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REVIEW ARTICLE

Interaction of Statins with Grapefruit Juice

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SUMMARY

Grapefruit juice, which discovered to interact with felodipine for the first time, is now known to interact with more than 80 drugs. Statins are among the drugs that interact with grapefruit juice. Grapefruit juice-statin interactions were first investigated in 1998 in human pharmacokinetic studies with lovastatin and simvastatin. The pharmacokinetic and pharmacodynamic basis of the interaction has been extensively investigated in studies. Flavonoids and furanocoumarins, the main components of grapefruit juice, have been reported to cause drug interactions. Furthermore, statin-grapefruit juice interactions occur mostly through inhibition of cytochrome-3A4 (CYP3A4), to a lesser extent through inhibition of P-glycoprotein (P-gp) and organic anion transporting polypeptides (OATPs). Changes in plasma drug levels as a result of interaction may increase the side-effect of statins or reduce their therapeutic efficacy. Therefore, patients using statins are generally advised to avoid grapefruit juice consumption.

Key Words: *Grapefruit juice, drug interaction, statins, CYP3A4, P-gp, OATP*

Statinlerin Greyfurt Suyu ile Etkileşimi

ÖZ

İlk kez felodipin ile etkileştiği keşfedilen greyfurt suyunun günümüzde 80'den fazla ilaçla etkileştiği bilinmektedir. Statinler de greyfurt suyuyla etkileşen ilaçlar arasında yer almaktadır. Greyfurt suyu-statin etkileşimleri ilk olarak 1998 yılında lovastatin ve simvastatin ile insanlarda yapılan farmakokinetik çalışmalarla araştırılmıştır. Yapılan çalışmalarda etkileşimin farmakokinetik ve farmakodinamik temeli kapsamlı bir şekilde araştırılmıştır. Greyfurt suyunun ana bileşenleri olan flavonoidler ve furanokumarinlerin ilaç etkileşimlerine neden olduğu belirtilmiştir. Ayrıca, statin-greyfurt suyu etkileşimleri çoğunlukla sitokrom-3A4'ün (CYP3A4) inhibisyonu yoluyla, daha az oranda P-glikoprotein (P-gp) ve organik anyon taşıyıcı polipeptitlerinin (OATPler) inhibisyonu yoluyla meydana gelmektedir. Etkileşim sonucu plazma ilaç seviyelerindeki değişiklikler, statinlerin yan etkilerini artırabilir veya terapötik etkinliklerini azaltabilir. Bu nedenle statin kullanan hastaların genellikle greyfurt suyu tüketiminden uzak durmaları önerilmektedir.

Anahtar Kelimeler: *Greyfurt suyu, ilaç etkileşimi, statinler, CYP3A4, P-gp, OATP*

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INTRODUCTION

Drug-food interactions significantly affect the success of drug therapy. Food-drug interactions can be divided into: pharmacokinetic and pharmacodynamic interactions depending on the content, amount, and consumption time of nutrients (Schmidt, 2002). The pharmacodynamic interactions in which dietary components affect pharmacological activity at the receptor level are limited. More frequent pharmacokinetic interactions may change the effectiveness of therapy or increase toxicity. This may adversely affect patient care, increase morbidity, and extend treatment or hospital stay (Shirasaka, 2011). In a study examining the interaction between ethanol and felodipine, grapefruit juice was used to mask the taste of ethanol and found that plasma concentrations of felodipine were several times higher when grapefruit juice was used (Bailey, 1989; Bailey, 1998). Because of this accidental discovery, the idea that grapefruit juice and drug interaction has emerged, and numerous studies have been conducted on the subject (Dahan, 2004). In 2016, it was reported that the number of drugs interacting with grapefruit juice was more than 85 (Lee, 2016). When therapeutic agents are co-administered with grapefruit juice, the drug exposure is significantly increased. The drugs that are best known to interact with grapefruit juice are statins, also called 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, used to treat hypercholesterolemia (Kafle, 2018). The main substances that cause grapefruit juice to interact with statins are the components in grapefruit juice (Mouly, 2017). As a result of thisinteraction, serious side effects such as rhabdomyolysis, ischemic heart disease, and changes in low-density lipoprotein (LDL) cholesterol values have been reported (Shirasaka, 2013). In this review, grapefruit juice components, their role in drug interactions, statins interacting with grapefruit juice and their properties are summarized.

GRAPEFRUIT JUICE COMPOSITION

Grapefruit, one of the world's most popular citrus fruits, is rich in vitamins, dietary fiber, sugar, and minerals. In addition, antioxidant, anti-inflammatory, anticancer, and neuroprotective effects of secondary metabolites in grapefruit juice are known (Hung, 2017). Antioxidant activity is caused by phenolic compounds such as anthocyanins, flavonoids, and ascorbic acid. These compounds are the largest group of secondary metabolites that attract attention due to their physiological effects (Sicari, 2018). Furanocoumarins and flavonoids are components in grapefruit juice that inhibit intestinal metabolism and/or transport of many drugs. The amounts of these components in grapefruit juice may vary depending on production procedure, storage conditions, source, and maturity of the fruit. The amount of active ingredients is important in terms of the grapefruit juice-drug interaction mechanism, reversibility, and comparison with clinical data (Castro, 2006).

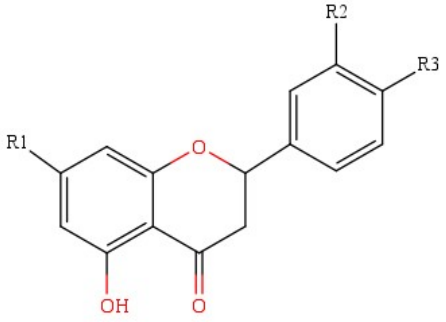
Flavonoids

There are six groups of flavonoids: Anthocyanins, flavan, flavanones, flavones, flavonols and isoflavones (Figure 1). Flavonones are abundant in citrus fruits and give their typical flavor. They exist in glycoside or aglycone forms (Igual, 2011). If sugar molecules are attached to the flavonoid core, which contains three-ring structure, they are called glycosides; and if there is no sugar, they are called aglycons (Zhang, 2007). Flavonoids are structurally similar to adenosine triphosphate (ATP). Therefore, they may be responsible for some biological effects by competing with ATP for binding to different enzymatic sites (Vanamala, 2006). Naringin is the most abundant flavonoid in grapefruit juice (200-2000 μmol/L). It is also the main component that causes the bitter taste in grapefruit juice and is an inhibitor of the cytochrome (CYP) enzymes. Naringenin is the aglycone form produced by the intestinal hydrolysis of naringin (Fukuda, 2000; Hanley, 2011). Many flavonoids such as narirutin, hesperidin, neohesperidin, quercetin, tangeretin, nobiletin, kemferol were detected in grapefruit juice (Ross, 2000).

Tangeretin and nobiletin increased the activity of benzopyrene hydroxylase and some CYP enzymes after oral administration, while naringin (capsule formulation) and quercetin did not show a significant inhibitory effect on CYP3A4 (Ho, 2001).

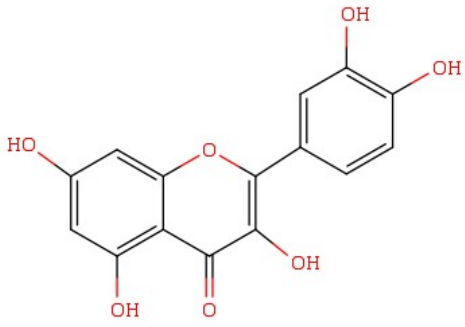
Furanocoumarins

Furanocoumarins have a three-ring head and an aliphatic tail. The furan ring is crucial for the production of a reactive precursor that binds irreversibly to the CYP apoprotein and inhibits enzymatic activity. Reported concentrations in grapefruit juice for bergamottin and dihydroxybergamottin are 1-37 μM and 0.2-52.5 μM, respectively (Hanley, 2011). Dihydroxybergamottin, one of the furanocoumarin derivatives found in the highest amount in grapefruit juice, has 1000 times the water solubility of bergamottin due to its hydroxyl groups. The CYP3A4 inhibitory effect of both components has been shown to be mechanism-based and reversible *in vitro* (Paine, 2004; Paine, 2006).



Flavanone

Flavonoid	R1	R2	R3
Naringenin	OH	H	OH
Narirutine	O-Ru	H	OH
Naringin	O-Nh	H	OH
Hesperidin	O-Ru	OH	OCH_3
Neohesperidin	O-Nh	OH	OCH_3
Didymin	O-Ru	H	OCH_3
Poncirin	O-Nh	H	OCH_3



Flavonol

Quercetin

Figure 1. Chemical structures of some flavonoids in grapefruit juice (Igual, 2011).

Furanocoumarin derivatives are divided into three groups: monomer, dimer, and trimer. The monomers can be angular with a furan ring attachment at 7,8-position or linear with a furan ring attachment at 6,7-position of coumarin. This structure is substituted at the 5 and/or 8 position with side chains of methoxy, prenyloxy or geranyloxy. Dimers are formed by an ether bond between the side chains of two linear furanocoumarin monomers or by attaching the side chain of one monomer to the pyrone ring of the other monomer (Guo, 2004). In 2006, chemical analogues of furanocoumarins were synthesized for the structural evaluation of their inhibitory effects on the CYP3A4 enzyme. According to the results of this study, the binding of geranyloxy chains with hydrophilic groups at the 6,7-positions to the structure increases the in-

hibitory effect. In this way, furanocoumarins interact with the CYP3A4 enzyme from both lipophilic and hydrophilic sites (Row, 2006). The chemical structure of some furanocoumarins in grapefruit juice is given in Figure 2 (Ohta, 2002). *In vitro* and *in vivo* studies have shown that furanocoumarins improve bone health as well as anti-inflammatory, antioxidative, and anticancer effects (Hung, 2017). It has also been used clinically in the treatment of skin diseases in some countries since the 2000s (Melough, 2018).

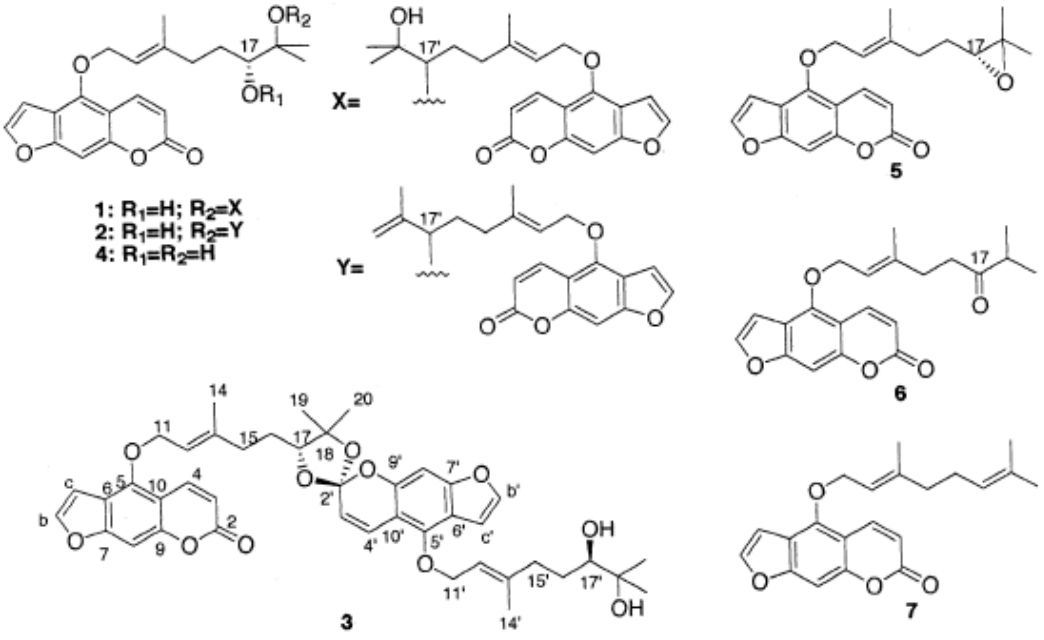


Figure 2. Some furanocoumarins in grapefruit juice (1: Paradisin A, 2: Paradisin B, 3: Paradisin C, 4: 17,18-dihydroxybergamottin, 5: 17-epoxybergamottin, 6: 17-ketobergamottin, 7: Bergamottin) (Ohta, 2002).

GRAPEFRUIT JUICE-DRUG INTERACTION MECHANISMS

Natural components in grapefruit juice cause drug interactions through different mechanisms. The most accepted interaction mechanism is the inhibition of CYP3A isoforms (Greenblatt, 2001). It is well known that grapefruit juice interacts with drugs that are substrates of intestinal CYP3A4, which controls the first-pass metabolism of many pharmaceuticals (Kiani, 2007). Recent research indicates that grapefruit-drug interactions may also occur by altering intestinal absorptive and efflux transporter proteins. These transporters are involved in the absorption of many drugs (De Castro, 2007). According to the literature, there are three mechanisms for grapefruit juice-drug interaction.

CYP3A4 Inhibition

CYP450 is a family of enzymes responsible for drug metabolism and more than 50 members have been elucidated. CYP3A4 is responsible for oxidative metabolization of many drugs in humans and is expressed at the apical surface of enterocytes and hepatocytes (Bailey, 2004; Bailey, 2013). The components in grapefruit juice cause competitive and non-competitive inhibition of this enzyme. To observe this inhibition, the drug should be taken orally, and grapefruit juice should be consumed as a glass (200 mL) of frozen concentrate, diluted from concentrate or freshly frozen (Bailey, 2004). Grapefruit

juice significantly increases the plasma concentration of many drugs that are CYP3A4 substrates, such as dihydropyridine, cyclosporine, midazolam, and terfenadine (Lilja, 1998). To examine the effect of grapefruit juice on the pharmacokinetics of midazolam, volunteers were administered midazolam with different amounts of grapefruit juice. When the pharmacokinetic parameters of midazolam, such as the area under the plasma drug concentration-time curve (AUC), maximum plasma concentration (C_{max}), elimination half-life ($t_{1/2}$) were evaluated, side effects of CYP3A4 substrates increased due to consumption of large amounts of grapefruit juice (Veronese, 2003). In another pharmacokinetic study, concomitant use of grapefruit juice and simvastatin in healthy volunteers increased the AUC_{0-24} by 3.6-fold and C_{max} by 3.9-fold. These results were attributed to the inhibition of CYP3A4-mediated first-pass metabolism of simvastatin in the intestinal wall (Lilja, 2004). Components in grapefruit juice (especially furanocoumarins) are converted into reactive intermediates that cause inactivation by covalently binding to the CYP3A4 enzyme system. In this condition, known as mechanism-based inhibition, defective CYP3A4 undergoes proteolysis. In this process, there is no change in the content of messenger RNA (mRNA) in enterocytes or a decrease in CYP3A4 production (Bailey, 2004). In another study, it was reported that furanocoumarins (such as 6,7-dihydroxybergamottin) cause irreversible inhibition of CYP3A4 (Pirmohamed, 2013). Evaluation of CYP3A4 and P-gp interaction with five grapefruit juice components (quercetin, naringin, naringenin, 6,7-dihydroxybergamottin and bergamottin) showed that 6,7-dihydroxybergamottin and bergamottin inhibited the CYP3A4-mediated metabolism of model drug saquinavir. However, none of these grapefruit juice components had a significant effect on P-gp activity *in vitro* (Eagling, 1999). In another study, the inhibitory effect of four furanocoumarin derivatives isolated from grapefruit juice on CYP3A4 was evaluated and the inhibitory effects of these components were found to be equivalent or greater than the specific CYP3A4 inhibitor ketoconazole (Fukuda, 1997). In addition, evaluation the effects of five grapefruit juice components (bergamottin, 6,7-dihydroxybergamottin, GF-I-1, GF-I-4 and nootkatone) on CYP450 isoforms showed that four furanocoumarin derivatives inhibited CYP3A4-mediated oxidation of nifedipine in a concentration- and time-dependent manner. On the other hand, bergamottin inhibited CYP1A2, CYP2C9, CYP2C19, CYP2D6, while dihydroxybergamottin inhibited only CYP1A2. Nootkatone, a sesquiterpene, had no significant effect on CYP450 activity, except for CYP2A6 and CYP2C19 (Tassaneeyakul, 2000).

P-gp Inhibition

P-gp is an ATP-dependent efflux pump that affects the disposition and clinical response of its substrates. It is localized in the blood-brain barrier, testes, proximal tubule of the kidneys, canalicular membrane of the liver, and luminal surfaces of small intestinal epithelial cells. It has been reported that grapefruit juice inhibits P-gp-mediated pitavastatin transport in rats and humans (Shirasaka, 2011). Although the mechanism of inhibition is not fully elucidated, flavonoids (naringin, naringenin) in grapefruit juice are known to inhibit P-gp-mediated transport (Chen, 2018). The oral bioavailability of digoxin, a good P-gp substrate, is increased when co-administered with grapefruit juice (Bailey, 2004). Naringin had no direct inhibitory effect on the P-gp substrate talinolol. However, naringin is converted to aglycone naringin, which regulates P-gp activity in the intestinal microflora, and exerts its inhibitory effect. In the same study, it was reported that bergamottin did not significantly affect P-gp activity, but 6,7-dihydroxybergamottin was a potential P-gp inhibitor (De Castro, 2007). In another study, the effect of grapefruit juice and its components on intestinal absorption of colchicine was investigated using the human colorectal adenocarcinoma (Caco-2) cell line and an intestinal rat perfusion method. The decreased mucosal secretion in the presence of known P-gp inhibitors verapamil and quinidine indicates that basolateral-to-apical (B→A) per-

meability is greater than apical-to-basolateral (A→B) permeability. In the presence of grapefruit juice and its components, A→B permeability increased, whereas B→A permeability decreased due to P-gp inhibition. In addition, in rats, grapefruit juice increased the ileal and jejunal permeability of colchicine 2 and 1.5 times, respectively (Dahan, 2009).

Organic anion transporting polypeptides Inhibition

Organic anion transporting polypeptides (OATP1A2, OATP1B1, OATP1B3, OATP2B1, OATP3A1, OATP4A1) are localized on the luminal surface of epithelial cells in the small intestine and facilitate the uptake of their substrates from the gastrointestinal tract into the portal circulation. OATPs localized on the basolateral membrane in the liver facilitate uptake of their substrates from the portal circulation to the hepatocytes. Grapefruit juice and its components (e.g. furanocoumarins and flavonoids) are potential inhibitors of OATPs. The oral bioavailability of fexofenadine (an OATP substrate) has been shown to be increased in humans when co-administered with grapefruit juice (Bailey, 2004). Grapefruit juice components, especially flavonoids (such as naringin, hesperidin) inhibit OATP. This directly affects the dose-response relationship by reducing substrate drug concentrations in the systemic circulation and tissues (Pirmohamed, 2013). In a pharmacokinetic study, co-administration of grapefruit juice with aliskiren dramatically decreased the plasma levels of aliskiren. OATP2B1 and OATP1A2 transfected cell lines were used to elucidate the mechanism of this effect. The accumulation of OATP1A2 substrates aliskiren and fexofenadine was significantly reduced in the presence of naringin (Rebello, 2012). Two views have been proposed regarding the OATP inhibitory effect of grapefruit juice. First, water absorbed faster than grapefruit juice, resulting in increased drug concentrations in the intestinal fluid and increased drug absorption due to higher drug exposure of OATP transporters. The second view is that non-specific osmotic effects of solutes increase the volume of intestinal fluid, and thus indirectly affect OATP function (Dresser, 2003).

STATINS

Statins are a class of drugs used to treat hypercholesterolemia. They are also known as HMG-CoA reductase inhibitors. In clinical studies with statins, it has been shown that morbidity and mortality rates due to cardiovascular dieseases are reduced (Bellosta, 2004). There are seven statins used in the clinic: Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin, pitavastatin. With the exception of cerivastatin, which was withdrawn from the market in 2001, all are safe and well-tolerated drugs. Although their chemical structures are different, they mainly consist of three parts. These moieties are the binding site to the HMG-CoA enzyme, the complex hydrophobic ring and the side groups responsible for the solubility of the drug attached to this ring (Figure 3) (Schachter, 2004).

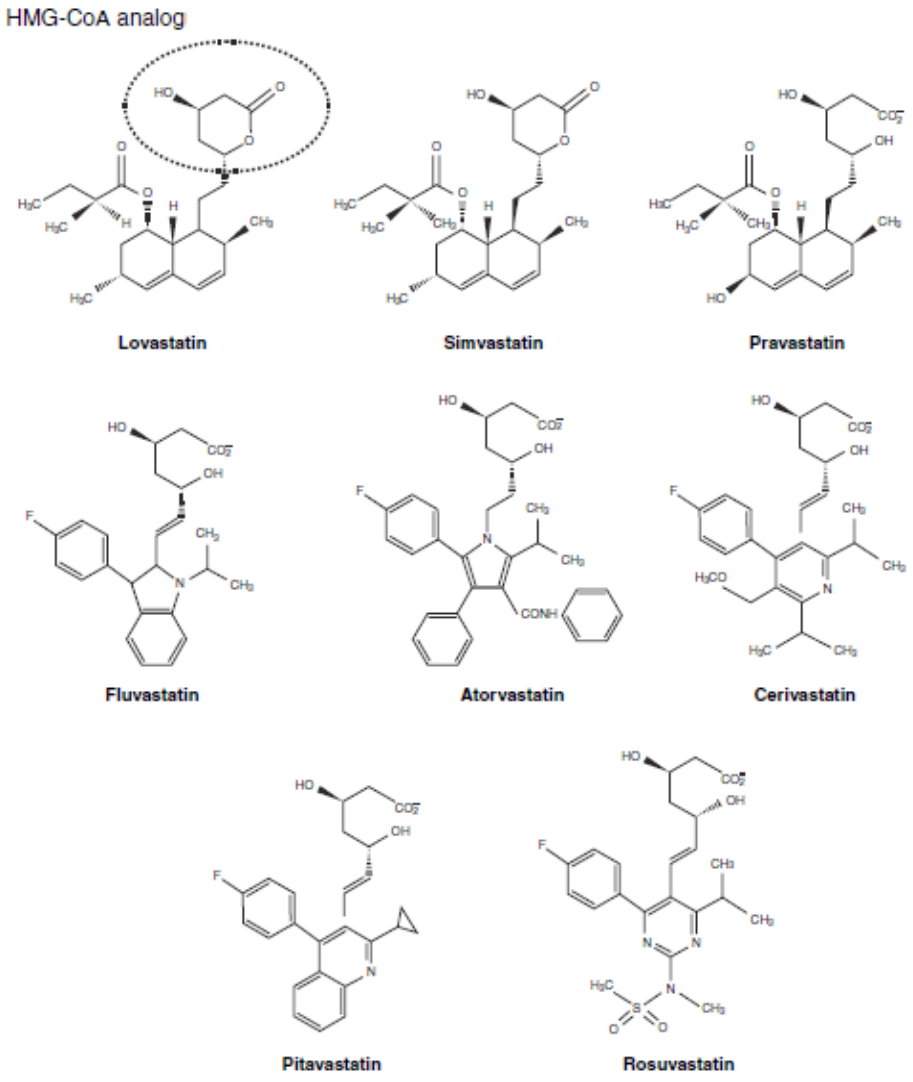


Figure 3. Chemical structures of statins (Schachter, 2004).

Statins competitively inhibit the HMG-CoA reductase enzyme, which is the rate-limiting step in cholesterol synthesis (Figure 4). Statins have 3 times higher affinity for the enzyme binding site than the natural substrate HMG-CoA, and reduce cholesterol synthesis by 10-60%, depending on dose and individual factors (Williams, 2002). The reduction of cholesterol in hepatocytes leads to an increase in hepatic LDL receptors, which reduces circulating LDL and its precursors (intermediate density - IDL and very low density - VLDL lipoproteins). After a single daily dose, all statins decrease LDL cholesterol in a non-linear and dose-dependent manner (Stancu, 2001). Table 1 shows statins-induced decreases in serum LDL cholesterol concentrations at different doses (Law, 2003). Additionally, HMG-CoA inhibition affects smooth muscle proliferation and platelet aggregation, and anti-inflammatory and antithrombotic effects can also be observed (Williams, 2002). The most known side effects of statins are on the musculoskeletal system. Possible side effects are muscle pain, fatigue, weakness and, in severe cases, rhabdomyolysis. In addition, a number of side effects such as gastrointestinal, neurological, psychiatric symptoms, sleep problems, and high blood sugar levels have also been reported (Golomb, 2008).

Table 1. Reductions in serum LDL cholesterol levels (%) based on daily dose of statins (Law, 2003).

	Daily dose (mg)				
	5	**10**	**20**	**40**	**80**
Atorvastatin	31%	37%	43%	49%	55%
Fluvastatin	10%	15%	21%	27%	33%
Lovastatin	-	21%	29%	37%	45%
Pravastatin	15%	20%	24%	29%	33%
Rosuvastatin	38%	43%	48%	53%	58%
Simvastatin	23%	27%	32%	37%	42%

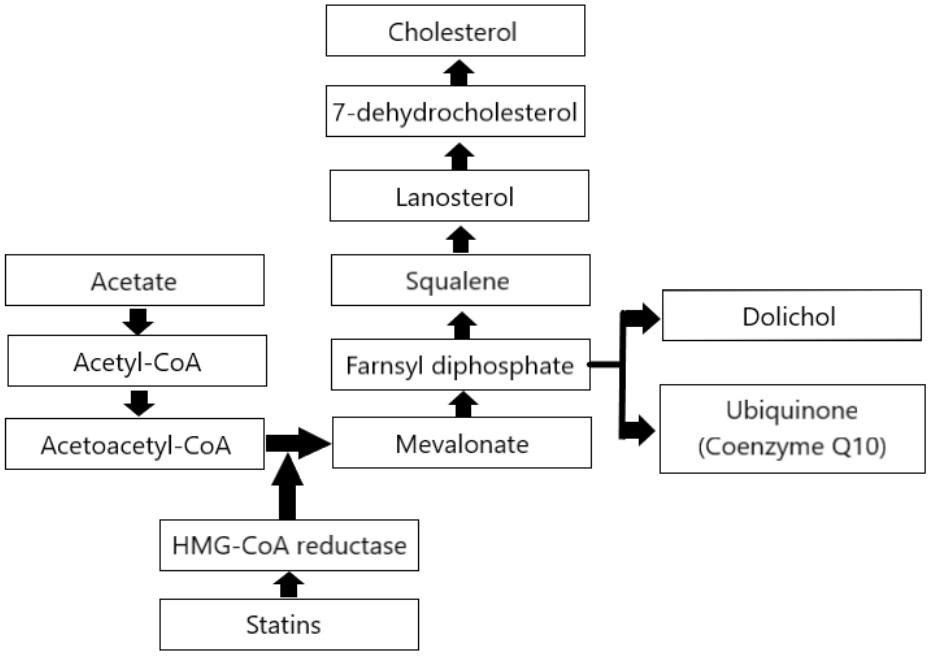


Figure 4. Cholesterol synthesis in the liver and the mechanism of action of statins (Williams, 2002).

Although statins have the same mechanism of action, their pharmacokinetic properties differ due to changes in their chemical structures (Amly, 2015). Their chemical structures also affect their binding potency to the HMG-CoA reductase enzyme, their lipophilicity, and their ability to enter hepatocytes. The pharmacokinetic parameters of statins are summarized in Table 2. Statins with 15-30% oral bioavailability have a short elimination half-life. Most statins are metabolized by CYP enzymes. Atorvastatin, cerivastatin, lovastatin, and simvastatin are metabolized by CYP3A4, while fluvastatin and rosuvastatin are metabolized by CYP2C9 (McKenney, 2003). CYP450 enzymes have no significant effect on the metabolism of pravastatin and pitavastatin (Schachter, 2004).

Table 2. Physicochemical and pharmacokinetic properties of statins.

	Lovastatin	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Cerivastatin	Rosuvastatin	Pitavastatin
[1]IC_{50} (nM)	-	11.2	44.1	27.6	8.2	10.0	5.4	-
[1]Absorption (%)	30	60-85	35	98	30	>98	50	80
[1]Bioavailability (%)	5	<5	18	24-30	12	60	20	60-80
[1]Hepatic extraction (%)	≥70	≥80	45	≥70	70	50-60	63	-
[1]Renal extraction (%)	10	13	20	6	<5	30	10	-
[1]Protein binding (%)	>98	>95	50	>98	>98	>99	90	96
[1]Half-life (h)	2-5	2-5	1-3	1-3	7-20	1-3	20	10-13
[1]Metabolism	+++	+++	+	+++	+++	+++	+	++
[1]Active metabolites	3	3	2	No	2	2	Minor	Minor
[1]CYP enzyme metabolism	3A4/5, 2C8	3A4/5, 2C8	3A4	2C9	3A4, 2C8	3A4, 2C8	2C9, 2C19	2C9
[1]Uptake transporters	SLCO1B1, MCT4	SLCO1B1	SLCO1B1/2B1 OAT3, MCT1	SLCO1B1	SLCO1B1	SLCO1B1	SLCO1B1/1B3 /2B1/1A2, SLC10A1	SLCO1B1/1B3
[1]Efflux transporters	ABCB1	ABCB1	ABCB1/B11 /C2/G2	ABCG2	ABCB1/G2	ABCB1/C2/G2	ABCB1/C2/G2	ABCB1/C2/G2
[2,3]BCS class	II	II	III	I	II	II	II	II
[4]Hydrophilicity/ Lipophilicity	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic
[5]log P (pH 7.0)	1.7	2.06	-0.23	1.67	1.61	2.05	0.13	-
[5]log D (pH 7.0)	3.91	4.4	-0.47	1.75	1.53	2.32	-	1.5
[6]Standard daily dose (mg)	10-40	10-40	10-40	80	10-80	-	5-40	1-4

r[1]Hu, 2009; [2]Lada, 2018; [3]Varma, 2012; [4]Bonsu, 2013; [5]Murphy, 2020, [6]Sirtori, 2014

IC_{50}: Half maximal inhibitory concentration, CYP: Cytochrome P450, BCS: Biopharmaceutics Classification System, log P: Partition coefficient, log D: Distribution coefficient,

SLC: Solute carrier organic anion transporters, MCT: Monocarboxylate transporters, ABC: ATP-binding cassette transporters

Atorvastatin

Atorvastatin is a second-generation statin and a reversible HMG-CoA reductase enzyme inhibitor. It is administered orally as the calcium salt of the active hydroxy acid form. It is used at doses of 10-80 mg/day in the clinic. Atorvastatin is converted to the lactone form in the body. The acid and lactone forms of the drug differ in solubility, lipophilicity, and octanol/water partition coefficient (Lennernas, 2003). Atorvastatin calcium salt is insoluble in aqueous solutions at pH ≤ 4.0 aqueous solutions, and slightly soluble in pH 7.4 phosphate buffer and water (Kim, 2008). According to the Biopharmaceutics Classification System (BCS), atorvastatin calcium is a Class II drug (low solubility, high permeability) and its oral bioavailability is approximately 12% (Shayanfar, 2013). Due to its high membrane permeability, it is rapidly absorbed and reaches its maximum plasma concentration within 1-3 hours after oral administration (Khan, 2017). Low solubility and first-pass elimination have been reported to be the causes of low bioavailability (Khan, 2011). The CYP3A4 enzyme in the gastrointestinal tract and liver, is responsible for the first-pass metabolism of atorvastatin (Kumar, 2017). The plasma protein binding of atorvastatin is greater than 98%, and the mean volume of distribution after 5 mg iv infusion is 381 L indicating high binding of atorvastatin to peripheral tissues (Khan, 2017).

There are many studies in the literature evaluating the interaction of atorvastatin with grapefruit juice. Co-administration with grapefruit juice increased the AUC of atorvastatin acid and pitavastatin acid (their active forms) in humans by 83% and 13%, respectively; this indicates that grapefruit juice inhibits the CYP3A4-mediated metabolism of atorvastatin, whereas the metabolism of pitavastatin does not extensively depend on CYP3A4. The time to maximum concentration (t_{max}) of 2-hydroxy atorvastatin acid (major active metabolite) was prolonged from 3.2 to 9.4 hours. $t_{1/2}$ and AUC of pitavastatin lactone (inactive form) were significantly increased (Ando, 2005). In another study, in the presence of grapefruit juice, the AUCs of atorvastatin acid and atorvastatin lactone increased by 1.4- and 1.56-fold, respectively, while there was no significant increase in the pharmacokinetic parameters of pravastatin (Fukazawa, 2003). Daily consumption of 240 mL grapefruit juice increased the AUC of atorvastatin by 37% after oral administration of 40 mg, but this increase was not clinically significant (Kellick, 2014). Concomitant use of atorvastatin (10, 20, or 40 mg/day) and grapefruit juice resulted in a 19-26% increase in serum atorvastatin concentrations in patients. When the daily dose was halved, serum concentration values increased by 12-25%. Additionally, myalgia and memory loss scoring were used to assess the quality of life of the patients. Serum creatine kinase (CPK) levels and liver function tests were evaluated. According to results, changes in serum atorvastatin levels did not cause liver and/or muscle toxicity (Reddy, 2011). Similarly, grapefruit juice consumption with 10 mg atorvastatin increased the serum levels by 1.8 times. Daily use of 10 mg of atorvastatin reduces LDL cholesterol level by 37%, reducing the risk of ischemic heart disease by 61%. When atorvastatin is taken with a glass of grapefruit juice, its blood level increases by approximately 80%. In this case, the reductions in LDL cholesterol level and ischemic heart disease risk are 42% and 66%, respectively (Lee et al., 2016). The intestinal concentration of CYP3A4 enzyme decreases by 50% within 4 h of drinking juice of a whole grapefruit. Inactivation of intestinal CYP3A4 increases the systemic bioavailability by affecting the presystemic degradation of statins (atorvastatin, lovastatin, simvastatin) metabolized by this enzyme. Therefore, it is not recommended to consume grapefruit juice while taking these statins. The half-life of drug, the time of consumption and the amount grapefruit juice consumed are important for interaction. It has been reported that with statins, this grapefruit juice effect is reduced to 10% of the maximum 24 hours after grapefruit juice ingestion, or using about a liter or more grapefruit juice poses a potential hazard as it increases the amount of

statin entering the circulation (Azemawah, 2019).

Simvastatin

Simvastatin is produced synthetically from the fermentation product of Aspergillus terreus. There is only one stable crystal form and no hydrate form. It is Class II drug (low solubility, high permeability) according to BCS (solubility at 25 ^{0}C 6.3x10^{-3} g/L, pH 1.0-7.0) (Graeser, 2008; Kong, 2017). After simvastatin lactone is administered as a prodrug, it is enzymatically hydrolyzed in the body and converted to its active acid form (Schachter, 2004). Although oral absorption is about 60-85%, the bioavailability of simvastatin is less than 5% due to pre-systemic elimination in the gastrointestinal tract via both CYP3A4 and P-gp. The CYP2C8 is also involved in metabolism of simvastatin. Lipophilic statins such as simvastatin tend to bind to peripheral tissues much more readily (Neuvonen, 2008). The major elimination organ of simvastatin is the kidneys, and its half-life is approximately 3 hours in adults with normal renal function (Srinivas, 2012). The t_{max} of simvastatin is between 1.3 and 2.4 hours after 40 mg oral dose (Bellosta, 2004). Total body clearance is 31.8 L/h, and protein bindings for simvastatin and simvastatin acid are 98% and 94%, respectively (Mauro, 1993). In nine healthy Malaysian male subjects, the mean volume of distribution was 232.57±132.54 L following a single oral dosage of 40 mg (Alakhali, 2013).

In a study investigating the effects of regular grapefruit juice consumption on the pharmacokinetics of simvastatin, 200 mL of grapefruit juice was given to 10 healthy volunteers every day for three days. Simvastatin (40 mg, single dose) was administered with 200 mL of grapefruit juice on the third day. The AUC values of simvastatin and simvastatin acid were increased by 3.6 and 3.3 times, respectively, following grapefruit juice administration (Lilja, 2004). In another study by the same researcher, the C_{max} of simvastatin increased 12-fold and the AUC increased 13.5-fold after consuming 200 mL grapefruit juice three times each day for three days, compared to the control group (consumed water only) (Lilja, 2000). Similarly, administration of 40 mg simvastatin daily with one grapefruit or one glass of grapefruit juice (approximately 240 mL) increased AUC by 3.6-fold, while excessive grapefruit juice consumption (equal to six grapefruits) increased AUC by 13.5-fold (Lee, 2016). In another study, 200 mL of double-strength (diluted 1/1) grapefruit juice was given 3 times a day for 2 days. On the 3rd day, 60 mg of simvastatin was administered with 200 mL of grapefruit juice. The increase in AUC values for simvastatin and simvastatin acid was 16 and 7-fold, respectively. Additionally, 200 mL of single-strength (diluted 1/3) grapefruit juice was consumed at breakfast for 3 days, and then 20 mg of simvastatin was administered in the evening on the 3rd day. The AUC of simvastatin and simvastatin acid increased 1.9 and 1.3 times, respectively. Based on the results, it was reported that the amount of grapefruit juice taken with simvastatin should not exceed 1 liter daily (Kellick, 2014). Bergamottin, a component of grapefruit juice, raises the plasma levels of simvastatin and simvastatin acid (the active metabolite) by preventing the CYP3A4-mediated first-pass metabolism of simvastatin in the intestines (Kiani, 2007). In a study using human and rat liver microsomes, bergamottin extracted from grapefruit juice was shown to inhibit the CYP450-dependent hepatic metabolism of simvastatin (Goff-Klein, 2004). Grapefruit juice and other CYP3A4 inhibitors have the potential to increase blood levels 20-fold. According to a case report published in Germany, a woman taking 80 mg of simvastatin developed rhabdomyolysis four days after she started consuming one grapefruit per day. Therefore, grapefruit juice consumption requires dose adjustment (Spence, 2016). Excessive consumption of grapefruit juice (400 mL 3 times daily, 3 days) increased the AUC of simvastatin by 700%, while this increase was 330% at low amounts (200 mL once daily, 3 days). Additionally, rhabdomyolysis has also been reported after consumption of fresh grapefruit for 10 days (Bailey, 2013).

Lovastatin

Lovastatin is a white crystalline powder and its

water solubility is 0.4 μg/mL at room temperature (Sharannavar, 2018). It is given as a prodrug in inactive lactone form and transformed into the active β-hydroxy acid form by carboxyesterases in the liver (Donovan, 2002). After oral administration, lovastatin is metabolized by CYP3A4 and reaches its maximum plasma concentration within 4 hours. The elimination half-life is 3 hours, and lovastatin is 95% protein bound. Renal and fecal excretion are approximately 10% and 83%, respectively. Lovastatin is a BCS Class II drug (low solubility, high permeability) and it should be taken twice daily (Zolkiflee, 2017). Due to its low water solubility and short half-life, its oral bioavailability is only 5%. It also undergoes extensive first-pass metabolism (Zhou, 2015).

Ten healthy volunteers were given 200 mL of grapefruit juice 3 times a day for 2 days, and 80 mg of lovastatin was co-administered with 200 mL of grapefruit juice on the 3rd day. In this pharmacokinetic study, AUC increased 15 times for lovastatin and 5 times for lovastatin acid. C_{max} of lovastatin and lovastatin acid increased approximately 12-fold and 4-fold, respectively. $t_{1/2}$ values remained unchanged (Kantola, 1998). In another study, AUC and C_{max} values of lovastatin increased by 2-fold, while for lovastatin acid these values increased by 1.6-fold with grapefruit juice (Rogers, 1999). A high daily intake of grapefruit juice (equivalent to six grapefruits) increases the systemic bioavailability of lovastatin by inhibiting its presystemic biotransformation. The time of consumption is as important as the amount of grapefruit juice taken. The pharmacokinetic properties of statins with short half-life, such as simvastatin and lovastatin are more affected when taken with grapefruit juice in the morning. This is because the effect of grapefruit juice is seen within 7-8 hours (Costache, 2019). In another study, a single dose of 40 mg lovastatin was administered after using 250 mL of single-strength grapefruit juice for 4 days. AUC values for lovastatin and lovastatin acid increased 1.94 and 1.57-fold, respectively (Kellick, 2014). When concomitant administration of 40 mg of lovastatin or simvastatin daily with grapefruit juice, the estimated reduction in LDL cholesterol level and heart disease risk is 48% and 70%, respectively. If grapefruit juice is consumed 12 hours before these statins, reductions are predicted to be 43% and 66%, respectively (Lee, 2016).

Pravastatin

Pravastatin is a hygroscopic, crystalline powder, readily soluble in water and methanol. Unlike other statins, it is a hydrophilic compound. The pH-dependent octanol-water partition coefficient is 0.59 at pH 7.0. It is an acidic drug with a pKa of 4.5. Although it is very rapidly absorbed after oral administration, its bioavailability is low (about 18%) due to low membrane permeability (Hatanaka, 2000; Quion, 1994; Bang, 2003). The protein binding of pravastatin is approximately 50% and the volume of distribution is 0.46 L/kg. Elimination of pravastatin occurs by renal (47%) or non-renal (53%) routes. Approximately 70% of the oral dose is excreted in the feces and 20% in the urine. Despite its high dissolution rate and solubility in water, pravastatin is unstable in acidic conditions. It is converted to an isomer (3α-isopravastatin) by chemical transformation in the stomach (Hatanaka, 2000; Quion, 1994; Bang, 2003).

Evaluation of the interaction of atorvastatin and pravastatin with grapefruit juice in healthy volunteers revealed that grapefruit juice raised the AUC of atorvastatin acid and atorvastatin lactone, while pharmacokinetic parameters of pravastatin remained unchanged. This observation was attributed to the insignificant role of CYP3A4 pravastatin metabolism (Lilja, 1999). It has been reported that grapefruit juice has no effect on statins that are not metabolized by CYP3A4, such as pravastatin, rosuvastatin, fluvastatin, and pitavastatin. On the other hand, taking CPY3A4 metabolized statins at least four hours after drinking grapefruit juice reduces the risk of interactions by more than 60%, as the effect of grapefruit juice on this enzyme system disappears within a few hours (Mouly, 2017). In a study with pravastatin and pitavastatin, drug interactions were investigated in rats using the *in*

situ intestinal closed-loop technique in the presence of grapefruit juice or naringin. Although both statins are OATP1A5 and OATP2B1 substrates, only pitavastatin is a P-gp substrate. Grapefruit juice and naringin decreased the plasma concentration of pravastatin, while increasing the plasma concentration of pitavastatin. Based on the results, it was stated that the inhibitory effect of naringin on OATP caused a decrease in the absorption of pravastatin, while P-gp inhibition caused an increase in the absorption of pitavastatin (Shirasaka, 2011). In another study by the same researchers using the same technique, pravastatin was administered together with elacridar (P-gp inhibitor) and naringin (OATP inhibitor). In the presence of naringin, rat intestinal permeability of pravastatin was significantly reduced, whereas there was no significant change with elacridar (Shirasaka, 2010). According to the results of these studies, although there is a cellular interaction between naringin and the OATP substrate pravastatin, there is no possible clinical interaction between grapefruit juice and pravastatin.

Pitavastatin

Clinically used pitavastatin calcium is white to light yellow and odorless powder. It is soluble in organic solvents such as pyridine and tetrahydrofuran, but slightly soluble in ethanol and water. Partition coefficient of pitavastatin is 31.7 (Hayashi, 2007). Pitavastatin is a synthetic lipophilic statin that was first used in the treatment of hyperlipidemia in Japan in 2003. Unlike other statins, the cyclopropyl group in the structure of pitavastatin binds to the hydrophobic regions of the HMG-CoA reductase enzyme with high affinity, leading to more effective inhibition. Pitavastatin is administered as the calcium salt in doses of 1 mg, 2 mg, and 4 mg. Its bioavailability is between 51-60% and C_{max} is reached within one hour after oral dosing. Plasma protein binding is greater than 99%, particularly to albumin and alpha(1)-acid glycoprotein. It is specifically distributed to the liver and its hepatic uptake is presumed to be mediated by OATP1B1 and OATP1B3. The elimination half-life of pitavastatin is 12 hours and the mean volume of distribution is 133 L. CYP2C9 and CYP2C8 play a minor role in pitavastatin metabolism. Although pitavastatin is a CYP3A4 substrate, cyclopropyl group increases the bioavailability of pitavastatin by inhibiting its metabolism by the cytochrome P450 system (Duggan, 2012; Carella, 2016; Saito, 2011).

Evaluation of the concomitant use of grapefruit juice and atorvastatin or pitavastatin showed that no significant change was observed in the pharmacokinetics of pitavastatin, while the atorvastatin concentration increased significantly. This observation supports the fact that pitavastatin is a better treatment option (Ando, 2005). In another study, grapefruit juice caused a modest increase in pitavastatin levels in the blood. The $AUC_{0\text{-}48h}$ of pitavastatin acid and pitavastatin lactone increased by 14%, while $t_{1/2}$ values remained unchanged. Apparent oral clearance (CL/F) and C_{max} of pitavastatin acid decreased by 10% and 12%, respectively. The reductions in these values for pitavastatin lactone are 15% and 13%, respectively (Hu, 2013). Investigation of the role of OATPs and P-gp (MDR1) in intestinal absorption of pitavastatin confirmed that pitavastatin is the substrate of human OATP1A2, OATP2B1, MDR1 and rat Oatp1a5, Oatp2b1, Mdr1a. When pitavastatin was co-administered with naringin (OATP and MDR1 inhibitor) and/or elacridar (MDR1 inhibitor), rat intestinal permeability of pitavastatin decreased at low naringin concentration while increased at high naringin concentration. Permeability of pitavastatin was increased when elacridar was used alone, but decreased when elacridar and naringin were used together. The results of this study showed that OATP/Oatp and MDR1/Mdr1 have effects on the intestinal absorption of pitavastatin (Shirasaka, 2010). Pitavastatin has been reported to be safer than other statins. It is poorly metabolized by the CYP450 system and no inhibitory effect of the lactone form on CYP3A4 was found. In isolated rat liver microsomes, the HMG-CoA reductase inhibitory effect of pitavastatin was 2.4 and 6.8 times greater than simvastatin and pravastatin, respectively. In human microsomes, the intrinsic clearance of lovastatin,

simvastatin, atorvastatin, and fluvastatin was 100, 50, 8, and 30 times greater than that of pitavastatin, respectively. Based on these results, pitavastatin has a relatively low intrinsic clearance and is much less metabolized than other statins. In addition, pitavastatin produces a clinical response equivalent to atorvastatin, the most preferred and most potent statin. Due to its favorable pharmacokinetic properties, the possibility of drug-drug and/or drug-food interactions is very low, and may be preferred for use in treatment (Kajinami, 2003).

Fluvastatin

Fluvastatin is the first HMG-CoA reductase inhibitor that is entirely synthetic. The pKa of fluvastatin is 5.5, indicating it is a weak acid. At pH 7.0, its octanol/water partition coefficient is 20. Its water solubility at pH 6.0 is 2 g/L. Fluvastatin has two enantiomers due to the presence of two asymmetric centers in the side chain. Commercially available product is a racemic mixture of these enantiomers (Scripture, 2001). Almost all of the orally administered dose is absorbed (98%), but its absolute bioavailability is only around 20% to 30% due to first-pass hepatic metabolism. Fluvastatin has a volume of distribution of 0.35 L/kg and is highly bound to plasma proteins (> 99%). Fluvastatin is mainly metabolized by CYP2C9, but to a lesser extent by CYP3A4 and CYP2D6, and is eliminated in the bile and feces. The elimination half-life is 1.2 hours and total body clearance is 0.97 L/h/kg (Langtry, 1999; Plosker, 1996).

There are no studies evaluating the interaction of fluvastatin with grapefruit juice (Gazzerro, 2012). It has been suggested for use as an alternative to other statins that interact with grapefruit juice because no interaction has been reported (Bailey, 2013).

Rosuvastatin

Rosuvastatin is a synthetic HMG-CoA inhibitor. In addition to the statin-specific pharmacophore group in its structure, the hydrophilic methane sulfonamide group provides low lipophilicity. The log D value at pH 7.4 is -0.33. Rosuvastatin has an absolute bioavailability of 20%. Food decreases the absorption rate of rosuvastatin by 20%, but the extent of absorption is not affected. Rosuvastatin is used in daily doses of 5-40 mg. The C_{max} of 6.1 μg/L is reached 5 hours after a single oral 20 mg dose, while the C_{max} of 19–25 μg/L is reached 3-5 hours after a single oral 40 mg dose. The mean volume of distribution of rosuvastatin is 134 L and plasma protein binding is 88%. Rosuvastatin is not extensively metabolized in humans. *In vitro* studies have shown that CYP2C9 and 2C19 are primary metabolic enzymes. Its $t_{1/2}$ varies between 18-24 hours depending on age (White, 2002; Scott, 2004; Carswell, 2002).

Rosuvastatin has been shown to be a substrate of OATP1B1, 1B3, 2B1, and 1A2 in studies (Ho, 2006). There is no known interaction between rosuvastatin and grapefruit juice (Bailey, 2010). However, given the inhibitory effect of grapefruit juice on OATPs, such an interaction is possible.

CONCLUSION

According to the reviewed studies, flavonoids (naringin, naringenin) and furanocoumarins (bergamottin, dihydroxybergamottin) in grapefruit juice are the main components that cause drug interactions. Grapefruit juice-drug interactions occur in different ways. CYP3A4 inhibition is the most accepted and investigated mechanism. When drugs that are metabolized by this enzyme are given together with grapefruit juice, their plasma concentration values increase. Other mechanisms are inhibition of absorptive (OATPs) and efflux transporters (P-gp) that regulate drug absorption in the gut. When OATPs are inhibited, blood level and bioavailability of substrate drugs are reduced. On the other hand, P-gp inhibition increases the bioavailability of substrates. Statins are a class of drugs that have a well-known interaction with grapefruit juice. While most statins interact with grapefruit juice via CYP3A4 inhibition, no interaction has been demonstrated for CYP2C9 substrates, fluvastatin and rosuvastatin. Although CYP450 enzymes do not play an important role in the metab-

olism of pitavastatin and pravastatin, the interaction of these statins with grapefruit juice occurs through OATP and/or P-gp inhibition. Except for cerivastatin and pitavastatin, statins have a maximum oral bioavailability of 30%. Interactions of statins, which are CYP3A4 and/or P-gp substrates, with grapefruit juice may require dose adjustment as they will increase the bioavailability of drug. Conversely, bioavailability will be further reduced when statins, which are OATP substrates, are co-administered with grapefruit juice. Therefore, when statins and grapefruit juice are used together, the mechanism of interaction should be known and clarified.

The grapefruit juice-statin interaction is also clinically important and depend on many factors such as genetic polymorphism, variability of grapefruit juice components, and the patient's sensitivity to side effects. Long-term and/or use of large amount of grapefruit juice makes interactions more likely. Grapefruit juice enhances the effect of statins (especially atorvastatin, lovastatin, simvastatin) by increasing plasma drug levels. Thus, they further reduce LDL levels and the risk of ischemic heart disease. Although the risk of rhabdomyolysis, one of the most important side effects of statins, increases, this increase is not significant. The inhibitory effects of flavonoids and furanocoumarins can last for several hours. The interaction is minimized by giving statins and grapefruit juice at least 4 hours apart. Patients taking atorvastatin, lovastatin, or simvastatin should be informed to avoid or drink too much grapefruit juice. The interaction of pitavastatin and pravastatin with grapefruit juice is more limited, and there are no available studies showing the interaction for fluvastatin and rosuvastatin. Therefore, the possibility of interaction can be reduced by choosing statins (pravastatin, pitavastatin, fluvastatin, rosuvastatin) not metabolized primarily by CYP3A4.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Choose the subject (S.S.), literature search and preparation of the manuscript (M.A.), evaluation and final editing of the review (S.S.)

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