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An Updated Mini Review on Grapefruit: Interactions with Drugs, Obesity and Cardiovascular Risk Factors

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ABSTRACT

The paper examines the effects of grapefruit consumption in relation to drugs, obesity and cardiovascular risk factors. The review includes the most updated studies found in Pub-Med. The grapefruit effect refers to the ability of grapefruit juice and supplements to interact with a wide variety of pharmaceuticals, either enhancing or limiting their systemic availability. Due to altering the active dosage of the pharmaceutical, Grapefruit juice is commonly not allowed to be used alongside with many drugs. Naringin is the most important one, which can inhibit absorption of some drugs but more commonly 6'7'-dihydroxybergamottin, which inhibits CYP3A4. Lately, grapefruit has been found both in rats and adults to reduce body weight, blood pressure, improve lipid and hepatic profile and decrease platelet aggregation. These promising results must be followed by additional studies in order to add to the importance of the role and effects of grapefruit as part of our diet.

KEYWORDS

Grapefruit; Drug Interactions; Obesity; Cardiovascular Risk Factors

1. Introduction

Grapefruit was first discovered in the forests of Caribbean island, Barbados. It is now one of the widely cultivated fruits in the United States, particularly in Florida, California, and the other semi-tropical Southern states. The fruit is a natural hybridization of pomelo and orange. The plant is a subtropical citrus tree and botanically belongs to the large Rutaceae family of citrus fruits of the genus: Citrus. Scientific name: *Citrus paradise* [1]. Each fruit is largely oblate, ranges in diameter from 3 - 4 in and weighs up to 150 g. Characteristically, the fruit has slightly thicker and tougher skin than oranges. Inside, its flesh is segmented as in oranges. The fruit is very juicy, acidic, and varying in color depending on the cultivars, which could be white, pink and red pulps of varying sweetness. While some varieties are seedless, there may be up to 50 white, elliptical, pointed seeds about 1/2 in, length [1].

Grapefruit juice is known to contain several potentially pharmacologically active compounds, including flavonoids (naringin and hesperidin, among others) and furanocoumarins (FC) (bergamottin and 6',7'-dihydroxybergamottin) [2,3]. Flavonoids have also been identified in the juice of both sweet (Citrus sinensis) and sour (Citrus aurantium) oranges, although furanocoumarins such as 6',7'-dihydroxybergamottin are found only in sour (Seville) oranges which are not usually consumed as juices owing to their poor taste [4,5]. The primary flavonoids in grapefruit juice and orange juice are naringin and hesperidin, respectively [3,6,7]. Naringin has been identified in some commercially available orange juice products [2] although it is not present in pure sweet orange juice suggesting that these juices may not contain pure orange juice. Naringin reported concentrations ranging from approximately 200 to 2000 μmol/L [8]. The variability in the concentrations of flavonoids and FCs in grapefruit juice may result from factors such as the type, origin [9] and quality of the grapefruits used to make the juice [10], the manufacturing process [11] and storage conditions

[2].

2. Nutrient Content of Grapefruit

Grapefruit is very low in calories, consists of just 42 calories per 100 g. Nonetheless, it is rich in dietary insoluble fiber pectin, which by acting as a bulk laxative helps to protect the colon mucous membrane by decreasing exposure time to toxic substances in the colon as well as binding to cancer-causing chemicals in the colon [12]. Also grapefruit contains very good levels of vitamin-A (provides about 1150 IU per 100 g). Furthermore, vitamin A is also required to maintain healthy mucus membranes and skin. Consumption of natural fruits rich in vitamin-A, and flavonoids additionally help to protect from lung and oral cavity cancers [13]. Grapefruit also contains appreciable amounts of lycopene, beta-carotene, xanthin and lutein. Studies suggest that these compounds have antioxidant properties and are essential for vision. The total antioxidant strength measured in terms of oxygen radical absorbance capacity (ORAC) of grapefruit is 1548 µmol TE/100 g. Red varieties of grapefruits are especially rich in the most powerful flavonoid antioxidant, lycopene. Research has shown that lycopene protects skin damage from UV rays, and offers protection against prostate cancer [13,14].

Grapefruit is also an excellent source of antioxidant vitamin-C, providing about 52% of DRI. Vitamin-C is a powerful natural anti-oxidant and helps the body develop resistance against infectious agents and scavenge harmful free radicals. Furthermore, it is required for the maintenance of healthy connective tissue and aids in early wound healing. It also facilitates dietary iron absorption from the intestine [15] Approximately 100 g of fresh fruit contains about 135 mg of potassium electrolyte. Potassium is an important component of cell and body fluids, helps controlling heart rate and blood pressure through countering sodium effects [14].

Finally, it contains moderate levels of B-complex group of vitamins such as folates, riboflavin, pyridoxine, and thiamin as well as some resourceful minerals such as iron, calcium, copper, and phosphorus [14].

3. Interactions with Drugs

The characteristics of medications that interact with grapefruit are well defined. The most significant of these characteristics is metabolism by the intestinal cytochrome P450 3A4 (CYP 3A4) system. CYP 3A4 is found in the liver and intestinal tract. Intestinal CYP 3A4 concentration can be decreased by 47 percent within four hours of grapefruit consumption [16]. One study [17] has shown that the interaction persists for up to 72 hours; therefore, it would be prudent to avoid grapefruit products for 72 hours before taking a medication with which they may interact.

Another study by Lundahl *et al*. [18] reported that consuming 8 oz of grapefruit juice can inhibit intestinal CYP 3A4 concentration for 24 to 72 hours. Therefore, separating the times of medication administration and grapefruit consumption is not a plausible solution. It is important to note that because of genetic polymorphism, people have varying amounts of intestinal CYP 3A4; consequently, the extent of an interaction is not predictable from patient to patient [19]. The substance or substances in grapefruit that inhibit intestinal CYP 3A4 have not been identified. In addition, grapefruit may decrease the intestinal transport of drugs into the circulation [19]. As intestinal CYP 3A4 is affected, the interaction will only occur with oral formulations. Studies of the intravenous form of drugs that are substrates of hepatic CYP 3A4 and have the potential to interact with grapefruit failed to demonstrate any effect on plasma concentration [16].

Table 1 shows how grapefruit is affecting different class drugs. Antiarrhythmic drugs may potentially be affected by consumption of grapefruit causing cardiotoxicity, bradycardia and liver injury [20,21]. Flushing, tachycardia, peripheral edema may also be a result in patients taking grapefruit together with calcium channel blockers drugs [9]. Increased plasma concentrations of grapefruit may also cause gastrointestinal complaints, hepatic inflammation, and myopathies in patients with statins intake [22-25]. Renal and hepatic toxicity may also be a result for patients taking immunosuppressant drug therapy [20,26-28] while headache, fatigue, insomnia, and anxiety may be a result in protease inhibitor therapy [29].

4. Interactions with Obesity

Grapefruit polyphenols do appear to be effective at reducing bodyweight, reliably but not outright potently. The efficacy of grapefruit polyphenols in reducing body weight may be better if consumed via the grapefruit itself (possibly through fibers also acting) and appear to be synergistic with anthocyanins (blue-red pigments in fruits like berries).

A human study using overweight/obese subjects that were otherwise healthy compared a control diet to a diet with a moderate amount of grapefruit (one half of a fresh Rio-Red grapefruit with each of three meals) for 6 weeks, and noted that grapefruit consumption was associated with modest weight loss (−0.61 +/− 2.23 kg) that came with a modest decrease in blood pressure (−3.21 +/− 10.13 mmHg) while no changes occurred in control [30]. Self-reported intake as assessed by 24-hour dietary recall did not differ between groups, and estimated intake of Naringenin and Hesperiden was 146.2 mg and 1.57 mg daily [30]. A previous study by Fujioka *et al*. [31] in obese people compared three groups, raw grapefruit, grapefruit

Table 1. List of drugs affected by grapefruit.

Drug class	Drugs potentially affected by grapefruit	Effects of interaction
Antiarrhythmics	Amiodarone (cordarone), disopyramide (norpace), quinidine	Increased plasma concentrations of amiodarone may cause thyroid or pulmonary toxicity, liver injury, prolongation, proarrhythmic disorders, and bradycardia. Increased plasma concentration of quinidine and disopyramide may be cardiotoxic causing torsades depointes.
Calcium channel blockers	Felodipine (plendil), nicardipine (cardene), nifedipine (procardia), nimodipine (nimotop), nisoldipine (sular)	Increased plasma concentration may lead to flushing, peripheral edema, headaches, tachycardia, symptomatic hypotension, and myocardial infarction in rare cases.
Statins	Atorvastatin (lipitor), lovastatin (mevacor), simvastatin (zocor)	Increased plasma concentration may cause headaches, gastrointestinal complaints, hepatic inflammation, and myopathies (e.g., rhabdomyolysis).
Immunosuppressants	Cyclosporine (sandimmune, neoral), tacrolimus (prograf)	Increased drug exposure without effects on peak concentration may cause increased adverse events or toxicity evidenced by renal toxicity, hepatic toxicity, and increased immunosuppression.
Protease inhibitors	Saquinavir (fortovase)	Increased plasma concentrations may cause increased side effects such as headache, fatigue, insomnia, and anxiety.

juice and grapefruit capsules of 500 mg extract and the authors noted that over the course of the 2 week period of study that all groups were able to lose weight, 1.6 kg, 1.5 kg and 1.1 kg, respectively. The fruit was significantly more effective than placebo at weight loss while the other two groups trended towards being more effective, and this trend towards increased efficacy also appeared to hold for blood pressure (although did not reach statistical significance) [31].

One study using a sinetrol mixture (grapefruit polyphenols, anthocyanins, Caffeine) noted that this mixture, when taken by healthy overweight/obese persons at 1.4 g daily (four capsules of 350 mg) over 12 weeks had their BMI reduced by 2.2 +/− 0.9 points from a baseline status of 28.1 +/− 2.45, which was accompanied by a reduction of their body fat percentage from 30.7 +/− 1.9% to 29.0 +/− 0.8% at 4 weeks (5.4% reduction) and 25.9 +/− 1.0% (15.6% reduction) at 12 weeks; this study did not disclose any affiliations with the patent owners or producers of sinetrol [32].

5. Interactions with Cardiovascular Disease

The fact that *Citrus* flavonoids are promising compounds against cardiovascular diseases is a dream becoming reality. Epidemiological studies are unanimous that increased dietary intake of flavonoids has been associated with reduced risk of ischaemic stroke and cardiovascular diseases [33,34]. The protective effects of flavonoids include: anti-ischaemic, antioxidant, vasorelaxant and antithrombotic properties. It has been suggested that flavonoids decrease the risk of coronary heart diseases by improving coronary vasodilatation, decreasing the ability of the platelets to clot, and preventing oxidation of low-density lipoproteins (LDL) [35]. Naringenin may inhibit secretion of apoB and enhances LDL receptor-mediated apoB uptake [36]. Hesperidin has similarly been reported to increase high-density lipoprotein (HDL) and lower LDL, plasma triglycerides and total lipids in rats [37]. Promising results are coming to light from a recent study in rats by Alam *et al*. [38] in which dietary supplementation with naringin (approximately 100 mg/kg/day) has been found to improve glucose intolerance and liver mitochondrial dysfunction, lower plasma lipid concentrations and improve the structure and function of the heart and liver.

Raw consumption of grapefruit has been also found to decrease platelet aggregation. In one study comparing grape juice, orange juice, and grapefruit juice on platelet aggregation, it was found that only grape juice was active [39] 5 - 7.5 mL/kg juice for 7 - 10 days in otherwise healthy people, prior to a collagen-induced clotting test, noted that Grapefruit was associated with a significant 77% reduction in clotting while grapefruit was not significantly different than control [39]. These observed effects may be due to Nootkatone being localized to the peel of the grapefruit and being in ethanolic rather than water extracts, both of which may preclude its exclusion in juice [40].

The effects of ingestion of grapefruit juice on the hypotensive effect have been examined by Nakawaga & Goto [41]. A single ingestion of grapefruit juice (500 ml) had no effect on decreased blood pressure while recently, another study by [30] found that consumption of a half a small grapefruit thrice a day for 6 weeks is associated with a moderate drop in systolic blood pressure (−3.21 +/− 10.13 mmHg) with no influence on diastolic or heart rate. More recently, naringin has also been found to normalize systolic blood pressure and improve vascular dysfunction and ventricular diastolic dysfunction in high carbohydrate, high fat-fed rats [38].

6. Summary

Polyphenols and anthocyanids found in grapefruit have been found to have a positive effect on weight reduction

and finally a total decrease of obesity risk. The greater effects of grapefruit are very promising in cardiovascular disease due to excellent results found in studies that grapefruit may have the capability of reducing blood pressure, platelet aggregation, LDL and improving HDL and the clinical picture of liver. In drugs, the characteristics of medications that interact with grapefruit are well defined. Naringin that is the most important substance of grapefruit, can inhibit the absorption of some drugs but more commonly the 6'7'-dihydroxybergamottin, which inhibits CYP3A4. Even though the results are very promising, additional studies are necessary to elucidate the role and effect of grapefruit in diet and disease.

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