The Interaction Between Grapefruit Juice and Statin Medications

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INDRODUCTION

Health care in the United States focuses on the use of biomedicine, which is defined as the branch of medical science that applies natural sciences both biologically and physically in clinical practice [1]. Therefore, the application of surgical procedures with combined usage of pharmacological drugs has become the most common method to treat pathological and genetic diseases. Medications prescribed to patients are typically meant for use outside medical facilities, and as a result the doctor responsible for prescribing the medication must provide clear direction on how to correctly take the drug. Guidelines given should include the correct dose, potential side effects, and interactions the drug has with other medications or foods. Additionally, drug manufacturers must provide directions on prescription bottles that should include directions for use, precautions, and drug strength [2]. Sadly, the warnings provided by both the healthcare provider and drug label are still inadequate. In 2007, the CDC stated that adverse drug reactions were thought to cause more than 700,000 visits to the emergency room and cause greater than 120,000 hospitalizations for that year [3].

Many drug-drug or food-drug interactions are commonly noted and understood, such as the reaction between green leafy vegetables, high in vitamin K, and prescribed blood thinners such as warfarin. However, there are some interactions that are not as commonly noted and must be brought to the patient’s attention by the physician. An example of one less-discussed interaction is the reaction between statin drugs and grapefruit juice.
Grapefruits belong to the genus Citrus and are frequently consumed for their high vitamin C content. Unlike other citrus species, grapefruit juice contains compounds responsible for inhibiting the metabolism of drugs, including statins [4]. Statins themselves are a group of drugs with a number of synthetic forms and used to treat high blood cholesterol (hypercholesterolemia) [5]. When statins and grapefruit juice are taken separately, the liver metabolizes both compounds safely. However, consumption of both compounds together cause harmful side effects such as myopathy or rhabdomyolosis, and in extreme cases these side effects result in fatalities [5]. General directions are given regarding the proper use of statins and are given as a means to prevent the interaction between the drug and the chemical components within grapefruit juice [5]. The purpose of the following discussion is to evaluate statin medications and to determine which statin medications have an interaction with grapefruit juice, and whether or not there are alternate options for individuals prescribed statin drug, but still desire to consume grapefruit juice.

METHODS

Access to the University of Pittsburgh Health Science Library System was provided, allowing access to databases such as PubMed and CINHAL. These databases were used to search for topics concerning supplemental use and drug interactions. After looking over potential topics and listening to advice given by the professor, the topic was narrowed down to grapefruit juice and cardiovascular medications. When ‘grapefruit juice and cardiovascular drugs’ was put in the search bar, a search returned a total of 152 hits. However, all of these articles concerned
different cardiovascular drugs. To narrow the topic down even further, ‘grapefruit juice and statin drugs’ was typed into the search bar. This returned 41 possible articles. Lastly, by limiting the search to articles that have been written in the last ten years and involved only human trials, 14 articles were provided by PubMed concerning the reaction between grapefruit juice and statin medications. Reading each articles abstract allowed identification of content similar to the research question being discussed. This resulted in three research articles on statin interactions with grapefruit juice and one article on the components of grapefruit juice that are responsible for the interaction.

**BACKGROUND/RESULTS**

*Cardiovascular Disease*

Statin drugs are used to treat hypercholesterolemia, a major risk factor in the development of cardiovascular disease (CVD). In 2007, the Center for Disease Control classified CVD as the leading cause of death in the United States, killing even more Americans than cancer [3]. Cardiovascular disease may be a result of hypercholesterolemia, which causes the buildup of plaque in arterial walls, causing inadequate blood flow and oxygen to the body’s essential organs (ischemia) [6]. If symptoms of ischemic heart disease are left untreated, CVD could result in a heart attack, stroke, pectoris, angina, and consequently death [6]. Therefore, prevention of cardiovascular disease has drawn the attention of numerous research studies that chiefly focus on reducing blood cholesterol levels as a means to prevent the disease.
The research studies focusing on reducing blood cholesterol levels have three possible approaches: decreasing cholesterol absorption within the small intestine, inhibiting the biosynthesis of cholesterol, or promoting cholesterol excretion from the body [6]. However, the most common approach involves inhibiting cholesterol biosynthesis, which was made possible with the creation of statin drugs [7]. Since the prevalence of cardiovascular disease has increased in the past few decades, the use of statin drugs has increased from 2%-25% within a period of 20 years, causing the necessity for research [3].

*Statin Forms*

Currently, there are a total of seven synthetic forms of statins. These forms include atorvastatin (Lipitor®), lovastatin (Mevacor®), simvastatin (Zocor®), rosvastatin (Crestor®), pravastatin (Pravachol®), fluvastatin (Lescol®), and pitavastatin (Livalo®) [8]. There used to be an eighth synthetic form; however, cerivastatin was recently withdrawn from the pharmaceutical market after being associated with deaths from rhabdomyolysis [9]. Rhabdomyolysis, the severe damage of both muscles and kidneys, resulted from the toxic accumulation of cerivastatin within the bloodstream [9]. The deaths caused by cerivastatin lead to the awareness of the dangers associated with statin use and brought about numerous studies concerning statin drugs. A few studies chose to focus on the drug-food interactions associated with statin medications, including the interaction between statins and grapefruit juice.
Statins are able to reduce cholesterol levels by acting as HMG-CoA reductase inhibitors [6]. HMG-CoA reductase, an enzyme mainly located within the liver, is responsible for converting HMG-CoA to mevalonate, an intermediate product and the committed step of cholesterol synthesis [10] (Figure 1).

![Mevalonate Pathway](image)

Figure 1: Mevalonate Pathway [10]

The chemical composition of statin drugs is similar to the structure of the HMG-CoA molecule [10]. Consequently, HMG-CoA reductase mistakenly interprets statin medications as HMG-CoA and satirically binds to the drug [10]. This prevents the attachment and chemical conversion of HMG-CoA to mevalonate, decreasing the biosynthetic formation of cholesterol and ultimately cholesterol levels within the blood [10].

Metabolism of Statins

However, like other drugs, statins are metabolized and excreted from the body within a certain time frame to prevent toxic levels from accumulating in the body.
blood. Metabolism of many drugs occurs within an enzyme complex known as cytochrome P450. This complex consists of a number of proteins that oxidize fat-soluble drugs to their water-soluble counterparts, allowing them to be more readily excreted in the urine [11]. However, the metabolism of statin drugs is dependent on the specific form of statin taken [11] (Figure 3).

![Table 1: Pharmacokinetic characteristics of statins](image1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fluvastatin</th>
<th>Pravastatin</th>
<th>Lovastatin</th>
<th>Simvastatin</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption (%)</td>
<td>98</td>
<td>34</td>
<td>30</td>
<td>60-80</td>
<td>30</td>
</tr>
<tr>
<td>Solubility</td>
<td>Fat soluble</td>
<td>Water soluble</td>
<td>Fat soluble</td>
<td>Fat soluble</td>
<td>Fat soluble</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>16-29</td>
<td>18</td>
<td>5</td>
<td>&lt;5</td>
<td>12</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Proteins bind (%)</td>
<td>&gt;98</td>
<td>50</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>&gt;98</td>
</tr>
<tr>
<td>Main metabolic pathway</td>
<td>CYP2C9</td>
<td>Conjugation</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Active metabolites</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>&lt;1</td>
<td>1-3</td>
<td>2-4</td>
<td>2-3</td>
<td>1-14</td>
</tr>
<tr>
<td>Unmodified urinary excretion (%)</td>
<td>NS</td>
<td>47</td>
<td>10</td>
<td>NS</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Transporters involved in liver</td>
<td>BSEP</td>
<td>OATP1B1</td>
<td>OATP1B1</td>
<td>OATP1B1</td>
<td>OATP1B1</td>
</tr>
<tr>
<td>uptake and bile excretion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS, Non-significant; BSEP, Bile salt exporting pump; OATP, Organic anion transporting polypeptide system; OAT, Organic anion transporter; MDR, Multidrug resistance-associated protein; BCRP, Breast cancer resistance protein; MRP, Multidrug resistance protein. Modified from Leimner and Figer.3

**Figure 3: Pharmacokinetic Characteristics of Statins [11]**

Three of the seven statin drugs, lovastatin, simvastatin, and atorvastatin are metabolized by the cytochrome P450-3A4 (CYP3A4) complex, while fluvastatin is metabolized by CYP2C9 [11]. Moreover, Pravastatin, as well as pitavastatin and rosuvastatin, are only metabolized in small amounts because they are already water-soluble and easily excreted in the urine [11]. The different metabolic routes of statin medications play an extensive role when determining potential food-drug interactions. The statin drugs metabolized by cytochrome P450 are more...
susceptible to these interactions as a result of the location of the cytochrome-P450, which is predominately located within hepatocytes and enterocytes [4].

**Grapefruit Juice**

Grapefruit juice, though not as highly consumed as other fruit beverages, has become popular due to the fruits association with vitamin C. The other components within the juice must be considered when looking at food-drug interactions. The grapefruit flavonoids, naringin and naringenin, as well as the furanocoumarins, bergamottin and 6',7'-dihydroxybergamottin, are generally thought to be the components responsible for inhibition of CYP3A4 [12]. However, research has shown to be inconclusive on the specific inhibitory components of GFJ [12].

Therefore, before looking at the interaction between statins and grapefruit juice, a study concerning the actual components in GFJ responsible for inhibiting CYP3A4 is necessary. Analysis of the results of this study would allow for a better understanding of the interaction between grapefruit juice and statin medications.

A randomized, 3-way crossover study by M. Paine and fellow scientists, took place at the University of North Carolina, and analyzed whether or not furanocoumarins were indeed the components in grapefruit juice responsible for the inhibition of the CYP3A4 complex [13].

The study consisted of 18 total volunteers, nine men and nine women. All participants were Caucasian, except three who were identified as African American. All participants came in on three separate occasions, and on each visit felodipine, a drug metabolized by CYP3A4, was consumed with one of three beverages [13].
Beverage distribution was determined by randomization of participants into six groups of n=3. Groups consisted of treatment orders 123, 231, 312, 213, 132 or 321 (1= GFJ; 2=OJ; 3= FC-free GFJ). The three beverages tested were grapefruit juice (GFJ), orange juice (OJ), or furanocoumarin-free grapefruit juice (FC-free GFJ). Orange juice served as the control because OJ was previously proven to have no affect on the CYP3A4 complex [13].

When choosing volunteers little exclusion criteria existed, and to ensure that each subject was healthy a series of tests including a blood screening, physical and a medical history check were carried out. Moreover, before the experiment, each participant was instructed not to consume any grapefruit juice a week before the study, nor to consume any caffeinated or alcoholic beverages the night before the study [13].

Blood was drawn from each participant before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after administration of felodipine. The samples were measured using liquid chromatography-mass spectrometry and analyzed statistically [13].

<table>
<thead>
<tr>
<th>Measures</th>
<th>GFJ</th>
<th>FC-free GFJ</th>
<th>OJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>110 (58-270)</td>
<td>48 (23-120)</td>
<td>54 (29-150)</td>
</tr>
<tr>
<td>Cmax</td>
<td>21 (7.6-50)</td>
<td>8.3 (3-16.6)</td>
<td>7.6 (3.4-13.9)</td>
</tr>
<tr>
<td>Tmax</td>
<td>2.5 (1.5-6)</td>
<td>2.5 (2-6)</td>
<td>2.8 (1.5-4)</td>
</tr>
<tr>
<td>t1/2</td>
<td>6.6 (4.2-13.6)</td>
<td>6.8 (2.6-14.4)</td>
<td>7.8 (4.4-13.2)</td>
</tr>
</tbody>
</table>

Table 1: Median Statistical Values of Blood Samples (Ranges are in parentheses) [13]

The area under the curve (AUC), as well as the max concentration of felodipine (Cmax), was significantly greater (P<0.0001) when consumed with GFJ,
contrary to OJ and FC-free GFJ [13]. However, the half-life and time to reach Cmax (tmax) did not have a significant difference (P >0.09) when GFJ, OJ or FC-free GFJ was consumed with felodipine [13](Table 1).

![Graph A: the plasma concentration-time profile for the smallest GFJ-mediated increase in a subject](image)

![Graph B: the largest increase in plasma concentration-time profile in a subject](image)

![Graph C: the median plasma concentration for all 18 subjects](image)

Orange juice, •; furanocoumarin-free grapefruit juice, □; grapefruit juice, △.

Figure 2 [13]:

A range was observed when comparing the alterations in plasma concentration of felodipine with GFJ consumption. All 18 subjects expressed different plasma felodipine concentration when the drug was consumed with GFJ [13]. The different concentration of each participant created an observable range, necessitating the calculation of an average concentration time profile [13].

A clearer understanding of the inhibitory properties of GFJ on CYP3A4 allow for a stronger analysis of the subsequent two-phase, randomized crossover study by J. Lilja and companions involving the interaction between simvastatin and GFJ [14]. The study took place at the University of Helsinki, Finland, consisted of 10 healthy
volunteers, and occurred in two phases. Each phase took place over a period of 3 consecutive days with a two-week interval between phases. On days one and two, the participants drank 200 mL of grapefruit juice or 200 mL of water. On day three, a 40 mg dose of simvastatin was given with grapefruit juice or water [14].

The participants in the study were all men between the ages of 20 and 24 years. Men who were on fixed medications or smoked were excluded. The volunteers were not allowed to consume grapefruit juice two weeks prior to testing.

Blood samples were taken from each participant before simvastatin application, as well as at 0.5, 1,2,3,4,6,8,12, and 24 hours after drug administration [14]. These samples were measured using a liquid chromatography-mass spectrometry, and analyzed for simvastatin and simvastatin acid (a metabolite of simvastatin) concentrations using the statistical program Systat. Concentrations were considered statistically significant with P values < 0.05 [14].

Results from the analysis of simvastatin and simvastatin acid showed a 3.6-fold increase in the AUC (area under the concentration curve) of simvastatin from 0-24 hours, and a 3.3-fold increase in the AUC(0-24) of simvastatin acid with the concomitant consumption of grapefruit juice (P<0.001) [14](Figure 3).
Figure 3: Simvastatin concentration with GFJ and water consumption [14]

There was no significant change in the Tmax or T1/2 values for either simvastatin or simvastatin acid [14].

As shown, effects of grapefruit juice on simvastatin, a statin drug metabolized by CYP3A4, caused an increase in plasma concentration simvastatin; however, alternate statin forms are metabolized by an alternate pathway [6,14]. At the Obara Hospital in Tokyo, Japan, I. Fukazawa and fellow scientists carried two, two-way randomized crossover studies comparing the interaction between grapefruit juice and atorvastatin (a statin metabolized by CYP3A4), and grapefruit juice and pravastatin (a statin not metabolized by CYP3A4) [6].

A total of 20 healthy male adults were split into two groups of 10 participants, forming studies I and II [6]. Study I and study II each lasted a length of three days. Participants received 250 ml of grapefruit juice or 250 mL of water three times a day for the first two days of the study. On the third day, a single 10mg dose of atorvastatin was given to the participants in study I, and 10 mg of pravastatin was given to the participants in study II, along with 250 ml of grapefruit juice or water. The studies were repeated, but the beverage reversed. In other words, those who
first received water now consumed GFJ with the statin and vice versa. This allowed each subject to act as his own control [6] (Table 2).

<table>
<thead>
<tr>
<th>Study I</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Study II</th>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GFJ + atorvostatin</td>
<td>Water + atorvastatin</td>
<td></td>
<td>GFJ + pravastatin</td>
<td>Water + pravastatin</td>
</tr>
</tbody>
</table>

Table 2: Randomization in Study I and Study II [15]

Participants were included after a thorough examination and review of medical history [6]. Individuals were excluded if they smoked, participated in a previous clinical study within the last few months, were alcohol or drug dependent, or consumed grapefruit juice, grapefruit, or any other drugs within the last two weeks preceding the study [6].

In study I, blood was drawn from each subject right before and at times 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after each dose of atorvastatin [6]. Blood was also taken from study group II at identical times when administered pravastatin; however, times 36 and 48 hours were excluded. The blood was then measure by using a liquid chromatography-mass spectrometer, and analyzed stastically [6].

The results for study I with atorvastatin acid showed a statistically significant increase in statin concentration (P<0.05) [6]. The AUC(0-48) increased by 1.40-fold when atorvastatin was consumed with grapefruit juice compared to the AUC(0-48) when taken with water. A metabolite of atorvastatin, atorvastatin lactone, showed a significant increase in plasma concentration (P<0.001) by 1.56-fold. However, in study II no significant difference in the pharmacokinetics of pravastatin was observed when consumed with grapefruit juice or water [6].
Additional analysis of the synthetic forms of statin drugs consumed with GFJ further explains the specificity of GFJ for statin medications metabolized by CYP3A4. A randomized four-phase crossover study was carried out by H. Ando and fellow scientists [15]. A total of eight healthy Japanese men were analyzed to determine the affects of grapefruit juice on atorvastatin, as well as a statin drug not metabolized by CYP3A4, pravastatin [15].

The participants were randomly given 250 mL of grapefruit juice or water for three consecutive days. On each study day, they were administered a single oral dose or either 4 mg pitavastatin or 20 mg atorvastatin with grapefruit juice or water [15]. All participants came in for 4 complete trials, allowing each participant to serve as his own control for both pitavastatin and atorvastatin. Order of administration of variables (GFJ, water, pitavastatin, atorvastatin) was dependent upon randomization at the start of the trial [15] (Table 3).

<table>
<thead>
<tr>
<th>Participant</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>GFJ + Pitavastatin</td>
<td>GFJ + Atorvastatin</td>
<td>Water + Pitavastatin</td>
<td>Water + Atorvastatin</td>
</tr>
</tbody>
</table>

Table 3: Example of Randomized Order for One Participant [16]

No significant exclusion criteria were considered when choosing the subjects [15]. The participants were advised not to smoke or consume any beverages containing caffeine one night prior to the study [15].

Blood samples were drawn from each subject right before and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after pitavastatin or atorvastatin administration [15]. The samples were analyzed using liquid chromatography-mass spectrometry.
Furancoumarins were additionally extracted from the grapefruit juice with ethyl acetate [15].

Furancoumarin extraction determined the amounts of compounds present in the grapefruit juice provided, since concentration of furancoumarins is dependent on each batch of juice [15]. Results showed a vast difference in atorvastatin concentration (83%) when taken with grapefruit juice, but only had a small increase (13%) in plasma concentrations with pitavastatin administration. The AUC(0-24) of atorvastatin had a mean 4.3-fold increase, but the Cmax did not reach statistical significance (P=0.09) [15].

DISCUSSION

The studies chosen were presented in an order that provided linear analysis of the research question at hand. The study performed by M. Paine et al. explained the components in grapefruit juice responsible for inhibiting the CYP3A4 complex, the furancoumarins, providing the background for GFJ and statin interactions [13]. The study by M. Paine allowed for a stronger analysis of the adverse side effects of consuming grapefruit juice with simvastatin, a drug metabolized cytochrome P450-3A4 and researched by J. Lilja et al. [14]. Consequently, the study by J. Lilja led to the question on whether or not all statin medications are affected by GFJ [14]. Therefore, studies by I. Fukazawa et al. and H. Ando et al. were incorporated to compare the effects of grapefruit juice on the plasma concentration levels of statins metabolized by CYP3A4, as well as statin medications metabolized by alternative routes [6,15].
There were strengths existent in all studies. The following table lists characteristics of the studies, and how they compare to one another.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Subjects</th>
<th>Sampling</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Pain et al.-North Carolina [13]</td>
<td>Randomized, 3 way, crossover study</td>
<td>18 volunteers (9 men &amp; 9 women)</td>
<td>Blood Sample measure by LCMS</td>
</tr>
<tr>
<td>J. Lilja et al.-Finaland [14]-</td>
<td>Randomized, two phase, crossover study</td>
<td>10 male volunteers</td>
<td>Blood Sample measure by LCMS</td>
</tr>
<tr>
<td>I. Fukazawa et al.-Japan [15]</td>
<td>Randomized, two way, crossover study</td>
<td>20 male volunteers</td>
<td>Blood Sample measure by LCMS</td>
</tr>
<tr>
<td>H. Ando et al.-Japan [16]</td>
<td>Randomized, four phase, crossover study</td>
<td>8 male volunteers</td>
<td>Blood Sample measure by LCMS</td>
</tr>
</tbody>
</table>

Table 4: Comparison of research studies [6,13,14,15]

A few important strengths between all the studies included randomization of participants, approximately similar amounts of GFJ provided to each subject during the study, the use of blood samples for analysis of statin concentration, and having the participants act as their own controls [6,13,14,15]. Moreover, there were no dropouts or unexpected deaths during any trials [6,13,14,15].

One major difference between studies concerned the dosage of statin medication given to participants; however, during trials the dose size did not seem to have an effect on the overall plasma statin concentration, thus no alterations in data were expressed due to the different doses of statins [6,13,14,15].

A common limitation in all studies consisted of the miniscule amount of participants involved, and failed to mention how determination of sufficient sample
sizes was carried out, leading to underpowered studies [6,13,14,15]. On the contrary, the sample sizes were large enough to give statistically significant results [6,13,14,15]. The importance of having large sample sizes is seen when the P value for the Cmax in the study by H. Ando et al. was P=0.09, which does not reach statistical importance (P=0.05) [15].

A specific strength in research carried out by H. Ando et al. performed an analysis of the furanocoumarin concentration in grapefruit juice provided to all subjects [15]. The concentration of furanocoumarins is dependent on the batch of GFJ taken [15]. Since grapefruit juice acts as the independent variable in all four studies, determining the concentration seems necessary to guarantee accurate results and provide reliable comparisons between groups studied; however, none of the other studies analyzed furanocoumarin concentrations in various batches of GFJ used during the studies [6,13,14,15].

In addition, all four studies express the inhibitory effects of grapefruit juice on the CYP3A4 complex in the intestinal cells of the GI tract [6,13,14,15]; however, only one of the studies drew conclusions about the components of grapefruit juice responsible for the inhibition of CYP3A4 [13]. M. Paine’s et al. found the furanocoumarins within grapefruit juice as the components responsible for the inhibitory actions of GFJ [13]; however, P. Ho et al. found both furanocoumarins and flavonoids as the components responsible for CYP3A4 inhibition [4]. Consequently, these results call for further studies focusing on determining the precise components of grapefruit juice responsible for CYP3A4 inhibition.
Furthermore, the contrasts that arose between the studies analyzing the interaction between GFJ and statin medications could be due to the different ethnicities between subjects, or a result of each participant’s different inherent ability to metabolize statins [6, 15]. The studies discussed occurred in Finland and Japan [6,14,15]. The subjects in Finland were all Caucasian, while Japanese participants made up the studies in Japan [6,14,15]. The different ethnicities of participants led to the concern that different expression levels of CYP3A4 resulted from genetic differences [6]. However, there is no current evidence supporting this theory [6]. Additionally, when looking at each study individually, the participant’s ability to metabolize statins with grapefruit juice rarely resulted with identical AUC and Cmax measurements [6,13,14,15]. An observable range between all subjects occurred, causing concern for multiple factors affecting statin metabolism, including the potential for polymorphisms in the CYP3A4 complex [6,13,14,15].

In conclusion, all four studies touched base concerning the interaction between grapefruit juice and statin drugs [6,13,14,15]. The studies provided experimental evidence showing the increase in concentration of statins within plasma with concurrent consumption of grapefruit juice; however, more research must be done to explain the range that occurred between individual participants during the studies [6,13,14,15]. These results all emphasize the importance of knowing the possible interactions between prescribed medications and foods in order to avoid dangerous consequences.
RECOMMENDATIONS/APPLICATIONS TO PRACTICE

Grapefruit juice, though a natural fruit juice, contains components that interact with statin medications [13]. Research has shown the food-drug interaction only occurs with three of the seven synthetic forms of statin drugs; therefore, if an individual was prescribed statins as a means to reduce his or her cholesterol levels, he or she should be well informed by the healthcare provider of the statin forms known to have detrimental interactions with GFJ [11]. Strong emphasis should be placed on the severity of the reaction between specific statin drugs and grapefruit juice, as well as emphasis on the fact that the effects of grapefruit juice last up to 72 hours after consumption since the body has to reproduce CYP3A4; therefore, consumption of grapefruit juice in the morning and taking statin medications at night can still result in a deleterious interaction [16]. The healthcare provider should not only consist of a primary care physician (PCP), but also a registered dietitian, who should also be included in future studies involving statin drugs and their interaction with grapefruit juice.

The main role of a dietitian when dealing with statins and grapefruit juice should be education. Dietitians can provide advice on how to affectively avoid grapefruit and grapefruit products, because even though research may be lacking when it comes to completely understanding the extensiveness of GFJ and cytochrome P450-3A4 interactions, studies have consistently shown an increase, whether small or large, does occur in the plasma statin concentrations of all participants. Therefore, to ensure individual safety, joint consumption of GFJ and CYP3A4 metabolized statins should be avoided [6, 13,14,15].
Thus, if a person does not want to follow these guidelines and desires to continue consumption of grapefruit juice, alternate options are possible. One such option would be to replace daily consumption of GFJ with orange juice to still retain a high intake of vitamin C, because OJ has been shown to have no interaction with statin medications. Another option, if grapefruit must be consumed, would be to take one of the other four synthetic forms of statins not affected by GFJ (fluvastatin, pravastatin, pitavastatin, or rosuvastatin) instead of taking a statin metabolized by CYP3A4 (atorvastatin, simvastatin, or lovastatin) [11].

However, the healthiest and safest alternative option for someone who wishes to decrease his or her cholesterol would be a change in lifestyle. Registered dietitians are professionals who have extensive knowledge on ways to lower cholesterol levels naturally, including guidelines on how to progressively lose weight, become more active, and consume healthier diets [17].

In conclusion, dietitians would be useful when trying to guide individuals in maintaining a healthier lifestyle, or a lifestyle void of grapefruit juice. Moreover, when dealing with the potentially adverse reactions with drugs and certain foods/food groups, direction should always come from a registered dietitian who has particular expertise in food-drug interactions.
REFERENCES


17. American Heart Association. Step I, Step II and TLC Diets. Available at: