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Research Article

# LIQUORICE BEVERAGE EFFECT ON THE PHARMACOKINETIC PARAMETERS OF ATORVASTATIN, SIMVASTATIN, AND LOVASTATIN BY LIQUID CHROMATOGRAPHY-MASS SPECTROSCOPY/MASS SPECTROSCOPY

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**ABSTRACT**

**Objective:** The objective of this study is to examine the effects of pre-consumption of freshly prepared liquorice beverage (4 ml/kg) on the pharmacokinetic (PK) parameters of (80 mg/kg) oral dose of atorvastatin, simvastatin, and lovastatin in healthy rats plasma.

**Methods:** A simple, rapid, and applicable analytical method was developed for the determination of each statin in rats' plasma. This method uses liquid chromatography-mass spectroscopy/mass spectroscopy. The mobile phase composed of methanol and formic acid in water and glimepiride as an internal standard. 108 rats were used in this study. Liquorice juice was given, and then each of the statins was given to test groups and liquorice only to the control groups, and then plasma samples were withdrawn on specific time schedule then PK analysis was performed.

**Results:** The analytical method showed acceptable linearity, recovery, precision, and accuracy. Administration of liquorice resulted in a significant increase in maximum concentration in plasma ($C_{max}$) of the three statins, also the area under plasma level-time curves (area under curve) was increased significantly. Moreover, the bioavailability of the drugs. On the other hand, the elimination of the three drugs showed no great changes, which suggests an interaction between liquorice and the transporting system of statins on the gut and biliary wall.

**Conclusion:** Consumption of liquorice results in increase bioavailability of atorvastatin, simvastatin, and lovastatin.

**Keywords:** Liquorice, Atorvastatin, Liquid chromatography-mass spectroscopy/mass spectroscopy, Simvastatin, Lovastatin, Pharmacokinetic parameters.



## INTRODUCTION

Atorvastatin, simvastatin, and lovastatin are drugs that belong to a group named statins. Statins lower plasma levels of lipid by decreasing endogenous cholesterol synthesis via inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in the liver. This enzyme catalyzes the conversion of HMG-CoA to mevalonate; an early and rate-limiting step in cholesterol biosynthesis [1,2].

Statins are widely used in many countries for the treatment of both severe familial and non-familial hypercholesterolemia [3,4]. Hypercholesterolemia is known as the imbalance of blood lipids that is considered as a high-risk factor for inducing atherosclerosis and cardiovascular diseases which are now considered one of the most leading causes of death over the world [5,6].

The pharmacokinetics (PK) of individual statin drugs is affected by their lipophilicity. The more hydrophilic compounds, such as atorvastatin, are actively transported into the liver and are less metabolized by the cytochrome P450 (CYP-450) family, and exhibit more pronounced active renal excretion, while the less hydrophilic compounds such as simvastatin and lovastatin may be transported partially by passive diffusion and are better substrates for both CYP enzymes and transporters involved in biliary excretion. Simvastatin and lovastatin are both given as lactone prodrugs and converted to the active beta-hydroxy form, and the mechanism for this does not appear to be via CYP pathways [7].

Atorvastatin is highly soluble and is completely absorbed after oral administration. However, atorvastatin suffers extensive first-pass metabolism in the gut wall as well as in the liver which results in low bioavailability (14%). The volume of distribution of atorvastatin acid is 381L, and plasma protein binding exceeds 98%. Atorvastatin is extensively metabolized in both the gut and liver by oxidation, lactonization, and glucuronidation; and the metabolites are eliminated by biliary secretion and direct secretion from blood to the intestine. *In vitro*, atorvastatin is a substrate for P-glycoprotein (P-gp), organic anion-transporting polypeptide C, and $H^+$-monocarboxylic acid co-transporter. The total plasma clearance of atorvastatin is 625 mL/min and the half-life is about 7 hrs. The renal route is of minor importance (<1%) for the elimination of atorvastatin. *In vivo*, CYP-450 3A4 is responsible for the formation of two active metabolites from the acid and the lactone forms of atorvastatin [8].

Simvastatin is the methyl analogue of lovastatin. It is well-absorbed from the gastrointestinal tract but is highly extracted by the liver, and only 7% of the dose reaches the general circulation intact. Simvastatin is eliminated mainly in the feces due to biliary excretion, but only a small percentage of the dose is found in the stool in the form of the parent compound or simvastatin acid. Since simvastatin is metabolized by the CYP-450 system, a potential for drug interactions exists [9].

Many previous studies have shown that the effect and activity of any drug may differ from the expected findings as many drugs are exposed to drug-drug or food/beverage-drug interaction [10]. Recent published data have proven the existence of an intrinsic interaction between many popular juices such as grapefruit juice, orange juice, pomegranate juice, and drugs. These juices can alter the metabolism of drugs, which mostly causes alterations in PK and/or pharmacodynamics (PD) of drugs. The interaction could also be on the absorption level, which results in altering oral bioavailability, or through induction, or inhibition of metabolizing enzymes in gut or liver. These effects would be indicated by changes in plasma concentration of drugs [11-13].