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Interactions with Drugs and Dietary Supplements Used For Weight Loss

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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. Sympathomimetic 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 $> 30 \text{ kg/m}^2$ 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

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

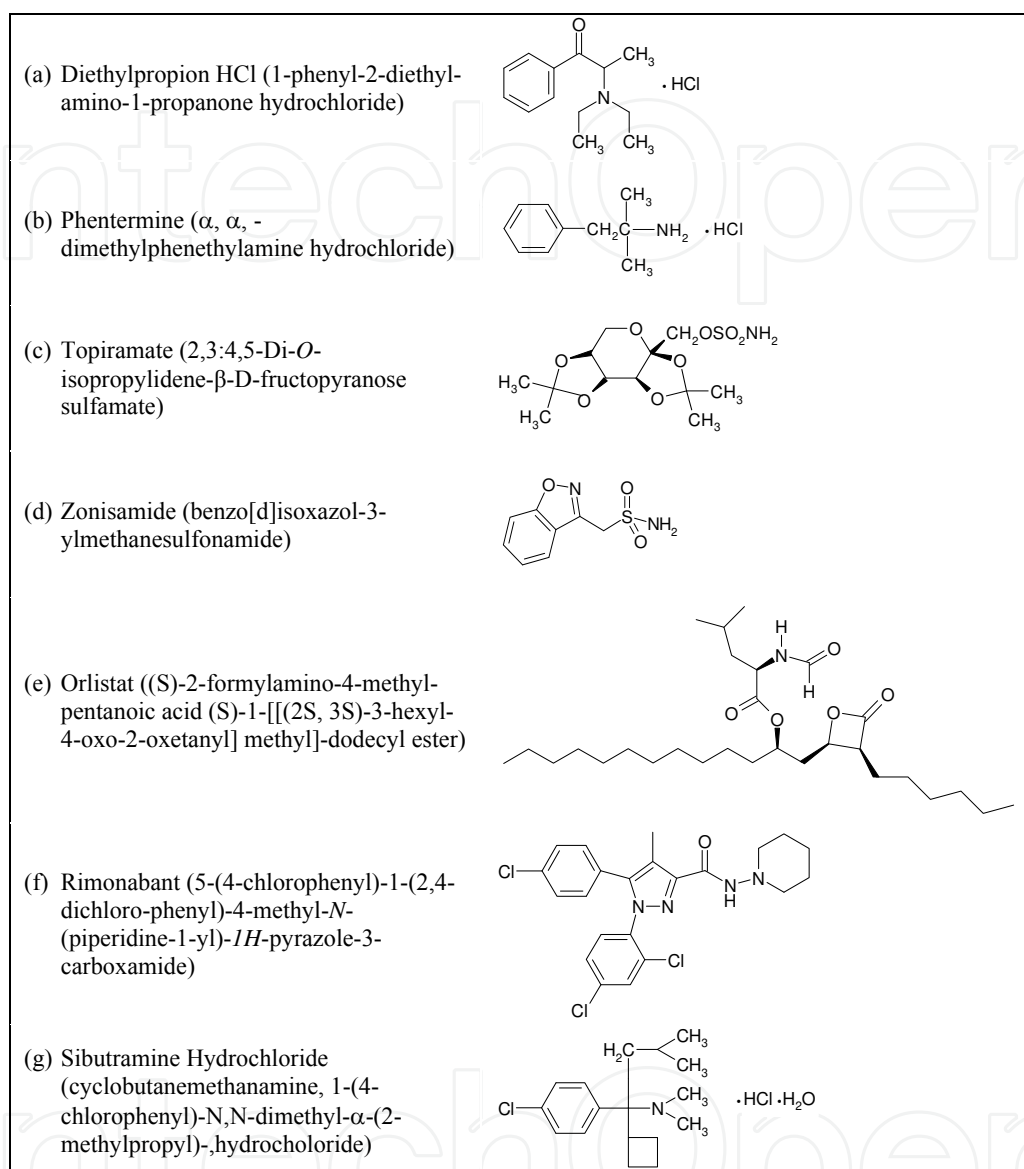


Figure 1. Molecular structures of anorectic drugs.

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/m² [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 penproprative 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

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 ($t_{1/2} = 60$ h) was decreased in patients receiving both zonisamide and phenytoin ($t_{1/2} = 27$ h), carbamazepine ($t_{1/2} = 38$ h, and sodium valproate ($t_{1/2} = 46$ 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 cannabinoid receptor antagonist that suppresses appetite by preventing activation of CB₁ receptors by the endogenous cannabinoids 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 (EMA), later studies indicating serious neuropsychiatric

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 hydrochloride (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. Açai (*Euterpe oleracea*)

The açai 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 açai 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 açai as an anorectic agent cannot be determined. There have been no reported adverse drug interactions or interactions with others herbs and açai [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].

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 EGCG 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 drug 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 $t_{1/2}$ 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].

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 chronotropic 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

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 anthraquinone 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 in 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 -glycyrrhetic 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,

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 experienced 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 erythema 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]. Phenolphthalein 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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