Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Low risk of the TMPRSS2 inhibitor camostat mesylate and its metabolite GBPA to act as perpetrators of drug-drug interactions

Johanna Weiss *, Gzona Bajraktari-Sylejmani, Walter Emil Haefeli

Department of Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Im Neuenheimer Feld 410, 69120, Heidelberg, Germany

A R T I C L E   I N F O

Keywords:
Camostat mesylate
GBPA
Drug-drug interactions
Drug transporters
SARS-CoV-2
COVID-19

A B S T R A C T

Camostat mesylate, a potent inhibitor of the human transmembrane protease, serine 2 (TMPRSS2), is currently under investigation for its effectiveness in COVID-19 patients. For its safe application, the risks of camostat mesylate to induce pharmacokinetic drug-drug interactions with co-administered drugs should be known. We therefore tested in vitro the potential inhibition of important efflux (P-glycoprotein (P-gp, ABCB1), breast cancer resistance protein (BCRP, ABCG2)), and uptake transporters (organic anion transporting polypeptides OATP1B1, OATP1B3, OATP2B1) by camostat mesylate and its active metabolite 4-(4-guanidinobenzoyloxy)phenylacetic acid (GBPA). Transporter inhibition was evaluated using fluorescent probe substrates in transporter over-expressing cell lines and compared to the respective parental cell lines. Moreover, possible mRNA induction of pharmacokinetically relevant genes regulated by the nuclear pregnane X receptor (PXR) and aryl hydrocarbon receptor (AhR) was analysed in LS180 cells by quantitative real-time PCR. The results of our study for the first time demonstrated that camostat mesylate and GBPA do not relevantly inhibit P-gp, BCRP, OATP1B1 or OATP1B3. Only OATP2B1 was profoundly inhibited by GBPA with an IC50 of 11 μM. Induction experiments in LS180 cells excluded induction of PXR-regulated genes such as cytochrome P450 3A4 (CYP3A4) and ABCB1 and AhR-regulated genes such as CYP1A1 and CYP1A2 by camostat mesylate and GBPA. Together with the summary of product characteristics of camostat mesylate indicating no inhibition of CYP1A2, 2C9, 2C19, 2D6, and 3A4 in vitro, our data suggest a low potential of camostat mesylate to act as a perpetrator in pharmacokinetic drug-drug interactions. Only inhibition of OATP2B1 by GBPA warrants further investigation.

1. Introduction

Camostat mesylate, a potent inhibitor of the human transmembrane protease, serine 2 (TMPRSS2), is approved in Japan for the treatment of chronic pancreatitis and postoperative reflux esophagitis. Because SARS-coronavirus 2 (SARS-CoV-2) needs the TMPRSS2 for its spike protein priming, this protease is essential for the cellular entry of this virus [1] and recent evidence indicates that camostat mesylate effectively inhibits SARS-CoV-2 entry into lung cells [1]. Therefore, several clinical studies are ongoing testing its effectiveness in coronavirus disease 2019 (COVID-19) patients.

In humans and animals, camostat mesylate is rapidly metabolised by carboxylesterases to its metabolite, 4-(4-guanidinobenzoyloxy) phenylacetic acid (GBA, FOY-251), which has a terminal half-life of 0.75–1.4 h in humans and is further metabolised to 4-guanidinobenzoic acid (GBA) [2–5] (Fig. 1). Whereas GBA has a low inhibition potency for TMPRSS2, GBPA is pharmacologically active but with an about 10-fold lower potency than the parent compound camostat.

Efficacy and safety of drugs can be influenced by drug–drug interactions. In pharmacokinetic interactions, the perpetrator drug leads to changes in absorption, metabolism, distribution, or excretion of the victim drug causing toxic side effects or non-response. Most pharmacokinetic drug-drug interactions can be attributed to inhibition or induction of drug-metabolising enzymes and drug transporters involved in

Abbreviations: AhR, aryl hydrocarbon receptor; BCRP, breast cancer resistance protein; calcein-AM, calcein acetoxymethylester; COVID-19, coronavirus disease 2019; CYP, cytochrome P450; DBF, 4’,5’-dibromofluorescein; FTC, fumitremorgin C; GBA, 4-guanidinobenzoic acid; GBPA, 4-(4-guanidinobenzoyloxy)phenylacetic acid; GU, glucuronidase β; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; PXR, pregnane X receptor; SARS-CoV-2, SARS-coronavirus 2; SPC, summary of product characteristics; TMPRSS2, transmembrane protease, serine 2.

* Corresponding author. University Hospital Heidelberg, Department of Clinical Pharmacology and Pharmacoepidemiology, Im Neuenheimer Feld 410, 69120, Heidelberg, Germany.

E-mail address: johanna.weiss@med.uni-heidelberg.de (J. Weiss).

https://doi.org/10.1016/j.cbi.2021.109428
Received 18 January 2021; Accepted 23 February 2021
Available online 27 February 2021
0009-2797/© 2021 Elsevier B.V. All rights reserved.
the absorption, distribution, and clearance of drugs. Up to now, nearly no published information exists whether camostat acts as a perpetrator in drug-drug interactions. The summary of product characteristics (SPC) of FOIPAN® only states that camostat and GBPA do not inhibit cytochrome P450 (CYP) 1A2, 2C9, 2C19, 2D6, and 3A4 in vitro [6] excluding one of the important mechanisms of drug-drug interactions. However, apart from CYPs and other metabolising enzymes, drug uptake or efflux transporters can also have substantial impact on the pharmacokinetics of drugs. Among them are efflux transporters such as P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2) and uptake transporters such as the organic anion transporting polypeptides (OATP) 1B1, 1B3, and 2B1 [7–11]. Thus far, no data are published on possible inhibiting effects of camostat or GBPA on drug transporters. Moreover, there is no information on possible inducing effects of these compounds on enzymes or transporters, which may lead to decreased exposure of co-administered drugs and thus to non-response. We therefore evaluated the inhibitory potential of camostat and GBPA on selected pharmacokinetically important drug transporters as well as their inducing potential on exemplary genes regulated by the pregnane X receptor (PXR) and the aryl-hydrocarbon receptor (AhR): CYP1A1, CYP1A2, CYP3A4, ABCB1, and ABCG2.

2. Material and methods

2.1. Materials

Cell culture medium M199, foetal calf serum (FCS), supplements, Hank’s buffered salt solution (HBSS), phosphate buffered saline (PBS), GenElute™ Mammalian Total RNA Miniprep Kit, Cytotoxicity Detection Kit (LDH), 4′,5′-dibromofluorescein (DBF), tetracycline, rifampicin, naringin, omeprazole, and camostat mesylate were obtained from Sigma-Aldrich (Taufkirchen, Germany). DMEM was purchased from PAN Biotech (Aidenbach, Germany). GBPA mesylate was purchased from Sigma-Aldrich (Taufkirchen, Germany). Vincristine was purchased from Biotrend (Co- logne, Germany). Fumitremorgin C (FTC) was obtained from Merck Millipore (Darmstadt, Germany). Calcein acetoxymethylester (calcein-AM) was obtained from Invitrogen (Karlsruhe, Germany), phenophorbid A from Frontier Scientific Europe (Carnforth, UK), LY335979 (zosuquidar) from Toronto Research Chemicals (Toronto, Canada), and 8-fluorescein-cAMP from BIOLOG Life Science Institute (Bremen, Germany). The RevertAid™ H Minus First Strand cDNA Synthesis Kit and the Absolute SYBR Green Mix were purchased from Thermo Fisher Scientific (Waltham, MA, USA). Primers were synthesised by Eurofins MWG Operon (Ebersberg, Germany).

2.2. Stock solutions

Stock solution of camostat mesylate was prepared in aqua bidest (50 mM) and of GBPA mesylate in DMSO (10 mM). Stock solutions of all other compounds were prepared in DMSO. All stock solutions were stored in aliquots at –20 °C.

2.3. Cytotoxicity assay

Because cytotoxic effects can influence transporter inhibition assays, we tested for possible cytotoxic effects of camostat mesylate and GBPA in all cell lines using the Cytotoxicity Detection Kit according to the manufacturer’s instructions. Neither camostat nor GBPA revealed any cytotoxic effects up to 100 μM. Moreover, in the flow cytometry assays, no shift of the cell populations in the forward versus side scatter occurred also confirming the absence of any short-term cytotoxic effects.

2.4. P-gp inhibition assay (calcein assay)

For assessing whether camostat and GBPA inhibit P-gp, a calcein assay was performed as validated and described in detail previously [12]. As a cell system, the L-MDR1 cell line over-expressing human P-gp [13] (kindly provided by A. H. Schinkel (The Netherlands Cancer Institute, Amsterdam, The Netherlands)) and the corresponding parental cell line LLC-PK1 were used. The two cell lines were cultured under standard cell culture conditions in medium M199 supplemented with 10% FCS, 2 mM glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin sulphate. To maintain P-gp expression, the medium used for L-MDR1 cells was amended with 0.64 μM vincristine. One day before the calcein assay, both cell lines were fed with vincristine-free culture medium.

Each concentration of camostat mesylate and GBPA mesylate (0.5–100 μM) was tested in octuplet and 1 μM LY335979 was used as a positive control. The experiment was performed in quadruplicate.

2.5. BCRP inhibition assay (flow cytometric phenophorbid A efflux assay)

For testing BCRP inhibition, the human BCRP-overexpressing cell line MDCKII-BCRP [14] (kindly provided by A. H. Schinkel (The Netherlands Cancer Institute, Amsterdam, The Netherlands)) and the corresponding parental cell line MDCKII were used. Cells were cultured under standard cell culture conditions in DMEM containing 10% FCS, 2 mM glutamate, 100 U/ml penicillin, and 100 μg/ml streptomycin sulphate.

The flow cytometric BCRP inhibition assay was conducted as validated and described previously [15] using the fluorescent phenophorbid A as a specific BCRP substrate. In each sample, 30,000 cells were counted. Living cells were gated in the forward versus side scatter. The inhibitory effect of test compounds was quantified by calculating the ratio between the median fluorescence with and without inhibitor and normalised to the effects in the parental cell line. For camostat and GBPA 0.5–100 μM were tested and as a positive control, 10 μM FTC was used. The experiment was performed in triplicate.

2.6. OATP1B1 and OATP1B3 inhibition assay (flow cytometric 8-fluo- rescein-cAMP uptake assay)

For measuring OATP1B1 and OATP1B3 inhibition, the human embryonic kidney cell line HEK293 stably transfected with OATP1B1 (HEK-
OATP1B1), OATP1B3 (HEK-OATP1B3), or the empty control vector (HEK293-VC G418) (kindly provided by D. Keppler (German Cancer Research Centre, Heidelberg, Germany)) were used [16,17]. Cells were cultured under standard cell culture conditions with DMEM supplemented with 10% FCS, 100 U/ml penicillin, 100 μg/ml streptomycin sulphate, and 800 μg/ml G418.

Inhibition of OATP1B1 and OATP1B3 was analysed by measuring the uptake of the fluorescent substrate 8-fluorescein-cAMP as described previously [18]. In each sample, 30,000 cells were counted. Cell debris was eliminated by gating the viable cells in the forward versus side scatter. For determination of the inhibitor effects, the ratio between the median fluorescence of intracellular 8-fluorescein-cAMP with and without inhibitor was calculated and normalised to the mock transfected control cell line. For camostat and GBPA 0.5–100 μM were tested and as a positive control 20 μM rifampicin was used. The experiments were conducted in triplicate.

### 2.7. OATP2B1 inhibition assay (flow cytometric DBF uptake assay)

HEK293 cells overexpressing OATP2B1 in presence of tetracycline [19] (Grosser et al., 2015) (kindly supplied by G. Grosser and J. Geyer (University of Gießen, Germany)) were used for measuring OATP2B1 inhibition as described previously [20]. Cells were cultured under standard cell culture conditions with DMEM/Ham’s F12 medium supplemented with 10% FCS, 100 U/ml penicillin, and 100 μg/ml streptomycin sulphate. To generate OATP2B1 over-expression, cells were treated for 72 h with 1 μg/ml tetracycline before the assay. In each sample, 30,000 cells were counted. Cell debris was eliminated by gating the viable cells in the forward versus side scatter. For determination of the inhibitor effects, the ratio between the median fluorescence of intracellular DBF with and without inhibitor was calculated and normalised to the control cell line. For camostat and GBPA 0.5–100 μM were tested and as a positive control 1 μM maringin was used. The experiments were conducted in triplicate.

### 2.8. Induction assay

For testing possible inducing effects of camostat and GBPA, the human colon adenocarcinoma cell line LS180 was used. LS180 cells are a well-established model for investigating induction mediated by PXR and AhR [21–27]. Cells were cultured under standard cell culture conditions in DMEM supplemented with 10% FCS, 100 U/ml penicillin, 100 μg/ml streptomycin sulphate, 0.1 mM non-essential amino acids, and 2 mM glutamine.

Antiproliferative effects can influence the results of induction assays. Thus, growth inhibition by camostat mesylate was investigated in LS180 before starting the induction assay. Proliferation was quantified by crystal violet staining and the assays were conducted as described previously [28]. Camostat mesylate was tested from 0.01 to 100 μM with each concentration tested in triplicate and the experiment was performed in quadruplicate. Camostat mesylate did not show any antiproliferative effects up to the maximum concentration tested (100 μM), which was therefore also the maximum concentration tested in the induction assay.

In FCS-containing medium, similar to the in vivo situation, camostat mesylate is rapidly metabolised to GBPA and further to GBA with a half-life of about 140 min [29]. Thus, we did not test GBPA separately in our induction assay, because during our 4-day incubation, the metabolites were present anyway.

To test induction, LS180 cells were treated for four days with camostat mesylate (5, 10, 50, 100 μM), omeprazole (150 μM, positive control for AhR-driven genes), rifampicin (20 μM, positive control for PXR-driven genes), or with medium only as a negative control. All media were adjusted to 0.1% DMSO. Immediately after harvesting the cells, RNA was extracted using the GenElute™ Mammalian Total RNA Mini-prep Kit, purity and concentration measured photometrically and stored at −80 °C until processing. The experiment was conducted in quintuplicate.

RNA was reverse transcribed to cDNA with the RevertAid™ H Minus First Strand cDNA Synthesis Kit according to the manufacturer’s instructions. mRNA expression was quantified by real-time RT-PCR with the LightCycler® 480 (Roche Applied Science, Mannheim, Germany) as described previously [30]. Primer sequences were also published previously: ABCB1 and ABCC2 [30], CYP1A1 [31], CYP1A2 [32], CYP3A4 [33], and glucuronidase β (GU) as housekeeping gene [34]. PCR amplification was carried out in 20 μl reaction volume containing 5 μl 1:10 diluted cDNA, 1x Absolute QPCR SYBR Green Mix, and 0.15 μM primers. The most suitable housekeeping gene for normalisation was identified using geNorm (version 3.4, Center for Medical Genetics, Ghent, Belgium), which determines the most stable reference gene from a set of tested genes in a given cDNA sample panel [35]. Among the 7 reference genes tested, GU proved to be the most stable in LS180 cells under our experimental conditions. Data were evaluated via calibrator-normalised relative quantification with efficiency correction using the LightCycler® 480 software version 1.5.1.62 (Roche Applied Science). Results were expressed as the target/reference ratio divided by the target/reference ratio of the calibrator. The results are therefore corrected for variance caused by detection and sample inhomogeneities. All samples were amplified in technical duplicate and the mean was used for further calculation.

![Fig. 2. Concentration-dependent effect of GBPA on intracellular calcine fluorescence in L-MDR 1 indicating P-gp inhibition. The curve depicts the results of 3 experiments with each concentration tested in octuplet and data are expressed as mean ± S.E.M. Due to the small errors, the error bars are not visible.](image)

![Fig. 3. Concentration-dependent effect of GBPA on the BCRP activity. For determination of the inhibitor effects, the ratio between the median fluorescence of intracellular phophorhode A with and without inhibitor was calculated in BCRP-overexpressing cells and normalised to the control cell line. Each data point depicts the results of 3 experiments with 30,000 cells each and is expressed as mean ± S.E.M. Due to the small errors, the error bars are not visible.](image)
activity of OATP2B1. For determination of the inhibitor effects, the ratio between the median fluorescence of intracellular 8-fluorescein-cAMP with and without inhibitor was calculated in OATP-overexpressing cells and normalised to the control cell line. Each data point depicts the results of 3 experiments with 30,000 cells each and is expressed as mean ± S.E.M.

2.9. Statistical analysis

Non-linear regression curves were calculated with GraphPad Prism version 9.0.0 (GraphPad Software Inc., La Jolla, CA, USA) using the four-parameter fit (sigmoidal dose-response curves with variable slope). Differences between mRNA expressions were tested using ANOVA with Dunnett’s post hoc test using InStat version 3.06 (GraphPad Software Inc., La Jolla, CA, USA). A p-value < 0.05 was considered significant.

3. Results

3.1. Inhibition of drug efflux transporters P-gp and BCRP by camostat and GBPA

Camostat neither inhibited P-gp nor BCRP up to 100 μM (data not shown). In contrast, its metabolite GBPA slightly increased intracellular calcein fluorescence at concentrations above 10 μM in P-gp-overexpressing L-MDR1 cells, but not in the parental cell line LLC-PK1 indicating very weak P-gp inhibition (Fig. 2). Similarly, GBPA had a small inhibitory effect on BCRP at concentrations above 10 μM. However, compared to the respective positive controls (LY335979 and FTC) the effect was very small (Figs. 2 and 3).

3.2. Inhibition of OATPs by camostat and GBPA

Camostat revealed only minor effects on OATP activities: it did not inhibit OATP1B3 and OATP2B1 (Figs. 4A and 5) and only slightly inhibited OATP1B1 at concentrations > 50 μM (Fig. 4A). GBPA also had no relevant effects on OATP1B3 activity (Fig. 4B), but inhibited OATP1B1 about 50% at 100 μM and potently inhibited OATP2B1 with an IC50 of 11.1 ± 3.3 μM (Fig. 5).

3.3. Induction of PXR- and AhR-regulated genes by camostat and GBPA

In contrast to substantial induction by the respective positive controls (rifampicin, omeprazole), incubation of LS180 cells for 4 days with camostat mesylate and thus also GBPA had no significant effect on the mRNA expression of CYP1A1, CYP1A2, CYP3A4, ABCB1, and ABCG2 clearly excluding the induction of genes regulated by PXR and/or AhR (Fig. 6).

4. Discussion

The pandemic caused by SARS-CoV-2 has triggered a feverish search for effective pharmacological treatment of infected patients. The development and approval of new drugs is a very time-consuming process, which can be abbreviated by repurposing already licensed drugs. One of those approved drugs proposed as possible treatment option for COVID-19 patients is camostat mesylate. This serine protease inhibitor, marketed in Japan as FOIPAN®, has already been clinically used for over two decades to treat pancreatitis and postoperative reflux esophagitis due to its potent inactivation of trypsin preventing auto-digestion [36]. Camostat mesylate also potently inhibits the transmembrane serine protease TMPRSS2, on which SARS-CoV-2 critically depends for cellular entry and subsequent virus spread in the host [1,29]. It is therefore currently tested for its efficacy in COVID-19 patients. Beyond its efficacy, possible drug-drug interactions provoked by camostat are also of concern, because they could harm the particularly vulnerable COVID-19 patients. So far, the possible perpetrator characteristics of camostat mesylate in pharmacokinetic drug-drug interactions have not been investigated in detail. Our study aimed to close this knowledge gap.

In humans and other mammals, after oral intake camostat mesylate itself does not reach systemic circulation in measurable concentrations, because it is rapidly metabolised during intestinal absorption to GBPA and GBA [2–5]. Thus, although GBPA is about 10-fold less potent than the parent compound, inhibition of TMPRSS2 in humans and thus its possible anti-SARS-CoV-2 activity has to be attributed to this metabolite [29]. For the same reason, systemic drug-drug interactions can only be provoked by GBPA, which reaches maximum plasma concentrations of about 87 ng/ml (±0.3 μM) after oral intake of 200 mg camostat mesylate [6]. In contrast, intestinal drug-drug interactions might also be provoked by both, the short-lived camostat itself and by its metabolite GBPA, which can reach concentrations in the intestine up to 1600 μM after oral intake of 200 mg according to the formula published by Zhang and co-workers [37].

Conclusive earlier data demonstrated that in FCS-containing medium camostat mesylate is rapidly metabolised to GBPA with a half-life of about 140 min [29]. Thus, we assume that in our induction assays, in which LS180 cells are incubated with camostat mesylate in FCS-containing medium, we also tested the influence of GBPA on the
mRNA expression of several drug metabolising genes and drug transporters. Our data clearly demonstrate that camostat mesylate/GBPA did not induce CYP3A4 and ABCB1 (PXR-regulated), ABCG2 (regulated by PXR and AhR), or CYP1A1 and CYP1A2 (AhR-regulated) genes. We therefore conclude that camostat will not act as a perpetrator in drug-drug interactions based on the induction of drug metabolising enzymes or drug transporters regulated by PXR or AhR.

In our inhibition assays, we tested both compounds individually, because these were short-term experiments and some of the buffers used did not contain FCS excluding the degradation of camostat mesylate. Our results demonstrated that neither camostat mesylate nor its metabolite GBPA are inhibitors of the efflux transporters P-gp and BCRP. Whereas camostat mesylate had no relevant effects on the uptake transporters OATP1B1, 1B3, and 2B1, GBPA exerted different effects on these OATPs: No pronounced inhibition of OATP1B3, weak inhibition of OATP1B1, and potent inhibition of OATP2B1 (IC_{50} about 11 μM). Although the small effect on OATP1B1 is most likely not relevant in vivo, because systemic concentrations of GBPA are too low for inhibition of this liver-specific uptake transporter, the potency for intestinal OATP2B1 inhibition is clearly high enough to be of clinical relevance. Inhibition of this uptake transporter represents a typical feature of several citrus flavonoids [38–40] and can lead to decreased bioavailability of respective substrates as already postulated e.g. for aliskiren [41,42], celiprolol [43], and rosuvastatin [44]. Whether therapy with camostat mesylate substantially influences the pharmacokinetics of OATP2B1 substrates should be investigated in clinical studies.

5. Conclusions

In conclusion, the capability of the potential COVID-19 therapeutic drug camostat mesylate to act as a perpetrator in pharmacokinetic drug-drug interactions appears to be low. The SPC of camostat mesylate (FOIPAN®) states that camostat mesylate and GBPA do not inhibit CYP1A2, 2C9, 2C19, 2D6, and 3A4 in vitro. Our data for the first time demonstrate that these compounds also do not relevantly inhibit P-gp, BCRP, OATP1B1, and OATP1B3 and do not induce drug transporters or

---

**Fig. 6.** Effects of camostat mesylate on mRNA expression in LS180 cells compared to untreated medium control after 4 days of incubation. Rifampicin (20 μM) served as a positive control for PXR-driven genes (CYP3A4, ABCB1, ABCG2) and omeprazole (150 μM) served as a positive control for AhR-driven genes (ABCG2, CYP1A1, CYP1A2). Expression data were normalised to the housekeeping gene GU. Data are expressed as mRNA changes ±SEM for n = 5 biological replicates. Data were analysed using ANOVA with Dunnett’s post hoc test compared to the medium control. **p < 0.01.
drug metabolising enzymes regulated by PXR or AhR in vitro. Only inhibition of OATP2B1 by GBPA might be of clinical relevance and should be further investigated.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

GBS was supported in part by the Physician Scientist program of the Faculty of Medicine of Heidelberg University, Germany. The authors thank Corina Mueller, Stephanie Rosenzweig, and Jutta Kocher for excellent technical assistance, Alfred Schinkel for providing the cell lines L-MDR1 and MDDCK-II-BCRP, Dietrich Keppler for providing the cell lines HEK-OATP1B1/1B3 and Gary Grosser and Joachim Geyer for providing the cell line HEK-OATP2B1.

References

[1] M. Hofmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Eichsen, T. S. Schierenges, G. Herrler, N.H. Wu, A. Nitsche, M.A. Müller, C. Drosten, S. Pohlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2020) 271–280, https://doi.org/10.1016/j.cell.2020.02.052, e25.
[2] K. Beck, B. Goke, R. Muller, A. Arnold, Elimination of the low-molecular weight proteinase inhibitor camostat (FOY 305) and its degradation products by the rat liver, Res. Exp. Med. 187 (1987) 401–406, https://doi.org/10.1007/BF01852177.
[3] K. Beck, H. Weidenbach, P. Weidenbach, R. Muller, G. Adler, Hepatitis virus infection, endocrine pancreatic metabolism and biliary excretion of the protease inhibitor camostat mesilate, Int. J. Pancreatology. 10 (1991) 197–205.
[4] S. Oikii, H. Nishiya, K. Ozeki, H. Ito, F. Hirata, Studies on absorption, distribution, metabolism and excretion of [14C] FOY-305, Gendai-Iryo 12 (1980) 764, https://doi.org/10.2133/dmpk.DMPK-10-RV-094.
[5] D. Yamasaki, T. Nakamura, N. Okamura, M. Kokudai, Effects of acid and lactone forms of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on the induction of MDR1 expression and function in L6100 cells, Eur. J. Pharmacol. Sci. 39 (2007) 129–132, https://doi.org/10.1016/j.ejps.2009.01.009.
[6] W. Li, P.A. Harper, B.K. Tang, A.B. Okey, Regulation of cytochrome P450 enzymes by aryl hydrocarbon receptor in human cells: CYP2E1 expression in the LS180, Pharmacol. Res. 57 (2008) 599–612, https://doi.org/10.1016/j.pr.2008.05.237651, biovia.08.05.237651. Preprint.
[7] N. Albermann, F.H. Schmitz-Winnenthal, K.Z. Gragger, C. Volk, M.M. Hoffmann, W.E. Haefeli, J. Weiss, Expression of the drug transporters MDR1/ABCB1, MRPs/ABCC, and BCRP/ABCG2, and PAR in peripheral blood mononuclear cells and their relationship with the expression in intestine and liver, Toxicol. In Vitro. 20 (2006) 949–958, https://doi.org/10.1016/j.ijtox.2005.06.018.
[8] Z. Dvorak, R. Vrazil, P. Henklova, P. Jancova, E. Anzenbacherova, P. Maurel, L. Svecova, P. Pavek, J. Ehrmann, R. Havlik, P. Bednar, K. Lemr, J. Ulrichova, JNK inhibitor SP600125 is a partial agonist of human aryl hydrocarbon receptor and induces CYP1A2 and CYP1A1 enzymes in human hepatocytes, Pharmacol. Res. 58 (2008) 580–588, https://doi.org/10.1016/j.phrs.2007.09.013.
[9] J. Ayed-Boussema, I.M. Fasuncu, P. Maier, A. Schirmer, Z. Zscholemann activates pregnane X receptor, constitutive androstane receptor and aryl hydrocarbon receptor and correspondingly phase I target genes mRNA in primary cultures of human hepatocytes, Environ. Toxicol. Pharmacol. 31 (2011) 79–87, https://doi.org/10.1016/j.etap.2011.04.008.
[10] L. Cerveny, L. Svecova, E. Anzenbacherova, R. Vrazil, F. Staud, Z. Dvorak, J. Ulrichova, P. Anzenbacher, P. Pavek, V.P. Kokudai, Valproic acid induces CYP3A4 and MDR1 gene expression by activation of constitutive androstane receptor and pregnane X receptor pathways, Drug Metab. Dispos. 35 (2007) 1032–1041, https://doi.org/10.1124/dmd.106.014456.
[11] J. Zisowsky, S. Koegel, S. Leyers, K. Devarakonda, M.U. Kassack, M. Osmak, C. Drosten, M. Winkler, T. Hempel, L. Raich, S. Olsson, J.F. Hagemann, J.M. Sheltzer, M. Kjolby, Camostat mesylate against SARS-CoV-2 activation by TMPRSS2-related Proteases and its Metabolite GBPA Exerts Antiviral Activity, 2020 Aug 5, 2020, https://doi.org/10.1124/jpet.120.257651, biovia.08.25.257651. Preprint.
[37] L. Zhang, Y.D. Zhang, J.M. Strong, K.S. Reynolds, S.M. Huang, A regulatory viewpoint on transporter-based drug interactions, Xenobiotica 38 (2008) 709–724, https://doi.org/10.1080/0049825080217715.

[38] S.J. McFeely, L. Wu, T.K. Ritchie, J. Unadkat, Organic anion transporting polypeptide 2B1 - more than a glass-full of drug interactions, Pharmacol. Ther. 196 (2019) 204–215, https://doi.org/10.1016/j.pharmthera.2018.12.009.

[39] E. Johnson, C.S. Won, K. Kock, M.F. Paine, Prioritizing pharmacokinetic drug interaction precipitants in natural products: application to OATP inhibitors in grapefruit juice, Biopharm Drug Disp. 3 (2017) 251–259, https://doi.org/10.1002/bdd.2061.

[40] G. Bajraktari-Sylejmani, J. Weiss, Potential Risk of Food-Drug Interactions: citrus polymethoxyflavones and flavanones as inhibitors of the organic anion transporting polypeptides (OATP) 1B1, 1B3, and 2B1, Eur. J. Drug Metab. Pharmacokinet. 45 (2020) 809–815, https://doi.org/10.1007/s13318-020-00634-4.

[41] T. Tapaninen, P.J. Neuvonen, M. Niemi, Grapefruit juice greatly reduces the plasma concentrations of the OATP2B1 and CYP3A4 substrate aliskiren, Clin. Pharmacol. Ther. 88 (2010) 339–342, https://doi.org/10.1038/clpt.2010.101.

[42] T. Tapaninen, P.J. Neuvonen, M. Niemi M, Orange and apple juice greatly reduce the plasma concentrations of the OATP2B1 substrate aliskiren, Br. J. Clin. Pharmacol. 71 (2017) 718–726, https://doi.org/10.1111/j.1365-2125.2010.03898.x.

[43] J.J. Lilja, J. Juutti-Patinen, P.J. Neuvonen, Orange juice substantially reduces the bioavailability of the beta-adrenergic-blocking agent celiprolol, Clin. Pharmacol. Ther. 75 (2004) 184–190, https://doi.org/10.1016/j.clpt.2003.11.002.

[44] M. Johnson, D. Patel, C. Matheny, M. Ho, L. Chen, H. Ellens, Inhibition of intestinal OATP2B1 by the calcium receptor antagonist ronacaleret results in a significant drug-drug interaction by causing a 2-fold decrease in exposure of rosuvastatin, Drug Metab. Dispos. 45 (2017) 27–34, https://doi.org/10.1124/dmd.116.072597.