Toxicology in Vitro 84 (2022) 105447

Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

Phloretin exhibits potential food-drug interactions by inhibiting human UDP-glucuronosyltransferases in vitro

Jinqian Chen [a,1], Hao Zhang [b,1], Xia Hu [c,1], Mengyuan Xu [b,1], Yanjun Su [d], Chunze Zhang [e], Yuan Yue [b], Xiaomin Zhang [b], Xinyu Wang [b], Wei Cui [f], Zhenyu Zhao [a,*], Xichuan Li [b,**]

[a] Departments of Pharmacy, NHC Key Laboratory of Hormones and Development, Tianjin Key Laboratory of Metabolic Diseases, Tianjin Medical University Chu Hsien-I Memorial Hospital, Tianjin 300134, PR China
[b] Tianjin Key Laboratory of Animal and Plant Resistance, College of Life Sciences, Tianjin Normal University, Tianjin 300387, PR China
[c] Department of Agriculture Insect, Institute of Plant Protection, Tianjin Academy of Agricultural Sciences, Tianjin 300384, PR China
[d] Department of Lung Cancer, Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin 300060, PR China
[e] Department of Colorectal Surgery, Tianjin Union Medical Center, Tianjin 300121, PR China
[f] School of Mathematical Sciences and LPMC, Nankai University, Tianjin 300070, PR China

ARTICLE INFO

Keywords:
Phloretin
Apple polyphenols
Food-drug interactions
UGTs
Enzymes inhibition
IVIVE

ABSTRACT

Phloretin is a well-known apple polyphenol possessing a wide variety of biological effects and has been widely used in many fields. However, it's unclear whether phloretin has an effect on the activity of human UGT enzymes. Our study indicated that phloretin inhibited human UGTs on a broad spectrum. Further kinetic analysis revealed that phloretin inhibited UGT1A1, 1A6, 1A9, 2B7, and 2B15 in a noncompetitive manner, with calculated K_i of 8.34 μM, 16.69 μM, 10.58 μM, 17.74 μM and 2.46μM, respectively, whereas phloretin inhibited UGT1A7 in an un-competitive manner, with calculated K_i of 5.70 μM. According to the quantitative risk prediction, co-administration of phloretin with drugs primarily metabolized by UGT1A7 and/or UGT2B15 may result in potential food-drug interactions. To sum up, when phloretin or phloretin-rich food is administered with medications metabolized by UGT1A7 and/or UGT2B15, concern should be exercised.

1. Introduction

Apples are popular worldwide due to their delicious flavors and health benefits (Bahar Aydin, 2015; Boyer and Liu, 2004), as well as their seasonal availability and widely geographic spread (Wang et al., 2018). Throughout the last few decades, numerous studies have confirmed the proverb "an apple a day keeps the doctor away from you", and scientific evidence attribute the health benefits to the high phenolic content (Boyer and Liu, 2004; Gimbrone Jr. and Garcia-Cardena, 2016; Rana and Bhushan, 2016) and fiber (Boyer and Liu, 2004; Veronese et al., 2018). Phenols are secondary metabolites of plants that have been shown to have a wide range of bioactive functions, including anti-metabolic syndrome (obesity, hyperlipidemia, hypertension and diabetes), and associated complications (Amiot et al., 2016), anti-cancer (Lall et al., 2015), cardiovascular disease prevention (Speer et al., 2019). Polyphenols are abound in fruits and beverages (Williamson, 2017). Apples contain high amounts of polyphenols in the forms of flavonoids (mainly quercetin, quercitin, proanthocyanidins, catechins, epicatechins), phenolic acids (mainly chlorogenic acid, caffeic acid, p-coumaric acid) and dihydrochalcones (phlorizin, phloretin) (Mizunoya et al., 2015; Vrhovsek et al., 2004; Yoshida et al., 2018). Apples are the largest dietary source of phenols, and apple polyphenols (APs) account for 22% of the phenolics in the human diet in the United States. (Vinson et al., 2001).

Strong evidence supports that chronic diseases are effectively prevented by changing dietary food (Köksal and Gulcin, 2008; Elmastas et al., 2006; Gulcin et al., 2011; Schulze et al., 2018), which is well accepted both in academic and non-academic worlds. Food and drugs, which are both important parts of a patient's treatment plan, may interact. Food-drug interactions (FDIs) are changes in the

* Correspondence to: Z. Zhao, Tianjin Medical University Chu Hsien-I Memorial Hospital, NO.6, Huanrui Bei Road, Beichen District, Tianjin 300134, PR China.
** Correspondence to: X. Li, Tianjin Normal University, NO.393, Binshuixi Road, Xiqing District, Tianjin 300387, China.
E-mail addresses: zhaozhenyu0858@163.com (Z. Zhao), xichuanli@tjnu.edu.cn (X. Li).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.tiv.2022.105447
Received 20 May 2022; Received in revised form 11 July 2022; Accepted 14 July 2022
Available online 19 July 2022

Table 1
Incubation conditions of 4-MU by recombinant UGTs.

UGTs	Protein(mg/mL)	Incubation(min)	4-MU (μM)
UGT1A1	0.125	120	110
UGT1A3	0.05	120	1200
UGT1A6	0.025	30	110
UGT1A7	0.05	30	30
UGT1A8	0.025	30	750
UGT1A9	0.05	30	30
UGT1A10	0.05	120	30
UGT2B4	0.25	120	1000
UGT2B7	0.05	120	350
UGT2B15	0.2	120	250
UGT2B17	0.5	120	2000

pharmacokinetics or pharmacodynamics of medicines caused by food or nutritional supplements. (Genser, 2008). FDIs, a potential threat to safe oral pharmacotherapy, result in therapeuticfailure or even toxic effects (Amadi and Mgbahurike, 2018). It poses a risk to elderly patients with oral medications. The prevalence reaches 58.5% as >30% of all the prescribed medications are taken by this population (Spinewine et al., 2007). The pharmacokinetic quality of drugs and phytochemicals is altered during absorption, distribution, metabolism and elimination (ADME), which is mainly related to the inhibition and/or induction of metabolic enzymes(Rushmore and Kong, 2002; Sorensen, 2002). The most significant phase II metabolic enzymes are the UGTs. UGTs catalyze glucuronidation, a crucial process for the clearance and detoxification of exogenous compounds including medicines. (Rowland et al., 2013), and UGTs are responsible for the elimination of 40–70% of human therapeutic medicines(Zhang et al., 2015).

Apple polyphenols are a catch-all term for a variety of naturally active phenols found in apples. Phloretin, one of the bioactive polyphenols in apples, is a substrate of CYP3A4 and CYP2C19 and is metabolized to 3-OH phloretin (Nguyen et al., 2020). It also inhibits the catalytic activity of human CYP1A1(Pohl et al., 2006), CYP1A2 and CYP3A4 (Gao et al., 2012). Quercetin and its metabolites showed weak to moderate inhibitory effects on CYP2C19 and 3A4 (Elbarbry et al., 2018; Mohos et al., 2020), and a strong inhibitory effect against CYP2D6 (Elbarbry et al., 2018). Quercetin was revealed to be a potent inhibitor of UGT1A9 and a moderate inhibitor of UGT1A1 and UGT1A3(Zhang et al., 2021). Previous research has verified that apple polyphenols have a variety of biological activities, which make them an excellent nutrition or even promising drug candidate. Nevertheless, whether the other main apple polyphenols have effects on the UGTs and lead to unexpected food-drug interactions remains unknown.

The objective of this study was to see if the primary apple polyphenols, such as procyanidin B2, catechins, epicatechins, chlorogenic acid, caffeic acid, p-coumaric acid, phloretin, and phlorizin, had any inhibitory effects on UGT activities. The risk of food-drug interactions in humans was also evaluated using in vitro inhibitory kinetics.

2. Materials and methods

2.1. Chemicals and reagents

Eight APs were obtained from Solarbio Co., with purity above 99%. Recombinant human UGT isoform expressed in baculovirus-infected cells, purchased from BD Gentest (Woburn, MA, USA). UDPGA (trisodium salt), 4-methylumbelliferone (4-MU), 4-MUG, 7-hydroxycoumarin were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other reagents are HPLC grade or the highest grade available on the market.

2.2. Preliminary inhibition screening of APs towards UGTs

The inhibition of UGT isoforms other than UGT1A4 by APs was observed using 4-MU as a non-selective probe substrate for recombinant UGTs (See Table 1.). UGT1A4 was not included in this study because it showed no catalytic activity towards 4-MU. The total volume of 200 μL incubations contained Aps (100 μM), UDPGA (5 mM), $MgCl_2$ (10 mM), Tris-HCl buffer (50 mM, pH = 7.4), recombinant UGTs and 4-MU. The concentration of 4-MU, the incubation time and the concentration of UGTs were adopted with slight modifications based on our previous study (Li et al., 2022). After preincubation at 37 °C for 5 min, UDPGA was added to the mixture to initiate the reaction. The incubation was ended by adding 200 L of ice-cold acetonitrile containing 100 μM 7-hydroxycoumarin as the internal standard. The APs were dissolved in DMSO, and the incubation mixture without the APs served as a negative control. After the incubation was completed, the incubated mixture was centrifuged at 12,000*g* for 10 min at 4 °C. HPLC (Waters) was used to measure the products in the supernatant. Chromatographic separation was carried out in accordance with our previous literature (Li et al., 2022). All of the experiments were performed in duplicates.

2.3. Determination of IC_{50} and inhibition kinetics

Further studies were conducted to assess the inhibition kinetics and types under the situation that the preliminary screening inhibition was increased by 80%. The IC_{50} values were established by administering different concentrations of APs ranging from 0 μM to 100 μM. Non-linear regression of various concentrations of 4-MU (1/5 K_m to 5 K_m) in the presence of varied concentrations of AP was used to determine the inhibition kinetics (K_i) and inhibition types(Bayrak et al., 2019; Gulcin et al., 2016; Kucuk and Gulcin, 2016). The first plot was made using the

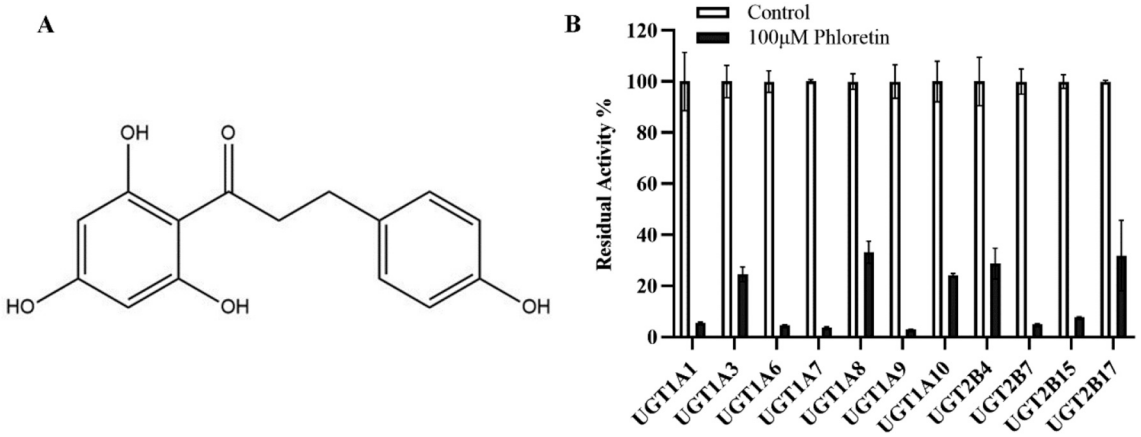

Fig. 1. Phloretin's chemical structure(A); inhibition of recombinant UGTs activity in the presence and absence of phloretin (100 μM), respectively(B). All data were displayed as mean ± S.D. All experiments were repeated in duplicates.

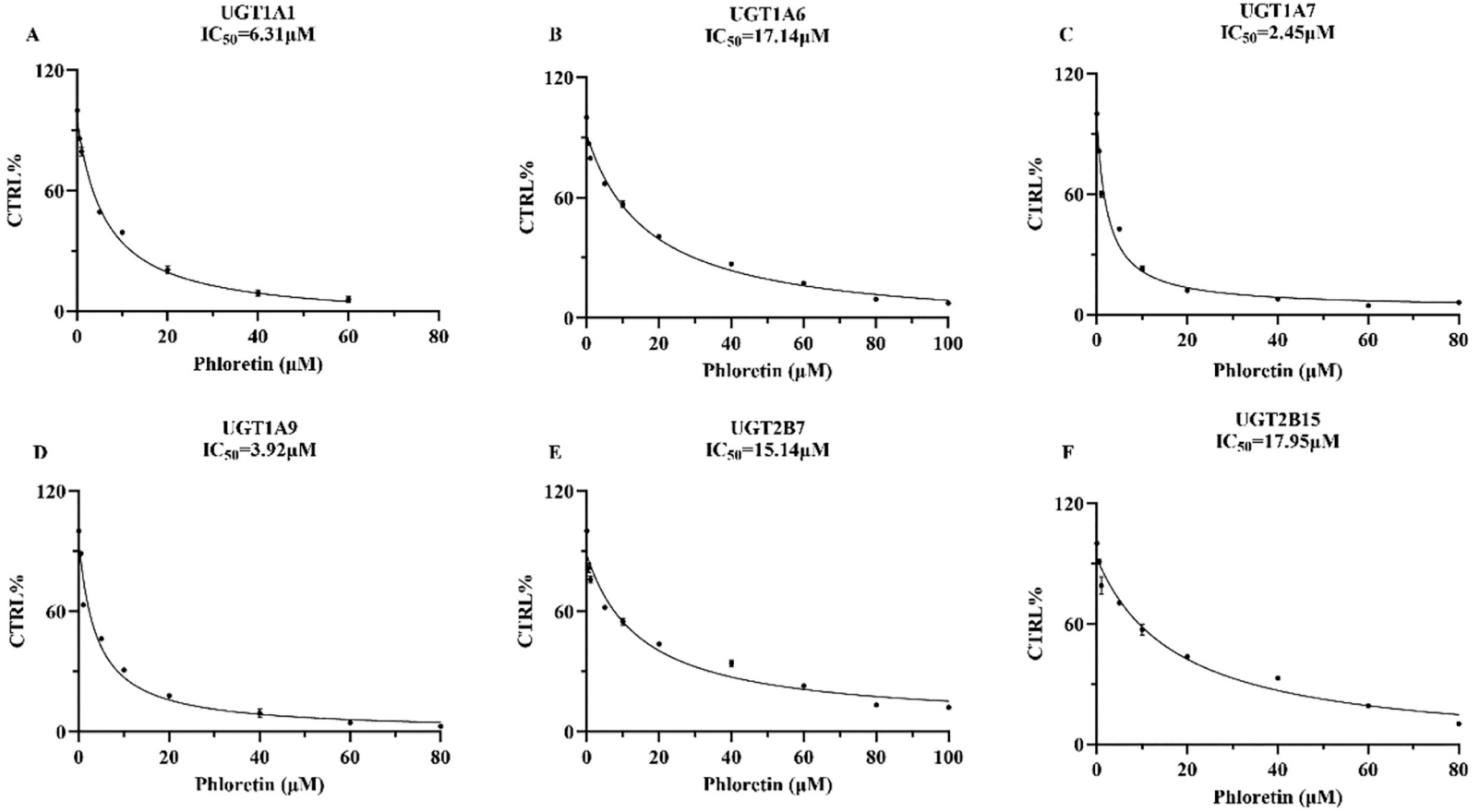

Fig. 2. Dose-dependent inhibition curves of the activity of recombinant UGTs by phloretin. UGT1A1(A); UGT1A6(B); UGT1A7(C); UGT1A9(D); UGT2B7(E); UGT2B15(F). All data were displayed as mean ± S.D.

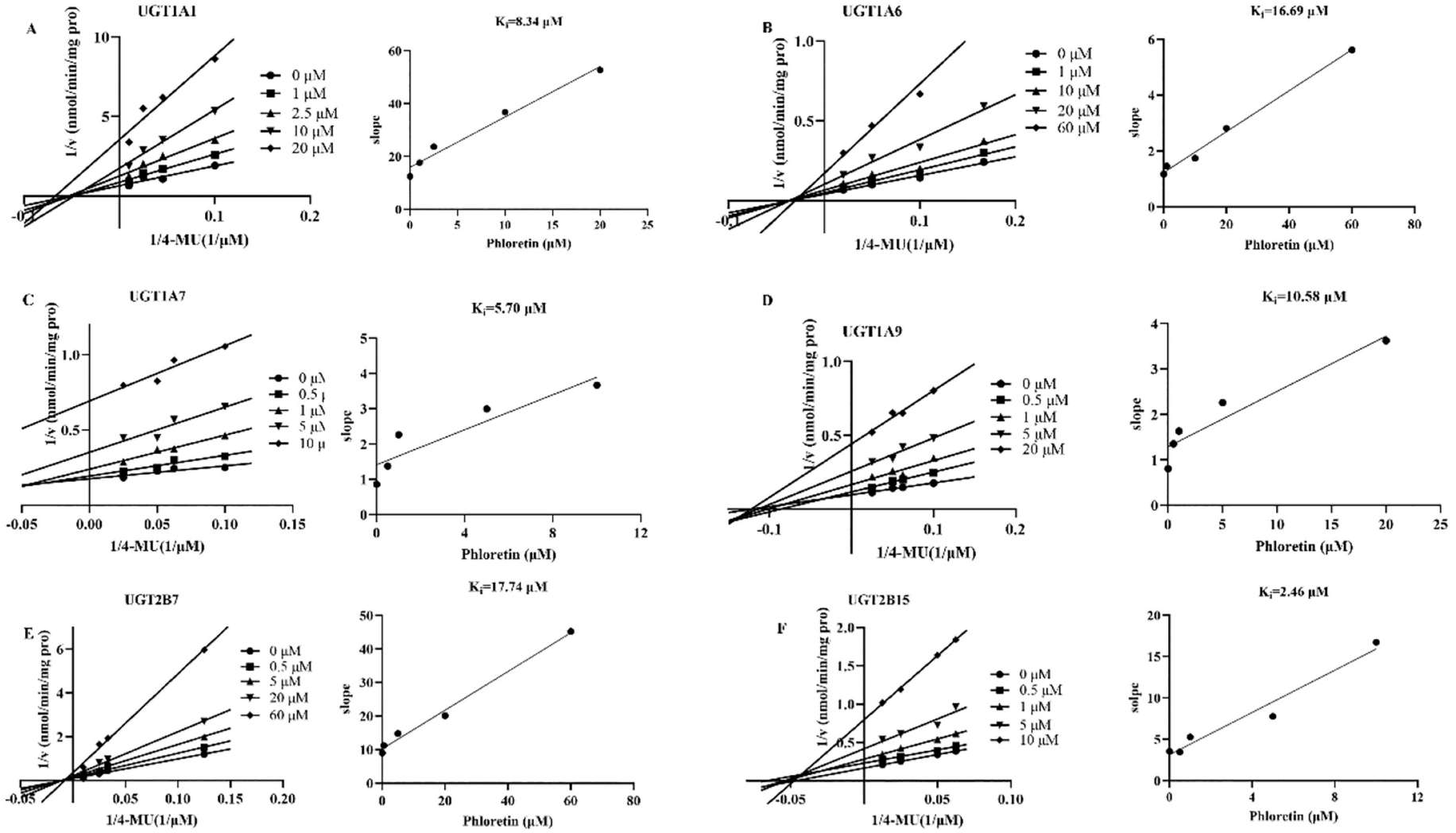

Fig. 3. Lineweaver-Burk and Dixon plots of phloretin's effect on 4-MU glucuronide formation against UGT1A1(A); UGT1A6(B); UGT1A7(C); UGT1A9(D); UGT2B7(E); and UGT2B15(F). All data were displayed as mean values of duplicates.

slopes of the lines in the Lineweaver–Burk plot versus AP to determine the type of inhibition kinetics, while the second plot is drawn using the slope of the line in the Lineweaver-Burk plot versus AP to calculate the inhibition constant K_i.

2.4. In vivo inhibition of APs-catalyzed metabolism of UGTs by in vitro-in vivo extrapolation (IVIVE)

Ratio of the area under the plasma concentration time curve in the presence and absence of inhibitors (AUC_i/AUC) was used to calculate the magnitudes of AP inhibition. The following equations were used to calculate the ratio (Miners et al., 2010):

$$\frac{AUC_i}{AUC} = \frac{1}{\frac{f_m}{1+\frac{[I]}{K_i}} + (1 - f_m)} \quad (1)$$

$$\frac{AUC_i}{AUC} = 1 + \frac{[I]}{K_{i.}} \quad (2)$$

The f_m is the proportion of substrate that is metabolized by the enzyme, and [I] is the in vivo AP exposure concentration. Eq. 1 is simplified to Eq. 2 if a substrate is metabolized by a single enzyme (f_m = 1). The possibility of the potential interaction is predicted by [I]/K_i, whose value is categorized into the following ranges: [I]/K_i < 0.1, low possibility; 0.1 < [I]/K_i < 1, medium possibility; [I]/K_i > 1, high possibility.

2.5. Autodocking to explain the inhibition of APs towards UGTs

The molecular interaction between APs and UGTs was shown using Autodocking. The structure of UGTs was created using the open-source MODELLER9v14 tool and homology modeling. Docking APs into the active cavity of UGTs was done using Autodock software (version 4.2). Nonpolar hydrogen atoms were merged and polar hydrogen atoms were introduced to the UGTs. The grid box was created using the coordinates 60*60*60 in X, Y, and Z, with a gridpoint spacing of 0.375 Å. The protein-fixed ligand-flexible docking computations were done using the Genetic Algorithm technique. To study the interactions between APs and UGTs, 50 docking runs were calculated for each AP, and the best conformation with the lowest docked energy was chosen (Liu et al., 2019).

2.6. Statistical analysis

The mean value plus standard deviation (S.D.) was used to present the experimental results. GraphPad Prism 8.0 was used for statistical analysis. A two-tailed unpaired Student's *t*-test was used to make comparisons between two groups. The one-way ANOVA was used to compare multiple groups.

3. Results

3.1. Primary inhibition assessment of APs towards UGTs

In vitro, the catalytic activities of UGT1A1, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, and 2B17 were measured using 100 μM AP or a vehicle control. A majority of the APs showed <80% of inhibition on the tested UGTs except phloretin. The results were showed in the supplementary materials. As illustrated in Fig. 1, phloretin showed broad inhibition on the activity of UGT1A1, 1A6, 1A7, 1A9, 2B7, 2B15. The activity of UGT1A1, 1A6, 1A7, 1A9, 2B7, 2B15 was inhibited by 95.08%, 95.34%, 96.30%, 96.92%, 95.12%, 92.11%, at 100 μM of phloretin, respectively. The primary assessment of the other seven APs towards UGTs was shown in Fig. S1 in the supplementary materials.

3.2. The inhibition kinetics analysis of phloretin against UGTs

The IC_{50} of phloretin was determined to characterize its inhibitory effects against UGT1A1, 1A6, 1A7, 1A9, 2B7, and 2B15. Phloretin inhibits all of the tested UGTs in a concentration-dependent manner, as illustrated in Fig. 2. The IC_{50} values for UGT1A1, 1A6, 1A7, 1A9, 2B7, and 2B15 were calculated to be 6.31 μM, 17.14 μM, 2.45 μM, 3.92 μM, 15.14 μM, and 17.95 μM, respectively. The findings suggested that phloretin is a potent inhibitor of UGT1A1, 1A7, and 1A9 (IC_{50} < 10 μM), but only a moderate inhibitor of UGT1A6, 2B7, and 2B15 (IC_{50} range 15.14 μM to 17.95 μM). Furthermore, the inhibition type and parameters were determined using the Lineweaver-Burk plots and the best fitting of the data to the equation in the nonlinear regression analysis in the dynamics module of Graphpad Prism 8.0. Phloretin inhibited UGT1A1, 1A6, 1A9, 2B7, 2B15 in a noncompetitive manner, as illustrated in Fig. 3, with K_i of 6.61 μM, 16.63 μM, 10.57 μM, 17.73 μM, and 2.46 μM, respectively. Phloretin inhibited UGT1A7 in a mixed manner, with a K_i value of 5.70 μM. All the results were summarized in Table 2.

3.3. In vivo inhibition of APs-catalyzed metabolism of UGTs by in vitro-in vivo extrapolation (IVIVE)

When [I]/K_i > 0.1, the compounds may inhibit UGTs-catalyzed metabolism in vivo, according to the simplified evaluation criteria. The C_{max} of phloretin in serum was 0.72 μM after one liter of cloudy apple juice of 2 h in healthy volunteers was consumed (Kahle et al., 2011). As showed in Table 3, the rates of [I]/K_i for UGT1A1, 1A6, 1A7, 1A9, 2B7, 2B15 were 0.09, 0.04, 0.13, 0.07, 0.04 and 0.29, respectively. Phloretin posed medium risk of inhibition towards UGT1A7 and UGT2B15. In the case of UGT1A7 and UGT2B15 with moderate risk FDIs, the effects of metabolic fraction f_m and in vivo phloretin concentration on the AUC of drugs metabolized by UGT1A7 and/or UGT2B15 were further explored. As illustrated in Fig. 4, assumed that 80% of a co-administration drug is catalyzed by UGT1A7, when the plasma concentration of phloretin is >4.07 μM, the AUC of the drug can be increased by >50%. Similarly, if a drug is 100% metabolized byUGT2B15, the AUC of the co-administration drug can be more than doubled when the plasma concentration of phloretin is >2.46 μM.

3.4. Autodocking of phloretin against UGTs

The interactions between phloretin, phlorizin, and inhibitory UGTs were studied using Autodocking. The Autodocking results of phloretin

Table 2
IC_{50}, K_i and inhibition type of phloretin towards UGTs.

UGTs	IC_{50} (μM)	K_i (μM)	Inhibition Type
UGT1A1	6.31	8.34	non-competitive
UGT1A6	17.14	16.69	non-competitive
UGT1A7	2.45	5.70	un-competitive
UGT1A9	3.92	10.58	non-competitive
UGT2B7	15.14	17.74	non-competitive
UGT2B15	17.95	2.46	non-competitive

Table 3
Quantitative prediction of the risk of inhibition of UGTs by phloretin in vivo.

UGTs	K_i	[I]/K_i	Possibility of in vivo inhibition on UGTs by phloretin
UGT 1A1	6.31	0.09	low
UGT 1A6	16.63	0.04	low
UGT 1A7	5.70	0.13	medium
UGT 1A9	10.57	0.07	low
UGT 2B7	17.73	0.04	low
UGT 2B15	2.46	0.29	medium

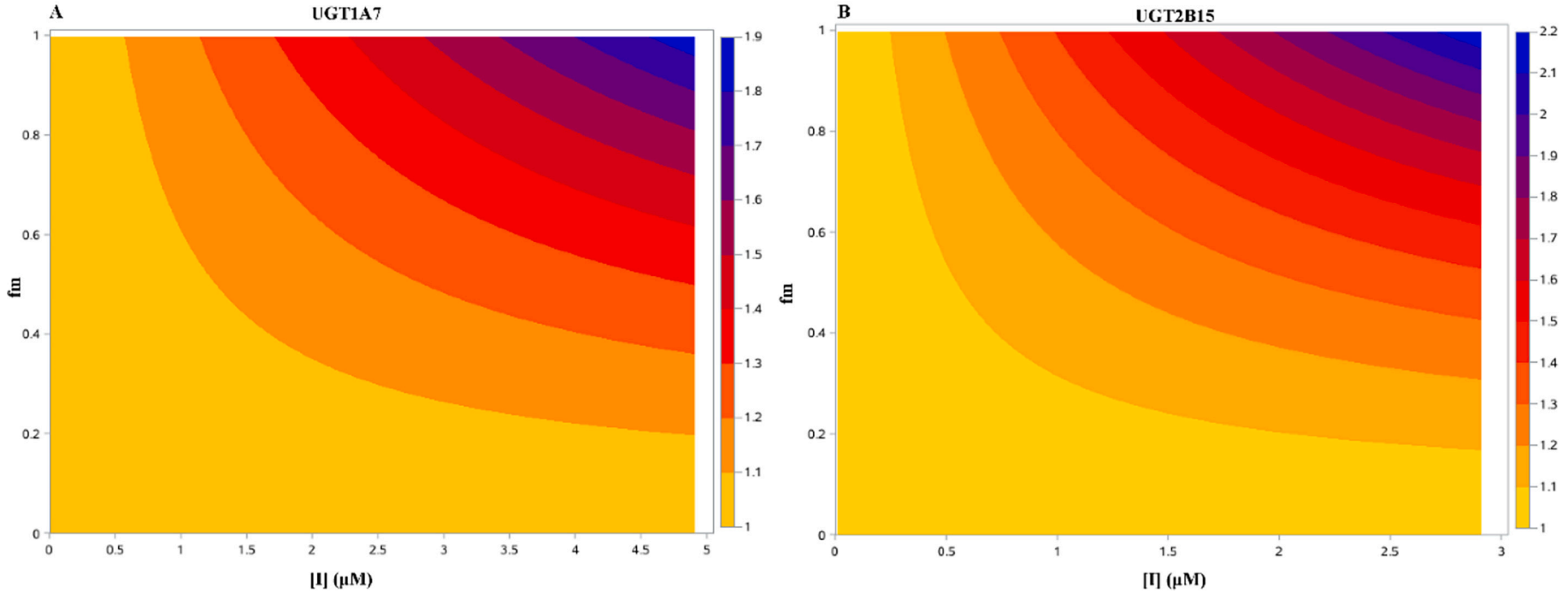

Fig. 4. Isolines plot for relationship of AUC ratio against plasma concentration of phloretin and f_m by UGT1A7 (A) and UGT2B15 (B).

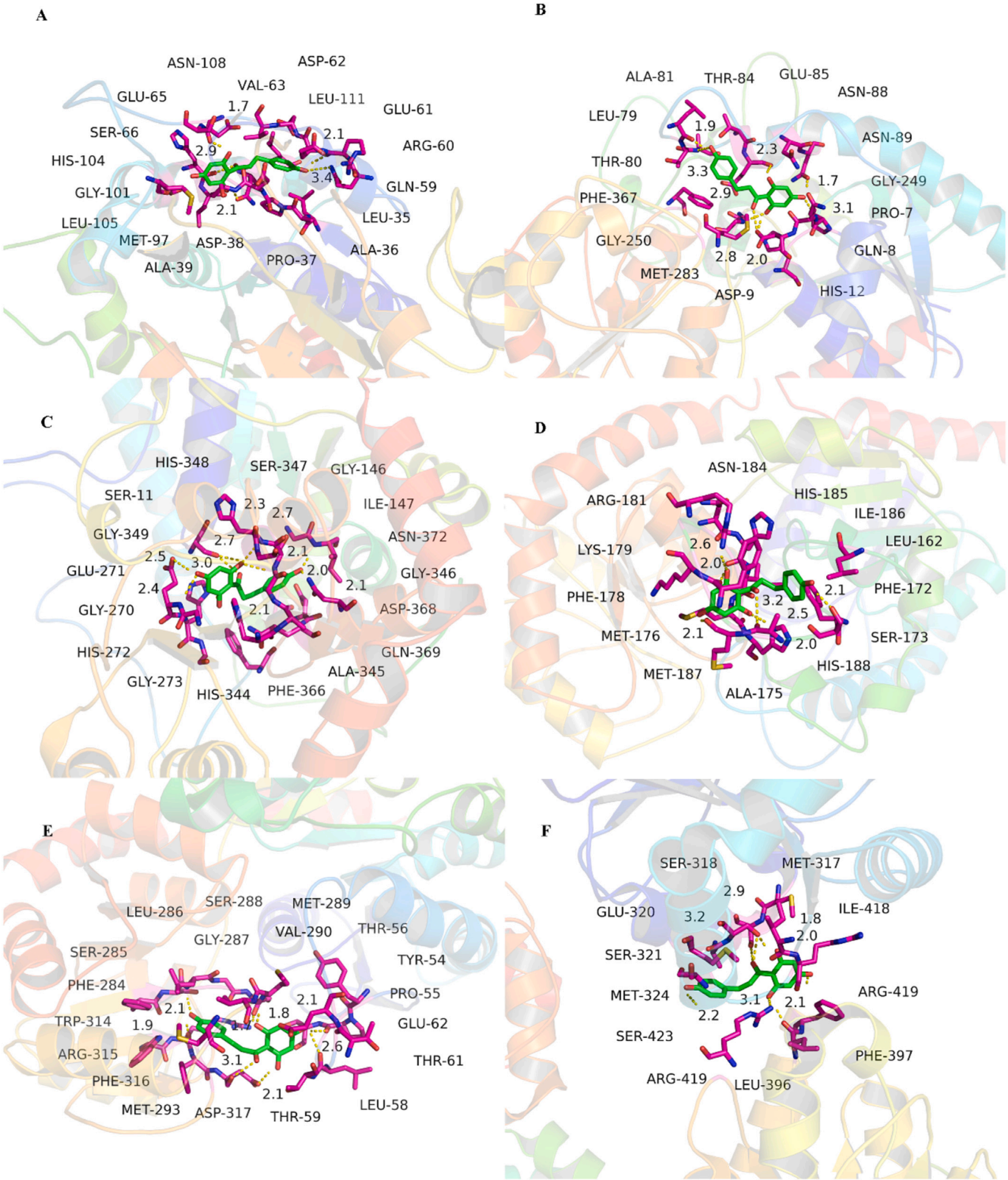

Fig. 5. Autodocking results of ligand with 4A amino acid residues and hydrogen bonds. Phloretin with UGT1A1(A); UGT1A6(B); UGT1A7(C); UGT1A9(D); UGT2B7 (E); UGT2B15(F).

were shown in Fig. 5, and the results of phlorizin were shown in Fig. S2. The binding free energies of phloretin towards UGT1A1, UGT1A6, UGT1A7, UGT1A9, UGT2B7 and UGT2B15 were −8.35, −7.37, −6.74, −7.36, −8.59 and −6.62 kcal/mol, respectively. While, the binding free energies of phlorizin towards UGT1A1, UGT1A6, UGT1A7, UGT1A9, UGT2B7 and UGT2B15 were −3.84, −3.03, −5.64, −3.79, 1.75 and −2.56 kcal/mol, respectively. The lower the score, the stronger the affinity of the ligand compound for UGTs. Apparently, the docking scores

of phloretin is lower than phlorizin with corresponding UGTs. The docking score orders of phloretin and phlorizin were basically consistent with the previous inhibition extent towards UGTs. The findings suggested that the ability of phloretin to inhibit UGTs was dependent on its structure-related binding affinities with UGTs. That is, the higher binding affinity of phloretin for UGTs resulted in more severe UGT inhibition.

4. Discussion

Polyphenols are consumed as part of our daily diet and have a variety of health-promoting properties(Durmaz et al., 2022; Gulcin, 2012, 2020). Phloretin is a well-known bioactive polyphenol found in apples. It was identified by French chemists in the root bark of *Malus domestica* and shown to be a competitive inhibitor of sodium-dependent glucose transporters (SGLTs). Phloretin has a wide spectrum of biological activities, including antioxidant, anti-inflammatory, anti-microbial, anti-allergic, and anti-tumor properties, as well as the ability to reduce vascular endothelial dysfunction and liver damage, according to subsequent research(Mariadoss et al., 2019). Phloretin and its glycoside phlorizin have been widely used in fields of foods, beverages, food additives, pharmaceuticals and cosmetics(Anunciato Casarini et al., 2020; Kim et al., 2014). As the principal flavonoids, phloretin and phlorizin are enriched in apples and apple-derived products such as apple cider, which are frequently consumed by humans. Phlorizin was first hydrolyzed to phloretin by an enzyme-catalyzed hydrolysis reaction after oral administration, then uptaken by epithelial cells in the intestine and converted into a glycose conjugate in the systemic circulation(De Oliveira, 2016; Marks et al., 2009; Wang et al., 2019). Despite the fact that daily apple consumption does not raise polyphenol levels in plasma or urine, (Stracke et al., 2010), alcohol can promote absorption of phloretin (Marks et al., 2009).The circumstances above may increase plasma concentration of phloretin.

Phloretin potently inhibited UGT1A1, 1A6, 1A7, 1A9, 2B7, 2B15, with IC_{50} values ranging from 2.45 μM to 17.95 μM in preliminary inhibition assays. Further kinetic analysis revealed that phloretin inhibited UGT1A1, 1A6, 1A9, 2B7, and 2B15 in a non-competitive manner, with K_i values ranging from 2.46 μM to 17.73 μM, while phloretin inhibited UGT1A7 in an un-competitive manner. The quantitative prediction of phloretin's in vivo inhibition of UGTs revealed that inhibition of UGT1A7 and UGT2B15 happened with medium possibilities. Autodocking outcomes were consistent with inhibition assessments. Phloretin and phlorizin showed various inhibition capacities due to the different structure caused different hydrophobic interactions and hydrogen bonds. Compare to phlorizin, phloretin is free of glycosyl and more conducive to dock into the hydrophobic cavity of UGTs.

UGT1A7 is absent from the liver and only expressed in the gastrointestinal tract, which catalyzes the metabolism of a large number of exogenous substances(Vrhovsek et al., 2004). UGT1A7 has detoxification effect on dietary derived carcinogens such as heterocyclic aromatic hydrocarbons and heterocyclic amines, and shows glucuronidation activity on various carcinogens. The inhibitory activity of UGT1A7 is closely related to the susceptibility to cancer (Yilmaz et al., 2015; Zhang et al., 2017). UGT2B15 was initially identified as an androgen metabolic enzyme. Subsequent studies showed that the enzyme metabolized drugs, including oxazepam, hydroxytamoxifen, lorazepam(Miners et al., 2006; Rowland et al., 2013). Therefore, the potent inhibition of phloretin towards UGT1A7 and UGT2B15 catalytic activities may lead food-drug interactions and result in an increased frequency of drug-adverse effects.

FDIs have emerged as a major threat to the safety of oral drug treatment, potentially leading to treatment failure and even toxic effects (Amadi and Mgbahurike, 2018). The risk of this interaction is higher in elderly patients using oral drugs, with a prevalence of 58.5%(Spinewine et al., 2007). Almost a quarter of all adults in the United States were found to be taking a prescription medication and a dietary supplement at the same time(Asher et al., 2017), and the situation may be more common in Asian countries. Phloretin possesses numerous biological activities, which enables it to be an excellent of nutrition supplement or even a candidate of new drug. Based on the inhibition of transporters, apple juice (1.2 l) reduced the average AUC of atenolol by 86%(Chen et al., 2018). Other literature reported that apple juice greatly reduce the plasma concentrations and renin-inhibiting effect of Aliskiren, probably by inhibiting its OATP2B1-mediated influx in the small intestine(Tapaninen et al., 2011). Phloretin inhibited OATP2B1-mediated uptake of estrone-3-sulfate with IC_{50} values of 1.31 ± 0.16 μM(Shirasaka et al., 2013). Taking above reasons and our experimental data in vitro into consideration, it is necessary to pay more attention to potential interactions between phloretin and drugs.

In conclusion, the findings show that phloretin is a potent broad-spectrum inhibitor of UGT isoforms. Food-drug interactions are likely to occur with medium risk following oral co-administration of large amounts of apples or apple-derived products with drugs that primarily undergo UGT1A7- and/or UGT1A9-catalyzed metabolism. As a result, due to the potential risk, caution should be exercised, and unexpected toxic and side effects caused by UGT inhibition should be avoided. The experimental data was, of course, based on an in vitro study. It remains to be seen whether phloretin and drugs interact in vivo, resulting in clinically relevant food-drug interactions.

Declaration of Competing Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grant No. 81872236 to Xichuan Li), the Natural Science Foundation of Tianjin (grant No. 18JCYBJC28100 to Xichuan Li, and No. 19JCYBJC29600 to Xia Hu), the Special Fund of Diseases Control and Prevention in Tianjin Science and Technology Major Projects (grant No. 18ZXDBSY00040 to Yanjun Su), the Key R&D Projects in Tianjin Science and Technology Pillar Program (grant No. 19YFZCSY00420 to Chunze Zhang, and grant No. 20KPHDRC00020 to Zhenyu Zhao), and the Innovative S&T Projects for Young Researchers of Tianjin Academy of Agricultural Science (grant No.201918 to Xia Hu).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tiv.2022.105447.

References

Amadi, C.N., Mgbahurike, A.A., 2018. Selected food/herb-drug interactions: mechanisms and clinical relevance. Am. J. Ther. 25, e423–e433.
Amiot, M.J., Riva, C., Vinet, A., 2016. Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review. Obes. Rev. 17, 573–586.
Anunciato Casarini, T.P., Frank, L.A., Pohlmann, A.R., Guterres, S.S., 2020. Dermatological applications of the flavonoid phloretin. Eur. J. Pharmacol. 889, 173593.
Asher, G.N., Corbett, A.H., Hawke, R.L., 2017. Common herbal dietary supplement-drug interactions. Am. Fam. Physician 96, 101–107.
Bahar Aydin, I.G.S.H.A., 2015. Purification and characterization of polyphenol oxidase from Hemşin apple (Malus communis L.). Int. J. Food Prop. 18, 2735–2745.
Bayrak, C., Taslimi, P., Karaman, H.S., Gulcin, I., Menzek, A., 2019. The first synthesis, carbonic anhydrase inhibition and anticholinergic activities of some bromophenol derivatives with S including natural products. Bioorg. Chem. 85, 128–139.
Boyer, J., Liu, R.H., 2004. Apple phytochemicals and their health benefits. Nutr. J. 3, 5.
Chen, M., Zhou, S.Y., Fabriaga, E., Zhang, P.H., Zhou, Q., 2018. Food-drug interactions precipitated by fruit juices other than grapefruit juice: an update review. J. Food Drug Anal. 26, S61–S71.
De Oliveira, M.R., 2016. Phloretin-induced cytoprotective effects on mammalian cells: a mechanistic view and future directions. Biofactors 42, 13–40.
Durmaz, L., Erturk, A., Akyuz, M., Polat Kose, L., Uc, E.M., Bingol, Z., Saglamtas, R., Alwasel, S., Gulcin, I., 2022. Screening of carbonic anhydrase, acetylcholinesterase,

butyrylcholinesterase, and alpha-glycosidase enzyme inhibition effects and antioxidant activity of coumestrol. Molecules 27.
Elbarbry, F., Ung, A., Abdelkawy, K., 2018. Studying the inhibitory effect of quercetin and thymoquinone on human cytochrome P450 enzyme activities. Pharmacogn. Mag. 13, S895–S899.
Elmastas, M., Turkekul, I., Ozturk, L., Gulcin, I., Isildak, O., Aboul-Enein, H.Y., 2006. Antioxidant activity of two wild edible mushrooms (Morchella vulgaris and Morchella esculanta) from North Turkey. Comb. Chem. High Throughput Screen. 9, 443–448.
Gao, S.S., Chen, X.Y., Zhu, R.Z., Choi, B.M., Kim, S.J., Kim, B.R., 2012. Dual effects of phloretin on aflatoxin B1 metabolism: activation and detoxification of aflatoxin B1. Biofactors 38, 34–43.
Genser, D., 2008. Food and drug interaction: consequences for the nutrition/health status. Ann. Nutr. Metab. 52 (Suppl. 1), 29–32.
Gimbrone Jr., M.A., Garcia-Cardena, G., 2016. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ. Res. 118, 620–636.
Gulcin, I., 2012. Antioxidant activity of food constituents: an overview. Arch. Toxicol. 86, 345–391.
Gulcin, I., 2020. Antioxidants and antioxidant methods: an updated overview. Arch. Toxicol. 94, 651–715.
Gulcin, I., Fevzi Topal, S., Sarıkaya, Beyza Öztürk, Bursal, Ercan, Bilsel, Gökhan, Gören, Ahmet C., 2011. Polyphenol contents and antioxidant properties of Medlar (Mespilus germanica L.). Records Nat. Prod. 5, 158–175.
Gulcin, I., Scozzafava, A., Supuran, C.T., Akincioglu, H., Koksal, Z., Turkan, F., Alwasel, S., 2016. The effect of caffeic acid phenethyl ester (CAPE) on metabolic enzymes including acetylcholinesterase, butyrylcholinesterase, glutathione S-transferase, lactoperoxidase, and carbonic anhydrase isoenzymes I, II, IX, and XII. J. Enzyme Inhib. Med. Chem 31, 1095–1101.
Kahle, K., Kempf, M., Schreier, P., Scheppach, W., Schrenk, D., Kautenburger, T., Hecker, D., Huemmer, W., Ackermann, M., Richling, E., 2011. Intestinal transit and systemic metabolism of apple polyphenols. Eur. J. Nutr. 50, 507–522.
Kim, M.S., Park, S.H., Han, S.Y., Kim, Y.H., Lee, E.J., Yoon Park, J.H., Kang, Y.H., 2014. Phloretin suppresses thrombin-mediated leukocyte-platelet-endothelial interactions. Mol. Nutr. Food Res. 58, 698–708.
Köksal, Ekrem, Gulcin, I., 2008. Antioxidant activity of cauliflower (Brassica oleracea L.). Turk. J. Agric. For. 32, 65–78.
Kucuk, M., Gulcin, I., 2016. Purification and characterization of the carbonic anhydrase enzyme from Black Sea trout (Salmo trutta Labrax Coruhensis) kidney and inhibition effects of some metal ions on enzyme activity. Environ. Toxicol. Pharmacol. 44, 134–139.
Lall, R.K., Syed, D.N., Adhami, V.M., Khan, M.I., Mukhtar, H., 2015. Dietary polyphenols in prevention and treatment of prostate cancer. Int. J. Mol. Sci. 16, 3350–3376.
Li, X., Wang, C., Chen, J., Hu, X., Zhang, H., Li, Z., Lan, B., Zhang, W., Su, Y., Zhang, C., 2022. Potential interactions among myricetin and dietary flavonols through the inhibition of human UDP-glucuronosyltransferase in vitro. Toxicol. Lett. 358, 40–47.
Liu, Y.Z., Zhang, Z.P., Fu, Z.W., Yang, K., Ding, N., Hu, L.G., Fang, Z.Z., Zhuo, X., 2019. Per- and polyfluoroalkyl substances display structure-dependent inhibition towards UDP-glucuronosyltransferases. Environ. Pollut. 254, 113093.
Mariadoss, A.V.A., Vinyagam, R., Rajamanickam, V., Sankaran, V., Venkatesan, S., David, E., 2019. Pharmacological aspects and potential use of phloretin: a systemic review. Mini-Rev. Med. Chem. 19, 1060–1067.
Marks, S.C., Mullen, W., Borges, G., Crozier, A., 2009. Absorption, metabolism, and excretion of cider dihydrochalcones in healthy humans and subjects with an ileostomy. J. Agric. Food Chem. 57, 2009–2015.
Miners, J.O., Knights, K.M., Houston, J.B., Mackenzie, P.I., 2006. In vitro-in vivo correlation for drugs and other compounds eliminated by glucuronidation in humans: pitfalls and promises. Biochem. Pharmacol. 71, 1531–1539.
Miners, J.O., Mackenzie, P.I., Knights, K.M., 2010. The prediction of drug-glucuronidation parameters in humans: UDP-glucuronosyltransferase enzyme-selective substrate and inhibitor probes for reaction phenotyping and in vitro-in vivo extrapolation of drug clearance and drug-drug interaction potential. Drug Metab. Rev. 42, 196–208.
Mizunoya, W., Miyahara, H., Okamoto, S., Akahoshi, M., Suzuki, T., Do, M.K., Ohtsubo, H., Komiya, Y., Lan, M., Waga, T., Iwata, A., Nakazato, K., Ikeuchi, Y., Anderson, J.E., Tatsumi, R., 2015. Improvement of endurance based on muscle fiber-type composition by treatment with dietary apple polyphenols in rats. PLoS One 10, e0134303.
Mohos, V., Fliszar-Nyul, E., Ungvari, O., Kuffa, K., Needs, P.W., Kroon, P.A., Telbisz, A., Ozvegy-Laczka, C., Poor, M., 2020. Inhibitory effects of quercetin and its main methyl, sulfate, and glucuronic acid conjugates on cytochrome P450 enzymes, and on OATP, BCRP and MRP2 transporters. Nutrients 12.
Nguyen, N.A., Cao, N.T., Nguyen, T.H.H., Le, T.K., Cha, G.S., Choi, S.K., Pan, J.G., Yeom, S.J., Kang, H.S., Yun, C.H., 2020. Regioselective hydroxylation of phloretin, a bioactive compound from apples, by human cytochrome P450 enzymes. Pharmaceuticals (Basel) 13.
Pohl, C., Will, F., Dietrich, H., Schrenk, D., 2006. Cytochrome P450 1A1 expression and activity in Caco-2 cells: modulation by apple juice extract and certain apple polyphenols. J. Agric. Food Chem. 54, 10262–10268.
Rana, S., Bhushan, S., 2016. Apple phenolics as nutraceuticals: assessment, analysis and application. J. Food Sci. Technol. 53, 1727–1738.
Rowland, A., Miners, J.O., Mackenzie, P.I., 2013. The UDP-glucuronosyltransferases: their role in drug metabolism and detoxification. Int. J. Biochem. Cell Biol. 45, 1121–1132.
Rushmore, T.H., Kong, A.N., 2002. Pharmacogenomics, regulation and signaling pathways of phase I and II drug metabolizing enzymes. Curr. Drug Metab. 3, 481–490.
Schulze, M.B., Martinez-Gonzalez, M.A., Fung, T.T., Lichtenstein, A.H., Forouhi, N.G., 2018. Food based dietary patterns and chronic disease prevention. BMJ 361, k2396.
Shirasaka, Y., Shichiri, M., Mori, T., Nakanishi, T., Tamai, I., 2013. Major active components in grapefruit, orange, and apple juices responsible for OATP2B1-mediated drug interactions. J. Pharm. Sci. 102, 3418–3426.
Sorensen, J.M., 2002. Herb-drug, food-drug, nutrient-drug, and drug-drug interactions: mechanisms involved and their medical implications. J. Altern. Complement. Med. 8, 293–308.
Speer, H., D'Cunha, N.M., Botek, M., McKune, A.J., Sergi, D., Georgousopoulou, E., Mellor, D.D., Naumovski, N., 2019. The effects of dietary polyphenols on circulating cardiovascular disease biomarkers and Iron status: a systematic review. Nutr. Metab. Insights 12 (1178638819882739).
Spinewine, A., Schmader, K.E., Barber, N., Hughes, C., Lapane, K.L., Swine, C., Hanlon, J. T., 2007. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 370, 173–184.
Stracke, B.A., Rufer, C.E., Bub, A., Seifert, S., Weibel, F.P., Kunz, C., Watzl, B., 2010. No effect of the farming system (organic/conventional) on the bioavailability of apple (Malus domestica Bork., cultivar Golden delicious) polyphenols in healthy men: a comparative study. Eur. J. Nutr. 49, 301–310.
Tapaninen, T., Neuvonen, P.J., Niemi, M., 2011. Orange and apple juice greatly reduce the plasma concentrations of the OATP2B1 substrate aliskiren. Br. J. Clin. Pharmacol. 71, 718–726.
Veronese, N., Solmi, M., Caruso, M.G., Giannelli, G., Osella, A.R., Evangelou, E., Maggi, S., Fontana, L., Stubbs, B., Tzoulaki, I., 2018. Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. Am. J. Clin. Nutr. 107, 436–444.
Vinson, J.A., Su, X., Zubik, L., Bose, P., 2001. Phenol antioxidant quantity and quality in foods: fruits. J. Agric. Food Chem. 49, 5315–5321.
Vrhovsek, U., Rigo, A., Tonon, D., Mattivi, F., 2004. Quantitation of polyphenols in different apple varieties. J. Agric. Food Chem. 52, 6532–6538.
Wang, N., Jiang, S., Zhang, Z., Fang, H., Xu, H., Wang, Y., Chen, X., 2018. Malus sieversii: the origin, flavonoid synthesis mechanism, and breeding of red-skinned and red-fleshed apples. Hortic. Res. 5, 70.
Wang, Z., Gao, Z., Wang, A., Jia, L., Zhang, X., Fang, M., Yi, K., Li, Q., Hu, H., 2019. Comparative oral and intravenous pharmacokinetics of phlorizin in rats having type 2 diabetes and in normal rats based on phase II metabolism. Food Funct. 10, 1582–1594.
Williamson, G., 2017. The role of polyphenols in modern nutrition. Nutr. Bull. 42, 226–235.
Yilmaz, L., Borazan, E., Aytekin, T., Baskonus, I., Aytekin, A., Oztuzcu, S., Bozdag, Z., Balik, A., 2015. Increased UGT1A3 and UGT1A7 expression is associated with pancreatic cancer. Asian Pac. J. Cancer Prev. 16, 1651–1655.
Yoshida, Y., Tsutaki, A., Tamura, Y., Kouzaki, K., Sashihara, K., Nakashima, S., Tagashira, M., Tatsumi, R., Nakazato, K., 2018. Dietary apple polyphenols increase skeletal muscle capillaries in Wistar rats. Phys. Rep. 6, e13866.
Zhang, N., Liu, Y., Jeong, H., 2015. Drug-drug interaction potentials of tyrosine kinase inhibitors via inhibition of UDP-glucuronosyltransferases. Sci. Rep. 5, 17778.
Zhang, Y., Hou, J., Feng, F., Li, D., Jiang, Q., Li, X., Zhao, Q., Li, B.A., 2017. Genetic polymorphisms in human UDP-glucuronosyltransferases 1A7 and the risk of gastrointestinal carcinomas: a systematic review and network meta-analysis. Oncotarget 8, 66371–66381.
Zhang, R., Wei, Y., Yang, T., Huang, X., Zhou, J., Yang, C., Zhou, J., Liu, Y., Shi, S., 2021. Inhibitory effects of quercetin and its major metabolite quercetin-3-O-beta-D-glucoside on human UDP-glucuronosyltransferase 1A isoforms by liquid chromatography-tandem mass spectrometry. Exp. Ther. Med. 22, 842.