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# Grapefruit Juice and Statins

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**ABSTRACT**

We determined the validity of current medical advice to avoid grapefruit juice consumption while taking 3 widely used statins. A daily glass of grapefruit juice increases blood levels of simvastatin and lovastatin by about 260% if taken at the same time (about 90% if taken 12 hours apart), and atorvastatin by about 80% (whenever taken). Simvastatin 40 mg, lovastatin 40 mg, and atorvastatin 10 mg daily reduce low-density lipoprotein (LDL) cholesterol levels in a 60-year-old man with an LDL cholesterol of 4.8 mmol/L by 37%, reducing ischemic heart disease risk by 61%. When simvastatin or lovastatin are taken at the same time as grapefruit juice, the estimated reduction in LDL cholesterol is 48%, and in heart disease is 70%. If the juice is taken 12 hours before these statins, the reductions are, respectively, 43% and 66%, and for atorvastatin, 42% and 66%. The increased rhabdomyolysis risk from grapefruit juice consumption due to the increased effective statin dose is minimal compared with the greater effect in preventing heart disease. Grapefruit juice should not be contraindicated in people taking statins.

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**KEYWORDS:** Drug interaction; Effect enhancer; Grapefruit juice; Ischemic heart disease; LDL cholesterol; Statins

Current medical advice is to avoid grapefruit juice consumption while taking a statin.[1-3] The action of grapefruit juice on the effect of drugs was discovered by accident in 1989 in an experiment designed to examine the effect of ethanol on the action of felodipine, a calcium channel blocker.[4] Grapefruit juice was used to mask the taste of alcohol but the results showed several-fold higher felodipine concentration in blood plasma than had been expected. Grapefruit juice has since been shown to interact with over 85 drugs, including statins,[5] which are widely used to reduce low-density lipoprotein (LDL) cholesterol to help prevent cardiovascular disease.[6]

The adverse effects of statins on muscles can range from mild discomfort (myalgia) to the more serious rhabdomyolysis, which requires hospitalization and, in extremely rare cases, causes death. Statins increase the risk of hyperglycemia, but the much greater cardiovascular benefits of statins outweigh this small increased risk, and statins are recommended in patients with diabetes. We here focus on rhabdomyolysis as the dominant adverse event of concern.

This review summarizes the pharmacokinetics of grapefruit juice−statin interactions, specifically, atorvastatin, simvastatin, and lovastatin, and quantifies how this interaction affects LDL cholesterol and ischemic heart disease risk and the risk of rhabdomyolysis, presenting results on which clinical advice can be based.

## CHEMISTRY OF THE GRAPEFRUIT JUICE EFFECT

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Different statins vary in their bioavailability, half-life, and method of metabolic degradation (see **Table 1**).[6] For example, as a consequence of their different half-lives, atorvastatin can be taken at any time during the day with a consistent efficacy, whereas simvastatin should be taken at night. Cytochrome P450 (CYP) 3A4 is the major enzyme involved in the metabolic degradation of many statins, including atorvastatin, simvastatin, and lovastatin.[7-12]

The main agents responsible for the grapefruit juice effect on statins are bergamottin in fresh grapefruit and its

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derivative, 6′,7′-dihydroxybergamottin (DHB) in juice concentrate, which are furanocoumarins.[13] Furanocoumarins are also found in other fruit (eg, pomegranates), and in vegetables (eg, parsnips and celery), however, they are especially concentrated in grapefruit juice and fresh grapefruits.[14-16]

Kinetic studies reveal that both bergamottin and DHB inactivate CYP3A4. Studies have shown a 50% reduction in intestinal CYP3A4 concentration within 4 hours of drinking one serving of grapefruit juice (equivalent to the juice in one whole grapefruit).[15,17] Inhibiting the activity of CYP3A4 in the intestines presumably inhibits the presystemic degradation of statins and so increases their systemic bioavailability. Lovastatin, simvastatin, and atorvastatin are all metabolized by CYP3A4, while statins such as fluvastatin and rosuvastatin are metabolized by CYP2C9 (Table 1) and pravastatin is metabolized enzymatically in the liver.[6] This explains why grapefruit juice interacts with atorvastatin, simvastatin, and lovastatin, but not with fluvastatin, rosuvastatin, or pravastatin.[11] Removal of furanocoumarins from grapefruit juice eliminates the grapefruit juice effect.[18]

**CLINICAL SIGNIFICANCE**

- Grapefruit juice enhances the efficacy of certain statins in reducing low-density lipoprotein cholesterol and heart disease.
- Recognizing the grapefruit juice effect as an effect enhancer and therapeutic benefit is already seen in cancer treatment.
- Moderate grapefruit juice consumption should not be regarded as contraindicated in people taking statins.
- The focus on the risk of rhabdomyolysis from grapefruit juice consumption with statins ignores the greater benefits for the higher effective statin dose.

## EFFECTS OF GRAPEFRUIT JUICE ON THE PHARMACOKINETICS OF STATINS

A study[19] showed that when 40 mg simvastatin was taken with unusually large intakes of grapefruit juice (equivalent to 6 whole grapefruits a day), the blood levels of the statin (expressed as the area under the curve [AUC] in a pharmacokinetic study) increased by about 13.5-fold. However, another study[20] examined the effect of a typical grapefruit juice intake (equivalent to an 8-oz [240-mL] glass or 1 grapefruit per day) consumed at breakfast, and 40 mg simvastatin was taken at the same time, as there was only a 3.6-fold increase in the AUC.

The grapefruit juice effect with statins has been shown to decrease to 10% of its maximum 24 hours after intake of grapefruit juice, suggesting that the half-life of the grapefruit juice effect is between 7 and 8 hours, similar to that of CYP3A4.[19] Therefore, it can be deduced that for statins that have relatively short half-lives (eg, simvastatin or lovastatin), grapefruit juice taken in the evening will have approximately half the effect of grapefruit juice taken in the morning. The results from a study[12] that observed a 1.9-fold increase in the AUC of lovastatin when grapefruit juice was taken at breakfast and 40 mg of lovastatin in the evening are consistent with this; they were approximately 50% lower than the study that observed a 3.6-fold increase with simvastatin and grapefruit juice both taken in the morning.

Another study[11] observed a 1.8-fold increase in the blood levels of 10 mg of atorvastatin when taken with grapefruit juice. This effect would be expected to be unaffected by the time of taking the grapefruit juice because the half-life of atorvastatin is relatively long.

## CLINICAL IMPLICATIONS OF CONSUMING GRAPEFRUIT JUICE WITH STATINS

### Effect on LDL Cholesterol and Heart Disease Risk

A meta-analysis by Law et al[21] estimated that 10 mg atorvastatin, 40 mg simvastatin, or 40 mg lovastatin reduce LDL cholesterol by 37%, and double these doses reduces LDL cholesterol by 43%, an extra 6 percentage points. For someone with a baseline LDL cholesterol of 4.8 mmol/L, these are equivalent to a 1.8-mmol/L reduction (0.37 × 4.8) and a 2.1 mmol/L reduction, respectively.

The effect of a standard serving of grapefruit juice is to increase the effective dose of simvastatin or lovastatin by about 3.6-fold when given at the same time as the statin, and by 1.9-fold when given 12 hours earlier. Therefore, the effect of grapefruit juice if consumed at the same time as taking simvastatin or lovastatin is to reduce LDL cholesterol by an additional 11.1% [log(3.6)/log(2) × 6%], equivalent to a 0.53 mmol/L (11.1% × 4.8 mmol/L) reduction (see Table 2). The effect of grapefruit juice if consumed 12 hours before taking simvastatin or lovastatin is to reduce LDL cholesterol by an additional 5.6% [log(1.9)/log(2) × 6%], equivalent to a 0.27-mmol/L (5.6% × 4.8 mmol/L) reduction (see Table 2).

A 1-mmol/L reduction in serum LDL cholesterol reduces the risk of ischemic heart disease (IHD) in a 60-year-old by 41%.[21] Using this, together with the absolute reduction in LDL shown

**Table 1** Time to Maximum Concentration, Half Life, and Method of Metabolic Degradation According to Statin*

| Statin | Approx. Time to Maximum Concentration (Hours) | Half Life (Hours) | Metabolic Degradation |
|---|---|---|---|
| Atorvastatin | 2 | 23 | CYP3A4 |
| Lovastatin | 3 | 3 | CYP3A4 |
| Simvastatin | 2 | 2 | CYP3A4 |
| Fluvastatin | 1 | 1 | CYP2C9 |
| Rosuvastatin | 3 | 21 | CYP2C9 |
| Pravastatin | 1 | 2 | Sulphation |

*Adapted from Bellosta et al.[6]