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Research Article/ Araştırma Makalesi

MODULATION OF CYP1A1 ACTIVITY IN RAT MICROSOMES BY *CITRUS* L. FRUIT JUICES

SIÇAN MİKROZOMLARINDA CYP1A1 AKTİVİTESİNİN CİTRUS L. MEYVE SULARI İLE MODÜLASYONU

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ABSTRACT

Objectives: *Juices prepared from citrus fruits make up almost two-thirds of the worldwide market for juice, which makes them one of the most common beverages in the diet. The simultaneous consumption of fruit juices and medicinal drugs poses a risk of herb-drug interactions. Previous studies have noted that Citrus paradisi Macfad., Citrus aurantifolia Linn., Citrus maxima (Burm) Merrill, and Citrus sinensis (L.) Osbeck juices affect cytochrome (CYP) 1A1 activity. Studies testing the effects of Citrus australasica F. Muell., Citrus limon (L.) Osbeck, Citrus reticulata Blanco× Citrus sinensis (L.) Osbeck, and Citrus japonica Thunb. fruit juices on CYP1A1 activity are lacking.*
Material and Methods: *This study evaluate the CYP1A1 activity of Citrus fruit juices on rat liver tissues using the 7-ethoxyresorufin O-deethylase (EROD) assay.*
Result and Discussion: *Among the six fruit juices studied, C. sinensis, C. japonica and C. australasica were found to inhibit CYP1A1 activity by 50%, 50% and 60%, respectively. These juices should be used with caution when taking medicines metabolized by the CYP1A1 isoenzyme.*
Keywords: *Citrus, CYP1A1, EROD, Fruit juice*

ÖZ

Amaç: *Citrus L. meyve suları, küresel meyve suyu pazarının yaklaşık üçte ikisini oluşturan diyette yaygın olarak tüketilen içeceklerden biridir. Meyve sularının tıbbi ilaçlarla eş zamanlı tüketilmesi bitki-ilaç etkileşim riskini ortaya çıkarmaktadır. Önceki çalışmalarda C. paradisi, C. aurantifolia, C. maxima ve C. sinensis meyve sularının sitokrom (CYP)1A1 aktivitesini etkilediği belirtilmiştir. C. australasica, C. limon, C. reticulata × C. sinensis ve C. japonica meyve sularının CYP1A1 aktivitesi üzerindeki etkisini değerlendiren bir çalışma bulunmamaktadır.*
Gereç ve Yöntem: *Bu çalışmada, narenciye meyve sularının sıçan karaciğer dokusu üzerindeki CYP1A1 aktivitesini 7-etoksirezorufin O-deetilaz yöntemi kullanarak değerlendirilmiştir.*
Sonuç ve Tartışma: *Çalışılan altı meyve suyu arasında C. sinensis, C. japonica ve C. australasica'nın CYP1A1 aktivitesini sırasıyla %50, %50 ve %60 oranında inhibe ettiği*

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bulunmuştur. Bu meyve suları, CYP 1A1 izoenzimi tarafından metabolize olan ilaçlar alınırken dikkatli kullanılmalıdır.
Anahtar Kelimeler: *Citrus, CYP1A1, EROD, Meyve suyu*

INTRODUCTION

Fruit juice is defined as the liquid portion of the fruit obtained from the edible, ripe, and fresh part and preserved by cooling or freezing. Except for its fiber content, it has similar nutritional and phytochemical content as whole fruit. In previous studies, it has been proven that different juices have a high antioxidant capacity, improve endothelial functions, reduce platelet aggregation, and exhibit anti-inflammatory activity [1]. Moreover, some studies have focused on the potential effects of fruit juices on diseases such as neurodegenerative diseases, cancer, urinary tract infections, diabetes, and metabolic syndrome [2].

Citrus L., a member of the Rutaceae family, is an important genus distributed in tropical and subtropical regions of Southeast Asia, Mediterranean countries of Europe and North Africa, America, South Africa, and Australia. The fruits of numerous species of this genus are cultivated in different regions of the world, and their annual production is growing significantly and rapidly due to increased consumer demand [3]. *Citrus* fruit juices are the most popular fruit juice with the largest trade volume worldwide, accounting for about two-thirds of the global juice market [4]. Among the *Citrus* species used as food or for processing, pomelo (*Citrus maxima* (Burm.) Merr.), sweet orange (*Citrus sinensis* (L.) Osbeck), mandarin (*Citrus reticulata* Blanco), lemon (*Citrus limon* (L.) Osbeck), lime (*Citrus aurantiifolia* (Christm.) Swingle), grapefruit (*Citrus paradisi* Macfad.), citron (*Citrus medica* L.), bergamot (*Citrus* × *bergamia* Risso & Poiteau), kumquat (*Citrus japonica* Thunb.), and their hybrids come to the fore [5]. It was stated that *Citrus* fruits contain flavonoids, carotenoids, limonoids, coumarin compounds, and essential oils. The flavonoids responsible for biological activity are particularly abundant in the peels [6-9]. Hesperidin, hesperetin, neohesperidoside, naringin, naringenin, naringenin, nobiletin, rutinoside, narirutin, and eriocitrin have been isolated from *Citrus* fruits in the structure of flavonoid [8,9]. The main furanocoumarin compounds in its composition are bergamottin, epoxybergamottin, and 6′,7′-dihydroxybergamottin [6]. Besides their high nutritional value, citrus fruits have been reported to possess pharmacological activities including antioxidant, anti-inflammatory, anticancer, anti-lipogenic, and neuroprotective effects [6,9]. The simultaneous use of herbal products with drugs increases the risk of herb-drug interaction. Several studies have noted that the use of *Citrus* fruit juices with drugs can cause herb-drug interactions. Grapefruit juice has been documented to interact with more than 85 different drugs, with about half of these interactions resulting in serious side effects. The simultaneous administration of simvastatin and grapefruit juice increased the mean peak serum concentration (C_{max}) and the area under the serum concentration-time curve of simvastatin by 12.0 and 13.5-fold, respectively [10,11]. According to clinical studies, orange juice causes a significant decrease in drug bioavailability and a potential reduction in the effects associated with it. In another study, the simultaneous use of Seville orange juice with felodipine significantly increased C_{max}. There is clinical evidence that lime juice improves the antimalarial efficacy of artemether and camoquine [11].

Cytochrome P450 (CYP) enzymes play an important role in the first-pass metabolism of drugs. The main function of CYP1A1 is to metabolically activate chemical carcinogens by oxidizing benzo[α]pyrene (BaP) and other polycyclic aromatic hydrocarbons (PAHs) to their toxic derivatives. It is also known that CYP1A1 is involved in the metabolism of riociguat, granisetron, axitinib, erlotinib, gefitinib, ningetinib, imiquimod, and conivaptan [12,13]. The main mechanism of action of *Citrus* juices in drug interactions is thought to be inactivation of CYP3A4 expressed in the intestines [10,11]. On the other hand, there is limited evidence on the interaction of *Citrus* juices with the CYP1A1 isozyme. In the previous study, *C. aurantiifolia, C. maxima*, *C. paradisi*, and *C. sinensis* fruit juices were shown to inhibit 7-ethoxyresorufin O-deethylase (EROD) activity, which predicted hepatic CYP1A1 interference [14,15]. To the best of our knowledge, there is no study in the literature predicting the effect of *Citrus australasica* F. Muell. (finger lime), *C. limon*, *Citrus reticulata* Blanco × *Citrus sinensis* (L.) Osbeck (Murcott mandarin), and *C. japonica* fruit juices on CYP1A1 activity. CYP1A1 is predominantly expressed in the liver but is also expressed in other tissues such as the heart, brain,

intestine, and gonads [16]. The goal of this study is to find out how Murcott mandarin, grapefruit, orange, kumquat, finger lime, and lemon juices affect the activity of the CYP1A1 enzyme in rat liver microsomes by using the EROD assay.

MATERIALS AND METHODS

Plant Material

Six *Citrus* fruits were obtained from local vegetable markets in the city of Trabzon, Türkiye in February and March 2024. The shell surfaces of *Citrus* fruits were washed clean by soaking in a sodium lauryl ether sulfate: water solution (1:800) for 10 minutes to remove dirt and residues. Then the fruits were rinsed with distilled water and peeled to expose the edible portion. The fleshy part was squeezed, and the total volume was measured. The fruit juice was frozen and lyophilized using a freeze-dryer, and then the dry powder was kept at 4°C. The dry powder of each fruit juice was accurately weighed and suspended in DMSO and distilled water.

Animals

Male Sprague-Dawley rats weighing 200–225 g were kept in single cages under controlled laboratory conditions. The animals had ad libitum access to standard rat chow and tap water. Food intake was discontinued in the 24 hours before sacrifiation. Following decapitation under anesthesia, the liver and brain tissues were carefully dissected. The liver and brain tissues of the rats were removed whole without any damage and cleaned with Krebs solution on ice. The tissues were stored in a freezer at -80°C.

Preparation of Liver Microsomal Fractions of Sprague-Dawley Rats

Microsomal fractions were prepared from the livers of a group of (n = 5) male Sprague-Dawley rats used as controls. Sprague-Dawley rats' liver tissues, which were crushed on ice, were added to a 1.15% potassium chloride solution at a rate of 3, 5 ml per 1 gram of tissue. After homogenization at 3000 rpm, the tissues were centrifuged at 11000 rpm for 25 minutes at 4°C. The supernatant fraction was centrifuged again at 4000 rpm at 4°C for 60 minutes. The pellet obtained at the end of the time contained the microsome. After the supernatant was removed from the pellet, the pellet part was transferred into the homogenization glass, and 20% glycerol was added as half of its weight, i.e., 0.5 ml per 1 gram of tissue. Subsequently, tissues were homogenized, and the resulting microsomal fractions were stored at -80°C for biological activity studies [17].

7-Ethoxyresorufin O-deethylase (EROD) Activity

The total bicinchoninic acid (BCA) protein determinations of microsomes before testing the EROD activity of fruit juices were performed based on the previously described method and using bovine serum albumin as a standard [17]. EROD is the enzyme that enables the conversion of 7-ethoxyresorfin to resorfin. The activity of this enzyme is based on a spectrofluorimetric measurement of the amount of resorufin formed. A mixture containing glucose-6-phosphate (2.5 mM), $NADP^+$ (2.5 mM), glucose-6-phosphate dehydrogenase (1 U/0.5 ml), $MgCl_2$ (2.5 mM), and potassium phosphate buffer (0.4 mM, pH 7.8) was used as a cofactor. Tris-HCl buffer (0.1 M, pH: 7.8) and methanol were added to the tubes to be used as blanks. Cofactor-free zero-time tubes consisted of Tris-HCl buffer, albumin substrate (0.5 mM, 7-ethoxyresorfin), fruit juice (5mg/ml) and microsomal protein. Tris-HCl buffer, albumin, substrate, juice, and microsomal protein were added to the tubes in which enzyme activity was to be determined and mixed with cofactor in a shaking water bath adjusted to 37°C. After incubation at 37 ˚C for 5 minutes, methanol was added to all tubes, and the reaction in the tube was arrested. The tubes were centrifuged at 5000 rpm for 20 minutes at 18°C to remove denatured proteins. The fluorescence intensity of the supernatant was measured at 538 nm excitation and 587 nm emission wavelengths, respectively Caffeine was chosen as the standard, while dimethyl sulfoxide (DMSO) and distilled water were used as controls [18]. In our study, there are a limited number of studies in the literature regarding the effects of the fruit juices of the plants we tested on CYP450 enzymes, particularly CYP1A1 enzyme activity. Therefore, when determining the working concentration of the fruit juices

included in our study, the study by Jarukamjorn and Chatuphonpraser (2020) was taken into consideration. In the researchers' study, the IC_{50} value for the EROD activity of the *C. sinensis* plant was referenced, and the working concentration of our fruit juices was determined to be 5 mg/ml [14].

RESULT AND DISCUSSION

The EROD activities on rat liver microsomes of fruit juices obtained from the plants *C. paradisi, C. reticulata × C. sinensis, C. sinensis, C. japonica, C. limon, and C. australasica* are presented in Table 1. The values presented in the table are shown as mean ± standard deviation (SD). DMSO was used as a control and caffeine was included in the study as a standard compound.

Table 1. EROD activity results of fruit juices

Fruit juice	**EROD activity X ± SD (pmol/mg/min)**	**% of control**
Citrus paradisi	0.63±.01	143
Citrus reticulata* × *Citrus sinensis	0.56 ±0.01	127
Citrus sinensis	0.23±0.02	50
Citrus japonica	0.22±0.02	50
Citrus limon	0.89±0.06	202
Citrus australasica	0.17±0.01	40
DMSO	0.44±0.07	100
Caffeine	0.19±0.01	44

The fruit juice from the *C. australasica* plant has a greater effect on the activity of the EROD enzyme than caffeine and the fruit juices from the other plants we tested. *C. sinensis*, *C. japonica*, and *C. australasica* juices inhibited EROD activity by 50%, 50%, and 60%, respectively. The percentage inhibition for the positive control caffeine was calculated as 56% (Figure 1). It was not observed that the fruit juices of *C. paradisi, C. reticulata × C. sinensis, and C. limon* plants inhibited EROD activity.

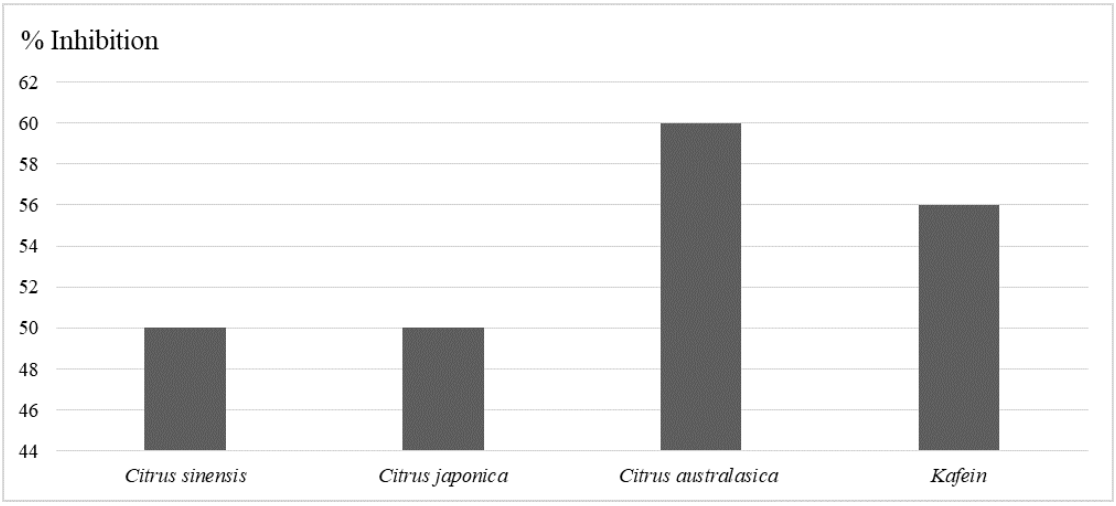

Figure 1. % Inhibition of EROD activity of fruit juices

There are a limited number of studies in the literature evaluating the activity of *Citrus* fruit juices and their components on CYP1A1. *C. aurantiifolia*, *C. maxima*, and *C. sinensis* inhibited EROD activity with calculated IC_{50} values of <0.01 mg/ml, 10.37±0.60 mg/ml, and 5.30±0.17 mg/ml, respectively [14]. It was revealed that administration of grapefruit juice (41.6 µl/g b.w., peroral) to BaP-treated mice inhibited EROD activity by 20% and 44% in liver and intestinal microsomes, respectively. Microsomes

prepared from untreated control mice were incubated with grapefruit juice at concentrations between 0.5 and 5% v/v. Grapefruit juice decreased EROD activity in microsomes by 85% in a concentration-dependent manner [15]. A previous study tested the effect of naringenin and 6′,7′-dihydroxybergamottin, the active components of grapefruit juice, on CYP1A1 in human and rat liver microsomes. Naringenin inhibited CYP1A1 in human and rat liver microsomes with a calculated IC_{50} value of 8.31±1.20 mM and 5.18±1.22 µM, respectively. It was reported that 6′,7′-dihydroxybergamottin inhibited CYP1A1 activity in human and rat liver microsomes with IC_{50} values of 1.43±0.11 mM and 11.14±0.19 µM, respectively. Naringenin and 6′,7′-dihydroxybergamottin are competitive inhibitors of CYP1A1 in human and rat livers. Computational docking studies have noted that the compounds can inhibit the oxidation of 7-ethoxyresorufin by binding to the CYP1A1 active site. Moreover, enzymes present in rat liver microsomes were shown to be approximately 1000 times more sensitive to inhibition than in human liver microsomes [12]. The interaction of bergamottin with CYP1A1 activity regulated by the aryl hydrocarbon receptor in rat hepatocytes was assayed both in the presence and absence of light. The treatment with bergamottin potently inhibited CYP1A1 activity in hepatocytes pretreated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the presence (IC_{50}: 10 nM) and absence (IC_{50}: 60 nM) of light [19]. In another study, male Wistar rats were administered a diet containing increasing doses of limonin or nomilin (1, 2, 5, and 10 mg/day) for ten days. Consequently, limonin and nomilin did not affect CYP1A1 activity in the liver and small intestinal microsomes [20]. CYP1A1 activities are generally measured as the rate of O-dealkylation of 7-ethoxyresorufin for EROD. CYP1A1 metabolizes a diverse range of substrates, including endogenous compounds such as arachidonic acid, eicosapentaenoic acid, 17*β*-estradiol, and melatonin, as well as exogenous substances like combustion and tobacco products, PAHs like BaP, heterocyclic aromatic amines in charred meat, industrial arylamines, the fluoroquinolone antibiotic difloxacin, and the drug theophyllin. CYP1A1 is primarily recognized as a crucial enzyme in the bioactivation of procarcinogens, producing reactive metabolites. These metabolites, generated through CYP1A1-mediated metabolism of environmental contaminants, can form DNA adducts, promoting mutagenesis and ultimately leading to tumor development. Notable CYP1A1 substrates include combustion and tobacco products, polycyclic aromatic hydrocarbons, heterocyclic aromatic amines present in charred meat, and industrial arylamines. CYP1A1-mediated epoxidation of BaP generates BaP-7,8-epoxide, which undergoes further oxidation to produce the carcinogenic compound BaP-7,8-dihydrodiol-9,10-epoxide. Given CYP1A1's involvement in carcinogenesis, inhibiting this P450 enzyme may serve as a promising strategy for cancer prevention [21]. *C. sinensis*, *C. japonica*, and *C. australasica* fruit juices were found to alter CYP1A1 activity in rat liver microsomes. This highlights the potential for fruit juice-drug interactions, which could result in clinically ineffective treatments or adverse and toxic effects. Therefore, patients taking medications with a narrow therapeutic index should avoid consuming especially these three fruit juices, *C. sinensis*, *C. japonica*, and *C. australasica*. Although previous studies have reported the inhibitory effects of certain *Citrus* juices-particularly grapefruit juice-on CYP1A1 activity, no such inhibition was observed in this study for *C. paradisi, C. reticulata* × *C. sinensis*, and *C. limon* at the tested concentration. This outcome may be attributed to several factors. Firstly, the concentration and composition of active secondary metabolites such as flavonoids and furanocoumarins can vary considerably depending on the fruit's geographical origin, cultivation conditions, harvest time, and storage methods. Secondly, the tested juices may lack sufficient levels of specific CYP1A1 inhibitors like naringenin or 6′,7′-dihydroxybergamottin. Thirdly, even if these compounds are present, they may exhibit low binding affinity to the active site of CYP1A1, resulting in weak or no inhibition. Additionally, other constituents in the juice matrix may act antagonistically or interfere with inhibitory mechanisms. Finally, the use of a single concentration (5 mg/ml) may not have been sufficient to observe inhibitory effects for some juices, and higher concentrations may reveal different outcomes. These possibilities highlight the need for further phytochemical analysis and dose-dependent studies to fully elucidate the interactions between *Citrus* juices and CYP1A1 activity. On the other hand, previous studies indicate that C. paradisi fruit juices inhibit EROD activity. This study revealed that *C. paradisi* juice did not affect EROD activity in liver microsomes. One of the limitations of this study is the use of a single test concentration (5 mg/ml) for all fruit juices. While this concentration was selected based on prior studies [14], it does not allow for the evaluation of dose-response relationships. It is possible that some juices that did not show inhibition

at this concentration, such as *C. paradisi*, *C. reticulata* × *C. sinensis*, and *C. limon*, might exhibit inhibitory effects at higher concentrations. Therefore, future studies using a range of concentrations are necessary to fully assess the inhibitory potential of these fruit juices on CYP1A1 activity. Previous studies have reported that flavonoid and furanocoumarin compounds such as naringenin and 6′,7′-dihydroxybergamottin play a role in the inhibition of EROD activity. The variety and quantity of secondary metabolites in plant composition change depending on geographical conditions, growing conditions, harvest timing, and processing methods. This may explain why our findings are not consistent with previous investigations. The lower concentrations of flavonoids and furanocoumarins in grapefruit juice may have affected the outcome. We recommend that further studies be designed by elucidating the phytochemical contents, considering the results of this study. The effects of different dosages on EROD activity can also be evaluated.

In conclusion, the simultaneous use of herbal products and drugs increases the risk of herb-drug interactions and associated adverse effects. There are limited studies evaluating the effects of *Citrus* fruit juices and their secondary metabolites on CYP1A1 activity. To the best of our knowledge, the results evaluating the effect of *C. paradisi*, *C. reticulata* × *C. sinensis*, *C. japonica*, *C. limon* fruit juices on EROD activity were presented for the first time in our study. The findings from this study predict the effect of *Citrus* fruit juices on CYP1A1. These results need to be supported by further studies.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

Before beginning the study, approval from the ethical committee was secured, as per a decision of the Ankara University Health Sciences Ethical Committee dated March 14, 2018, and numbered 2018-6-45.

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