit, widely used in Brazil, has gained in popularity as a food product and dietary supplement in the past several years, mainly due to its antioxidant and anti-inflammatory effects related to high polyphenol content [122-126]. Although there is little scientific evidence to support the berry for any of its purported health benefits, it can be found in several dietary supplements promoted for weight loss. In a pilot study investigating the effect of açaí supplementation on metabolic parameters in healthy overweight patients, the authors found a significant decrease in fasting glucose, insulin and cholesterol levels and a mild decrease in LDL-cholesterol and ratio of total cholesterol to HDL-cholesterol [127]. However, the authors did not assess weight loss in this study and therefore the activity of açaí as an anorectic agent cannot be determined. There have been no reported adverse drug interactions or interactions with others herbs and açaí [27].

3.2. Bitter orange (*Citrus aurantium, Citrus naringin, synephrine*)

Bitter orange is the fruit of *Citrus aurantium* or *Citrus naringin*, used as both a food product and the medicinal properties of the juice and peel [27]. There are multiple active constituents in bitter orange including several flavonoids (e.g. naringin) and the adrenergic agonists synephrine and octopamine [128-134]. Synephrine is structurally similar to ephedrine, therefore prompting the replacement of ephedra with bitter orange in weight loss supplements, although the fruit has been used dichotomously as both an appetite stimulant and for weight loss [27]. However, there is insufficient evidence to confirm the efficacy of bitter orange as an anti-obesity agent, especially given its inclusion in combination products [27].

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Interactions with bitter orange are varied. Synephrine, like ephedrine, is known to cause adverse cardiovascular effects at high doses, the risk of which are heightened when combination products also including caffeine are ingested and therefore patients taking cardiac medications should be cautioned on its use [135, 136]. Some evidence demonstrates that bitter orange can inhibit cytochrome P450 3A4, although to a lesser extent than with grapefruit [137-140]. A 76% increase in AUC was observed following administration of 10 mg extended release felodipine administered with 240 mL Seville orange juice compared to control [139]; while a significant increase in indinavir t_{max} was observed with administration of 8 ounces of Seville orange juice compared to control [140]. Because synephrine and octopamine, both endogenous substances, can interact with monoamine oxidase there is a theoretical interaction of bitter orange with MAOIs [141, 142].

3.3. Caffeine-containing herbs

Caffeine is a methylxanthine that is commonly found in food, beverages, and dietary supplements. It is used as an additive in beverages and dietary supplements for its energy enhancing properties. Many dietary supplements marketed for weight loss contain high levels of caffeine, often from multiple sources, for increased thermogenesis and lipid metabolism [143, 144]. Most studies investigating the anti-obesity effects of caffeine have been done using combination products that include ephedra, or have looked at enhancement of athletic endurance [145-151]. Therefore, it is difficult to assess the effect of caffeine alone on weight loss. One study demonstrated an increase in thermogenic metabolic rate in subjects drinking coffee along with food, compared to ingestion of decaffeinated coffee [144].

Adverse effects associated with caffeine consumption include restlessness, jitteriness, anxiety, insomnia, and cardiovascular effects [152-156]. Most drug and herb interactions with caffeine are mild to moderate and are related to increased adverse effects resulting from decreased caffeine elimination or additive effects with other methylxanthine containing products [157]. For example, estrogen drugs (e.g. oral contraceptives and estrogen replacement therapy) have been shown to decrease clearance of caffeine up to 50 – 65% [158, 159]. The most significant caffeine interaction occurs with coadministration of *Ephedra* or ephedrine containing products (see *Ephedra* below). The ban on ephedra in the United States has resulted in marketing of "ephedra-free" dietary supplements using ephedra alternatives, including caffeine containing herbs and bitter orange (see *Bitter Orange* above). In one randomized controlled trial study, subjects were administered products containing *Citrus aurantium* standardized to either a high dose of synephrine (46.9 mg) or a product containing caffeine and a low synephrine dose (5.5 mg) [136]. A significant increase on blood pressure was observed in patients taking the product containing both caffeine and synephrine, but not high dose synephrine alone, suggesting an interaction between the two herbs.

3.3.1. Green tea (Camellia sinensis; EGCG)

Green tea has gained in popularity for the treatment of a wide variety of diseases and for promotion of general wellbeing. The addition of green tea to weight loss supplements is due in part to the caffeine content of *Camellia sinensis*. However, in addition to alkaloid content

(caffeine, theobromine, theophylline) green tea also contains polyphenols, most notably the catechin epigallocatechin-3-gallate (EGCG) [160-164]. EGCG, in concert with caffeine, is proposed to elicit anti-obesity effects via inhibition of catechol O-methyl transferase and phosphodiesterase [164]. A meta-analysis of clinical trials involving green tea in weight loss concluded that weight loss is decreased, relative to placebo, in treatment involving both green tea ECGC and caffeine but not with decaffeinated green tea products [165].

As expected, the majority of drug interactions associated with green tea are related to caffeine content. However, a few interactions described in the literature are due to other constituents of green tea. Green tea may be contraindicated, especially at high doses, in patients taking anticoagulants such as warfarin due to the high Vitamin K content of the herb. There is one case report of a patient taking warfarin who experienced a significant reduction in INR following initiation of daily consumption of one-half to one gallon of green tea [166]. Once green tea consumption was stopped INR normalized. Green tea is also thought to cause decreased estrogen levels and combination products containing the herb have been used to improve fertility and relieve menopausal symptoms [167-170]. Therefore, use of high doses of green tea in patients taking oral contraceptives or estrogen replacement therapy may be cautioned.

3.3.2. Guarana (Paullinia cupana)

Guarana (*Paullinia cupana*) is a plant native to South America that is used traditionally and in anti-obesity supplements for its high caffeine content, although other minor constituents including theophylline, theobromine, catechin and epicatechin are found in these extracts [171-176]. There are no studies investigating the effects of Guarana alone on weight loss so it is difficult to determine the anti-obesity properties of the herb. In one double-blind, parallel, placebo controlled trial 47 subjects were administered three capsules containing yerba mate (*Ilex paraguayensis*, 112 mg), guarana (95 mg) and damiana (*Turnera diffusa*, 36 mg) daily for 45 days, resulting in significant weight loss (-5.1 ± 0.5 kg) compared to placebo (-0.3 ± 0.08 kg) [145]. One of the few interactions reported with guarana not related to caffeine content suggests possible interference with anticoagulants since platelet aggregation was observed *in vitro* and in animal studies [177].

3.4. Dandelion (*Taraxacum officinale*)

Dandelion is a perennial herb of multiple global varieties that has traditionally been used for liver, spleen, kidney, and gastrointestinal disorders, although there have been no clinical trials investigating the effects of dandelion in weight loss [27, 178]. It is commonly added to weight loss supplements, mainly for its diuretic properties, although the herb does possess some mild laxative properties [179-181]. There are no known drugs interactions between *Taraxacum* and other herbs or drugs, although one study in rats suggests a probable interaction with quinolone antibiotics due to the high mineral content of *Taraxacum* [182]. In the study, ciprofloxacin (20 mg/kg) C_{max} significantly decreased while V_d and $t_{½}$ significantly increased when administered with crude dandelion extract (2 g/kg) compared to control. There is one case report of hypoglycemia in a 58 year old diabetic patient following a 2-week period of dandelion consumption in salads [183].

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The patient denied changes in calorie consumption, exercise, or insulin dosing. Diabetic patients taking hypoglycemic agents while consuming dandelion should be monitored.

3.5. Ephedra (*Ephedra sinica*, ma huang)

Ephedra, derived from the evergreen shrub *Ephedra sinica*, contains multiple plant alkaloids including ephedrine and pseudoephedrine that are chemically related to amphetamines. These compounds act by increasing availability and activity of endogenous neurotransmitters such as epinephrine and norepinephrine, resulting in brain and cardiovascular catecholamine receptor stimulation [184]. The herb has traditionally been used for bronchodilation in the treatment of respiratory ailments such as asthma, as an athletic performance enhancer, and for its thermogenic properties in weight loss [148, 185-189]. Ephedra as a weight loss dietary supplement is commonly found in combination products also containing caffeine or caffeine-containing herbs. In one study a product containing 90 mg and 192 mg of ephedra alkaloids and caffeine, respectively, administered daily over six months in a randomized, double-blind placebo controlled trial resulted in significant decreases in body weight, body fat and LDL-cholesterol with an increase in HDL-cholesterol [148]. The addition of aspirin to ephedrine containing products can potentiate the thermogenic properties of ephedra, improving weight loss compared to products containing ephedra alone [190-201]. Due to high risk of cardiovascular toxicities and cardiomyopathies, ephedra has been banned in the United States [202-211]. However, the herb is still available in other countries [212].

Because of the controversial nature of ephedra related to cardiac toxicity and its eventual ban via the U.S. FDA, there are a significant number of clinical studies and case reports related to toxicities and interactions with ephedra and ephedrine. Ephedra can potentially interact with anesthetics since it is known that administration of ephedrine can reverse anesthesia induced hypotension and regression of analgesia following epidural blockade [213, 214]. Ephedrine has both chrontropic and inotropic effects, and therefore interactions with cardiovascular agents may be possible [184, 211, 215, 216]. However, no effects on heart rate or blood pressure were seen in clinical trials investigating the efficacy of ephedra in weight loss [192, 217, 218]. Theoretically interactions with antiadrenergic agents and MAOIs can occur due to sympathomimetic effects of ephedrine, potentially increasing risk of hypertensive crisis. There is a case report of a patient taking a product containing caffeine, ephedrine, and theophylline who experienced multiple adverse effects including encephalopathy, hypotension, tachycardia, and hypothermia 24 hours following discontinuation of phenelzine [219]. Interactions with ephedrine and tricyclic antidepressants are also possible [220]. Some evidence from clinical trials suggests that ephedra in combination with caffeine can cause hyperglycemia, and therefore interactions with antidiabetic agents is possible [147, 148, 221]. A lowering of seizure threshold has been observed in patients taking ephedrine, and therefore use of ephedra in this patient population is cautioned [222]. A major interaction between ephedra and methylxanthines (e.g. caffeine, theophylline) is possible due to increased risk of cardiovascular, neurologic and psychiatric adverse effects due to additive sympathomimetic and CNS stimulant activity [184, 223, 224]. One case study reports a 21 year old male patient admitted to the hospital emergency room with a blood pressure of 220/110 mmHg and ventricular arrhythmia following ingestion of a caffeine/ephedra containing product (“Herbal Ecstasy”) [225].

3.6. Glucomannan (*Amorphophallus konjac*)

Glucomannan is a soluble but highly viscous dietary fiber derived from the root of the *Amorphophallus konjac* (elephant yam) plant that grows native to Asia [27]. Although traditionally used as a food, the plant has gained popularity as an additive in weight loss supplements since the dietary fiber absorbs water in the gastrointestinal tract, helping to promote a sense of satiety and act as a bulk laxative [226-228]. There is also evidence that fiber content of glucomannan helps to reduce cholesterol levels [67, 229-232]. In a double blind crossover study involving 63 healthy males, 3.9 grams of glucomannan administered daily for four weeks resulted in a 10% reduction in total cholesterol, 7.2% reduction in LDL cholesterol, and a 23% decrease in triglyceride levels [67]. A meta-analysis of clinical trials involving glucomannan reported overall decreases in the above markers as well as fasting blood glucose [230].

There are relatively few reported drug interactions with glucomannan, most of which are likely due to associated decreases in cholesterol and lipid levels as well as interference with absorption of some drugs. Monitoring of patients taking antihypertensives, antilipemics, and other anti-obesity agents is warranted. Several studies note a significant decrease in fasting blood glucose levels following glucomannan administration while decreased absorption of the sulfonylurea drugs is possible [230, 231, 233-237]. Glucomannan can significantly decrease circulating levels of T3, T4, and FT3 in the treatment of thyrotoxicosis and therefore its use may be contraindicated in patients taking thyroid medications [238]. Glucomannan can potentially affect the absorption of certain drugs and supplements as demonstrated in one study in which absorption of the fat soluble Vitamin E was decreased potentially via the reduction of bile acids necessary for absorption of the vitamin [239].

3.7. *Hoodia gordonii*

Hoodia gordonii, a small succulent of the Apocynaceae family native to the Kalahari Desert, has been used traditionally by native tribes for its appetite and thirst suppressing properties [240, 241]. The active constituent of Hoodia (P57 or P57AS3) is an oxypregnane steroidal glycoside which is purported to increase ATP production in the hypothalamus, resulting in a feeling of satiety [242]. There is little known regarding potential drug or herb interactions with *Hoodia*, although *in vitro* studies suggest a potential interaction with drugs metabolized by CYP 3A4 [243].

3.8. Hydroxycitric acid (HCA, *Garcinia cambogia*)

Garcinia cambogia is a plant native to Southeast Asia which yields a small purple fruit used in weight loss products for its hydroxycitric acid (HCA) content [27, 244]. The anorectic activity of HCA is due to the inhibition of the adenosine triphosphate-citrate (pro-3S)-lyase, which catalyzes the formation of acetyl-CoA, resulting in decreased fatty acid synthesis and lipogenesis [245]. The evidence for HCA as an effective weight loss agent is contradictory. One randomized controlled trial reported a 5-6% reduction in weight and BMI following approximately a 4.5 gram daily dose of HCA, while two other studies reported no significant weight loss or effect on appetite at lower doses of 1.5 – 2.4 gram daily HCA doses [246-248]. There are

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a minimal number of reported interactions with *Garcinia* or HCA. Antilipemic agents such as HMG-CoA reductase inhibitors should be avoided due to an increased risk of rhabdomyolysis. In one case report a healthy 54 year old female patient reported chest pain following ingestion of an herbal product containing ephedra, guarana, chitosan, *Gymnena sylvestre*, *Garcinia cambogia* (50% HCA), and chromium. Lab results indicated elevated serum creatine kinase (1028 IU/mL), which declined following cessation of the supplement [249]. Although the exact interaction was not determined, cautionary use of HCA-containing products in patients at risk of rhabdomyolysis is warranted.

3.9. Herbal laxatives

Frequently laxatives and diuretics are used alone or in combination products to promote weight loss. However, there is little to no evidence supporting these supplements as anti-obesity agents, although subgroups of this patient population may abuse laxatives and diuretics for the purpose of weight loss [250].

3.9.1. Bulk laxatives

Bulk laxatives generally consist of soluble dietary fiber which expands in the gastrointestinal tract in the presence of water resulting in improved bowel function. Common sources of bulk laxatives include *Amorphophallus konjac* (glucomannan, *see above*), guar gum (*Cyamopsis tetragonoloba*), and psyllium husk (*Plantago psyllium*). Although the efficacy of bulk laxatives for weight loss is not proven, adsorption of dietary glucose and lipids to these agents in the gastrointestinal tract results in decreased absorption of lipids, cholesterol, and carbohydrates into the body, thereby promoting weight loss [230, 234, 251-253]. Because of changes in carbohydrate and glucose absorption, dosing of antidiabetic agents may require modification and therefore patients in this population should be monitored when taking bulk laxatives [254-261]. Bulk laxatives appear to have some effect on the absorption of orally administered medications, which can result in changes in drug plasma levels [262-272]. For example, in one study the effect of guar gum on digoxin and phenoxymethyl penicillin absorption was studied in 10 healthy volunteers, with significant reductions in both peak penicillin plasma concentrations and AUC, but little effect on overall digoxin levels [269]. In one case report of a patient with adrenal insufficiency treated with fludrocortisone and prednisolone, the patient experienced symptoms of acute adrenal crisis including fatigue, nausea, abdominal pain, and weakness approximately 3 – 4 days after initiation of psyllium [262]. The authors postulated that psyllium inhibited absorption of fludrocortisone and/or prednisolone. Other evidence related to changes in absorption of ethinyl estradiol, metformin, and lithium have also been reported [264-266, 270, 272].

3.9.2. Stimulant laxatives

Stimulant laxatives act by irritating the lining of the gastrointestinal tract, resulting in increased propulsive muscle contractions that aid elimination of intestinal contents. Because of the quick and efficacious activity, stimulant laxatives are most frequently abused to promote weight loss by increasing gastrointestinal transit time [273, 274]. The most common stimulant laxative

herbs are senna (*Cassia senna*), aloe latex (*Aloe vera*), and Cascara sagrada (*Frangula purshiana*). The leaves and pods from *Cassia senna* contain anthroquinone stimulant laxative compounds effective in the treatment of constipation and for bowel evacuation prior to medical procedures [27, 275-295]. The herb has been approved by the U.S. FDA as a non-prescription medication. Similarly, aloe latex, derived from the peripheral bundle sheath cells of the aloe leaf, contains anthracene compounds that are cleaved in the colon by bacterial enzymes into active anthrone compounds with stimulant laxative properties [296-299]. However, concerns over possible carcinogenic properties of certain anthraquinones in aloe latex, along with lack of safety evidence, prompted the U.S. FDA to ban aloe latex in 2002, although the herb is still used in other countries [178, 300, 301]. The bark of the deciduous buckthorn shrub Cascara sagrada is effective for the treatment of constipation due to the stimulant laxative properties of its anthraglycoside constituents [27, 302]. Like aloe latex, Cascara had previously been approved by the U.S. FDA as a non-prescription medication, but the designation was withdrawn into 2002 based on lack of safety and efficacy evidence, although the herb is still available as a supplement [300].

Stimulant laxatives share multiple common adverse effects and potential drug interactions. Because of decreased gastrointestinal transit time, absorption of some drugs, especially those with poor permeability, may be decreased [303, 304]. Experimental evidence in rats suggests absorption of carbohydrates may result in decreased blood glucose levels and therefore monitoring of patients receiving hypoglycemic agents or insulin is warranted [305-307]. Concomitant use of stimulant laxatives with diuretics, cardiac glycosides and licorice is contraindicated due to hypokalemic effects, especially with long term use of these laxatives [27, 178, 304, 308, 309]. Senna can potentially interfere with antiplatelet and anticoagulant activity by causing excessive bleeding [310]. There is one case report of a possible interaction of aloe and sevoflurane, in which a 35 year old female patient undergoing surgery for hemangioma experienced perioperative bleeding [311]. Although the size and vascularization of the hemangioma were noted as partial root causes of the bleeding episodes, the authors felt that the combination of anesthetic and aloe administration (4 tablets daily for 2 weeks prior to surgery) may have contributed to the adverse event.

3.10. Licorice (*Glycyrrhiza glabra*)

Licorice has historically been used both medicinally and as a food product and its relative safety at low doses has placed it on the U.S. FDA GRAS (generally recognized as safe) list, although at high doses licorice can cause severe adverse effects [27]. The main active components of licorice are glycyrrhizin and glycyrrhizic acid, although several other active constituents have been identified [312, 313]. One of the main adverse effects of high licorice consumption includes mineralocorticoid excess syndrome and resulting hypokalemia with associated increases in blood pressure, as well as secondary pseudohyperaldosteronism [314-338]. Licorice consumption may also alter blood glucose levels, potentially via binding to PPAR-γ [339, 340]. Although licorice is used in dietary supplements for weight loss, contradictory evidence reports weight gain with licorice consumption [341-343]. However, one study in which 3.5 grams daily licorice consumption was administered to 15 normal

weight subjects for two months reports a significant decrease in body fat mass but not body mass index [344, 345].

Acquisition of mineralocorticoid excess syndrome following high dose consumption of licorice results in the potential for licorice-drug interactions with multiple drug classes, including aldosterone receptor antagonists, antiarrhythmics, antihypertensives, cardiac glycosides, corticosteroids, diuretics, and potassium lowering agents [321-324, 326]. In one study, 10 healthy subjects were given 32 grams of licorice daily for two weeks along with 25 mg of hydrochlorothiazide (HCTZ); a significant reduction in potassium levels was observed, while two patients experience hypokalemia, compared to HCTZ alone [346]. Glycyrrhizin and β-glycyrrhetinic acid may also affect complement activity and decrease neutrophil generated oxides and peroxides, resulting in anti-inflammatory activity [347-350]. Therefore, licorice should be used with caution in patients taking other anti-inflammatory medications. Licorice constituents may also have an effect on hormonal agents via anti-estrogenic activity, inhibition of 17β-hydroxysteroid dehydrogenase, or associated decreases in prolactin levels [351-358]. In *in vitro* and animal studies it has been shown that constituents in licorice can promote the intestinal absorption of some drugs and therefore it is recommended that oral drugs be taken at least an hour before or two hours after licorice consumption [359]. Theoretically licorice may interact with antidepressant agents, since increases in norepinephrine and dopamine have been observed in mice while *in vitro* cell culture studies suggest potential serotonin reuptake inhibition [360, 361].

3.11. St. John's Wort (*Hypericum perforatum*)

St. John's Wort (SJW) is a perennial herb native to Europe that is commonly used to treat depression, anxiety, post-menopausal symptoms, attention deficit hyperactivity disorder (ADHD), and other mood disorders [362-367]. The active constituents of SJW are hypericin and hyperforin, which are thought to act by inhibiting the synaptic uptake of serotonin (5-HT), GABA, noradrenaline, dopamine, and L-glutamate via a novel mechanism compared to synthetic antidepressants [362, 368-373]. Although there are no official studies regarding the use of SJW for weight loss, anecdotal reports suggest a positive effect on satiety, which may be attributable to the serotonergic uptake inhibition (see *Sibutramine* above). Following the removal of fenfluramine, an anorectic agent commonly used in the combination product "Phen-Fen" (phentermine – fenfluramine), from the market in 1997, SJW was combined with *Ephedra* or *Citrus aurantium* (see above) and marketed for weight loss as "Herbal Phen-Fen". Because of the expanding popularity of SJW in the 1990s – 2000s, a great deal of research on the mechanism of action and herb-drug interactions has been reported.

Drug interactions with SJW are primarily related to binding of active constituents to the pregnane X receptor leading to induction of cytochrome P450 metabolizing or induction of p-glycoprotein efflux mechanisms via the MDR-1 drug transporter [374-388]. As a result, pharmacokinetics of many cytochrome P450 drug substrates is altered, often leading to decreased plasma concentrations and reduced efficacy [27]. There have been numerous studies that have demonstrated potential metabolism-related drug interactions with CYP 3A4, 1A2, 2C9 and 2C19 [389]. Kinetics of antiplatelet and anticoagulant agents may be altered in the

presence of SJW [390, 391]. In one open-label, three-way crossover randomized study, 12 healthy male subjects were given 1 gram of SJW (standardized to hypericin 0.825 mg/g and hyperforin 12.5 mg/g) for 21 days, with administration of a single 25 mg dose of warfarin on day 14 [390]. A significant increase in warfarin (Cl/F) was observed compared to warfarin alone, with a corresponding decrease in AUC and half-life. However, there was no significant impact on INR or platelet aggregation. The interaction is likely caused not only by alteration of drug metabolism via CYP 450 induction, but also binding of warfarin to the SJW constituents hypericin and pseudohypericin, leading to decreased absorption of the drug [392]. In another study, patients not responding to clopidogrel therapy alone experienced an increase in therapeutic activity when clopidogrel and SJW were coadministered; therefore it is possible that patients responding to stand alone clopidogrel treatment may be at increased risk of bleeding [391]. There has been one case report of a possible interaction between theophylline and SJW in which theophylline levels significantly increased following discontinuation of SJW in a smoker also taking 11 other drugs [393]. However, another study in healthy subjects showed no impact of SJW on theophylline kinetics [394]. Plasma concentrations of protease inhibitors such as indinavir may be reduced in the presence of SJW due to induction of p-glycoprotein efflux in the gastrointestinal tract [395-398]. Decreased plasma levels of the "statins" simvastatin and atorvastatin have been reported in controlled, randomized, cross-over studies [399, 400]. Reports of pharmacokinetic interactions have also been reported for digoxin, gliclazide, imatinib, irinotecan, methadone, omeprazole, verapamil, and voriconazole have also been published [401-412]. In general, coadministration of SJW with drugs significantly eliminated via these enzymes should be avoided.

Several studies and case reports describe interactions between SJW and oral contraceptives, resulting in breakthrough or irregular bleeding and unplanned pregnancy [413-416]. In one case report, an unwanted pregnancy occurred in a 36-year old patient while taking an ethinyl estradiol/dinogesterol oral contraceptive (Valette®). The patient had previously been taking fluvastatin (20 mg/day) for 2 years, but had discontinued the drug and started 1700 mg SJW extract daily for 3 months prior to conception [414]. One randomized controlled trial in 18 female subjects taking low dose oral contraceptives (0.02 mg ethinyl estradiol / 0.150 mg desogestrel) in combination with 300 mg SJW twice daily reported a significant increase in breakthrough bleeding compared to subjects taking oral contraceptive alone [417]. Progestins and estrogens contained in oral contraceptives are known to be metabolized by various CYP enzymes and therefore induction of these enzymes by SJW results in decreased plasma concentrations and therapeutic failure [417-420].

Interactions between SJW and with drugs used in the prevention of organ transplant rejection such as tacrolimus and cyclosporine have been reported [421-431]. Several transplant patients have experienced transplant rejection potentially related to coadministration of SJW. In one case report a patient treated with 75 mg cyclosporine daily for several years following kidney transplant experienced a drop in cyclosporin plasma levels attributed to SJW administration [427]. Levels returned to normal when SJW was discontinued and dropped upon rechallenge with SJW extract. Similarly, tacrolimus plasma levels markedly decreased in a study involving 10 stabilized renal transplant patients administered 600 mg SJW extract for two weeks,

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requiring dosage adjustments during and for up to two weeks following discontinuation of SJW [431].

SJW may interact with selective serotonin reuptake inhibitors (SSRIs), monoamines, and other antidepressant and psychiatric medications due to the serotonin uptake inhibitory properties of hypericin and hyperforin, although metabolic induction plays a role for some drugs [368, 370-373, 432-446]. In one case report, a patient who had been taking paroxetine 40 mg daily for treatment of depression discontinued her medication and began taking SJW 600 mg daily [434]. No adverse events were reported with the switch, but upon coadministration of a 20 mg dose of paroxetine to aid in sleep the patient experience extreme grogginess, weakness, fatigue, and incoherency. The author cited the potential for additive serotonin uptake inhibition resulting in "serotonin syndrome". One case of a male adult patient stabilized on methylphenidate for attention deficit hyperactivity disorder (ADHD) is reported in which the patient experienced increased ADHD symptoms after taking SJW 600 mg daily for four months [438]. The mechanism of the interaction is unknown. Interactions have also been reported for amitriptyline, clozapine, fexofenadine, and sertraline; therefore administration of SJW in patients taking these and similar drugs should be avoided [440, 443, 444, 446, 447].

An interaction between SJW and drugs known to cause phototoxic adverse reactions is also possible, due to the photosensitizing nature of hypericin [448-450]. In one study, 11 subjects were exposed to UVA1 radiation at baseline and following 10 days treatment with 1020 mg (3000 mcg hypericin) extract [449]. Minimum erythemal dose (MED) as measured 8, 24 and 48 hours after exposure to radiation and was found to be significantly lower at 8 and 48, but not 24 hours, after exposure compared to control. There is one case report of a patient experiencing severe phototoxicity upon exposure to laser light (532 nm) and pulsed dye laser light (585 nm), presumably due to ingestion of SJW [451]. SJW may also increase the sensitivity and skin toxicity of radiation treatment in patients undergoing radiation therapy, possibly through photosensitizing effects although the exact underlying mechanism is not known [452].

3.12. Willow bark (*Salix alba*)

Willow bark from the *Salix alba* tree is often contained in weight loss supplements, presumably due to earlier studies that noted enhanced thermogenic properties of ephedra in combination products also including aspirin (see *Ephedra* above). The active constituents of white willow are predominantly the salicylates (acetylsalicylic acid) and, therefore, the bark has traditionally been used in the treatment of pain [27, 453, 454]. The analgesic and anti-inflammatory activity of willow bark is due to inhibition of cyclooxygenase-2 (COX-2) mediated prostaglandin E2 release [455, 456]. Although there are few case reports dealing with willow bark extract specifically, drug and herb interactions seen with other salicylates are possible [455, 457]. Generally, caution should be used in concomitant administration of drugs contraindicated for aspirin, such as beta-blockers, NSAIDs, carbonic anhydrase inhibitors (e.g. acetazolamide), probenecid, alcohol, and salicylates, while the kinetics of protein bound drugs can also be modified [27]. Salicin may also have an effect on platelet aggregation, and therefore interactions with anticoagulants and antiplatelet drugs are possible [458, 459]. In one randomized

double-blind study involving 16 patients administered standardized extracts of *Salicis cortex* (240 mg salicin/day), mean arachidonic induced platelet aggregation was reduced (61% compared to 78% in placebo group), but not as significantly as in the acetylsalicylic acid group (13% reduction) [458]. One randomized placebo-controlled trial investigating the efficacy of willow bark extract in osteoarthritis reported an increase in triglyceride levels, suggesting a potential interaction between willow bark and antihyperlipidemics [460]. Some patients in another randomized controlled trial, who were given 240 mg salicin daily for four weeks, suffered blood pressure instability and edema; use of willow bark in patients taking antihypertensives should be cautioned [461].

4. Adulteration of dietary supplements

A final note is necessary regarding the adulteration of weight loss supplements with drug products and other chemical substances. This adulteration is often the underlying cause for the purported activity of a dietary supplement and can result in serious toxicity. The most commonly cited contaminant in weight loss supplements is sibutramine (Meridia®; see above), a weight loss supplement removed from the market in October 2010 for significant cardiac toxicities [462-466]. One U.S. FDA report cites 72 different herbal products containing adulterants, 94.4% of which contained sibutramine as an additive [102]. Multiple products listed in the report were contaminated with phenolphthalein (11.1%) or the anti-seizure drug phenytoin (2.8%). Other reported contaminants (1.4%) included the experimental anti-obesity agent cetilistat, the recalled anti-obesity agent rimonabant (see above), the anti-obesity amphetamine stimulant drug fenproporex, the antidepressant fluoxetine, or the diuretics furosemide and bumetanide[103]. Phenophthalein was previously used as a laxative in over-the-counter products but was removed from the U.S. market in 1999 due to concerns of carcinogenicity and genotoxicity [467]. Another study investigating contamination of 20 different dietary supplements using 1H-NMR methods found contamination of 14 of the products (70%), with eight products containing sibutramine, five containing both sibutramine and phenolphthalein, and one formulation containing undeclared synephrine [468]. There have been other reports of contamination of weight loss supplements with the diuretic hydrochlorothiazide [462, 469]. Given that tainting of weight loss supplements is common, patients and health care professionals should be made aware of the risks associated with ingestion of herbal products, especially those with minimal evidence backing their claims of efficacy.

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References

[1] World Health Organization, *Obesity: Facts and Figures*, 2012; Available from: http://www.euro.who.int/en/what-we-do/health-topics/noncommunicable-diseases/obesity/facts-and-figures [accessed 06/20/12].

[2] World Health Organization, *WHO Global Infobase*, 2012; Available from: https://apps.who.int/infobase/Comparisons.aspx [accessed 06/20/12]

[3] Ogden, C.L., et al., *Prevalence of overweight and obesity in the United States, 1999-2004.* JAMA, 2006. 295(13): p. 1549-55.

[4] Flegal, K.M., et al., *Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010.* JAMA, 2012. 307(5): p. 491-7.

[5] James, W.P., *WHO recognition of the global obesity epidemic.* Int J Obes (Lond), 2008. 32 Suppl 7: p. S120-6.

[6] Ogden, C.L., et al., *Prevalence of obesity in the United States, 2009-2010.* NCHS Data Brief, 2012(82): p. 1-8.

[7] Samaranayake, N.R., et al., *Management of obesity in the National Health and Nutrition Examination Survey (NHANES), 2007-2008.* Ann Epidemiol, 2012. 22(5): p. 349-53.

[8] Manton, K.G., *The global impact of noncommunicable diseases: estimates and projections.* World Health Stat Q, 1988. 41(3-4): p. 255-66.

[9] Wang, Y., et al., *Will all Americans become overweight or obese? estimating the progression and cost of the US obesity epidemic.* Obesity (Silver Spring), 2008. 16(10): p. 2323-30.

[10] Wolf, A.M. and G.A. Colditz, *Current estimates of the economic cost of obesity in the United States.* Obes Res, 1998. 6(2): p. 97-106.

[11] *European Charter on Counteracting Obesity*, in *WHO European Ministerial Conference on Counteracting Obesity*. 2006, World Health Organization: Istanbul, Turkey.

[12] U.S. Department of Agriculture, Cente rfor Nutrition Policy and Promotion, 2012. *ChooseMyPlate.gov*; Available from: http://www/ChooseMyPlate.gov [accessed 06/20/12].

[13] J. Steenhuysen, S.H., J. Lentz, L. Richwine, *Factbox: A troubled history for weight-loss drugs*, in *Reuters*. 2011, Thomson Reuters.

[14] Sam, A.H., V. Salem, and M.A. Ghatei, *Rimonabant: From RIO to Ban.* J Obes, 2011. 2011: p. 432607.

[15] U.S. Food and Drug Adminsitration, *FDA Drug Safety Communication: FDA Recommends Against the Continued Use of Meridia (sibutramine)*, 2010: Silver Spring, MD.

[16] Basch, E.M., J.C. Servoss, and U.B. Tedrow, *Safety assurances for dietary supplements policy issues and new research paradigms.* J Herb Pharmacother, 2005. 5(1): p. 3-15.

[17] Harris, I.M., *Regulatory and ethical issues with dietary supplements.* Pharmacotherapy, 2000. 20(11): p. 1295-302.

[18] Jordan, S.A., D.G. Cunningham, and R.J. Marles, *Assessment of herbal medicinal products: challenges, and opportunities to increase the knowledge base for safety assessment.* Toxicol Appl Pharmacol, 2010. 243(2): p. 198-216.

[19] Tsutani, K. and H. Takuma, *[Regulatory sciences in herbal medicines and dietary supplements].* Yakugaku Zasshi, 2008. 128(6): p. 867-80.

[20] Garcia-Mijares, M., A.M. Bernardes, and M.T. Silva, *Diethylpropion produces psychostimulant and reward effects.* Pharmacol Biochem Behav, 2009. 91(4): p. 621-8.

[21] Ollo, C., et al., *Lack of neurotoxic effect of diethylpropion in crack-cocaine abusers.* Clin Neuropharmacol, 1996. 19(1): p. 52-8.

[22] Samanin, R. and S. Garattini, *Neurochemical mechanism of action of anorectic drugs.* Pharmacol Toxicol, 1993. 73(2): p. 63-8.

[23] *Prescribing Information. Tenuate (diethylpropion hydrochloride)*. November 2003, Aventis Pharmaceuticals, Inc.: Bridgewater, NJ.

[24] Martin, C.A. and E.T. Iwamoto, *Diethylpropion-induced psychosis reprecipitated by an MAO inhibitor: case report.* J Clin Psychiatry, 1984. 45(3): p. 130-1.

[25] Seedat, Y.K. and J. Reddy, *Diethylpropion hydrochloride (Tenuate Dospan) in combination with hypotensive agents in the treatment of obesity associated with hypertension.* Curr Ther Res Clin Exp, 1974. 16(5): p. 398-413.

[26] Carruba, M.O., et al., *Dopaminergic and serotoninergic anorectics differentially antagonize insulin- and 2-DG-induced hyperphagia.* Life Sci, 1985. 36(18): p. 1739-49.

[27] Jellin, J. et al. (Eds), *Natural Medicines Comprehensive Database*. 1995 - 2012, Therapeutic Research Faculty.

[28] *Suprenza (phentermine hydrochloride) Prescribing Information*. 2011, Akrimax Pharmaceuticals, LLC: Cranford, NJ.

[29] Haddock, C.K., et al., *Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials.* Int J Obes Relat Metab Disord, 2002. 26(2): p. 262-73.

[30] Fleming, R.M. and L.B. Boyd, *The longitudinal effects of fenfluramine-phentermine use.* Angiology, 2007. 58(3): p. 353-9.

[31] Barasch, A. and M.M. Safford, *Diet medications and valvular heart disease: the current evidence.* Spec Care Dentist, 2002. 22(3): p. 108-14.

[32] Stephens, L.C. and S.G. Katz, *Phentermine and anaesthesia.* Anaesth Intensive Care, 2005. 33(4): p. 525-7.

[33] Biton, V., *Clinical pharmacology and mechanism of action of zonisamide.* Clin Neuropharmacol, 2007. 30(4): p. 230-40.

[34] Antel, J. and J. Hebebrand, *Weight-reducing side effects of the antiepileptic agents topiramate and zonisamide.* Handb Exp Pharmacol, 2012(209): p. 433-66.

[35] *Topamax (topiramate) Prescribing Information*. 2009, Janssen Pharmaceuticals, Inc.: Titusville, NJ.

[36] Czuczwar, S.J., *[GABA-ergic system and antiepileptic drugs].* Neurol Neurochir Pol, 2000. 34 Suppl 1: p. 13-20.

[37] White, H.S., et al., *Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism.* Epilepsia, 2000. 41 Suppl 1: p. S17-20.

[38] Eliasson, B., et al., *Weight loss and metabolic effects of topiramate in overweight and obese type 2 diabetic patients: randomized double-blind placebo-controlled trial.* Int J Obes (Lond), 2007. 31(7): p. 1140-7.

[39] Gordon, A. and L.H. Price, *Mood stabilization and weight loss with topiramate.* Am J Psychiatry, 1999. 156(6): p. 968-9.

[40] Littrell, K.H., et al., *Weight loss with topiramate.* Ann Pharmacother, 2001. 35(9): p. 1141-2.

[41] Roy Chengappa, K.N., et al., *Long-term effects of topiramate on bipolar mood instability, weight change and glycemic control: a case-series.* Eur Psychiatry, 2001. 16(3): p. 186-90.

[42] Shapira, N.A., T.D. Goldsmith, and S.L. McElroy, *Treatment of binge-eating disorder with topiramate: a clinical case series.* J Clin Psychiatry, 2000. 61(5): p. 368-72.

[43] Allison, D.B., et al., *Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP).* Obesity (Silver Spring), 2012. 20(2): p. 330-42.

[44] Bays, H.E. and K.M. Gadde, *Phentermine/topiramate for weight reduction and treatment of adverse metabolic consequences in obesity.* Drugs Today (Barc), 2011. 47(12): p. 903-14.

[45] Powell, A.G., C.M. Apovian, and L.J. Aronne, *The combination of phentermine and topiramate is an effective adjunct to diet and lifestyle modification for weight loss and measures of comorbidity in overweight or obese adults with additional metabolic risk factors.* Evid Based Med, 2012. 17(1): p. 14-5.

[46] Shah, K. and D.T. Villareal, *Combination treatment to CONQUER obesity?* Lancet, 2011. 377(9774): p. 1295-7.

[47] Mack, C.J., et al., *Interaction of topiramate with carbamazepine: two case reports and a review of clinical experience.* Seizure, 2002. 11(7): p. 464-7.

[48] Cano-Zuleta, A., et al., *Report of three cases of hyperammonaemic encephalopathy associated with valproic acid due to possible synergism with phenobarbital and topiramate.* Farm Hosp, 2012.

[49] Deutsch, S.I., J.A. Burket, and R.B. Rosse, *Valproate-induced hyperammonemic encephalopathy and normal liver functions: possible synergism with topiramate.* Clin Neuropharmacol, 2009. 32(6): p. 350-2.

[50] Gomez-Ibanez, A., E. Urrestarazu-Bolumburu, and C. Viteri-Torres, *Hyperammonemic encephalopathy related to valproate, phenobarbital, and topiramate synergism.* Epilepsy Behav, 2011. 21(4): p. 480-2.

[51] *Metabolic acidosis due to topiramate.* Prescrire Int, 2004. 13(73): p. 186.

[52] Burmeister, J.E., et al., *Topiramate and severe metabolic acidosis: case report.* Arq Neuropsiquiatr, 2005. 63(2B): p. 532-4.

[53] Fernandez-de Orueta, L., et al., *Topiramate-induced metabolic acidosis: a case study.* Nefrologia, 2012. 32(3): p. 403-404.

[54] Ko, C.H. and C.K. Kong, *Topiramate-induced metabolic acidosis: report of two cases.* Dev Med Child Neurol, 2001. 43(10): p. 701-4.

[55] Ozer, Y. and H. Altunkaya, *Topiramate induced metabolic acidosis.* Anaesthesia, 2004. 59(8): p. 830.

[56] Vivius, I., *VI-0521 (Qnexa) Advisory Committee Briefing Document*, E.a.M.D.A. Committee, Editor. 2012, Vivius, Inc.: Mountain View, CA. p. 1 - 166.

[57] Leppik, I.E., *Zonisamide: chemistry, mechanism of action, and pharmacokinetics.* Seizure, 2004. 13 Suppl 1: p. S5-9; discussion S10.

[58] Czapinski, P., B. Blaszczyk, and S.J. Czuczwar, *Mechanisms of action of antiepileptic drugs.* Curr Top Med Chem, 2005. 5(1): p. 3-14.

[59] Suzuki, S., et al., *Zonisamide blocks T-type calcium channel in cultured neurons of rat cerebral cortex.* Epilepsy Res, 1992. 12(1): p. 21-7.

[60] Okada, M., et al., *Effects of zonisamide on dopaminergic system.* Epilepsy Res, 1995. 22(3): p. 193-205.

[61] Okada, M., et al., *Biphasic effects of zonisamide on serotonergic system in rat hippocampus.* Epilepsy Res, 1999. 34(2-3): p. 187-97.

[62] Gadde, K.M., et al., *Zonisamide for weight loss in obese adults: a randomized controlled trial.* JAMA, 2003. 289(14): p. 1820-5.

[63] Ojemann, L.M., et al., *Comparative pharmacokinetics of zonisamide (CI-912) in epileptic patients on carbamazepine or phenytoin monotherapy.* Ther Drug Monit, 1986. 8(3): p. 293-6.

[64] Orito, K., et al., *Pharmacokinetics of zonisamide and drug interaction with phenobarbital in dogs.* J Vet Pharmacol Ther, 2008. 31(3): p. 259-64.

[65] Shinoda, M., et al., *The necessity of adjusting the dosage of zonisamide when coadministered with other anti-epileptic drugs.* Biol Pharm Bull, 1996. 19(8): p. 1090-2.

[66] *Zonegran (zonisamide) Package Insert*. 2006, Eisai Inc.: Teaneck, NJ.

[67] Arvill, A. and L. Bodin, *Effect of short-term ingestion of konjac glucomannan on serum cholesterol in healthy men.* Am J Clin Nutr, 1995. 61(3): p. 585-9.

[68] Nagatomo, I., et al., *Alcohol intake decreases brain Zonisamide concentration in inbred EL mice.* Neuroreport, 1997. 8(2): p. 391-4.

[69] *Xenical Prescribing Information*. 2012, Genentech USA, Inc.: South San Francisco, CA.

[70] Drent, M.L. and E.A. van der Veen, *Lipase inhibition: a novel concept in the treatment of obesity.* Int J Obes Relat Metab Disord, 1993. 17(4): p. 241-4.

[71] Li, Z., et al., *Meta-analysis: pharmacologic treatment of obesity.* Ann Intern Med, 2005. 142(7): p. 532-46.

[72] Davidson, M.H., et al., *Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial.* JAMA, 1999. 281(3): p. 235-42.

[73] Torgerson, J.S., et al., *XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients.* Diabetes Care, 2004. 27(1): p. 155-61.

[74] Colman, E. and M. Fossler, *Reduction in blood cyclosporine concentrations by orlistat.* N Engl J Med, 2000. 342(15): p. 1141-2.

[75] Errasti, P., et al., *Reduction in blood cyclosporine concentration by orlistat in two renal transplant patients.* Transplant Proc, 2002. 34(1): p. 137-9.

[76] Evans, S., et al., *Drug interaction in a renal transplant patient: cyclosporin-Neoral and orlistat.* Am J Kidney Dis, 2003. 41(2): p. 493-6.

[77] Le Beller, C., et al., *Co-administration of orlistat and cyclosporine in a heart transplant recipient.* Transplantation, 2000. 70(10): p. 1541-2.

[78] Nagele, H., et al., *Effect of orlistat on blood cyclosporin concentration in an obese heart transplant patient.* Eur J Clin Pharmacol, 1999. 55(9): p. 667-9.

[79] Schnetzler, B., et al., *Orlistat decreases the plasma level of cyclosporine and may be responsible for the development of acute rejection episodes.* Transplantation, 2000. 70(10): p. 1540-1.

[80] Barbaro, D., et al., *Obesity in transplant patients: case report showing interference of orlistat with absorption of cyclosporine and review of literature.* Endocr Pract, 2002. 8(2): p. 124-6.

[81] McDuffie, J.R., et al., *Effects of orlistat on fat-soluble vitamins in obese adolescents.* Pharmacotherapy, 2002. 22(7): p. 814-22.

[82] Melia, A.T., S.G. Koss-Twardy, and J. Zhi, *The effect of orlistat, an inhibitor of dietary fat absorption, on the absorption of vitamins A and E in healthy volunteers.* J Clin Pharmacol, 1996. 36(7): p. 647-53.

[83] Zhi, J., et al., *The effect of orlistat, an inhibitor of dietary fat absorption, on the pharmacokinetics of beta-carotene in healthy volunteers.* J Clin Pharmacol, 1996. 36(2): p. 152-9.

[84] Bigham, S., C. McGuigan, and B.K. MacDonald, *Reduced absorption of lipophilic anti-epileptic medications when used concomitantly with the anti-obesity drug orlistat.* Epilepsia, 2006. 47(12): p. 2207.

[85] Madhava, K. and A. Hartley, *Hypothyroidism in thyroid carcinoma follow-up: orlistat may inhibit the absorption of thyroxine.* Clin Oncol (R Coll Radiol), 2005. 17(6): p. 492.

[86] Zhi, J., et al., *The effect of orlistat on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers.* J Clin Pharmacol, 1996. 36(7): p. 659-66.

[87] Xie, S., et al., *The endocannabinoid system and rimonabant: a new drug with a novel mechanism of action involving cannabinoid CB1 receptor antagonism--or inverse agonism--as potential obesity treatment and other therapeutic use.* J Clin Pharm Ther, 2007. 32(3): p. 209-31.

[88] Banerji, M.A. and M. Tiewala, *Rimonabant--the RIO North America trial: a new strategy to sustaining weight loss and related morbidity.* Curr Diab Rep, 2006. 6(3): p. 228-9.

[89] Kintscher, U., *The cardiometabolic drug rimonabant: after 2 years of RIO-Europe and STRADIVARIUS.* Eur Heart J, 2008. 29(14): p. 1709-10.

[90] Nissen, S.E., et al., *Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial.* JAMA, 2008. 299(13): p. 1547-60.

[91] Pan, C., H.J. Yoo, and L.T. Ho, *Perspectives of CB1 Antagonist in Treatment of Obesity: Experience of RIO-Asia.* J Obes, 2011. 2011: p. 957268.

[92] Pi-Sunyer, F.X., et al., *Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial.* JAMA, 2006. 295(7): p. 761-75.

[93] Scheen, A.J., *CB1 receptor blockade and its impact on cardiometabolic risk factors: overview of the RIO programme with rimonabant.* J Neuroendocrinol, 2008. 20 Suppl 1: p. 139-46.

[94] Topol, E.J., et al., *Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial.* Lancet, 2010. 376(9740): p. 517-23.

[95] Van Gaal, L.F., et al., *Long-term effect of CB1 blockade with rimonabant on cardiometabolic risk factors: two year results from the RIO-Europe Study.* Eur Heart J, 2008. 29(14): p. 1761-71.

[96] Despres, J.P., A. Golay, and L. Sjostrom, *Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia.* N Engl J Med, 2005. 353(20): p. 2121-34.

[97] Rasmussen, E.B., et al., *Rimonabant reduces the essential value of food in the genetically obese Zucker rat: an exponential demand analysis.* Physiol Behav, 2012. 105(3): p. 734-41.

[98] Verty, A.N., et al., *Anti-obesity effects of the combined administration of CB1 receptor antagonist rimonabant and melanin-concentrating hormone antagonist SNAP-94847 in diet-inudced obese mice.* Int J Obes (Lond), 2012.

[99] Zaitone, S.A. and S. Essawy, *Addition of a low dose of rimonabant to orlistat therapy decreases weight gain and reduces adiposity in dietary obese rats.* Clin Exp Pharmacol Physiol, 2012. 39(6): p. 551-9.

[100] Taj Pharmaceuticals Limited, *Indian Pharmaceuticals Company Taj Pharmaceuticals receives FDA Approval for Generic Rimonabant*. 2010; Available from: http://www.tajpharma.com/media/media_r/Indian%20Pharmaceuticals%20Company%20Taj%20Pharmaceuticals%20receives%20FDA%20approval%20for%20Generic%20Rimonabant.pdf [accessed 06/20/12].

[101] Venhuis, B.J., et al., *The identification of rimonabant polymorphs, sibutramine and analogues of both in counterfeit Acomplia bought on the internet.* J Pharm Biomed Anal, 2011. 54(1): p. 21-6.

[102] U.S. Food and Drug Adminsitration, Department of Health and Human Services, *Questions and Answers about FDA's Initiative Against Contaminated Weight Loss Products*, 2008: Silver Spring, MD.

[103] U.S. Food and Drug Adminsitration, Department of Health and Human Services, *FDA Uncovers Additional Tainted Weight Loss Products: Agency Alerts Consumers to the Finding of New Undeclared Drug Ingredients.*, 2009: Rockville, MD.

[104] European Medicines Agency (EMEA), *Acomplia: EPAR - Product Information*, 2009.

[105] Mandhane, S., et al., *Induction of Glucose Intolerance by Acute Administration of Rimonabant.* Pharmacology, 2012. 89(5-6): p. 339-347.

[106] *Meridia (sibutramine hydrocholoride) Package Insert*. 2010, Abbott Laboratories: North Chicago, IL.

[107] Heal, D.J., et al., *Sibutramine: a novel anti-obesity drug. A review of the pharmacological evidence to differentiate it from d-amphetamine and d-fenfluramine.* Int J Obes Relat Metab Disord, 1998. 22 Suppl 1: p. S18-28; discussion S29.

[108] Liu, Y.L., D.J. Heal, and M.J. Stock, *Mechanism of the thermogenic effect of Metabolite 2 (BTS 54 505), a major pharmacologically active metabolite of the novel anti-obesity drug, sibutramine.* Int J Obes Relat Metab Disord, 2002. 26(9): p. 1245-53.

[109] McNeely, W. and K.L. Goa, *Sibutramine. A review of its contribution to the management of obesity.* Drugs, 1998. 56(6): p. 1093-124.

[110] Nisoli, E. and M.O. Carruba, *An assessment of the safety and efficacy of sibutramine, an anti-obesity drug with a novel mechanism of action.* Obes Rev, 2000. 1(2): p. 127-39.

[111] Bailey, D.G. and G.K. Dresser, *Interactions between grapefruit juice and cardiovascular drugs.* Am J Cardiovasc Drugs, 2004. 4(5): p. 281-97.

[112] Greenway, F.L. and M.K. Caruso, *Safety of obesity drugs.* Expert Opin Drug Saf, 2005. 4(6): p. 1083-95.

[113] Wellman, P.J., S.L. Jones, and D.K. Miller, *Effects of preexposure to dexfenfluramine, phentermine, dexfenfluramine-phentermine, or fluoxetine on sibutramine-induced hypophagia in the adult rat.* Pharmacol Biochem Behav, 2003. 75(1): p. 103-14.

[114] Yalcin, A.A., et al., *Elevation of QT dispersion after obesity drug sibutramine.* J Cardiovasc Med (Hagerstown), 2010. 11(11): p. 832-5.

[115] Caterson, I.D., et al., *Maintained intentional weight loss reduces cardiovascular outcomes: results from the Sibutramine Cardiovascular OUTcomes (SCOUT) trial.* Diabetes Obes Metab, 2012. 14(6): p. 523-30.

[116] Coutinho, W.F., *The obese older female patient: CV risk and the SCOUT study.* Int J Obes (Lond), 2007. 31 Suppl 2: p. S26-30; discussion S31-2.

[117] Maggioni, A.P., *SCOUT trial reports on the safety profile of sibutramine in patients with cardiovascular diseases.* Phys Sportsmed, 2009. 37(3): p. 95-7.

[118] Torp-Pedersen, C., et al., *Cardiovascular responses to weight management and sibutramine in high-risk subjects: an analysis from the SCOUT trial.* Eur Heart J, 2007. 28(23): p. 2915-23.

[119] Benazzi, F., *Organic hypomania secondary to sibutramine-citalopram interaction.* J Clin Psychiatry, 2002. 63(2): p. 165.

[120] Clerbaux, G., E. Goffin, and Y. Pirson, *Interaction between sibutramine and cyclosporine.* Am J Transplant, 2003. 3(7): p. 906.

[121] Jordan, J. and A.M. Sharma, *Potential for sibutramine-yohimbine interaction?* Lancet, 2003. 361(9371): p. 1826.

[122] Chin, Y.W., et al., *Lignans and other constituents of the fruits of Euterpe oleracea (Acai) with antioxidant and cytoprotective activities.* J Agric Food Chem, 2008. 56(17): p. 7759-64.

[123] Jensen, G.S., et al., *In vitro and in vivo antioxidant and anti-inflammatory capacities of an antioxidant-rich fruit and berry juice blend. Results of a pilot and randomized, double-blinded, placebo-controlled, crossover study.* J Agric Food Chem, 2008. 56(18): p. 8326-33.

[124] Lichtenthaler, R., et al., *Total oxidant scavenging capacities of Euterpe oleracea Mart. (Acai) fruits.* Int J Food Sci Nutr, 2005. 56(1): p. 53-64.

[125] Mertens-Talcott, S.U., et al., *Pharmacokinetics of anthocyanins and antioxidant effects after the consumption of anthocyanin-rich acai juice and pulp (Euterpe oleracea Mart.) in human healthy volunteers.* J Agric Food Chem, 2008. 56(17): p. 7796-802.

[126] Xie, C., et al., *Acai juice attenuates atherosclerosis in ApoE deficient mice through antioxidant and anti-inflammatory activities.* Atherosclerosis, 2011. 216(2): p. 327-33.

[127] Udani, J.K., et al., *Effects of Acai (Euterpe oleracea Mart.) berry preparation on metabolic parameters in a healthy overweight population: a pilot study.* Nutr J, 2011. 10: p. 45.

[128] Allison, D.B., et al., *Exactly which synephrine alkaloids does Citrus aurantium (bitter orange) contain?* Int J Obes (Lond), 2005. 29(4): p. 443-6.

[129] Dandekar, D.V., G.K. Jayaprakasha, and B.S. Patil, *Simultaneous extraction of bioactive limonoid aglycones and glucoside from Citrus aurantium L. using hydrotropy.* Z Naturforsch C, 2008. 63(3-4): p. 176-80.

[130] Haaz, S., et al., *Citrus aurantium and synephrine alkaloids in the treatment of overweight and obesity: an update.* Obes Rev, 2006. 7(1): p. 79-88.

[131] Liu, L., et al., *Naringenin and hesperetin, two flavonoids derived from Citrus aurantium up-regulate transcription of adiponectin.* Phytother Res, 2008. 22(10): p. 1400-3.

[132] Nelson, B.C., et al., *Mass spectrometric determination of the predominant adrenergic protoalkaloids in bitter orange (Citrus aurantium).* J Agric Food Chem, 2007. 55(24): p. 9769-75.

[133] Pellati, F., et al., *Determination of adrenergic agonists from extracts and herbal products of Citrus aurantium L. var. amara by LC.* J Pharm Biomed Anal, 2002. 29(6): p. 1113-9.

[134] Penzak, S.R., et al., *Seville (sour) orange juice: synephrine content and cardiovascular effects in normotensive adults.* J Clin Pharmacol, 2001. 41(10): p. 1059-63.

[135] Bui, L.T., D.T. Nguyen, and P.J. Ambrose, *Blood pressure and heart rate effects following a single dose of bitter orange.* Ann Pharmacother, 2006. 40(1): p. 53-7.

[136] Haller, C.A., N.L. Benowitz, and P. Jacob, 3rd, *Hemodynamic effects of ephedra-free weight-loss supplements in humans.* Am J Med, 2005. 118(9): p. 998-1003.

[137] Di Marco, M.P., et al., *The effect of grapefruit juice and seville orange juice on the pharmacokinetics of dextromethorphan: the role of gut CYP3A and P-glycoprotein.* Life Sci, 2002. 71(10): p. 1149-60.

[138] Edwards, D.J., et al., *6',7'-Dihydroxybergamottin in grapefruit juice and Seville orange juice: effects on cyclosporine disposition, enterocyte CYP3A4, and P-glycoprotein.* Clin Pharmacol Ther, 1999. 65(3): p. 237-44.

[139] Malhotra, S., et al., *Seville orange juice-felodipine interaction: comparison with dilute grapefruit juice and involvement of furocoumarins.* Clin Pharmacol Ther, 2001. 69(1): p. 14-23.

[140] Penzak, S.R., et al., *Effect of Seville orange juice and grapefruit juice on indinavir pharmacokinetics.* J Clin Pharmacol, 2002. 42(10): p. 1165-70.

[141] Suzuki, O., et al., *Oxidation of synephrine by type A and type B monoamine oxidase.* Experientia, 1979. 35(10): p. 1283-4.

[142] Visentin, V., et al., *Dual action of octopamine on glucose transport into adipocytes: inhibition via beta3-adrenoceptor activation and stimulation via oxidation by amine oxidases.* J Pharmacol Exp Ther, 2001. 299(1): p. 96-104.

[143] Acheson, K.J., et al., *Metabolic effects of caffeine in humans: lipid oxidation or futile cycling?* Am J Clin Nutr, 2004. 79(1): p. 40-6.

[144] Acheson, K.J., et al., *Caffeine and coffee: their influence on metabolic rate and substrate utilization in normal weight and obese individuals.* Am J Clin Nutr, 1980. 33(5): p. 989-97.

[145] Andersen, T. and J. Fogh, *Weight loss and delayed gastric emptying following a South American herbal preparation in overweight patients.* J Hum Nutr Diet, 2001. 14(3): p. 243-50.

[146] Astrup, A., et al., *The effect of ephedrine/caffeine mixture on energy expenditure and body composition in obese women.* Metabolism, 1992. 41(7): p. 686-8.

[147] Astrup, A., et al., *Thermogenic synergism between ephedrine and caffeine in healthy volunteers: a double-blind, placebo-controlled study.* Metabolism, 1991. 40(3): p. 323-9.

[148] Boozer, C.N., et al., *Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial.* Int J Obes Relat Metab Disord, 2002. 26(5): p. 593-604.

[149] Coffey, C.S., et al., *A randomized double-blind placebo-controlled clinical trial of a product containing ephedrine, caffeine, and other ingredients from herbal sources for treatment of overweight and obesity in the absence of lifestyle treatment.* Int J Obes Relat Metab Disord, 2004. 28(11): p. 1411-9.

[150] Dulloo, A.G., *Herbal simulation of ephedrine and caffeine in treatment of obesity.* Int J Obes Relat Metab Disord, 2002. 26(5): p. 590-2.

[151] Dulloo, A.G., J. Seydoux, and L. Girardier, *Peripheral mechanisms of thermogenesis induced by ephedrine and caffeine in brown adipose tissue.* Int J Obes, 1991. 15(5): p. 317-26.

[152] Cannon, M.E., C.T. Cooke, and J.S. McCarthy, *Caffeine-induced cardiac arrhythmia: an unrecognised danger of healthfood products.* Med J Aust, 2001. 174(10): p. 520-1.

[153] Heseltine, D., et al., *The effect of caffeine on postprandial hypotension in the elderly.* J Am Geriatr Soc, 1991. 39(2): p. 160-4.

[154] Heseltine, D., et al., *The effect of caffeine on postprandial blood pressure in the frail elderly.* Postgrad Med J, 1991. 67(788): p. 543-7.

[155] Katan, M.B. and E. Schouten, *Caffeine and arrhythmia.* Am J Clin Nutr, 2005. 81(3): p. 539-40.

[156] Nurminen, M.L., et al., *Coffee, caffeine and blood pressure: a critical review.* Eur J Clin Nutr, 1999. 53(11): p. 831-9.

[157] Upton, R.A., *Pharmacokinetic interactions between theophylline and other medication (Part I).* Clin Pharmacokinet, 1991. 20(1): p. 66-80.

[158] Del Rio, G., et al., *Increased cardiovascular response to caffeine in perimenopausal women before and during estrogen therapy.* Eur J Endocrinol, 1996. 135(5): p. 598-603.

[159] Pollock, B.G., et al., *Inhibition of caffeine metabolism by estrogen replacement therapy in postmenopausal women.* J Clin Pharmacol, 1999. 39(9): p. 936-40.

[160] Dulloo, A.G., et al., *Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans.* Am J Clin Nutr, 1999. 70(6): p. 1040-5.

[161] Dulloo, A.G., et al., *Green tea and thermogenesis: interactions between catechin-polyphenols, caffeine and sympathetic activity.* Int J Obes Relat Metab Disord, 2000. 24(2): p. 252-8.

[162] Jagdeo, J. and N. Brody, *Complementary antioxidant function of caffeine and green tea polyphenols in normal human skin fibroblasts.* J Drugs Dermatol, 2011. 10(7): p. 753-61.

[163] Samanidou, V., A. Tsagiannidis, and I. Sarakatsianos, *Simultaneous determination of polyphenols and major purine alkaloids in Greek Sideritis species, herbal extracts, green tea, black tea, and coffee by high-performance liquid chromatography-diode array detection.* J Sep Sci, 2012. 35(4): p. 608-15.

[164] Westerterp-Plantenga, M.S., *Green tea catechins, caffeine and body-weight regulation.* Physiol Behav, 2010. 100(1): p. 42-6.

[165] Phung, O.J., et al., *Effect of green tea catechins with or without caffeine on anthropometric measures: a systematic review and meta-analysis.* Am J Clin Nutr, 2010. 91(1): p. 73-81.

[166] Taylor, J.R. and V.M. Wilt, *Probable antagonism of warfarin by green tea.* Ann Pharmacother, 1999. 33(4): p. 426-8.

[167] Sun, J., *Morning/evening menopausal formula relieves menopausal symptoms: a pilot study.* J Altern Complement Med, 2003. 9(3): p. 403-9.

[168] Westphal, L.M., M.L. Polan, and A.S. Trant, *Double-blind, placebo-controlled study of Fertilityblend: a nutritional supplement for improving fertility in women.* Clin Exp Obstet Gynecol, 2006. 33(4): p. 205-8.

[169] Westphal, L.M., et al., *A nutritional supplement for improving fertility in women: a pilot study.* J Reprod Med, 2004. 49(4): p. 289-93.

[170] Wu, A.H., et al., *Tea and circulating estrogen levels in postmenopausal Chinese women in Singapore.* Carcinogenesis, 2005. 26(5): p. 976-80.

[171] Abourashed, E.A., et al., *Two new flavone glycosides from paullinia pinnata.* J Nat Prod, 1999. 62(8): p. 1179-81.

[172] Avato, P., et al., *Seed oil composition of Paullinia cupana var. sorbilis (Mart.) Ducke.* Lipids, 2003. 38(7): p. 773-80.

[173] Belliardo, F., A. Martelli, and M.G. Valle, *HPLC determination of caffeine and theophylline in Paullinia cupana Kunth (guarana) and Cola spp. samples.* Z Lebensm Unters Forsch, 1985. 180(5): p. 398-401.

[174] Saldana, M.D., et al., *Extraction of methylxanthines from guarana seeds, mate leaves, and cocoa beans using supercritical carbon dioxide and ethanol.* J Agric Food Chem, 2002. 50(17): p. 4820-6.

[175] Weckerle, C.S., M.A. Stutz, and T.W. Baumann, *Purine alkaloids in Paullinia.* Phytochemistry, 2003. 64(3): p. 735-42.

[176] Zamble, A., et al., *Paullinia pinnata extracts rich in polyphenols promote vascular relaxation via endothelium-dependent mechanisms.* J Cardiovasc Pharmacol, 2006. 47(4): p. 599-608.

[177] Bydlowski, S.P., R.L. Yunker, and M.T. Subbiah, *A novel property of an aqueous guarana extract (Paullinia cupana): inhibition of platelet aggregation in vitro and in vivo.* Braz J Med Biol Res, 1988. 21(3): p. 535-8.

[178] Blumenthal, M., W.R. Busse, and Bundesinstitut für Arzneimittel und Medizinprodukte (Germany), *The complete German Commission E monographs, Therapeutic guide to herbal medicines*. 1998, Austin, Texas; Boston: American Botanical Council ;Integrative Medicine Communications. xxii, 685 p.

[179] Escudero, N.L., DeArellano, M.L., Fernandez, S., Albarracin, G., and Mucciarelli, S., *Taraxacum officinale as a food source.* Plant Foods for Human Nutrition, 2003. 58(3): p. 1 - 10.

[180] Tabassum, N., Qazi, M.A., and Shah, A., *Curative Activity of Ethanol Extract of Taraxacum officinale Weber. Against CCl4 Induced Hepatocellular Damage in Albino Rats.* J. Pharmacy Res., 2011. 4(3): p. 687 - 689.

[181] Clare, B.A., R.S. Conroy, and K. Spelman, *The diuretic effect in human subjects of an extract of Taraxacum officinale folium over a single day.* J Altern Complement Med, 2009. 15(8): p. 929-34.

[182] Zhu, M., P.Y. Wong, and R.C. Li, *Effects of taraxacum mongolicum on the bioavailability and disposition of ciprofloxacin in rats.* J Pharm Sci, 1999. 88(6): p. 632-4.

[183] Goksu, E., et al., *First report of hypoglycemia secondary to dandelion (Taraxacum officinale) ingestion.* Am J Emerg Med, 2010. 28(1): p. 111 e1-2.

[184] Kalix, P., *The pharmacology of psychoactive alkaloids from ephedra and catha.* J Ethnopharmacol, 1991. 32(1-3): p. 201-8.

[185] Greenway, F.L., et al., *Effect of a dietary herbal supplement containing caffeine and ephedra on weight, metabolic rate, and body composition.* Obes Res, 2004. 12(7): p. 1152-7.

[186] Hackman, R.M., et al., *Multinutrient supplement containing ephedra and caffeine causes weight loss and improves metabolic risk factors in obese women: a randomized controlled trial.* Int J Obes (Lond), 2006. 30(10): p. 1545-56.

[187] Magkos, F. and S.A. Kavouras, *Caffeine and ephedrine: physiological, metabolic and performance-enhancing effects.* Sports Med, 2004. 34(13): p. 871-89.

[188] Williams, A.D., et al., *The effect of ephedra and caffeine on maximal strength and power in resistance-trained athletes.* J Strength Cond Res, 2008. 22(2): p. 464-70.

[189] Willis, S.L., et al., *Hypertensive retinopathy associated with use of the ephedra-free weight-loss herbal supplement Hydroxycut.* MedGenMed, 2006. 8(3): p. 82.

[190] *Ephedrine, Xanthines, Aspirin and Other Thermogenic Drugs to Assist the Dietary Management of Obesity. Proceedings of an international symposium. Geneva, 24-26 September 1992.* Int J Obes Relat Metab Disord, 1993. 17 Suppl 1: p. S1-83.

[191] Battig, K., *Acute and chronic cardiovascular and behavioural effects of caffeine, aspirin and ephedrine.* Int J Obes Relat Metab Disord, 1993. 17 Suppl 1: p. S61-4.

[192] Daly, P.A., et al., *Ephedrine, caffeine and aspirin: safety and efficacy for treatment of human obesity.* Int J Obes Relat Metab Disord, 1993. 17 Suppl 1: p. S73-8.

[193] Dulloo, A.G., *Ephedrine, xanthines and prostaglandin-inhibitors: actions and interactions in the stimulation of thermogenesis.* Int J Obes Relat Metab Disord, 1993. 17 Suppl 1: p. S35-40.

[194] Dulloo, A.G. and D.S. Miller, *Aspirin as a promoter of ephedrine-induced thermogenesis: potential use in the treatment of obesity.* Am J Clin Nutr, 1987. 45(3): p. 564-9.

[195] Dulloo, A.G. and D.S. Miller, *Ephedrine, caffeine and aspirin: "over-the-counter" drugs that interact to stimulate thermogenesis in the obese.* Nutrition, 1989. 5(1): p. 7-9.

[196] Geissler, C.A., *Effects of weight loss, ephedrine and aspirin on energy expenditure in obese women.* Int J Obes Relat Metab Disord, 1993. 17 Suppl 1: p. S45-8.

[197] Horton, T.J. and C.A. Geissler, *Aspirin potentiates the effect of ephedrine on the thermogenic response to a meal in obese but not lean women.* Int J Obes, 1991. 15(5): p. 359-66.

[198] Horton, T.J. and C.A. Geissler, *Post-prandial thermogenesis with ephedrine, caffeine and aspirin in lean, pre-disposed obese and obese women.* Int J Obes Relat Metab Disord, 1996. 20(2): p. 91-7.

[199] Krieger, D.R., et al., *Ephedrine, caffeine and aspirin promote weight loss in obese subjects.* Trans Assoc Am Physicians, 1990. 103: p. 307-12.

[200] Loose, I. and M. Winkel, *Clinical, double-blind, placebo-controlled study investigating the combination of acetylsalicylic acid and pseudoephedrine for the symptomatic treatment of nasal congestion associated with common cold.* Arzneimittelforschung, 2004. 54(9): p. 513-21.

[201] Lucker, P.W., et al., *Pharmacokinetic interaction study of a fixed combination of 500 mg acetylsalicylic acid/30 mg pseudoephedrine versus each of the single active ingredients in healthy male volunteers.* Arzneimittelforschung, 2003. 53(4): p. 260-5.

[202] Chen, C., et al., *Ischemic stroke after using over the counter products containing ephedra.* J Neurol Sci, 2004. 217(1): p. 55-60.

[203] Clark, B.M. and R.S. Schofield, *Dilated cardiomyopathy and acute liver injury associated with combined use of ephedra, gamma-hydroxybutyrate, and anabolic steroids.* Pharmacotherapy, 2005. 25(5): p. 756-61.

[204] Dhar, R., et al., *Cardiovascular toxicities of performance-enhancing substances in sports.* Mayo Clin Proc, 2005. 80(10): p. 1307-15.

[205] Figueredo, V.M., *Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart.* Am J Med, 2011. 124(6): p. 480-8.

[206] Flanagan, C.M., et al., *Coronary artery aneurysm and thrombosis following chronic ephedra use.* Int J Cardiol, 2010. 139(1): p. e11-3.

[207] Miller, S.C., *Safety concerns regarding ephedrine-type alkaloid-containing dietary supplements.* Mil Med, 2004. 169(2): p. 87-93.

[208] Peters, C.M., et al., *Is there an association between ephedra and heart failure? a case series.* J Card Fail, 2005. 11(1): p. 9-11.

[209] Shekelle, P.G., et al., *Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis.* JAMA, 2003. 289(12): p. 1537-45.

[210] Thomas, J.E., et al., *STEMI in a 24-year-old man after use of a synephrine-containing dietary supplement: a case report and review of the literature.* Tex Heart Inst J, 2009. 36(6): p. 586-90.

[211] White, L.M., et al., *Pharmacokinetics and cardiovascular effects of ma-huang (Ephedra sinica) in normotensive adults.* J Clin Pharmacol, 1997. 37(2): p. 116-22.

[212] Siegrid Keline, C.R., Robert Rister, *The Complete German Commissions E Monographs: Therapeutic Guide to Herbal Medicines*. 1998, Boston, MA: Integrative Medicine Communications. 685.

[213] Kanaya, N., et al., *Propofol anesthesia enhances the pressor response to intravenous ephedrine.* Anesth Analg, 2002. 94(5): p. 1207-11, table of contents.

[214] Ueda, W., et al., *Ephedrine-induced increases in arterial blood pressure accelerate regression of epidural block.* Anesth Analg, 1995. 81(4): p. 703-5.

[215] Lee, A., W.D. Ngan Kee, and T. Gin, *Prophylactic ephedrine prevents hypotension during spinal anesthesia for Cesarean delivery but does not improve neonatal outcome: a quantitative systematic review.* Can J Anaesth, 2002. 49(6): p. 588-99.

[216] Lee, A., W.D. Ngan Kee, and T. Gin, *A dose-response meta-analysis of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for elective cesarean delivery.* Anesth Analg, 2004. 98(2): p. 483-90, table of contents.

[217] Astrup, A., et al., *The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. A double blind trial.* Int J Obes Relat Metab Disord, 1992. 16(4): p. 269-77.

[218] Martinet, A., K. Hostettmann, and Y. Schutz, *Thermogenic effects of commercially available plant preparations aimed at treating human obesity.* Phytomedicine, 1999. 6(4): p. 231-8.

[219] Dawson, J.K., S.M. Earnshaw, and C.S. Graham, *Dangerous monoamine oxidase inhibitor interactions are still occurring in the 1990s.* J Accid Emerg Med, 1995. 12(1): p. 49-51.

[220] Boada, S., et al., *[Hypotension refractory to ephedrine after sympathetic blockade in a patient on long-term therapy with tricyclic antidepressants].* Rev Esp Anestesiol Reanim, 1999. 46(8): p. 364-6.

[221] Astrup, A. and S. Toubro, *Thermogenic, metabolic, and cardiovascular responses to ephedrine and caffeine in man.* Int J Obes Relat Metab Disord, 1993. 17 Suppl 1: p. S41-3.

[222] Samenuk, D., et al., *Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine.* Mayo Clin Proc, 2002. 77(1): p. 12-6.

[223] Tormey, W.P. and A. Bruzzi, *Acute psychosis due to the interaction of legal compounds--ephedra alkaloids in 'vigueur fit' tablets, caffeine in 'red bull' and alcohol.* Med Sci Law, 2001. 41(4): p. 331-6.

[224] Theoharides, T.C., *Sudden death of a healthy college student related to ephedrine toxicity from a ma huang-containing drink.* J Clin Psychopharmacol, 1997. 17(5): p. 437-9.

[225] Zahn, K.A., R.L. Li, and R.A. Purssell, *Cardiovascular toxicity after ingestion of "herbal ecstacy".* J Emerg Med, 1999. 17(2): p. 289-91.

[226] Cairella, M. and G. Marchini, *[Evaluation of the action of glucomannan on metabolic parameters and on the sensation of satiation in overweight and obese patients].* Clin Ter, 1995. 146(4): p. 269-74.

[227] Chen, H.L., et al., *Konjac acts as a natural laxative by increasing stool bulk and improving colonic ecology in healthy adults.* Nutrition, 2006. 22(11-12): p. 1112-9.

[228] Chen, H.L., et al., *Supplementation of konjac glucomannan into a low-fiber Chinese diet promoted bowel movement and improved colonic ecology in constipated adults: a placebo-controlled, diet-controlled trial.* J Am Coll Nutr, 2008. 27(1): p. 102-8.

[229] Chen, H.L., et al., *Konjac supplement alleviated hypercholesterolemia and hyperglycemia in type 2 diabetic subjects--a randomized double-blind trial.* J Am Coll Nutr, 2003. 22(1): p. 36-42.

[230] Sood, N., W.L. Baker, and C.I. Coleman, *Effect of glucomannan on plasma lipid and glucose concentrations, body weight, and blood pressure: systematic review and meta-analysis.* Am J Clin Nutr, 2008. 88(4): p. 1167-75.

[231] Vuksan, V., et al., *Beneficial effects of viscous dietary fiber from Konjac-mannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial.* Diabetes Care, 2000. 23(1): p. 9-14.

[232] Yoshida, M., et al., *Effect of plant sterols and glucomannan on lipids in individuals with and without type II diabetes.* Eur J Clin Nutr, 2006. 60(4): p. 529-37.

[233] Shima, K., et al., *Effect of dietary fiber, glucomannan, on absorption of sulfonylurea in man.* Horm Metab Res, 1983. 15(1): p. 1-3.

[234] Doi, K., *Effect of konjac fibre (glucomannan) on glucose and lipids.* Eur J Clin Nutr, 1995. 49 Suppl 3: p. S190-7.

[235] Doi, K., et al., *Treatment of diabetes with glucomannan (konjac mannan).* Lancet, 1979. 1(8123): p. 987-8.

[236] Huang, C.Y., et al., *Effect of Konjac food on blood glucose level in patients with diabetes.* Biomed Environ Sci, 1990. 3(2): p. 123-31.

[237] Vuksan, V., et al., *Konjac-Mannan and American ginsing: emerging alternative therapies for type 2 diabetes mellitus.* J Am Coll Nutr, 2001. 20(5 Suppl): p. 370S-380S; discussion 381S-383S.

[238] Azezli, A.D., T. Bayraktaroglu, and Y. Orhan, *The use of konjac glucomannan to lower serum thyroid hormones in hyperthyroidism.* J Am Coll Nutr, 2007. 26(6): p. 663-8.

[239] Doi, K., et al., *Influence of dietary fiber (konjac mannan) on absorption of vitamin B12 and vitamin E.* Tohoku J Exp Med, 1983. 141 Suppl: p. 677-81.

[240] van Heerden, F.R., *Hoodia gordonii: a natural appetite suppressant.* J Ethnopharmacol, 2008. 119(3): p. 434-7.

[241] Vermaak, I., J.H. Hamman, and A.M. Viljoen, *Hoodia gordonii: an up-to-date review of a commercially important anti-obesity plant.* Planta Med, 2011. 77(11): p. 1149-60.

[242] MacLean, D.B. and L.G. Luo, *Increased ATP content/production in the hypothalamus may be a signal for energy-sensing of satiety: studies of the anorectic mechanism of a plant steroidal glycoside.* Brain Res, 2004. 1020(1-2): p. 1-11.

[243] Madgula, V.L., et al., *In vitro metabolic stability and intestinal transport of P57AS3 (P57) from Hoodia gordonii and its interaction with drug metabolizing enzymes.* Planta Med, 2008. 74(10): p. 1269-75.

[244] Jena, B.S., et al., *Chemistry and biochemistry of (-)-hydroxycitric acid from Garcinia.* J Agric Food Chem, 2002. 50(1): p. 10-22.

[245] Soni, M.G., et al., *Safety assessment of (-)-hydroxycitric acid and Super CitriMax, a novel calcium/potassium salt.* Food Chem Toxicol, 2004. 42(9): p. 1513-29.

[246] Heymsfield, S.B., et al., *Garcinia cambogia (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial.* JAMA, 1998. 280(18): p. 1596-600.

[247] Preuss, H.G., et al., *Effects of a natural extract of (-)-hydroxycitric acid (HCA-SX) and a combination of HCA-SX plus niacin-bound chromium and Gymnema sylvestre extract on weight loss.* Diabetes Obes Metab, 2004. 6(3): p. 171-80.

[248] Mattes, R.D. and L. Bormann, *Effects of (-)-hydroxycitric acid on appetitive variables.* Physiol Behav, 2000. 71(1-2): p. 87-94.

[249] Mansi, I.A. and J. Huang, *Rhabdomyolysis in response to weight-loss herbal medicine.* Am J Med Sci, 2004. 327(6): p. 356-7.

[250] Levy, A.S. and A.W. Heaton, *Weight control practices of U.S. adults trying to lose weight.* Ann Intern Med, 1993. 119(7 Pt 2): p. 661-6.

[251] Boban, P.T., B. Nambisan, and P.R. Sudhakaran, *Hypolipidaemic effect of chemically different mucilages in rats: a comparative study.* Br J Nutr, 2006. 96(6): p. 1021-9.

[252] Pittler, M.H. and E. Ernst, *Guar gum for body weight reduction: meta-analysis of randomized trials.* Am J Med, 2001. 110(9): p. 724-30.

[253] Salas-Salvadó, J., et al., *Effect of two doses of a mixture of soluble fibres on body weight and metabolic variables in overweight or obese patients: a randomised trial.* Br J Nutr, 2008. 99(6): p. 1380-7.

[254] Blackburn, N.A., et al., *The mechanism of action of guar gum in improving glucose tolerance in man.* Clin Sci (Lond), 1984. 66(3): p. 329-36.

[255] Frati-Munari, A.C., et al., *Effect of Plantago psyllium mucilage on the glucose tolerance test.* Arch Invest Med (Mex), 1985. 16(2): p. 191-7.

[256] Jenkins, D.J. and A.L. Jenkins, *Dietary fiber and the glycemic response.* Proc Soc Exp Biol Med, 1985. 180(3): p. 422-31.

[257] Leclere, C.J., et al., *Role of viscous guar gums in lowering the glycemic response after a solid meal.* Am J Clin Nutr, 1994. 59(4): p. 914-21.

[258] McCarty, M.F., *Glucomannan minimizes the postprandial insulin surge: a potential adjuvant for hepatothermic therapy.* Med Hypotheses, 2002. 58(6): p. 487-90.

[259] Ou, S., et al., *In vitro study of possible role of dietary fiber in lowering postprandial serum glucose.* J Agric Food Chem, 2001. 49(2): p. 1026-9.

[260] Russo, A., et al., *Guar attenuates fall in postprandial blood pressure and slows gastric emptying of oral glucose in type 2 diabetes.* Dig Dis Sci, 2003. 48(7): p. 1221-9.

[261] Torsdottir, I., et al., *Dietary guar gum effects on postprandial blood glucose, insulin and hydroxyproline in humans.* J Nutr, 1989. 119(12): p. 1925-31.

[262] Ahi, S., et al., *A bulking agent may lead to adrenal insufficiency crisis: a case report.* Acta Med Iran, 2011. 49(10): p. 688-9.

[263] Chiu, A.C. and S.I. Sherman, *Effects of pharmacological fiber supplements on levothyroxine absorption.* Thyroid, 1998. 8(8): p. 667-71.

[264] Garcia, J.J., et al., *Influence of two dietary fibers in the oral bioavailability and other pharmacokinetic parameters of ethinyloestradiol.* Contraception, 2000. 62(5): p. 253-7.

[265] Gin, H., M.B. Orgerie, and J. Aubertin, *The influence of Guar gum on absorption of metformin from the gut in healthy volunteers.* Horm Metab Res, 1989. 21(2): p. 81-3.

[266] González, A., et al., *Effect of glucomannan and the dosage form on ethinylestradiol oral absorption in rabbits.* Contraception, 2004. 70(5): p. 423-7.

[267] Heaney, R.P. and C.M. Weaver, *Effect of psyllium on absorption of co-ingested calcium.* J Am Geriatr Soc, 1995. 43(3): p. 261-3.

[268] Holt, S., et al., *Effect of gel fibre on gastric emptying and absorption of glucose and paracetamol.* Lancet, 1979. 1(8117): p. 636-9.

[269] Huupponen, R., P. Seppala, and E. Iisalo, *Effect of guar gum, a fibre preparation, on digoxin and penicillin absorption in man.* Eur J Clin Pharmacol, 1984. 26(2): p. 279-81.

[270] Perlman, B.B., *Interaction between lithium salts and ispaghula husk.* Lancet, 1990. 335(8686): p. 416.

[271] Reissell, P. and V. Manninen, *Effect of administration of activated charcoal and fibre on absorption, excretion and steady state blood levels of digoxin and digitoxin. Evidence for intestinal secretion of the glycosides.* Acta Med Scand Suppl, 1982. 668: p. 88-90.

[272] Toutoungi, M., et al., *[Probable interaction of psyllium and lithium].* Therapie, 1990. 45(4): p. 358-60.

[273] Roerig, J.L., et al., *Laxative abuse: epidemiology, diagnosis and management.* Drugs, 2010. 70(12): p. 1487-503.

[274] Tozzi, F., et al., *Features associated with laxative abuse in individuals with eating disorders.* Psychosom Med, 2006. 68(3): p. 470-7.

[275] Amato, A., et al., *Half doses of PEG-ES and senna vs. high-dose senna for bowel cleansing before colonoscopy: a randomized, investigator-blinded trial.* Am J Gastroenterol, 2010. 105(3): p. 675-81.

[276] Branco, A., et al., *Anthraquinones from the bark of Senna macranthera.* An Acad Bras Cienc, 2011. 83(4): p. 1159-64.

[277] Brouwers, J.R., et al., *A controlled trial of senna preparations and other laxatives used for bowel cleansing prior to radiological examination.* Pharmacology, 1980. 20 Suppl 1: p. 58-64.

[278] El-Gengaihi, S., A.H. Agiza, and A. El-Hamidi, *Distribution of anthraquinones in Senna plants.* Planta Med, 1975. 27(4): p. 349-53.

[279] Franz, G., *The senna drug and its chemistry.* Pharmacology, 1993. 47 Suppl 1: p. 2-6.

[280] Godding, E.W., *Laxatives and the special role of senna.* Pharmacology, 1988. 36 Suppl 1: p. 230-6.

[281] Gould, S.R. and C.B. Williams, *Castor oil or senna preparation before colonoscopy for inactive chronic ulcerative colitis.* Gastrointest Endosc, 1982. 28(1): p. 6-8.

[282] Hietala, P., et al., *Laxative potency and acute toxicity of some anthraquinone derivatives, senna extracts and fractions of senna extracts.* Pharmacol Toxicol, 1987. 61(2): p. 153-6.

[283] Izard, M.W. and F.S. Ellison, *Treatment of drug-induced constipation with a purified senna derivative.* Conn Med, 1962. 26: p. 589-92.

[284] Khafagy, S.M., et al., *Estimation of sennosides A, B, C and D in Senna leaves, pods and formulations.* Planta Med, 1972. 21(3): p. 304-9.

[285] Kinnunen, O., et al., *Safety and efficacy of a bulk laxative containing senna versus lactulose in the treatment of chronic constipation in geriatric patients.* Pharmacology, 1993. 47 Suppl 1: p. 253-5.

[286] Kositchaiwat, S., et al., *Comparative study of two bowel preparation regimens for colonoscopy: senna tablets vs sodium phosphate solution.* World J Gastroenterol, 2006. 12(34): p. 5536-9.

[287] Krumbiegel, G. and H.U. Schulz, *Rhein and aloe-emodin kinetics from senna laxatives in man.* Pharmacology, 1993. 47 Suppl 1: p. 120-4.

[288] Lamphier, T.A. and R. Ehrlich, *Evaluation of standardized senna in the management of constipation.* Am J Gastroenterol, 1957. 27(4): p. 381-4.

[289] Lemli, J., *The Estimation of Anthracene Derivatives in Senna and Rhubarb.* J Pharm Pharmacol, 1965. 17: p. 227-32.

[290] Marlett, J.A., et al., *Comparative laxation of psyllium with and without senna in an ambulatory constipated population.* Am J Gastroenterol, 1987. 82(4): p. 333-7.

[291] Mc, N.G., *The effect of a standardised senna preparation on the human bowel.* J Pharm Pharmacol, 1958. 10(8): p. 499-506.

[292] Monias, M.B., *Standardized senna concentrate in postpartum bowel rehabilitation.* Md State Med J, 1966. 15(2): p. 32-3.

[293] Putalun, W., et al., *Sennosides A and B production by hairy roots of Senna alata (L.) Roxb.* Z Naturforsch C, 2006. 61(5-6): p. 367-71.

[294] Radaelli, F., et al., *High-dose senna compared with conventional PEG-ES lavage as bowel preparation for elective colonoscopy: a prospective, randomized, investigator-blinded trial.* Am J Gastroenterol, 2005. 100(12): p. 2674-80.

[295] Valverde, A., et al., *Senna vs polyethylene glycol for mechanical preparation the evening before elective colonic or rectal resection: a multicenter controlled trial. French Association for Surgical Research.* Arch Surg, 1999. 134(5): p. 514-9.

[296] Ishii, Y., H. Tanizawa, and Y. Takino, *[Studies of aloe. II. Mechanism of cathartic effect].* Yakugaku Zasshi, 1988. 108(9): p. 904-10.

[297] Ishii, Y., H. Tanizawa, and Y. Takino, *Studies of aloe. III. Mechanism of cathartic effect. (2).* Chem Pharm Bull (Tokyo), 1990. 38(1): p. 197-200.

[298] Ishii, Y., H. Tanizawa, and Y. Takino, *Studies of aloe. V. Mechanism of cathartic effect. (4).* Biol Pharm Bull, 1994. 17(5): p. 651-3.

[299] Ishii, Y., H. Tanizawa, and Y. Takino, *Studies of aloe. IV. Mechanism of cathartic effect. (3).* Biol Pharm Bull, 1994. 17(4): p. 495-7.

[300] *Status of certain additional over-the-counter drug category II and III active ingredients. Final rule.* Fed Regist, 2002. 67(90): p. 31125-7.

[301] *Final report on the safety assessment of AloeAndongensis Extract, Aloe Andongensis Leaf Juice,aloe Arborescens Leaf Extract, Aloe Arborescens Leaf Juice, Aloe Arborescens Leaf Protoplasts, Aloe Barbadensis Flower Extract, Aloe Barbadensis Leaf, Aloe Barbadensis Leaf Extract, Aloe Barbadensis Leaf Juice,aloe Barbadensis Leaf Polysaccharides, Aloe Barbadensis Leaf Water, Aloe Ferox Leaf Extract, Aloe Ferox Leaf Juice, and Aloe Ferox Leaf Juice Extract.* Int J Toxicol, 2007. 26 Suppl 2: p. 1-50.

[302] Quercia, V., *[Separation of anthraquinone compounds of Cascara sagrada by means of high-pressure liquid chromatography].* Boll Chim Farm, 1976. 115(4): p. 309-16.

[303] Fugh-Berman, A., *Herb-drug interactions.* Lancet, 2000. 355(9198): p. 134-8.

[304] Laitinen, L., et al., *Anthranoid laxatives influence the absorption of poorly permeable drugs in human intestinal cell culture model (Caco-2).* Eur J Pharm Biopharm, 2007. 66(1): p. 135-45.

[305] Huseini, H.F., et al., *Anti-hyperglycemic and anti-hypercholesterolemic effects of Aloe vera leaf gel in hyperlipidemic type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial.* Planta Med, 2012. 78(4): p. 311-6.

[306] Musabayane, C.T., P.T. Bwititi, and J.A. Ojewole, *Effects of oral administration of some herbal extracts on food consumption and blood glucose levels in normal and streptozotocin-treated diabetic rats.* Methods Find Exp Clin Pharmacol, 2006. 28(4): p. 223-8.

[307] Rajasekaran, S., et al., *Hypoglycemic effect of Aloe vera gel on streptozotocin-induced diabetes in experimental rats.* J Med Food, 2004. 7(1): p. 61-6.

[308] Lewis, S.J., et al., *Lower serum oestrogen concentrations associated with faster intestinal transit.* Br J Cancer, 1997. 76(3): p. 395-400.

[309] Lewis, S.J., R.E. Oakey, and K.W. Heaton, *Intestinal absorption of oestrogen: the effect of altering transit-time.* Eur J Gastroenterol Hepatol, 1998. 10(1): p. 33-9.

[310] Kittisupamongkol, W., V. Nilaratanakul, and W. Kulwichit, *Near-fatal bleeding, senna, and the opposite of lettuce.* Lancet, 2008. 371(9614): p. 784.

[311] Lee, A., et al., *Possible interaction between sevoflurane and Aloe vera.* Ann Pharmacother, 2004. 38(10): p. 1651-4.

[312] Kitagawa, I., et al., *Chemical studies of Chinese licorice-roots. I. Elucidation of five new flavonoid constituents from the roots of Glycyrrhiza glabra L. collected in Xinjiang.* Chem Pharm Bull (Tokyo), 1994. 42(5): p. 1056-62.

[313] Mitscher, L.A., et al., *Antimicrobial agents from higher plants. Antimicrobial isoflavanoids and related substances from Glycyrrhiza glabra L. var. typica.* J Nat Prod, 1980. 43(2): p. 259-69.

[314] Grossman, E. and F.H. Messerli, *Drug-induced hypertension: an unappreciated cause of secondary hypertension.* Am J Med, 2012. 125(1): p. 14-22.

[315] Kaleel, M., et al., *Licorice: a patient's shocking presentation.* Del Med J, 2011. 83(7): p. 211-5.

[316] Knobel, U., et al., *Gitelman's syndrome with persistent hypokalemia - don't forget licorice, alcohol, lemon juice, iced tea and salt depletion: a case report.* J Med Case Rep, 2011. 5: p. 312.

[317] Brayley, J. and J. Jones, *Life-threatening hypokalemia associated with excessive licorice ingestion.* Am J Psychiatry, 1994. 151(4): p. 617-8.

[318] Famularo, G., F.M. Corsi, and M. Giacanelli, *Iatrogenic worsening of hypokalemia and neuromuscular paralysis associated with the use of glucose solutions for potassium replacement in a young woman with licorice intoxication and furosemide abuse.* Acad Emerg Med, 1999. 6(9): p. 960-4.

[319] Joseph, R. and J. Kelemen, *Paraparesis due to licorice-induced hypokalemia.* N Y State J Med, 1984. 84(6): p. 296.

[320] Mumoli, N. and M. Cei, *Licorice-induced hypokalemia.* Int J Cardiol, 2008. 124(3): p. e42-4.

[321] Pelner, L., *Licorice induced hypokalemia.* N Y State J Med, 1984. 84(12): p. 591.

[322] Yasue, H., et al., *Severe hypokalemia, rhabdomyolysis, muscle paralysis, and respiratory impairment in a hypertensive patient taking herbal medicines containing licorice.* Intern Med, 2007. 46(9): p. 575-8.

[323] Yoshida, S. and Y. Takayama, *Licorice-induced hypokalemia as a treatable cause of dropped head syndrome.* Clin Neurol Neurosurg, 2003. 105(4): p. 286-7.

[324] Armanini, D., et al., *Further studies on the mechanism of the mineralocorticoid action of licorice in humans.* J Endocrinol Invest, 1996. 19(9): p. 624-9.

[325] Stoving, R.K., et al., *Is glycyrrhizin sensitivity increased in anorexia nervosa and should licorice be avoided? Case report and review of the literature.* Nutrition, 2011. 27(7-8): p. 855-8.

[326] Wynn, G.J., G.K. Davis, and B. Maher, *Trick or treat? Pseudohyperaldosteronism due to episodic licorice consumption.* J Clin Hypertens (Greenwich), 2011. 13(3): p. E3-4.

[327] Armanini, D., M. Wehling, and P.C. Weber, *Mineralocorticoid effector mechanism of liquorice derivatives in human mononuclear leukocytes.* J Endocrinol Invest, 1989. 12(5): p. 303-6.

[328] Berlango Jimenez, A., et al., *[Acute rhabdomyolysis and tetraparesis secondary to hypokalemia due to ingested licorice].* An Med Interna, 1995. 12(1): p. 33-5.

[329] Brasseur, A. and J. Ducobu, *[Severe hypokalemia after holidays return].* Rev Med Brux, 2008. 29(5): p. 490-3.

[330] Carretta, R. and S. Muiesan, *[Pseudohyperaldosteronism caused by the abuse of licorice].* G Clin Med, 1986. 67(1): p. 55-6.

[331] Cataldo, F., et al., *[Pseudohyperaldosteronism secondary to licorice poisoning associated with hemorrhagic gastritis].* Pediatr Med Chir, 1997. 19(3): p. 219-21.

[332] Ferrari, P. and B.N. Trost, *[A case from practice (169). Liquorice-induced pseudohyperaldosteronism in a previously alcoholic woman caused by the drinking of an alcohol-free Pastis substitute beverage].* Schweiz Rundsch Med Prax, 1990. 79(12): p. 377-8.

[333] Ghielmini, C. and A. Hoffmann, *[A case from practice (171). Pseudohyperaldosteronism in licorice abuse].* Schweiz Rundsch Med Prax, 1990. 79(15): p. 472-3.

[334] Gomez Fernandez, P., et al., *[Primary pseudohyperaldosteronism produced by chronic licorice consumption].* Rev Clin Esp, 1981. 163(4): p. 277-8.

[335] Holmes, A.M., et al., *Pseudohyperaldosteronism induced by habitual ingestion of liquorice.* Postgrad Med J, 1970. 46(540): p. 625-9.

[336] Russo, S., et al., *Low doses of liquorice can induce hypertension encephalopathy.* Am J Nephrol, 2000. 20(2): p. 145-8.

[337] Scali, M., et al., *Pseudohyperaldosteronism from liquorice-containing laxatives.* J Endocrinol Invest, 1990. 13(10): p. 847-8.

[338] Sontia, B., et al., *Pseudohyperaldosteronism, liquorice, and hypertension.* J Clin Hypertens (Greenwich), 2008. 10(2): p. 153-7.

[339] Kimura, I., et al., *The antihyperglycaemic blend effect of traditional chinese medicine byakko-ka-ninjin-to on alloxan and diabetic KK-CA(y) mice.* Phytother Res, 1999. 13(6): p. 484-8.

[340] Kuroda, M., et al., *Phenolics with PPAR-gamma ligand-binding activity obtained from licorice (Glycyrrhiza uralensis roots) and ameliorative effects of glycyrin on genetically diabetic KK-A(y) mice.* Bioorg Med Chem Lett, 2003. 13(24): p. 4267-72.

[341] Bardhan, K.D., et al., *Clinical trial of deglycyrrhizinised liquorice in gastric ulcer.* Gut, 1978. 19(9): p. 779-82.

[342] Engqvist, A., et al., *Double-blind trial of deglycyrrhizinated liquorice in gastric ulcer.* Gut, 1973. 14(9): p. 711-5.

[343] MacKenzie, M.A., et al., *The influence of glycyrrhetinic acid on plasma cortisol and cortisone in healthy young volunteers.* J Clin Endocrinol Metab, 1990. 70(6): p. 1637-43.

[344] Armanini, D., et al., *Effect of licorice on the reduction of body fat mass in healthy subjects.* J Endocrinol Invest, 2003. 26(7): p. 646-50.

[345] Armanini, D., et al., *Glycyrrhetinic acid, the active principle of licorice, can reduce the thickness of subcutaneous thigh fat through topical application.* Steroids, 2005. 70(8): p. 538-42.

[346] Hukkanen, J., O. Ukkola, and M.J. Savolainen, *Effects of low-dose liquorice alone or in combination with hydrochlorothiazide on the plasma potassium in healthy volunteers.* Blood Press, 2009. 18(4): p. 192-5.

[347] Kawakami, F., Y. Shimoyama, and K. Ohtsuki, *Characterization of complement C3 as a glycyrrhizin (GL)-binding protein and the phosphorylation of C3alpha by CK-2, which is potently inhibited by GL and glycyrrhetinic acid in vitro.* J Biochem, 2003. 133(2): p. 231-7.

[348] Kroes, B.H., et al., *Inhibition of human complement by beta-glycyrrhetinic acid.* Immunology, 1997. 90(1): p. 115-20.

[349] Akamatsu, H., et al., *Mechanism of anti-inflammatory action of glycyrrhizin: effect on neutrophil functions including reactive oxygen species generation.* Planta Med, 1991. 57(2): p. 119-21.

[350] Rackova, L., et al., *Mechanism of anti-inflammatory action of liquorice extract and glycyrrhizin.* Nat Prod Res, 2007. 21(14): p. 1234-41.

[351] Armanini, D., et al., *Licorice consumption and serum testosterone in healthy man.* Exp Clin Endocrinol Diabetes, 2003. 111(6): p. 341-3.

[352] Armanini, D., G. Bonanni, and M. Palermo, *Reduction of serum testosterone in men by licorice.* N Engl J Med, 1999. 341(15): p. 1158.

[353] Armanini, D., et al., *History of the endocrine effects of licorice.* Exp Clin Endocrinol Diabetes, 2002. 110(6): p. 257-61.

[354] Armanini, D., et al., *Licorice reduces serum testosterone in healthy women.* Steroids, 2004. 69(11-12): p. 763-6.

[355] Kraus, S.D., *Glycyrrhetinic acid--a triterpene with antioestrogenic and anti-inflammatory activity.* J Pharm Pharmacol, 1960. 12: p. 300-6.

[356] Kraus, S.D. and A. Kaminskis, *The anti-estrogenic action of beta-glycyrrhetinic acid.* Exp Med Surg, 1969. 27(4): p. 411-20.

[357] Yamada, K., et al., *Effectiveness of shakuyaku-kanzo-to in neuroleptic-induced hyperprolactinemia: a preliminary report.* Psychiatry Clin Neurosci, 1996. 50(6): p. 341-2.

[358] Yamada, K., et al., *Effectiveness of herbal medicine (shakuyaku-kanzo-to) for neuroleptic-induced hyperprolactinemia.* J Clin Psychopharmacol, 1997. 17(3): p. 234-5.

[359] Imai, T., et al., *In vitro and in vivo evaluation of the enhancing activity of glycyrrhizin on the intestinal absorption of drugs.* Pharm Res, 1999. 16(1): p. 80-6.

[360] Ofir, R., et al., *Inhibition of serotonin re-uptake by licorice constituents.* J Mol Neurosci, 2003. 20(2): p. 135-40.

[361] Dhingra, D. and A. Sharma, *Antidepressant-like activity of Glycyrrhiza glabra L. in mouse models of immobility tests.* Prog Neuropsychopharmacol Biol Psychiatry, 2006. 30(3): p. 449-54.

[362] Tadros, M.G., et al., *Involvement of serotoninergic 5-HT1A/2A, alpha-adrenergic and dopaminergic D1 receptors in St. John's wort-induced prepulse inhibition deficit: a possible role of hyperforin.* Behav Brain Res, 2009. 199(2): p. 334-9.

[363] Shelton, R.C., et al., *Effectiveness of St John's wort in major depression: a randomized controlled trial.* JAMA, 2001. 285(15): p. 1978-86.

[364] Kasper, S., et al., *Better tolerability of St. John's wort extract WS 5570 compared to treatment with SSRIs: a reanalysis of data from controlled clinical trials in acute major depression.* Int Clin Psychopharmacol, 2010. 25(4): p. 204-13.

[365] Niederhofer, H., *St. John's wort may improve some symptoms of attention-deficit hyperactivity disorder.* Nat Prod Res, 2010. 24(3): p. 203-5.

[366] Canning, S., et al., *The efficacy of Hypericum perforatum (St John's wort) for the treatment of premenstrual syndrome: a randomized, double-blind, placebo-controlled trial.* CNS Drugs, 2010. 24(3): p. 207-25.

[367] Balk, J., *The effects of St. John's wort on hot flashes.* Menopause, 2010. 17(5): p. 1089-90.

[368] Chatterjee, S.S., A. Biber, and C. Weibezahn, *Stimulation of glutamate, aspartate and gamma-aminobutyric acid release from synaptosomes by hyperforin.* Pharmacopsychiatry, 2001. 34 Suppl 1: p. S11-9.

[369] Gobbi, M., et al., *In vitro binding studies with two hypericum perforatum extracts--hyperforin, hypericin and biapigenin--on 5-HT6, 5-HT7, GABA(A)/benzodiazepine, sigma, NPY-Y1/Y2 receptors and dopamine transporters.* Pharmacopsychiatry, 2001. 34 Suppl 1: p. S45-8.

[370] Muller, W.E., A. Singer, and M. Wonnemann, *Hyperforin--antidepressant activity by a novel mechanism of action.* Pharmacopsychiatry, 2001. 34 Suppl 1: p. S98-102.

[371] Muller, W.E., et al., *Hyperforin represents the neurotransmitter reuptake inhibiting constituent of hypericum extract.* Pharmacopsychiatry, 1998. 31 Suppl 1: p. 16-21.

[372] Roz, N., et al., *Inhibition of vesicular uptake of monoamines by hyperforin.* Life Sci, 2002. 71(19): p. 2227-37.

[373] Singer, A., M. Wonnemann, and W.E. Muller, *Hyperforin, a major antidepressant constituent of St. John's Wort, inhibits serotonin uptake by elevating free intracellular Na+1.* J Pharmacol Exp Ther, 1999. 290(3): p. 1363-8.

[374] Wentworth, J.M., et al., *St John's wort, a herbal antidepressant, activates the steroid X receptor.* J Endocrinol, 2000. 166(3): p. R11-6.

[375] Weber, C.C., et al., *Modulation of P-glycoprotein function by St John's wort extract and its major constituents.* Pharmacopsychiatry, 2004. 37(6): p. 292-8.

[376] Wang, Z., et al., *The effects of St John's wort (Hypericum perforatum) on human cytochrome P450 activity.* Clin Pharmacol Ther, 2001. 70(4): p. 317-26.

[377] Wang, L.S., et al., *St John's wort induces both cytochrome P450 3A4-catalyzed sulfoxidation and 2C19-dependent hydroxylation of omeprazole.* Clin Pharmacol Ther, 2004. 75(3): p. 191-7.

[378] Wang, E.J., M. Barecki-Roach, and W.W. Johnson, *Quantitative characterization of direct P-glycoprotein inhibition by St John's wort constituents hypericin and hyperforin.* J Pharm Pharmacol, 2004. 56(1): p. 123-8.

[379] Ott, M., et al., *St. John's Wort constituents modulate P-glycoprotein transport activity at the blood-brain barrier.* Pharm Res, 2010. 27(5): p. 811-22.

[380] Obach, R.S., *Inhibition of human cytochrome P450 enzymes by constituents of St. John's Wort, an herbal preparation used in the treatment of depression.* J Pharmacol Exp Ther, 2000. 294(1): p. 88-95.

[381] Noldner, M. and S. Chatterjee, *Effects of two different extracts of St. John's wort and some of their constituents on cytochrome P450 activities in rat liver microsomes.* Pharmacopsychiatry, 2001. 34 Suppl 1: p. S108-10.

[382] Markowitz, J.S., et al., *Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme.* JAMA, 2003. 290(11): p. 1500-4.

[383] Markowitz, J.S., et al., *Effect of St. John's wort (Hypericum perforatum) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers.* Life Sci, 2000. 66(9): p. PL133-9.

[384] Karyekar, C.S., N.D. Eddington, and T.C. Dowling, *Effect of St. John's Wort extract on intestinal expression of cytochrome P4501A2: studies in LS180 cells.* J Postgrad Med, 2002. 48(2): p. 97-100.

[385] Dresser, G.K., et al., *Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects.* Clin Pharmacol Ther, 2003. 73(1): p. 41-50.

[386] Dostalek, M., et al., *Effect of St John's wort (Hypericum perforatum) on cytochrome P-450 activity in perfused rat liver.* Life Sci, 2005. 78(3): p. 239-44.

[387] Chaudhary, A. and K.L. Willett, *Inhibition of human cytochrome CYP 1 enzymes by flavonoids of St. John's wort.* Toxicology, 2006. 217(2-3): p. 194-205.

[388] Durr, D., et al., *St John's Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4.* Clin Pharmacol Ther, 2000. 68(6): p. 598-604.

[389] Zhou, S.F. and X. Lai, *An update on clinical drug interactions with the herbal antidepressant St. John's wort.* Curr Drug Metab, 2008. 9(5): p. 394-409.

[390] Jiang, X., et al., *Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects.* Br J Clin Pharmacol, 2004. 57(5): p. 592-9.

[391] Lau, W.C., et al., *The effect of St John's Wort on the pharmacodynamic response of clopidogrel in hyporesponsive volunteers and patients: increased platelet inhibition by enhancement of CYP3A4 metabolic activity.* J Cardiovasc Pharmacol, 2011. 57(1): p. 86-93.

[392] Groning, R., J. Breitkreutz, and R.S. Muller, *Physico-chemical interactions between extracts of Hypericum perforatum L. and drugs.* Eur J Pharm Biopharm, 2003. 56(2): p. 231-6.

[393] Nebel, A., et al., *Potential metabolic interaction between St. John's wort and theophylline.* Ann Pharmacother, 1999. 33(4): p. 502.

[394] Morimoto, T., et al., *Effect of St. John's wort on the pharmacokinetics of theophylline in healthy volunteers.* J Clin Pharmacol, 2004. 44(1): p. 95-101.

[395] *Toxicity. St. John's wort--interactions with indinavir and other drugs.* TreatmentUpdate, 2000. 12(2): p. 9-11.

[396] Ho, Y.F., et al., *Effects of St. John's wort extract on indinavir pharmacokinetics in rats: differentiation of intestinal and hepatic impacts.* Life Sci, 2009. 85(7-8): p. 296-302.

[397] Miller, J.L., *Interaction between indinavir and St. John's wort reported.* Am J Health Syst Pharm, 2000. 57(7): p. 625-6.

[398] Piscitelli, S.C., et al., *Indinavir concentrations and St John's wort.* Lancet, 2000. 355(9203): p. 547-8.

[399] Andren, L., A. Andreasson, and R. Eggertsen, *Interaction between a commercially available St. John's wort product (Movina) and atorvastatin in patients with hypercholesterolemia.* Eur J Clin Pharmacol, 2007. 63(10): p. 913-6.

[400] Eggertsen, R., A. Andreasson, and L. Andren, *Effects of treatment with a commercially available St John's Wort product (Movina) on cholesterol levels in patients with hypercholesterolemia treated with simvastatin.* Scand J Prim Health Care, 2007. 25(3): p. 154-9.

[401] Andelic, S., *[Bigeminy--the result of interaction between digoxin and St. John's wort].* Vojnosanit Pregl, 2003. 60(3): p. 361-4.

[402] Birdsall, T.C., *St. John's wort and irinotecan-induced diarrhea.* Toxicol Appl Pharmacol, 2007. 220(1): p. 108; author reply 109-10.

[403] Dasgupta, A., *Herbal supplements and therapeutic drug monitoring: focus on digoxin immunoassays and interactions with St. John's wort.* Ther Drug Monit, 2008. 30(2): p. 212-7.

[404] Frye, R.F., et al., *Effect of St John's wort on imatinib mesylate pharmacokinetics.* Clin Pharmacol Ther, 2004. 76(4): p. 323-9.

[405] Hu, Z., et al., *St. John's Wort modulates the toxicities and pharmacokinetics of CPT-11 (irinotecan) in rats.* Pharm Res, 2005. 22(6): p. 902-14.

[406] Hu, Z.P., et al., *A mechanistic study on altered pharmacokinetics of irinotecan by St. John's wort.* Curr Drug Metab, 2007. 8(2): p. 157-71.

[407] Mathijssen, R.H., et al., *Effects of St. John's wort on irinotecan metabolism.* J Natl Cancer Inst, 2002. 94(16): p. 1247-9.

[408] Mueller, S.C., et al., *Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin.* Clin Pharmacol Ther, 2004. 75(6): p. 546-57.

[409] Rengelshausen, J., et al., *Opposite effects of short-term and long-term St John's wort intake on voriconazole pharmacokinetics.* Clin Pharmacol Ther, 2005. 78(1): p. 25-33.

[410] Tannergren, C., et al., *St John's wort decreases the bioavailability of R- and S-verapamil through induction of the first-pass metabolism.* Clin Pharmacol Ther, 2004. 75(4): p. 298-309.

[411] Xie, H.G., *Additional discussions regarding the altered metabolism and transport of omeprazole after long-term use of St John's wort.* Clin Pharmacol Ther, 2005. 78(4): p. 440-1.

[412] Eich-Hochli, D., et al., *Methadone maintenance treatment and St. John's Wort - a case report.* Pharmacopsychiatry, 2003. 36(1): p. 35-7.

[413] Sarino, L.V., et al., *Drug interaction between oral contraceptives and St. John's Wort: appropriateness of advice received from community pharmacists and health food store clerks.* J Am Pharm Assoc (2003), 2007. 47(1): p. 42-7.

[414] Schwarz, U.I., B. Buschel, and W. Kirch, *Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception.* Br J Clin Pharmacol, 2003. 55(1): p. 112-3.

[415] Will-Shahab, L., et al., *St John's wort extract (Ze 117) does not alter the pharmacokinetics of a low-dose oral contraceptive.* Eur J Clin Pharmacol, 2009. 65(3): p. 287-94.

[416] Hall, S.D., et al., *The interaction between St John's wort and an oral contraceptive.* Clin Pharmacol Ther, 2003. 74(6): p. 525-35.

[417] Pfrunder, A., et al., *Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial.* Br J Clin Pharmacol, 2003. 56(6): p. 683-90.

[418] Bhavnani, B.R., *Pharmacokinetics and pharmacodynamics of conjugated equine estrogens: chemistry and metabolism.* Proc Soc Exp Biol Med, 1998. 217(1): p. 6-16.

[419] Tsuchiya, Y., M. Nakajima, and T. Yokoi, *Cytochrome P450-mediated metabolism of estrogens and its regulation in human.* Cancer Lett, 2005. 227(2): p. 115-24.

[420] Ranney, R.E., *Comparative Metabolism of 17alpha-Ethynyl Steroids Used in Oral-Contraceptives.* Journal of Toxicology and Environmental Health, 1977. 3(1-2): p. 139-166.

[421] Alscher, D.M. and U. Klotz, *Drug interaction of herbal tea containing St. John's wort with cyclosporine.* Transpl Int, 2003. 16(7): p. 543-4.

[422] Barone, G.W., et al., *Drug interaction between St. John's wort and cyclosporine.* Ann Pharmacother, 2000. 34(9): p. 1013-6.

[423] Bauer, S., et al., *Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients.* Br J Clin Pharmacol, 2003. 55(2): p. 203-11.

[424] Breidenbach, T., et al., *Profound drop of cyclosporin A whole blood trough levels caused by St. John's wort (Hypericum perforatum).* Transplantation, 2000. 69(10): p. 2229-30.

[425] Karliova, M., et al., *Interaction of Hypericum perforatum (St. John's wort) with cyclosporin A metabolism in a patient after liver transplantation.* J Hepatol, 2000. 33(5): p. 853-5.

[426] Mai, I., et al., *Hyperforin content determines the magnitude of the St John's wort-cyclosporine drug interaction.* Clin Pharmacol Ther, 2004. 76(4): p. 330-40.

[427] Mai, I., et al., *Hazardous pharmacokinetic interaction of Saint John's wort (Hypericum perforatum) with the immunosuppressant cyclosporin.* Int J Clin Pharmacol Ther, 2000. 38(10): p. 500-2.

[428] Moschella, C. and B.L. Jaber, *Interaction between cyclosporine and Hypericum perforatum (St. John's wort) after organ transplantation.* Am J Kidney Dis, 2001. 38(5): p. 1105-7.

[429] Bolley, R., et al., *Tacrolimus-induced nephrotoxicity unmasked by induction of the CYP3A4 system with St John's wort.* Transplantation, 2002. 73(6): p. 1009.

[430] Hebert, M.F., et al., *Effects of St. John's wort (Hypericum perforatum) on tacrolimus pharmacokinetics in healthy volunteers.* J Clin Pharmacol, 2004. 44(1): p. 89-94.

[431] Mai, I., et al., *Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients.* Nephrol Dial Transplant, 2003. 18(4): p. 819-22.

[432] Buchholzer, M.L., et al., *Dual modulation of striatal acetylcholine release by hyperforin, a constituent of St. John's wort.* J Pharmacol Exp Ther, 2002. 301(2): p. 714-9.

[433] Chatterjee, S.S., et al., *Hyperforin as a possible antidepressant component of hypericum extracts.* Life Sci, 1998. 63(6): p. 499-510.

[434] Gordon, J.B., *SSRIs and St.John's Wort: possible toxicity?* Am Fam Physician, 1998. 57(5): p. 950,953.

[435] Hirano, K., et al., *Effects of oral administration of extracts of Hypericum perforatum (St John's wort) on brain serotonin transporter, serotonin uptake and behaviour in mice.* J Pharm Pharmacol, 2004. 56(12): p. 1589-95.

[436] Kiewert, C., et al., *Stimulation of hippocampal acetylcholine release by hyperforin, a constituent of St. John's Wort.* Neurosci Lett, 2004. 364(3): p. 195-8.

[437] Kobak, K.A., et al., *St. John's wort in generalized anxiety disorder: three more case reports.* J Clin Psychopharmacol, 2003. 23(5): p. 531-2.

[438] Niederhofer, H., *St. John's wort may diminish methylphenidate's efficacy in treating patients suffering from attention deficit hyperactivity disorder.* Med Hypotheses, 2007. 68(5): p. 1189.

[439] Saraga, M. and D.F. Zullino, *[St. John's Wort, corticosteroids, cocaine, alcohol... and a first manic episode].* Praxis (Bern 1994), 2005. 94(23): p. 987-9.

[440] Schneck, C., *St. John's wort and hypomania.* J Clin Psychiatry, 1998. 59(12): p. 689.

[441] Turkanovic, J., S.N. Ngo, and R.W. Milne, *Effect of St John's wort on the disposition of fexofenadine in the isolated perfused rat liver.* J Pharm Pharmacol, 2009. 61(8): p. 1037-42.

[442] Uebelhack, R. and L. Franke, *In vitro effects of St. John's wort extract and hyperforin on 5 HT uptake and efflux in human blood platelets.* Pharmacopsychiatry, 2001. 34 Suppl 1: p. S146-7.

[443] Van Strater, A.C. and J.P. Bogers, *Interaction of St John's wort (Hypericum perforatum) with clozapine.* Int Clin Psychopharmacol, 2012. 27(2): p. 121-4.

[444] Wang, Z., et al., *Effect of St John's wort on the pharmacokinetics of fexofenadine.* Clin Pharmacol Ther, 2002. 71(6): p. 414-20.

[445] Wonnemann, M., A. Singer, and W.E. Muller, *Inhibition of synaptosomal uptake of 3H-L-glutamate and 3H-GABA by hyperforin, a major constituent of St. John's Wort: the role of amiloride sensitive sodium conductive pathways.* Neuropsychopharmacology, 2000. 23(2): p. 188-97.

[446] Johne, A., et al., *Decreased plasma levels of amitriptyline and its metabolites on comedication with an extract from St. John's wort (Hypericum perforatum).* J Clin Psychopharmacol, 2002. 22(1): p. 46-54.

[447] Barbenel, D.M., et al., *Mania in a patient receiving testosterone replacement postorchidectomy taking St John's wort and sertraline.* J Psychopharmacol, 2000. 14(1): p. 84-6.

[448] *Final report on the safety assessment of Hypericum perforatum extract and Hypericum perforatum oil.* Int J Toxicol, 2001. 20 Suppl 2: p. 31-9.

[449] Beattie, P.E., et al., *Can St John's wort (hypericin) ingestion enhance the erythemal response during high-dose ultraviolet A1 therapy?* Br J Dermatol, 2005. 153(6): p. 1187-91.

[450] Traynor, N.J., et al., *Photogenotoxicity of hypericin in HaCaT keratinocytes: implications for St. John's Wort supplements and high dose UVA-1 therapy.* Toxicol Lett, 2005. 158(3): p. 220-4.

[451] Cotterill, J.A., *Severe phototoxic reaction to laser treatment in a patient taking St John's Wort.* J Cosmet Laser Ther, 2001. 3(3): p. 159-60.

[452] Putnik, K., et al., *Enhanced radiation sensitivity and radiation recall dermatitis (RRD) after hypericin therapy -- case report and review of literature.* Radiat Oncol, 2006. 1: p. 32.

[453] Kammerer, B., et al., *HPLC-MS/MS analysis of willow bark extracts contained in pharmaceutical preparations.* Phytochem Anal, 2005. 16(6): p. 470-8.

[454] Li, L.S., et al., *[Determination of salicin in extract of willow bark by high performance liquid chromatography].* Se Pu, 2001. 19(5): p. 446-8.

[455] Fiebich, B.L. and K. Appel, *Anti-inflammatory effects of willow bark extract.* Clin Pharmacol Ther, 2003. 74(1): p. 96; author reply 96-7.

[456] Wagner, I., et al., *Influence of willow bark extract on cyclooxygenase activity and on tumor necrosis factor alpha or interleukin 1 beta release in vitro and ex vivo.* Clin Pharmacol Ther, 2003. 73(3): p. 272-4.

[457] Khayyal, M.T., et al., *Mechanisms involved in the anti-inflammatory effect of a standardized willow bark extract.* Arzneimittelforschung, 2005. 55(11): p. 677-87.

[458] Krivoy, N., Pavltzky, F., Eisenberg, E., et al., *Salix coretex (willow bark dry extract) effect on platelet aggregation.*. Drug Monitor, 1999. 21: p. 202.

[459] Krivoy, N., Pavlotzky, E., Chrubasik, S., Eisenberg, E., and Brook, G., *Effect of salicis cortex extract on human platelet aggregation.* Planta Med., 2001. 67(3): p. 209-212.

[460] Schmid, B., et al., *Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: randomized placebo-controlled, double blind clinical trial.* Phytother Res, 2001. 15(4): p. 344-50.

[461] Chrubasik, S., et al., *Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study.* Am J Med, 2000. 109(1): p. 9-14.

[462] U.S. Food and Drug Adminsitration, *Tainted Products Marketed as Dietary Supplements Potnetially Dangerous*. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm236967.htm [accessed 06/20/12].

[463] Deitel, M., *Sibutramine warning: hypertension and cardiac arrhythmias reported.* Obes Surg, 2002. 12(3): p. 422.

[464] Ernest, D., et al., *Sibutramine-associated QT interval prolongation and cardiac arrest.* Ann Pharmacother, 2008. 42(10): p. 1514-7.

[465] Geyer, H., et al., *Nutritional supplements cross-contaminated and faked with doping substances.* J Mass Spectrom, 2008. 43(7): p. 892-902.

[466] Wooltorton, E., *Obesity drug sibutramine (Meridia): hypertension and cardiac arrhythmias.* CMAJ, 2002. 166(10): p. 1307-8.

[467] Coogan, P.F., et al., *Phenolphthalein laxatives and risk of cancer.* J Natl Cancer Inst, 2000. 92(23): p. 1943-4.

[468] Vaysse, J., et al., *Analysis of adulterated herbal medicines and dietary supplements marketed for weight loss by DOSY 1H-NMR.* Food Addit Contam Part A Chem Anal Control Expo Risk Assess, 2010. 27(7): p. 903-16.

[469] Halbsguth, U., et al., *Necrotising vasculitis of the skin associated with an herbal medicine containing amfepramone.* Eur J Clin Pharmacol, 2009. 65(6): p. 647-8.