

The Effect of Pomegranate and Liquorice on Pharmacokinetics Parameters of Theophylline in Rat Plasma by using HPLC Technique

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Food or drinks may significantly alter the pharmacokinetics and pharmacodynamics of medicine which can cause adverse events. A drug such as theophylline is widely used to treat asthma and chronic obstructive pulmonary disease. Pomegranate and liquorice have been identified to help in cough management. However, the interactions of the later with theophylline pharmacokinetics were not studied. Therefore, we aimed to study the impact of pomegranate and liquorice on theophylline pharmacokinetics in rats. An HPLC method of study was developed and partially validated successfully consistent with the ecu Medical Agency Guideline to live theophylline in rat plasma. Pomegranate and liquorice juices were given to rats for two days and half an hour before theophylline (5 mg/kg) was orally administered as solution. Blood samples, then, were collected at scheduled time intervals, processed and analysed using the validated reliable HPLC method. Plasma profile of theophylline was obtained and pharmacokinetic parameters (C-max, T-max and Area under the curve (AUC)), were calculated for each group. Values of the pharmacokinetic parameters were compared statistically using ANOVA, t-test with corresponding control values on 95% confidence interval. It was found that consumption of pomegranate or liquorice juice prior oral administration of theophylline didn't end in significant pharmacokinetic interaction.

The consumption of herbs as beverages has increased in recent years. It has been estimated that approximately 1 out of 5 Asian take prescription medications concurrently with at least 1 herbal product or more (Shane-McWhorter, 2001). In many cases, patients consume such products to treat various disorders such as anxiety, dementia and memory impairment, headache, weight loss, and others (Marcus and Grollman, 2002). Concurrent use of herbal beverage with approved medications may result in therapeutic failures or adverse effects and should produce variable outcomes of clinical importance if this concomitant consumption is not controlled (Sinh and Saratchandra 2005, Hamad et al. 2017). In this regard, several juices have shown to change enzymes and transporters that modulate the pharmacokinetic parameters (PKP) and thus might end in undesired pharmacodynamic (PD) outcomes (Abu Dayyih et al. 2016, Mima et al. 2017). Most of the previously reported drug-juice interactions focused mainly on fruit juice. On the other hand, interactions with several other juices with drugs are generally unnoticed which still need to be investigated and addressed (Garvan and Lipsky 2000).

Pomegranate (*Punica granatum* from the family-Lythraceae) has become highly recommended supplements as a natural antioxidant consumed as fruit or juice (Komperda 2009, Awad et al. 2017). However, it showed pharmacokinetic interaction with various drugs like antiarrhythmic, calcium channel blockers and statins (Abu Dayyih et al, 2014). Studies proved that pomegranate inhibits CYP3A in the body, in addition, it was reported that pomegranate juice interfered with the intestinal absorption of certain drugs probably through an effect on transporters responsible for the absorption process (Hidaka et al. 2005, Hamad et al. 2017). Licorice (*Glycyrrhiza glabra* of the Leguminosae Family), on the other hand, is one of the well-known traditional drinks particularly in the Middle East region. It is known for its antiinflammatory, hypocholesterolemic and antioxidant effects (Cantelli-Forti, et al. 1994). However, licorice was found to interact with some drugs' kinetics like digoxin, thiazides and spironolactone (Shaikhli, 2015). It was also reported that licorice significantly reduced cyclosporine bioavailability by interfering with P-glycoprotein and CYP3A4 (Chua, et al. 2015). Theophylline (1,3-dimethylxanthine) is a naturally occurring alkaloid which has been classified as bronchodilator in the treatment of asthma and chronic obstructive pulmonary diseases (COPD) due to its effect in relaxation of bronchial smooth muscle. It has a narrow therapeutic index starting from 5 to twenty mg/ml of serum concentration (Piafsky and Ogilvie 1975). Theophylline is mainly (85-90%) metabolized by liver cytochrome P-450 in both human and rats. Oxidation at carbon no. 8 is the major metabolic pathway in human performed mainly by CYP1A2 as well as N-demethylation to 3-methylxanthine and conjugation (Ogilvie 1978, Khan and Jones 2014). CYP1A2 is stimulated by smoking and many drugs, and there is significant inter-individual variation in the level of this enzyme (Weinberger and Hendeles 1996). In rats, the 8-hydroxy derivative composes more than 95% of the total recovered metabolites. It was subjected to induction and inhibition by different xenobiotics as well (Kim et al, 2003). Furthermore, many studies showed interaction of the theophylline with other drugs, food, beverages or dietary supplements on its effect and activity (Khan and Jones 2014). Aqueous licorice and pomegranate root extract is one of the widely used juices worldwide as multi-target agents, and may exert a pronounced effect on several diseases. Therefore, we aimed here to study the impact of pomegranate and licorice on theophylline pharmacokinetics (PK) in rats.

A study by Fuhr et al. since 1995 proved lack of grape fruit juice on theophylline pharmacokinetic (Fuhr et al.1995), but there was an effect on Tmax after administration of modified release tablet of theophylline in adult human males as investigated by Gupta. (Gupta et al., 1999). It was found that grape fruit does not interfere either with the PK of caffeine which shares the xanthan nucleus with theophylline (Maish et al., 1996). Many studies focused on grapefruit as famous beverage which is known to interact with several medication. But pomegranate juice and licorice juice are widely consumed and they might have potential interactions with medications. The metabolism of theophylline as mentioned above is highly similar between

man and rat, that's why we can say that the result of this work give a good indication of this combination.

Results of this work show there is no a beverage - drug interaction between pomegranate or licorice and theophylline in rats. This was expressed by statistically nonsignificant differences between Cmax, Tmax and AUC(0-24hr) between groups of rats that received theophylline alone and those which received theophylline with pomegranate juice and licorice juice orally. This could be of important value if extended to human and can provide important information regarding theophylline administration and uses.