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Review article

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# NEW INSIGHT INTO ORGANIC ANION TRANSPORTERS FROM THE PERSPECTIVE OF POTENTIALLY IMPORTANT INTERACTIONS AND DRUGS TOXICITY

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The family of organic anion transporters (OATs) includes a group of over 10 transmembrane transporting proteins belonging to the solute carrier 22 subfamilies of the major facilitator superfamily. Their function is related to the transport of a great variety of organic anions against the electrical and chemical gradient. OATs are present in most types of human tissues, including the kidneys, liver, placenta, olfactory epithelium, retina, and choroid plexus tissues. The OATs family plays an important role in the cellular uptake, distribution, excretion, and detoxification of many water-soluble drugs, endogenous compounds, nutrition ingredients, environmental contaminants and toxins, and significantly impacts their efficacy, pharmacokinetics and toxicity, both in a preferable and unfavorable way. OATs demonstrated great potential to participate in many potentially relevant interactions, which may lead to unexpected, but not always detrimental, effects. Wider knowledge about their specific functions in the body, role in disease states, pharmacokinetics interactions, and intraindividual response to therapeutic treatment will allow to predict and prevent OAT-related adverse effects or use favorable interactions in pharmacotherapy, as well as to rationally design therapeutics targeted at individual transporter drugs with improved bioavailability, prolonged half-life or reduced toxicity, and improve safety guidelines concerning drug dosage. This review gathers recent reports regarding OAT-related essential interactions involving components of popular therapeutic herbal products, dietary supplements, and clinically important drugs, their significance and potential suitability in modulating the severity of drug-related side effects and toxicity mechanisms.

Key words: *organic anion transporters, drug-drug interactions, herbal preparations, dietary supplements, pharmacokinetic interactions*

## INTRODUCTION

The family of organic anion transporters (OATs in humans, Oats in animals) includes a group of over 10 transmembrane transporting proteins belonging to the solute carrier 22 subfamily of the major facilitator superfamily (1). This subfamily counts at least 31 identified/putative proteins and besides organic anion comprises the organic cation transporters and organic carnitine transporters (2, 3). The OATs family is highly similar within these subclasses of superfamily proteins (2, 4). Several subtypes of OATs have been identified in humans (OAT1-8, OAT10, and urate transporter 1 (URAT1)). Eight of them (OAT1-5, OAT7, OAT10, and URAT1) have been functionally characterized (5-7). All known OATs are built up of 536-563 amino acids. The structure of OATs comprises several critical regions that control their function, subcellular localization, and trafficking mechanisms. All the identified OATs have several common structural features, such as 12 transmembrane domains (1, 8), multiple glycosylation sites localized in the first extracellular loop between transmembrane domains 1 and 2, multiple potential phosphorylation sites present in the intracellular loop transmembrane domains 6 and 7 and at the carboxyl end (*Fig. 1*). OATs have many smaller extracellular and intracellular loops between other transmembrane domains and the intracellular carboxyl and amino terminal regions. Potential N-glycosylation and other regulatory regions identified in several OATs transporter regions could possibly affect OATs post-translational regulation (8).

OATs are present in most types of tissues (9, 10). A large part of them shows expression in human renal proximal tubules. OAT1-3 are located on the basolateral membrane of renal proximal tubule epithelial cells (RPTC), whereas OAT4, OAT10, and URAT1 are expressed on the luminal membrane (*Fig. 2*) (2, 3, 6). Besides the kidneys, four OATs have been detected in the human liver: OAT2, OAT3, OAT5, and OAT7 (6, 9, 11). In turn, OAT1 and OAT4 expression was discovered in the placenta, Oat1 and Oat6 in a murine olfactory epithelium, and OAT1 and OAT3 in human retina and choroid plexus tissues (1, 3, 10). The affinity of human OATs for most drug classes was reported; the authors compared the putative importance of individual OATs for its bioavailability and efficacy for specific organs and renal tubular drug secretion and/or reabsorption (3).

The function of OATs is related to the transport of organic anions against electrical and chemical forces. They have the ability to distribute anions against their chemical gradient to reach levels intracellularly several times higher than in the extracellular fluid, and in addition they are able to force anions into an already negatively charged cellular environment (12-14).

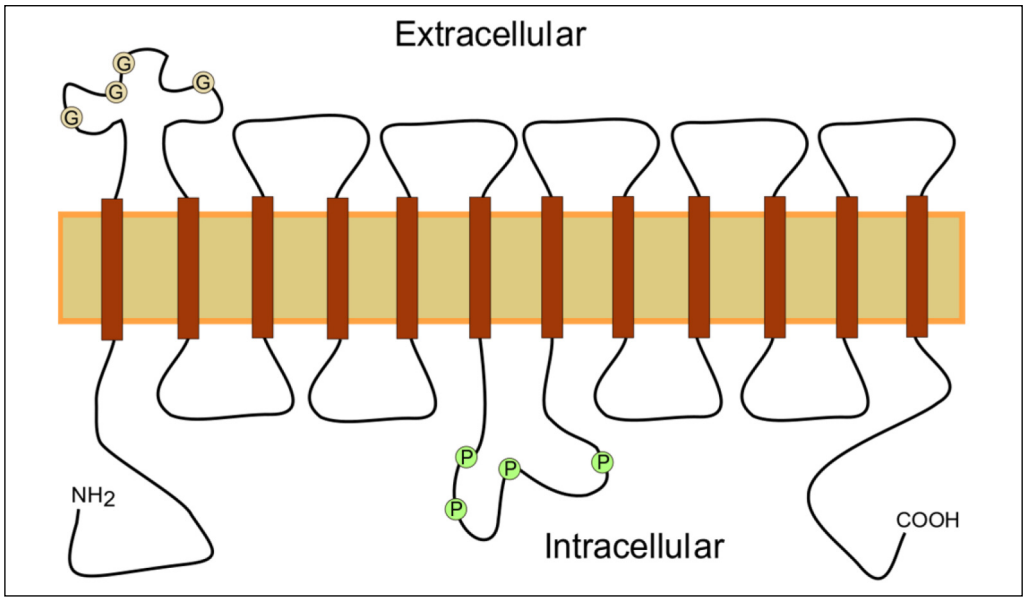


*Fig. 1.* Illustration of the predicted topology of organic anion transporters in the cellular membrane. G - glycosylation site, P - phosphorylation site.

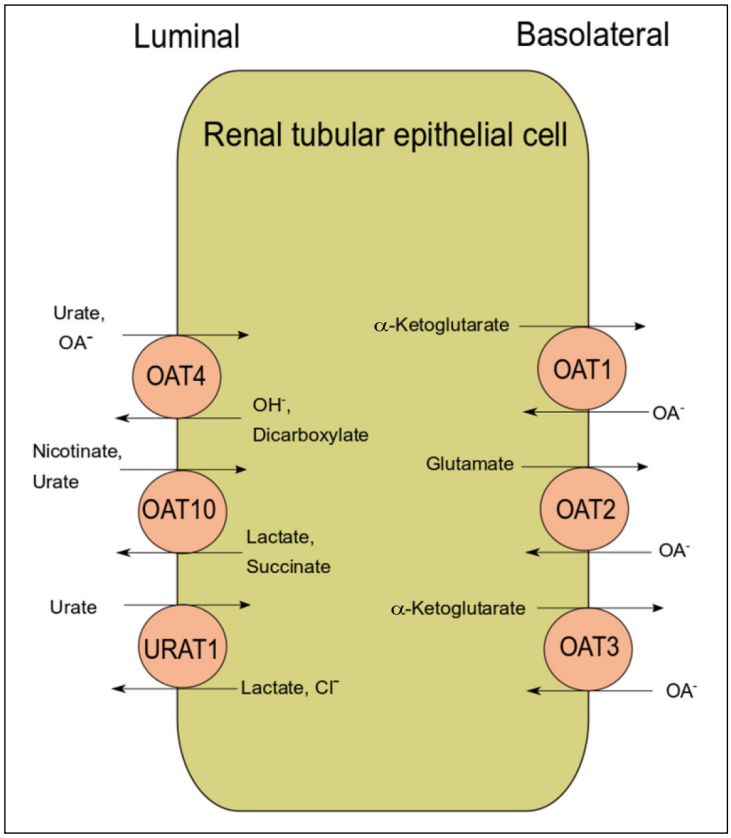


*Fig. 2.* Scheme of localization and simplified organic anionic compounds transport mechanism by OATs in renal tubular epithelial cells.
Cl, chloride anion; $OA^-$, organic anions; OAT, organic anion transporter; $OH^-$, hydroxyl anion; URAT1, urate transporter 1.

OATs transport a great variety of structurally diverse organic anions. The OATs family plays an important role in renal excretion and detoxification of many water-soluble drugs (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), anti-hypertensives, anti-viral therapeutics, anti-neoplastic drugs, cholesterol-lowering drugs, diuretics, and antibiotics), endogenous compounds (*e.g.* steroid hormones, neurotransmitter metabolites, uremic toxins), nutrition ingredients, (*e.g.* furocoumarins, phenolic acids, anthraquinones, and flavonoids), environmental contaminants and toxins (*e.g.* herbicide/pesticide components and mycotoxins), and impacts their efficacy and pharmacokinetics (*Fig. 3*) (12).

The nature of OATs substrate also suggests that, similarly to other transmembrane transporters, such as aquaporins, the proper function of these proteins is significant in maintaining total body homeostasis, that their altered function (and/or expression) is a key factor in the progression of some disease states and may play a role in the intraindividual variability in therapeutic or toxic responses observed patients (1, 3, 6, 9, 15). As many of these compounds are directly toxic to epithelial cells and are constantly exposed to them, their detoxification is thought to be crucial for the maintenance of body homeostasis. OATs function is a principal determinant of the ability for weakening substrate toxicity, whether derived from an

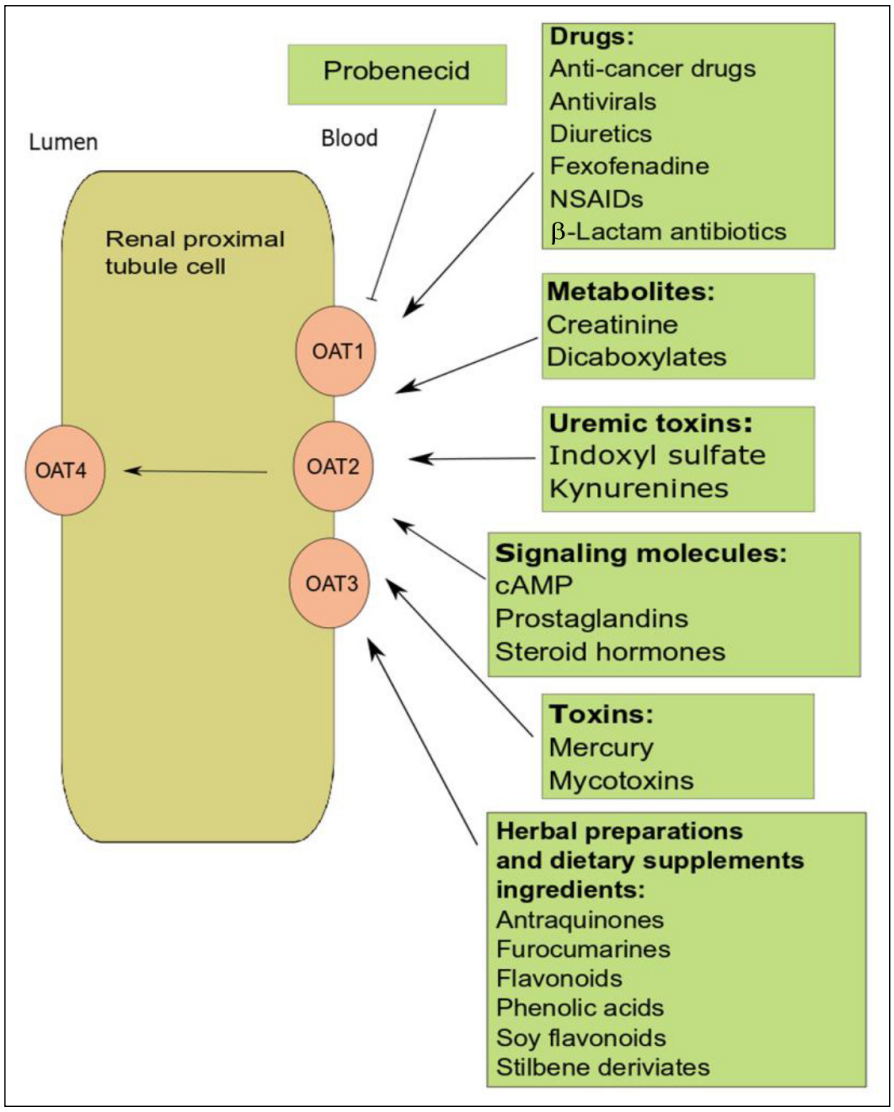


*Fig. 3.* Scheme of potential interactions between OATs' substrates caused by competition for tubular secretion at the transporter level. OATs trafficking may be inhibited by OATs inhibitor, such as probenecid (1).
cAMP, cyclic adenosine monophosphate; NSAIDs, nonsteroidal anti-inflammatory drugs; OAT, organic anion transporter.

exogenous or endogenous origin. Furthermore, the intraindividual variation in therapeutic response within human populations are associated with altered OATs expression levels, affinity and/or spatial distribution as a result of genetic factors.

A more thorough understanding of their function is necessary to accurately assess their impact on drug pharmacokinetics and effectiveness, as well as the severity of endogenous and xenobiotic toxins/ toxicant actions (16-19). There is growing evidence from both *in vitro* and *in vivo* studies implicating OATs in the renal targeting of these molecules. Inhibition of OATs protects against nephrotoxicity induced by OAT-substrate drugs. On the other hand, an increase in transporters dysfunction is necessary during the progression of acute renal injury because OATs and efflux transporters are able to work together to excrete uremic toxins (20).

This review gathers recent reports regarding OATs-related essential interactions involving components of popular therapeutic herbal products and dietary supplements or clinically important drugs and their significance in modulating the severity of side effects affecting the kidneys and other organs (*i.a.* liver, placenta, and choroid plexus). It also summarizes the current knowledge about OATs-related mechanisms of toxicity connected with taking clinically important therapeutics and the impact of the co-administration of other drugs, herbal preparations, dietary supplement ingredients that are OATs inhibitors on severity of these mechanisms.

## OATS-RELATED INTERACTIONS INVOLVING DRUGS, HERBAL PREPARATIONS, AND FOOD AND DIETARY SUPPLEMENT INGREDIENTS (*Table 1*)

OATs expressed in the kidney, liver, placenta, and choroid plexus tissues have a significant impact on the pharmacokinetics profiles of many nutritional substances, endogenous compounds, therapeutics, and toxins, demonstrating a significant effect on their pharmacokinetics, pharmacodynamics, dosing regimens, and toxicity (*Fig. 3*). These substances are characterized by a different inhibitory potential for OATs represented by half maximal inhibitory concentration ($IC_{50}$). Additionally, the possibility of interaction with drugs and herbal ingredients transported by OATs cannot be taken into consideration without a comparison of the values of this coefficient with peak concentrations ($C_{max}$) of the discussed substances in serum. However, for many of these compounds, $IC_{50}$ values for particular OATs still remain unknown (*Table 2* and *3*).

OATs have great potential to participate in many potentially relevant herb-drug, herb-endogenous compound, dietary supplement-drug, and drug-drug interactions (DDIs). Conclusive identification of their contributions to these interactions is still developing. Such interactions are not always detrimental (2, 10, 13). OATs-related interactions can result from both beneficial and harmful effects associated with drug

*Table 1.* Herbal preparations ingredients and clinically important drugs being OATs' substrates and involved in OAT-dependent interactions.

| OAT | Compound/ group of compounds | References |
|---|---|---|
| OAT1 | • anthraquinones, caffeine, cinnamic acid, cynarin, ellagic acid, ferulic acid, flavonoids, phenolic acids<br>• antiviral drugs, benzbromarone, bendroflumethiazide, chlorothiazide, cilostazol, cimetidine, cisplatin, fluvastatin, furosemide, Mesna, methotrexate, N-acetylcysteine, nilotinib, non-steroidal anti-inflammatory drugs, probenecid, pravastatin simvastatin, tazobactam, β-lactam antibiotics | (10, 34, 41, 86 105)<br>(10, 14, 18, 22, 34, 35, 45, 49, 52, 62, 65, 67, 69, 77) |
| Oat1 | • flavonoids, furocumanines, lycopene, steviol, stilbene derivatives<br>• antiviral drugs, bendroflumethiazide, chlorothiazide, cisplatin, enprofylline, methotrexate, non-steroidal anti-inflammatory drugs, β-lactam antibiotics | (18, 39, 94, 104, 109)<br>(18, 24, 29, 33, 52, 68, 71, 81, 130) |
| OAT2 | • antiviral drugs, bendamustine, bumetanide, irinotecan, Mesna, methotrexate, pravastatin, theophylline, β-lactam antibiotics | (10, 18, 24, 26, 34, 52, 71, 77, 81) |
| Oat2 | • methotrexate, non-steroidal anti-inflammatory drugs, β-lactam antibiotics | (18, 24, 34, 52) |
| OAT3 | • anthraquinones, cinnamic acid, cynarin, ellagic acid, ferulic acid, flavonoids, phenolic acids<br>• antiviral drugs, bendamustine, bendroflumethiazide, captopril, chlorothiazide, cilostazol, cimetidine, cispaltin, fexofenadine, fluvastatin, furosemide, gemcabene, gemfibrozil, Mesna, lansoprazole, methotrexate, N-acetylcysteine, nilotinib, non-steroidal anti-inflammatory drugs, omeprazole, pemetrexed, pravastatin, probenecid, quinapril (Quinaprilat), rosuvastatin, simvastatin, tazobactam, β-lactam antibiotics | (10, 40, 86, 91, 105)<br>(10, 14, 34, 35, 45, 48, 50, 52, 66, 68, 71, 73, 75, 76, 77, 83) |
| Oat3 | • flavonoids, furocumanines, lycopene, steviol<br>• antiviral drugs, atorvastatin, bendroflumethiazide, bumetanide, chlorothiazide, cisplatin, enprofylline, furosemide, non-steroidal anti-inflammatory drugs, β-lactam antibiotics | (39, 40 94, 109)<br>(10, 14, 34, 68, 71, 77, 81, 130) |
| OAT4 | • soy isoflavones<br>• antiviral drugs, cilostazol, levocetirizine, non-steroidal anti-inflammatory drugs, probenecid, β-lactam antibiotics | (93)<br>(10, 18, 25, 29, 33, 34, 61) |
| OAT6 | • salicytale | (119) |
| Oat6 | • antiviral drugs | (130) |

OAT, organic anion transporter.

administration. Favorable results of OATs-related interactions are always connected with decreasing or inhibiting OAT-mediated transport of toxic compounds. This may lead to a reduction of the hepatotoxicity, nephrotoxicity, or neurotoxicity of certain clinically important drugs with a low therapeutic index, (*e.g.* furosemide, anticancer drugs, NSAIDs, antivirals, or antibiotics) and consequently to alleviate their side effects (10, 18). Mitigation of drug toxicity by OATs substrates or non-competitive inhibitors is connected with a decrease in the intracellular accumulation of therapeutics, which are OATs substrates exhibiting cytotoxic properties or generating oxidative stress in renal and hepatic or choroid plexus cells, among others. Other beneficial effects connected with the inhibition of OATs substrate transmembrane transport are associated with improved bioavailability, prolonged half-life of drugs, and other pharmacokinetic properties caused by diminished renal excretion of these substances. Inhibition of the cellular uptake of drugs to cells of certain organs (*e.g.* kidneys, liver, choroid plexus) may also contribute to a partial reduction of drug toxicity in these organs (1, 2, 10). On the other hand, inhibition of OATs-dependent anion transport may also cause detrimental effects, leading to the aggravation of side effects and increased toxicity of the above-mentioned therapeutics (2, 18). In this case, the increase of systemic toxicity is connected with decreased clearance and renal elimination, increased serum concentrations and prolonged half-life of toxic OATs substrates, both endogenous and exogenous. This can lead to serious disorders connected with increases in endogenous and exogenous substance bioavailability. In turn, inhibition of the cellular uptake of drugs to the cells of different organs may lead to weakening their effectiveness. This may be particularly important in the case of anticancer drugs (10, 13, 17, 18).

## DRUG-DRUG INTERACTIONS (*Table 2*)

### *Nonsteroidal anti-inflammatory drugs*

NSAIDs are a one of the most popular classes of therapeutics. In conjunction with their popular use, an enormous variety of adverse reactions, including nephrotoxicity, hepatotoxicity, gastrointestinal irritation, and neurological dysfunction, have been reported. Early studies indicated that penicillin's urinary excretion was significantly inhibited by

NSAIDs co-administration, while their renal secretion was strongly inhibited by probenecid. This suggested that NSAIDs may interact with the renal OATs system (9, 21, 22). Several later studies based on human cell lines and animal models proved that certain NSAIDs are OATs substrates (9, 22, 23). Many of these compounds, including ketoprofen, ibuprofen, indomethacin, diclofenac, naproxen, mefenamic acid, phenacetin, piroxicam, and sulindac, can markedly modulate organic anion transport mediated by OAT1, Oat1 Oat2, OAT3, Oat3, and OAT4. In general, the inhibitory properties of these NSAIDs are much stronger for OAT1, Oat1, OAT3, and Oat3, than for other OATs (9, 21, 23-25). Thus, there seems to be significant potential for DDIs and supplement-drug interactions between NSAIDs and other drugs or herbal and dietary supplement components at the OATs level. Whether or not these interactions result in positive or negative effects will greatly depend on the careful management of the chosen therapeutic regimen (23, 25). Acetylsalicylate, salicylate, ibuprofen, and mefenamic acid have been related with the induction of proximal tubular nephropathy and renal papillary necrosis. Interactions of

*Table 2.* Mean $IC_{50}$ and $C_{max}$ values [μM] of clinically important drugs participating in OAT-related interactions.

| No. | Compound/ Group of compounds | OAT1 | OAT2 | OAT3 | OAT4 | OAT6 | $C_{max}$ value | References |
|---|---|---|---|---|---|---|---|---|
| 1. | *NSAIDs* | | | | | | | (64, 112, |
| | Acetylsalicylate | 769 | >2000 | 717 | >2000 | N/A | 131.5 | 113, 114, |
| | Diclofenac | 4.46 | 14.3 | 7.78 | 34.5 | N/A | 6.6 | 115, 116, |
| | Ibuprofen | 55 | 692 | 6 | 103 | N/A | 300 | 117, 118, |
| | Indomethacin | 3.83 | 64.1 | 0.61 | 10.1 | N/A | 2.3 | 119) |
| | Ketoprofen | 4.34 | 400 | 5.98 | 70.3 | N/A | 31.5 - | |
| | Naproxen | 5.67 | 486 | 4.67 | 85.4 | N/A | 47.2 | |
| | Phenacetin | 275 | 1878 | 19.4 | >2000 | N/A | 281.9 | |
| | Piroxicam | 62.8 | 70.3 | 2.52 | 84.9 | N/A | 10.27 | |
| | Salicylate | 325 | >2000 | 50 | >2000 | 49 | 5.74 | |
| | Sulindac | 36.2 | 440 | 3.62 | 617 | N/A | 543.1 | |
| | | | | | | | 0.02 | |
| 2. | *β-lactam antibiotics* | | | | | | | (35, 47, |
| | Benzylpenicillin | N/A | N/A | 52.1 | N/A | N/A | 314 | 120, 121, |
| | Carbenicillin | N/A | N/A | N/A | N/A | N/A | (mice) | 122, 123, |
| | Cefamandole | 30 | 430 | 46 | 1.14 | N/A | 364.7 | 124, 125, |
| | Cefazolin | 100.6 | 5090 | 116.6 | 1.74 | N/A | 77.6 | 126, 127, |
| | Cefoperazone | 210 | 1140 | 1890 | 2.8 | N/A | (dogs) | 128, 129) |
| | Cefotiam | 640 | N/A | 212.6 | N/A | N/A | 440 | |
| | Ceftibuten | 563.1 | N/A | 247.3 | N/A | N/A | 461,5 | |
| | Ceftriaxone | 230 | 6760 | 4390 | N/A | N/A | 182.1 | |
| | Cephalothin | 220 | 1040 | 40 | N/A | N/A | 56.8 | |
| | Piperacilllin | 54.32 | N/A | 89.04 | N/A | N/A | 148.2 | |
| | | | | | | | 97.6 | |
| | | | | | | | 511-710 | |
| 3. | *Antiviral drugs ( $IC_{50}$ values measured for murine oats)* | | | | | | *($C_{max}$ values measures for human OATs)* | (130, 131, 132,123, 134, 135, 136, 137, 138) |
| | Didanosine | 600 | N/A | 136 | N/A | >2000 | 2.2 - | |
| | Stavudine | 628 | N/A | 2113 | N/A | 1671 | 11.81 | |
| | Zalcitabane | 1479 | N/A | 203 | N/A | 729 | 0.05 - 0.5 | |
| | Lamivudine | 104 | N/A | 140 | N/A | >2000 | 0.03 | |
| | Zidovudine | 78 | 81 | 38 | N/A | 218 | 6.72 | |
| | Adefovir | 36 | N/A | 597 | N/A | >2000 | 1.3 - 1.63 | |
| | Tenofovir | 81 | N/A | 384, | N/A | >2000 | 13.8 - | |
| | Cidofovir | 25.7 | N/A | >2000 | N/A | >2000 | 47.2 | |
| | Acyclovir | 209 | >2000 | 729 | N/A | >2000 | 0.73 - | |
| | | | | | | | 1.03 | |
| | | | | | | | 11.2 - | |
| | | | | | | | 84.4 | |
| | | | | | | | 44.6 | |
| 4. | *Anti-neoplastic drugs* | | | | | | | (82, 83, 120, 139, |
| | Bendamustine | N/A | 16.88 | 0.8 | N/A | N/A | 16,3 | 140, 141, |
| | Methotrexate | 16.9 | 8.9 | 27.9 | N/A | N/A | 1.1 | 142, 143) |
| | Irinotecan | N/A | 7.55 | N/A | N/A | N/A | 7.65 | |
| | Nilotinib | N/A | N/A | N/A | N/A | N/A | 3.5 | |
| | Pemetrexed | N/A | N/A | N/A | N/A | N/A | 266 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5. | *Histamine receptor antagonists* | | | | | | | (144, 145, 146, 147) |
| | Cimetidine | 492 | >2000 | 92.4 | >2000 | N/A | 9.9 | |
| | Fexofenadine | N/A | N/A | N/A | N/A | N/A | 0.4 | |
| | Levocetirizine | N/A | N/A | N/A | N/A | N/A | 1.6 | |
| 6. | *Uricosuric drugs* | | | | | | | (62, 106, 111, 147) |
| | Benzbromarone | 4.6 | N/A | N/A | N/A | N/A | 9.22 | |
| | Probenecid | 12.3, 18.34 | 668 | 4.93, 5.83 | 25.4, 44.4-67.7 | N/A | 245 | |
| 7. | *Diuretics* | | | | | | | (59, 68, 69, 148, 149, 150, 151) |
| | Bendroflumethiazide | 8 | N/A | 8 | N/A | N/A | 0.11 | |
| | Bumetanide | N/A | N/A | N/A | N/A | N/A | 0.27 | |
| | Chlorothiazide | N/A | N/A | N/A | N/A | N/A | 9.8 | |
| | Furosemide | 18.0 | 603 | 7.31 | 44.5 | N/A | (dogs) 0.48 | |
| 8. | *Lowering lipids level agents* | | | | | | | (144, 148, 152, 153, 154, 155, 156) |
| | Gemcabene | N/A | N/A | N/A | N/A | N/A | N/A | |
| | Gemfibrozil | N/A | N/A | N/A | N/A | N/A | N/A | |
| | Atorvastatin | >2000 | N/A | 13.1 | N/A | N/A | 0.45 | |
| | Fluvastatin | 26.3 | N/A | 5.79 | N/A | N/A | 0.033 | |
| | Pravastatin | 408 | 352 | 76.3 | 591 | N/A | 0.92 | |
| | Rosuvastatin | N/A | N/A | 25.7 | N/A | N/A | 0.011 | |
| | Simvastatin | 73.6 | N/A | 32.3 | N/A | N/A | 0.016 | |
| 9. | *Phosphodiesterase inhibitors* | | | | | | | (80) |
| | Cilostazol | N/A | N/A | N/A | N/A | N/A | 2.1-5.1 | |
| 10. | *Bronchodilators* | | | | | | | (85, 86, 157) |
| | Enprofylline | N/A | N/A | N/A | N/A | N/A | 8.75 | |
| | Theophylline | N/A | 54.6 | N/A | N/A | N/A | 24.4 | |
| 11. | *Mucolitics* | | | | | | | |
| | N-acetylcysteine | N/A | N/A | N/A | N/A | N/A | 2.1 - 23.6 | (158) |
| 12. | Mesna | N/A | N/A | N/A | N/A | N/A | 147 | (85) |
| 13. | *Proton pump inhibitors* | | | | | | | (48, 56, 159) |
| | Lansoprazole | N/A | N/A | 0.4, 0.57 | N/A | N/A | 2.5-4.9 | |
| | Omeprazole | N/A | N/A | 5.5 | N/A | N/A | 1.73 | |
| 14. | *Angiotensin-converting enzyme inhibitors*, | | | | | | | (56, 160, 161) |
| | Captopril | N/A | N/A | N/A | N/A | N/A | 3.3 | |
| | Quinapril | N/A | N/A | 6.2 (Quinaprilat) | N/A | N/A | 2.25 | |
| 15. | Tazobactam | N/A | N/A | N/A | N/A | N/A | 96-129 | (120) |

$C_{max}$ - peak concentration
$IC_{50}$ - half maximal inhibitory concentration
N/A - no data available
NSAIDs - nonsteroidal anti-inflammatory drugs
OAT- organic anion transporter

these therapeutics with OAT1, OAT3, and OAT4 suggest that these renal anion transporters may play an important role in modulating OATs-related drug-induced nephrotoxicity (23-25). OATs-mediated NSAIDs renal transport may also be a key factor enhancing the efficacy of NSAIDs-induced inhibition of prostaglandin expression, which leads to a reduction of renal blood flow and the onset of acute renal failure (24). In turn, the presence of Oat2 in the basolateral membrane of hepatocytes indicated that Oat2-related uptake of hepatotoxic substrates, *e.g.* acetylsalicylate, diclofenac, and sulindac, is potentially a causative factor of NSAIDs-related hepatotoxicity. Other Oat2 substrates, such as theophylline, as competitive inhibitors of this anion transporter, demonstrated the ability to reduce this adverse effect in the animal model. Whereas, OATs expression in the choroid plexus and brain capillary endothelium potentially connects NSAIDs administration and central nervous system (CNS) dysfunctions, which include confusion, somnolence, dizziness, and seizures (23-25).

*β-lactam antibiotics*

β-lactam antibiotics are modified versions of occurring in nature microorganism metabolites that demonstrated a wide spectrum of antimicrobial properties (26). In most cases, these modifications resulted in the presence of accompanying nephrotoxicity that leads to acute proximal tubular necrosis and renal failure. This fact, resulted in the development of nephroprotective agents (*e.g.* cilastatin, probenecid, and

betamipron), which in further studies turned out to be OATs inhibitors. After co-administration with β-lactams, they caused an increase of their serum half-life and a reduction of their nephrotoxicity (11, 17, 27, 28). This suggested that OATs might mediate the RPTC accumulation of these antibiotics. Accordingly, several studies proved the inhibitor-sensitive transport of compounds belonging to the three main β-lactam subgroups (penicillins, cephalosporins, and penems) by OAT1, Oat1, OAT2, Oat2, OAT3, Oat3, and OAT4 for renal elimination (9, 27, 29-32). An effective reduction of β-lactam nephrotoxicity and an increase of in their neurotoxicity during the co-administration of OATs competitive inhibitors, such as other drugs or herbs, and food or dietary supplement components was observed (23, 27, 29, 32, 33). An explanation for this might be the fact that OATs expression in the choroid plexus and brain capillary cells, as well as in RPTC, is linked with a decreased CNS tolerance of these compounds. Newer compounds, such as carbapenems and carbacephems have shown wider antibacterial range. However, they are accompanied by larger nephrotoxic potential, which may be reduced by the co-administration of certain flavonoids (23, 34). A complete understanding of OATs functions and the mechanisms controlling their substrate specificity should help in the design of a new, safer generation of these antibiotics and avoid their renal accumulation or brain efflux (23, 27, 30).

Piperacillin/tazobactam is an intravenous β-lactam/β-lactamase inhibitor combination commonly used in the treatment of various infections. Tazobactam is a β-lactamase inhibitor, which inactivates β-lactamases and that is why it is used to reduce piperacillin hydrolysis. It results in increased plasma concentration of this antibiotic and improved therapy effectiveness. According to the latest state of knowledge, both piperacillin and tazobactam are substrates and competitive inhibitors of OAT1 and OAT3, and piperacillin has a stronger affinity for both transporting proteins than tazobactam. Research conducted in cell cultures and human kidney slices revealed that the aforementioned OATs mediate the DDIs between these substances, affecting their effectiveness and pharmacokinetics (35). This proves that when this β-lactam/β-lactamase inhibitor combination is co-administered with other OATs substrate drugs (*e.g.* probenecid) attention should be paid to the potential unfavorable OAT1- and OAT3-mediated DDIs leading to changes in the pharmacokinetics and efficacy of these substances when determining their dosage regimen.

*Antivirals*

Long-term antiviral therapy is often associated with strong adverse effects that include nephrotoxic and neurotoxic changes. Dose-dependent nephrotoxicity is the most important adverse effect associated with the administration of antiviral nucleoside phosphonates, such as adefovir and cidofovir (9, 22). This nephrotoxicity was inhibited by probenecid, among others. This suggests that active drug accumulation through OATs expressed in RPTC is a determining factor in their nephrotoxicity (9). Subsequently, it has been proved on the human cell cultures and animal models that adefovir and cidofovir are high affinity substrates of OAT1 and Oat1. These transporters' expression is strongly correlated with the cytotoxicity of these antivirals through increased entry from OAT1 and decreased efflux into the tubular lumen (22-24, 29). Further studies showed that the co-administration of NSAIDs efficiently reduced the OAT1-mediated transport and cytotoxicity of adefovir. Thus, use of a dietary supplement-drug and DDIs mediated by OAT1 might be considered when creating a clinical strategy for mitigating the nephrotoxicity of these antivirals without losing their therapeutic value. In turn, administration of acyclovir and ganciclovir is associated with neurotoxicity and nephrotoxicity. Both substances were identified as OAT1, OAT2, and OAT3 substrates (9, 27, 37, 38). These findings might deliver a potential explanation for the DDIs of these compounds observed clinically, strictly concerning the decrease of renal clearance of acyclovir in combination with probenecid or NSAIDs and the risk of convulsions when ganciclovir is taken in conjunction with imipenem (22, 29, 37). All antivirals transported by OAT1 and OAT3 are capable of interacting with herbal preparation and dietary supplement components that are competitive inhibitors of these renal (10, 33, 39-42). This is confirmed, among others, by research conducted on human embryonic kidney cells 293 (HEK293) colonies, as well as human and rat kidney slices, which proved that benzylpenicillin is able to reduce the renal cellular uptake and excretion of acyclovir *via* the OAT1 and OAT3 inhibition mechanism (29, 33). Entecavir is the OAT1 and OAT3 substrate and participates in supplement-drug and DDIs with other substrates of OAT1 and OAT3 (23, 38, 42). The OAT1-mediated cytotoxicity of cidofovir was significantly decreased by probenecid co-administration. High-dose probenecid administration parallel to cidofovir in HIV patients led to a decrease in its clearance to a level near glomerular filtration. This proved that probenecid is an effective nephroprotectant during cidofovir therapy (18, 27, 33, 36). Renal excretion of the anti-HIV drug azidothymidine was efficiently inhibited by probenecid. Recent *in vitro* studies demonstrated that azirtomydine is transported by OAT1, OAT2, OAT3, and OAT4. These would explained the source of reported DDIs with acetaminophen, indomethacin, cimetidine, probenecid, and salicylate. This information suggests that renal excretion of azirtimydine may be inhibited by herbal and dietary supplements components, being that are OATs inhibitors (*e.g.* flavonoids, phenolic acids, ellagic acid, anthraquinones, furocoumarins or caffeine). OAT1 is directly responsible for adefovir, cidofovir, and tenofovir cytotoxicity, while interactions with zidovudine did not decrease cell viability (23, 33, 36, 37, 44). Thus, OATs expressed in the choroid plexus' apical membrane and in the basolateral membrane of brain capillaries are considered to play an important role in the clearance of antivirals from the CNS and can negatively impact the therapeutic effect of these compounds during viral CNS infection treatment (24, 43).

*Anti-neoplastic drugs*

Anti-neoplastic drugs are probably the most toxic therapeutic used in present times. There is little information concerning potentially relevant interactions accompanying their use. Due to the narrow therapeutic window of most of anti-neoplastic substances and their great potential for severe life-threatening side-effects, this is a critical issue (39).

Cisplatin is a well-known and widely used antineoplastic agent. It is effective in the treatment of a wide range of solid tumors. Its administration during anti-tumor therapy is associated with severe nephrotoxicity. One of the cisplatin-induced renal injury pathways is mediated by OAT1- and OAT3-dependent transport. The function of these transporter proteins can be simultaneously inhibited by nilotinib without compromising the anticancer properties of cisplatin (45). Nilotinib was primarily designed as the BCR-Abl tyrosine kinase inhibitor used for the treatment of chronic myeloid leukemia (46). *In vitro* research showed that it can potently inhibit both OAT1 and OAT3 function. However, it is not a substrate of OAT1 or OAT3, thus suggesting that the mechanism of OATs inhibition by this compound is noncompetitive (45). This finding provides a rationale for the future development of new targeted adjuvant therapies with the use of OATs inhibitors to mitigate the adverse effects related to cisplatin treatment.

Pemetrexed is a multitargeted antifolate drug transported and excreted by tubular secretion through OAT3 with a higher affinity

and capacity for this transport protein than methotrexate (MTX), which is an anti-neoplastic factor and immune system suppressant used in the treatment of certain malign neoplasms and in the management of autoimmune diseases, such as rheumatoid arthritis or severe psoriasis (22, 39, 47, 48). Some commonly used drugs, *e.g.* NSAIDs, could lead to DDIs connected with pemetrexed tubular secretion through OAT3 at high concentrations (10, 47, 48). Both *in vitro*, *in vivo*, and clinical studies proved that the co-administration of lansoprazole, a proton-pump inhibitor used in the treatment of gastroesophageal reflux disease and ulcers of the stomach and duodenum, could aggravate the hematologic toxicity of pemetrexed, at least in part, by competitive inhibition of renal OAT3 (10, 48).

Greater attention needs to be paid to MTX, due to its strong toxicity and low therapeutic index. For this reason, its administration is strongly associated with the occurrence of severe nephrotoxicity, myelotoxicity, and hepatotoxicity (22, 39, 49-51). The co-administration of MTX with OATs inhibitors, such as probenecid, and NSAIDs, such as diclofenac, naproxen, indomethacin or ketoprofen (10, 52, 53), decreases its renal clearance and increases its plasma concentrations and half-life. These types of changes in MTX pharmacokinetics under the influence of OATs inhibitors are associated with the increased systemic toxicity of this drug (48, 51, 54). They also indicated that OATs are involved in its transport (9, 22, 52). Consequently, later studies based on animal and cellular models have directly demonstrated that OAT1, Oat1, OAT2, Oat2, and OAT3 participate in MTX cellular uptake, transport, and toxicity.

In addition, MTX treatment down-regulated the expression levels of Oat1 and Oat3 in rats. This effect was recovered by leucovorin. Therefore, it might be an effective adjuvant used to reduce MTX toxicity in normal cells (55). Moreover, these OATs are considered an important site of harmful DDIs reported between NSAIDs and this therapeutic (10, 52, 53). NSAIDs' glucuronides, similarly to their parent compounds, can inhibit both OAT1 and OAT3-mediated MTX transport in HEK293 cell lines. Stereoselectivity was not found to be effective against the inhibitory effects of either OAT1 or OAT3. These findings suggest that the inhibition of OAT1 and OAT3-mediated MTX cellular uptake by NSAID glucuronides may be a significant competitive site underlying the comprehensive DDIs between MTX and NSAIDs, in addition to the inhibition of basolateral OATs by parent NSAIDs (52).

*In vitro* and clinical studies identified proton pump inhibitors (*i.a.* omeprazole) as an important class of OATs inhibitors that decreases OAT3-mediated MTX cellular uptake and its renal excretion. They also confirmed that this antifolate has a greater affinity for OAT3 than OAT1, and indicated that OAT1do not participate in the interaction between MTX and this class of drugs. These studies largely explain the source of DDIs between MTX and these drugs. Proton pump inhibitors should be evaluated for interactions with other OATs substrates (50). The growing use these drugs in the treatment of reflux disease and peptic ulcers as well as the broad use of MTX for a wide range of tumor diseases suggest that many patients may be at risk for MTX-dependent toxicity, and more intensive pharmacotherapy monitoring is advised (10, 50, 56).

Certain immunosuppressive drugs, commonly used, among others after renal transplantation to prevent allograft rejection, (*e.g.* mycophenolic acid, tacrolimus, hydrocortisone, cyclophosphamide, vincristine, mitoxantrone, 6-mercaptopurine, and dexamethasone) can also modulate, stimulate or inhibit OAT1- and OAT3-mediated MTX transport and excretion to different extents (57, 58). Additionally the effectiveness of immunosuppressants depends on polymorphisms of proinflammatory cytokines associated with the onset of organ rejection, *e.g.* tumor necrosis factor-α (TNF-α). This polymorphism may possibly modulate the interaction of these drugs with methotrexate. However, this issue requires further research to confirm (58). In turn, cetuximab, that is the epidermal growth factor receptor recombinant antibody, significantly reverses epidermal growth factor receptor-induced OAT1 expression up-regulation leading to its down-regulation and impairs MTX-induced toxicity in proximal tubular epithelial cell cultures (53). These data allow to better understand the renal mechanisms underlying OATs-related interactions and nephrotoxicity affecting the dosing regimens of these compounds during pharmacotherapy (57).

These reports indicate that anion transporters may play an important role in the efficacy of MTX therapy, as well as in modulating the intensity of hepatotoxicity, gastrointestinal disorders, myelosuppression, and nephrotoxicity associated with its administration (22, 52).

*Histamine $H_1$ receptor antagonists*

Fexofenadine is a selective histamine $H_1$ receptor antagonist used in the therapy of *e.g.* allergic rhinitis and chronic idiopathic urticaria. It is mainly eliminated through biliary excretion after oral administration, but renal clearance also makes an important contribution to its total body clearance. Research carried out on the cellular model has shown that fexofenadine is an OAT3 substrate. Recent studies also reported that probenecid, as an OATs inhibitor, demonstrated a high potency to inhibit fexofenadine uptake in OAT3-expressing cells, leading to an increase in the fexofenadine serum level and decrease in its clearance. This indicates that the inhibition of OAT3-mediated renal fexofenadine is the main mechanism associated with the occurrence of observed probenecid-fexofenadine interactions (6, 10, 18, 59, 60). Certain NSAIDs being OAT3 substrates, such as ibuprofen, indomethacin, and ketoprofen, similarly to probenecid, are able interact with fexofenadine causing a decrease in clearance and urinary excretion of fexofenadine and an increase in its plasma concentration leading to an increased risk of its accumulation in the body, which may cause intensification of its adverse effects or toxicity (22). In turn, levocetirizine is the pharmacologically active enantiomer of cetirizine, a nonsedating $H_1$ antihistamine drug. OAT4 mediates its uptake but is unlikely to mediate the efflux in cells expressing this transporter (61). It can be responsible for interactions related to OAT4 substrate uptake. This matter ought to be taken into consideration when establishing safety recommendations concerning the use of these therapeutics.

*Uricosuric drugs*

Probenecid and benzbromarone belong to the group of medications that increases uric acid excretion in the urine. They are primarily used in treating gout and hyperuricemia (14, 17, 18, 62, 63). It has been proved that they are both inhibitors for the renal organic anion secretion system. Probenecid shows strong inhibition potency for OAT1 and less inhibitory effects with OAT3 and apical OAT4 (*Fig. 3*) (14, 17, 18, 30, 64). Benzbromarone exhibited even higher affinity for OAT1 than probenecid (*Table 2*), (63). However, the results of studies concerning its affinity for OAT4 are controversial. In different studies, either inhibition or no inhibition of these proteins was observed (65, 66). Clinical reports concerning probenecid-mediated DDIs showed that its co-administration caused a decrease in renal elimination and improved distribution of a variety of drugs, including β-lactams, cephalosporin antibiotics, fluoroquinolone antimicrobials, diuretics, histamine H1 receptor antagonists, and chemotherapeutic agents. Modern studies based on cloned transporters and knockout mouse cell lines have clearly demonstrated a primary role for OATs in mediating, at least to a certain extent, in most of these DDIs (1, 10, 18, 63, 67).

*Diuretics*

Furosemide is a loop diuretic, which exerts its pharmacological effects by inhibiting the Na-K-Cl co-transporters present in the luminal membrane of Henle's loop bendroflumethiazide and chlorothiazide belong to thiazides. They inhibit the protein-chloride protein transporter in the distal canal of the nephron, which reduces the passage of sodium and chlorine from its light to the epithelial cells. The consequence is increased excretion of sodium and secondary water accumulation in the body (68, 69). The main elimination pathway for these diuretics is renal excretion. Due to high albumin binding, their glomerular filtration is limited. Therefore, active tubular secretion is possibly the main route for both their renal elimination and delivery of these diuretics to their effective site. Studies based on cell colonies have shown furosemide, chlorothiazide, and bendroflumethiazide are the OAT1, Oat1, OAT3, and Oat3 substrates. Probenecid significantly reduced furosemide and chlorothiazide clearance and urinary excretion while increasing their systemic exposure. In many *in vivo* and clinical studies, pretreatment with probenecid even increased the overall response to furosemide. Mixed results were reported towards on its impact on the diuretic effect of furosemide. The effect of probenecid on furosemide's pharmacodynamics in humans is complex and cannot be simply predicted from changes in plasma or urinary drug levels (2, 6, 17-19, 66). Whereas, bendroflumethiazide inhibited Oat1- and Oat3-mediated uptake of a labeled para-aminohippurate in Xenopus oocytes injected with cRNA (68). Moreover, *in vitro* and *in vivo* studies proved that another loop diuretic, bumetanide, is transported by OAT2 and Oat3 (70, 71). Research based on both animal and cellular models, which demonstrated that certain NSAIDs (*i.a.* acetylsalicylate, ibuprofen, ketoprofen, indomethacin, and salicylate) are Oat1, OAT1, Oat3, and OAT3 substrates, suggest that this group of drugs may interact with the above-mentioned diuretics by decreasing its clearance and urinary excretion and increasing its plasma concentration and half-life (9, 21, 23, 39). This interaction leads to the accumulation of this drug; the severity of dose-associated side effects or toxicity that should potentially be taken into account when creating safety recommendations regarding the use of these medicines (23).

*Lipid-lowering agents*

Patients taking pravastatin and gemfibrozil in combination to control their triglyceride and cholesterol levels have experienced changes in pravastatin pharmacokinetics (increased plasma levels and decreased renal clearance). It has been reported that these patients suffer from increased pravastatin-associated side effects, such as muscle pain, tenderness, or weakness, lack of energy, fever, jaundice, yellowing of the skin or eyes, pain in the upper right part of the stomach, nausea, extreme tiredness, and unusual bleeding or bruising (72-74). These DDIs might be the effect of OAT3-mediated pravastatin transport inhibition by gemfibrozil in these patients (75-77). Clinical and *in vivo* research proved that another lipid altering agent, gemcabene, has been involved in lowering blood pressure when co-administered with the angiotensin-converting enzyme inhibitor, quinapril, in hypertensive rats and patients (2, 49, 74). Gemcabene was found to inhibit OAT3 transport of the pharmacologically active metabolites of quinapril and captopril - quinaprilat and captoprilat in a dose-dependent way in HEK293 lines, suggesting DDIs on OAT3 as the molecular basis for the observed increase in pharmacological activity (49, 74). Administration of another lipid altering agent, atorvastatin, evokes a nephroprotective effect against the nephrotoxic gentamicin by reducing oxidative stress and improving renal function and renal Oat3 function and expression in the animal model (75, 76). Alleviation of oxidative stress is the main factor that helps preserve renal function and Oat3 activity, as well as induces its expression. This proves that atorvastatin may be used in conjunction with gentamicin to protect against renal damage induced by gentamicin uptake by decreasing oxidative stress in renal cells (75). It was also revealed that pravastatin is transported by other protein transporters, organic anion transporting protein 1B1 (OATP1B1) and OATP2B1, expressed in the apical membrane of the small intestine (77). In turn, gemfibrozil, as well as its glucuronides are able to inhibit the OATP1B1-mediated pravastatin hepatic uptake. This could, at least in part, contribute to the known OAT-related DDIs between pravastatin and gemfibrozil (77, 78). One of the side effects associated with administration of statins, as well as angiotensin-converting enzyme inhibitors is the increased risk of hyperkalemia in hypertensive patients. Although one of the last studies has not shown that the co-administration of these drugs does not affect changes in serum potassium concentration there is still the possibility of interactions between these drug groups at the level of OATs, because therapeutics belonging to them are also the substrates of these transporters and the mechanism of hyperkalemia associated with statins use is poorly examined (79).

*Phosphodiesterase inhibitors*

Cilostazol is a quinolinone-derived therapeutic used in the alleviation of intermittent claudication symptoms in individuals with the peripheral vascular disease. It is also known as an effective and quickly acting antithrombotic factor (80). Numerous studies carried out on human cell lines and animal models proved that OAT3 and Oat3 play a primary role in its renal excretion, while OAT1 and Oat1 do not. Oat3 and drug-metabolizing enzymes are the aims of the DDIs between probenecid and cilostazol in the kidneys and liver. Probenecid, as an OATs inhibitor, decreases the renal clearance and total urinary excretion of cilostazol (14, 16, 21). At the same time, acetylsalicylic acid is able to inhibit the OAT3-mediated uptake and renal excretion of this drug (15, 21). Drugs such as cyclooxygenase-2 inhibitors or angiotensin-converting enzyme inhibitors and herbal dietary supplement components, such as flavonoids, phenolic acids, and anthraquinones, can change OAT3 activity or function that affects the pharmacokinetics of co-administered substances belonging to OAT3 substrates. This may also reduce cilostazol clearance and urinary excretion and increases its plasma concentration and a half-life that probably is associated with adverse effects intensification and ought to be considered when determining its safety and dosing regimen (9, 21).

*Bronchodilators*

Theophylline (1,3-dimethylxanthine) and enprofylline (3-propylxanthine) have been commonly used as bronchodilatory drugs for the treatment of neonatal apnea in premature newborns and patients with chronic obstructive airway diseases such as asthma and bronchitis (26, 81). Theophylline occurs in natural products such as tea and cocoa. OAT2 is highly expressed in the liver. It was shown that the OAT2-mediated uptake of theophylline and erythromycin was inhibited in a cellular model by adding erythromycin and theophylline, respectively. This indicates the possible involvement of OAT2 on theophylline-erythromycin interaction at the sinusoidal membrane of the human liver (26). Bendamustine and irinotecan are anti-tumor drugs, which are both OAT2 substrates (82). Bendamustine is also an OAT3 inhibitor (83). OAT2 showed potent interactions with these antineoplastic drugs, but it is still unclear if OAT2 contributes DDIs in healthy hepatocytes during tumor treatment or if it mediates the uptake of any of these therapeutics in the treatment of hepatocellular carcinoma (82). Other research indicated that Oat1 and Oat3 are

involved in the renal tubular transport of enprofylline in rats (81), which indicates that it may be able to modulate the pharmacokinetics of co-administered OAT3 substrates.

*Mucolytics*

N-acetylcysteine is a therapeutic used during paracetamol overdose treatment and to loosen thick mucus in patients with cystic fibrosis or chronic obstructive pulmonary disease. The latest research based on HEK293 cell lines has shown that N-acetylcysteine is an OAT1 and OAT3 substrate. It has been proved that probenecid, as an OAT1 and OAT3 inhibitor, reduces its clearance and increases plasma and brain exposure (84). This explains how N-acetylcysteine crosses biological barriers and suggests a promising therapeutic strategy to increase its exposure.

*2-mercaptoethanesulfonic acid sodium salt (Mesna)*

Mesna is a cancer chemotherapy adjuvant used to reduce renal nephrotoxicity of some chemotherapeutic agents (cyclophosphamide and cisplatin). Some research showed that it is an OATs substrate. Clinical studies proved that when probenecid was co-administered simultaneously with Mesna, its renal clearance significantly decreased. There were also *in vitro* studies that demonstrated that OAT1-, OAT3-, and OAT4-mediated probenecid-sensitive transport of Mesna and Dimesna may have a significant role in the DDIs between them and affect the effectiveness of the therapy with their use (2, 9, 10, 85).

## INTERACTIONS WITH HERBAL PREPARATIONS AND FOOD AND DIETARY SUPPLEMENT INGREDIENTS (*Table 3*)

*Caffeine*

Caffeine (1,3,7-trimethylxanthine) is widely consumed daily in beverages, food, and dietary supplements. It is mainly metabolized to 1,7-dimethylxanthine and 1-methylxanthine. Research conducted on OAT1-expressing cell cultures indicated

*Table 3.* Mean $IC_{50}$ and $C_{max}$ values [μM] of herbal preparations and dietary supplement ingredients participating in OAT-related interactions.

| No. | Compound/ Group of compounds | OAT1 | OAT2 | OAT3 | OAT4 | OAT6 | $C_{max}$ value | References |
|---|---|---|---|---|---|---|---|---|
| 1. | Caffeine (1-methylxanthine) | 10,3 | N/A | N/A | N/A | N/A | 10.68 | (87, 96) |
| 2. | *Flavonoids* | | | | | | | (34, 40, 91, |
| | Apigenin | 0.737 | N/A | N/A | N/A | N/A | 0.87 | 162, 163, |
| | Luteolin | 0.5 | N/A | N/A | N/A | N/A | 3.1 | 164, 165, |
| | Morin | <0.3, 0.5 | N/A | N/A | N/A | N/A | 14 | 166) |
| | Silibinin | 25 | N/A | N/A | N/A | N/A | 12.5 | |
| | dicaffeoylquinic acid | 0.8-1.6 | N/A | N/A | N/A | N/A | 1,17 | |
| | 18$\beta$-glycyrrhetinic acid. | 2.3-3.1 | N/A | N/A | N/A | N/A | 0,1 | |
| 3. | *Phenolic acids* | | | | | | | (93, 106, |
| | Ferulic acid | 9.01, | N/A | 7.35 | N/A | N/A | 0.012- | 167) |
| | Gallic acid | 3.69 | N/A | 9.02 | N/A | N/A | 1.04 | |
| | Gentisic acid | 1.24 | N/A | 86.81 | N/A | N/A | 0.22-10 | |
| | Protocatechuic acid | N/A | N/A | 86.83 | N/A | N/A | 0.7-6290 | |
| | Sinapinic acid | 18.08 | N/A | 25.74 | N/A | N/A | 0.12-0.49 | |
| | Vanillic acid | 11.02 | | N/A | N/A | N/A | N/A | |
| | | 7.65 | | | | | 0.03-0.10 | |
| 4. | *Anthraquinones* | | | | | | | (43, 95, 96, |
| | Rhein | 0.23 | N/A | 0.08 | N/A | N/A | 67-387 | 168) |
| | Emodin | 0.61 | N/A | 1.22 | N/A | N/A | 1.25 | |
| | Aloe-emodin | 2.29 | N/A | 5.37 | N/A | N/A | 11.0 | |
| | Resveratrol | N/A | N/A | N/A | N/A | N/A | 0.28 | |
| 5. | *Soy isoflavones* | | | | | | | (169) |
| | Daidzein | N/A | N/A | N/A | N/A | N/A | 0.38 | |
| | Genistein | N/A | N/A | N/A | N/A | N/A | 0.97 | |
| 6. | Cinnamic acid | 133.87 | N/A | N/A | N/A | N/A | 0.83 | (106, 170) |
| 7. | Cynarin | 6.03 | N/A | N/A | N/A | N/A | N/A | (106) |
| 8. | Ellagic acid | 0,207 | N/A | N/A | N/A | N/A | 74.8 | (97, 171) |
| 9. | Steviol | 11.1 | N/A | 62.6 | N/A | N/A | 1.69 - 6.15 | 109, 172) |

$C_{max}$ - peak concentration
$IC_{50}$ - half maximal inhibitory concentration
N/A - no data available
NSAIDs - nonsteroidal anti-inflammatory drugs
OAT- organic anion transporter

that one caffeine metabolite, 1-methylxanthine, inhibits OAT1 transport activity (86, 87). OAT1 involvement in the renal excretion of numerous drugs suggests that this inhibition possibly alters the pharmacokinetics of a series of commonly used drugs in humans (87). Thus, wide consumption of caffeine may increase the inhibitory effect of its metabolite, 1-methylxanthine, on renal tubular secretion mediated by OAT1 and contributes to the pharmacokinetics variability of drugs, such as MTX, antivirals, diuretics, β-lactam antibiotics, or NSAIDs that can result in their accumulation and the appearance of harmful side effects or toxicity (86, 87). On the other hand, OAT1 inhibition by 1-methylxanthine can be a potential beneficial mechanism alleviating OAT1-dependent, drug-induced nephrotoxicity and neurotoxicity. Both types of interactions should be potentially considered when administering these medications.

*Flavonoids*

Nowadays, taking dietary supplements has become increasingly popular. Certain components, like flavonoids (*e.g.* apigenin, catechin, epicatechin, and morin), belongs to the polyphenolic compounds widely distributed in fruits and vegetables, as well as red wine, tea and coffee, which belong to the most frequently consumed beverages in the world. They are known for their various beneficial pharmacological properties, such as anti-oxidant, antiviral, antitumor, antiallergic, anti-inflammatory, and antibacterial activities (40). Some research indicates that polyphenols present in the green tea shows a positive effect on the intestinal microbiota and improve renal functions in diabetic nephropathy in rats and mice by alleviation of oxidative stress in renal cells (88-90). In turn, both *in vitro* and *in vivo* studies have shown that certain flavonoids have the ability to regulate its activity. Apigenin inhibits OAT1 activity, while catechin inhibits OAT4 (40, 91). They may cause herb-drug interactions used in combination with antivirals and antibiotics. Therefore, the aforementioned flavonoids could be nephroprotective adjuvants in combination with the nephrotoxic OAT1 or OAT4 substrates. Morin and epicatechin have been demonstrated to be protective against the nephrotoxicity induced by imipenem, which was mediated by OAT3 and led to the accumulation of this antibiotic in the RPTC (34, 40, 91). The latest studies have also shown that epicatechin, catechin, and its derivative compounds (epigallocatechin-3-gallate, epicatechin-3-gallate, epigallocatechin and epicatechin gallocatechingallate) significantly down-regulated URAT1 expression and up-regulated Oat1 and Oat3 expression and thereby inhibited urate reabsorption and enhanced its secretion in mice (29). These data suggest that flavonoids are a possible cause of OAT1-, Oat1-, OAT3-, Oat3-, OAT4-, and Oat4-mediated herbal-drug interactions, as well as that they are probably able to modulate urate transport and increase its elimination in cellular and animal models. Therefore, they should be considered when determining dosing rules for drugs that are OAT1, OAT3, and OAT4 substrates and in future drug development (34, 40, 91, 92).

*Phenolic acids*

Phenolic acids exert beneficial health effects such as anti-oxidant, anti-carcinogenic, and anti-inflammatory activities. They occur in common fruits, vegetables, and beverages (*i.a.* tea and coffee). Belonging to this group, lithospermic acid, rosmarinic acid, and salvianolic acid A were found to be potent competitive inhibitors of OAT1- and OAT3-mediated transport. They demonstrated the capability to elicit cumulative inhibitory effects on OAT1- and OAT3-mediated substrate uptake in HEK293 and genetically modified OAT1-expressing Madin-Darby Canine Kidney cell lines (91, 93). Other phenolic acids, such as caffeic acid, dihydrocaffeic acid, ferulic acid, and dihydroferulic acid, demonstrated the potential to supplement-drug interactions by competitive inhibition of OAT1- and OAT3-mediated transport of antivirals and antifolates observed in the cellular model (41, 91, 93). Inhibition of OAT1 and OAT3 by phenolic acids was identified as having strong potential for significant supplement-drug interactions (41, 91). These compounds might support treatment in the management of OATs-mediated nephrotoxicity (93).

*Stilbene derivatives*

Stilbene derivatives, such as resveratrol, 4-stilbenol, pterostilbene, polydatin, and mulberroside A, are commonly found in fruits (*e.g.* grapes and berries), red wine, and peanuts and exhibit possible beneficial effects on human health (18). The newest research indicates that they exhibited antihyperuricemic and nephroprotective effects in the animal model (84). These effects were mediated by the modulation of renal expression levels of Oat1 for resveratrol, Urat1 for pterostilbene and 4-stilbenol, and Oat1 and for mulberroside and polydatin A in hyperuricemic mice (18, 94). The stilbene derivative 2-stilbenol showed renal protective capability, demonstrated by a decrease in the renal level of uromodulin, the most abundant protein in normal urine associated with hyperuricemia and kidney damage severity, in hyperuricemic mice (94). This proves the protective effect on hyperuricemia with renal dysfunction by resverartol analogues. Foods and dietary supplements containing these stilbene derivatives, or the administration of cytostatic (*i.a.* cisplatin, fludarabine or vinblastine) or diuretics (*e.g.* loop diuretics and thiazidies), are probably natural medicaments to prevent hyperuricemia accompanied by kidney dysfunction in adults (18, 94). Therefore, there is a real chance that the use of dietary supplements containing stilbene derivatives might result in a potential hypouricaemic effect supporting the treatment of patients with kidney injury-, and drug-associated hyperucemia. It is also suggested that DDIs mediated by OAT1 and OAT3 might appear while MTX is co-administered with resveratrol. Increased MTX absorption in the intestine and decreased renal uptake and elimination by resveratrol-dependent inhibition of OAT1 and OAT3 was proven during research on human cell cultures and animals. Despite a significant decrease in renal clearance of MTX, this compound reduces the cytotoxic effects of MTX in renal cells without increasing intestinal toxicity. This suggests that resveratrol could be an effective adjunctive candidate for the clinical application of MTX (51, 94). On the other hand, there is a high risk that the co-administration of this compound, and thus inhibition of MTX excretion, may lead to increased systemic toxicity of this anticancer drug.

*Anthraquinones*

Anthraquinones are components of numerous herbal preparations. They occur in aloe latex, senna, rhubarb, and lichens, among others. Compounds belonging to this group, such as rhein, chrysophanol, physcion emodin, and aloe-emodin, are widely used all over the world due to their laxative, antioxidant, antiviral, anti-cancer, vasodilatory, anti-inflammatory, and antipyretic properties (95, 96). Recent studies showed significant inhibitory effects of the aforementioned compounds on OAT1- and OAT3-mediated substrate uptake in cell lines at clinically relevant concentrations (10, 40, 41, 95). Chrysophanol or physcion significantly increased OAT1 inhibition. Emodin, aloe-emodin, chrysophanol, and physcion markedly increased OAT3 inhibition (10, 95, 96). However, they are not OAT1 and OAT3 substrates. Studies concerning OATs-mediated interactions with rhein based on cellular and animal models

showed strong potential for its interactions at the OAT1, Oat1, OAT3, and Oat3 level, as a result of a combination of this compound and drugs that are OATs substrates (*e.g.* antifolates, antibiotics or NSAIDs) (96, 97). An OATs-mediated herb-drug interaction may also occur when these compounds are co-administered with other anthraquinones. This mechanism potentially explains the influence of rhein and lithospermic acid on blood pressure regulation, *e.g.* by inhibiting the uptake of endogenous OAT3 and Oat3 substrates involved in this process (40, 95). In turn, the inhibition of OATs and Oats by rhein and its metabolites, administered in cell cultures and animal models reflecting osteoarthritis and diabetic nephropathy, significantly reduced the cellular uptake and renal accumulation of MTX, resulting in its decreased renal exposure and a subsequent lowering of MTX-induced nephrotoxicity. On the other hand, it leads to slowed elimination and an increased serum half-life of MTX, which are associated with increased systemic toxicity of this drug (22, 51, 54). Studies based on cell lines also proved that rhein acyl glucuronide can significantly decrease MTX transport by both OAT1 and OAT3. Therefore, diacerein, the rhein, may be a rational, effective adjuvant for MTX clinical application during rheumatoid arthritis pharmacotherapy (98). In addition, even nanomolar concentrations of this antraquinone can cause OAT1- and OAT3-mediated changes in uptake and excretion of many important endogenous compounds, *e.g.* prostaglandins or steroid hormones. This indicates the possibility of significant herb-endogenous molecule interactions as well (10, 42). These data allow speculating that the intake of anthraquinones in the form of dietary supplements possibly suppresses renal excretion and increases the plasma level of OAT1 and OAT3 substrate drugs or endogenous compounds and leads to their accumulation in the body, which may result in the occurrence of toxicity or severity of their adverse effects. On the other hand, OAT1, and OAT3 inhibition by the anthraquinones administration can be a potentially desired protective mechanism against OAT1- and OAT3-dependent, drug-induced hepatotoxicity, neurotoxicity, and nephrotoxicity. All these interactions, both adverse and beneficial, should be included in safety guidelines concerning dosage.

*Soy isoflavones*

Soy and its proteins are common in food and dietary supplement components. Soy is rich in phytoestrogenic isoflavones, such as daidzein and genistein, which are phytoestrogens that interact with estrogen receptors, which are extensively metabolized by glucuronosyltransferases and sulfotransferases, leading to the modulation of their estrogenic activity. Certain phase II metabolites of daidzein (e.g. daidzein-4'-sulfate and daidzein-7'-sulfate) were identified as OAT4 substrates, while conjugates of genistein (genistein-4'-O-sulfate and genistein-7-O-glucuronide) turned out to be OAT1 and OAT3 substrates, respectively, based on HEK293 cell line research. In addition, they were able to inhibit carrier-dependent estrone-sulfate uptake (99, 100).

*Furocoumarins*

Furocoumarins (e.g. psoralen, isopsoralen, and xanthotoxin) are a group of natural products with many biological activities that occur in many herbs (*e.g. Ammi majus*, *Angelica dahurica*, *Carum carvi*, *Levisticum officinale*, *Pimpinella saxifraga*, and *Psolarea corylifolia*), which are consumed daily in large quantities by the population around the world. Furocoumarins exhibit phototoxic properties (101). They are able to settle between DNA base pairs and form non-covalent complexes with DNA. UVA radiation leads to the transformation of these complexes to covalent photoadducts. This may lead to the formation of cyclobutane monoadducts with pyrimidine bases (101-103). Clinical evidence also indicated that the co-administration of furocoumarins can contribute to the toxicity of some nutrients, herbal compounds, and drugs (39, 101, 102). This may be related to their impact on OATs expression. The latest research has proved that Oat1, Oat3, Urat1 mRNA, and protein expression levels in a mouse model were significantly altered after furocoumarin administration (39). These findings suggest that furocoumarins are potentially able to modulate the bioavailability and excretion of many endogenous (*i.a.* uremic toxins) and exogenous compounds (*e.g.* antivirals, NSAIDs, and antibiotics) and impair liver as well as kidney functions in humans mediated by modifying the renal organic anion transport system.

*Lycopene*

Downregulation of Oat1 and Oat3 was observed in rodent's kidneys after cisplatin exposure. Lycopene is a carotenoid pigment and a strong antioxidant with singlet oxygen quenching capacity usually occurring in tomatoes and other fruits and vegetables, such as carrots, watermelons, or papayas (98). Its administration to rats with induced acute renal injury significantly reduces the adverse effects of anti-neoplastic drug cisplatin administration, leading to an increase of Oat1 and Oat3 expression level (45, 104). This indicates that the anti-oxidative effect of lycopene induces a nephroprotective effect against cisplatin-induced acute kidney injury and Oats expression in rats. It also suggests that this compound may be able to protect the kidneys from injury caused by cisplatin nephrotoxicity in humans (104).

*Ellagic acid*

Ellagic acid, a polyphenol present in many fruits (*e.g.* raspberries, strawberries, cranberries, peaches, grapes, and pomegranate) prevented the development of esophageal and colon cancer in animal models. Research based on OAT1- and OAT4-expressing cell lines indicated that OAT1 and OAT4 mediate the efficient transport of ellagic acid, with a very high affinity for OAT1. Its administration caused a dose-dependent, potent inhibition of OAT1 and OAT4 substrate uptake, which indicates possible interactions of ellagic acid with therapeutics and/or endogenous substances through OATs expressed in the kidney and/or the blood-brain barrier (105).

*Cinnamic acid, ferulic acid, and cynarine*

Cinnamic acid, ferulic acid, and cynarine occur in popular food components (*e.g.* cinnamon, corn, Shea butter, and artichoke). They were validated as competitive inhibitors of OAT1 and OAT3 and *in vitro* showed a potent inhibitory effect on OAT1-mediated para-aminohippurate uptake and OAT3-mediated estrone sulfate uptake (106). Therefore, attention should be paid to the daily intake of these compounds during the process of pharmacotherapy, because they may influence the pharmacokinetics and renal elimination of OAT1 and OAT3 substrates (*e.g.* furosemide, acyclovir, adefovir, cidofovir, ibuprofen, indomethacin, ketoprofen, pravastatin, rosuvastatin, cimetidine, quinaprilat, and benzylpenicillin) (10, 106).

*Stevioside and steviol*

The natural sweetener stevioside and its aglycone metabolite, steviol, are becoming increasingly popular in use. It has been shown that they both are able to inhibit the transepithelial

transport of para-aminohippurate in studies on isolated rabbit renal proximal tubules by interfering with basolateral entry. However, early studies did not assess the interactions of stevioside and its metabolite with specific basolateral Oats (107, 108). Later research proved that stevioside is not transported by basolateral Oats. In contrast, both Oat1 and Oat3 potently participate in the cellular transport of steviol. Furthermore, it distinguishes a high affinity for both Oat1 and Oat3 and, hence, it also presented a significant potential to reduce the renal clearance of certain anionic drugs and their metabolites that are OATs substrates *via* human variants of these proteins (109). The basolateral transport of stevioside is possibly connected with the presence of OATP4C1, which is a novel transport protein discovered in the human kidney, among others (111). It seems that this protein is involved in the transport of organic anions, as well as ouabain, digoxin, and large neutral cardiac glycosides, and may play a possible role in stevioside cellular uptake, but this issue still needs to be clarified (109-111).

## SUMMARY

The OATs family participates in the uptake, distribution, and excretion of a great number of endogenous and exogenous organic substances, having a potent effect on their pharmacokinetics, effectiveness, and toxicity. Many herbal preparations and components of dietary supplements, as well as several classes of drugs used in the treatment of major diseases are able to affect each other's pharmacokinetics, efficacy, and toxicity by interactions at the OATs level. These interactions result mainly from the fact that administration of OATs substrates modulates the transmembrane transport of a diverse array of anionic environmental toxins, clinically important therapeutics or herbal preparations and food ingredients, *via* OATs, through the mechanism of competitive inhibition leading to different changes in systemic and local exposures of these compounds. The potential for the above-mentioned substances to interact at the level of OATs resulting in potent interactions with clinically important drugs, emphasizes the need to better understand the impact of transmembrane transport processes on the pharmacokinetics and efficacy of these substances. In addition, some of these substances are able to change OATs expression. Wider knowledge about OATs, especially concerning their specific functions in the body, role in disease states, and intraindividual response to therapeutic treatment, will allow to predict and prevent OATs-related adverse effects or use favorable interactions in pharmacotherapy as well as to rationally design therapeutics targeted to individual transporters and improve safety guidelines concerning drugs dosage. Overall, this might lead to more efficient and safer pharmacotherapy and could be helpful to design drugs with improved bioavailability or predict and reduce adverse dietary supplement-drug and drug-drug interactions or side effects or to take advantage of beneficial interactions, including a prolonged half-life or reduced renal or hepatic toxicity in drug development and their clinical application.

*Abbreviations:* cAMP, cyclic adenosine monophosphate; $Cl^-$, Choride anion; $C_{max}$, peak serum concentration; CNS, central nervous system; DDIs, drug-drug interactions; G, glycosylation site; HEK293, human embryonic kidney cells (line 293); $IC_{50}$, half maximal inhibitory serum concentration; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; P, phosphorylation site; $OA^-$, organic anions; $OH^-$, hydroxyl anion; OAT, organic anion transporter; OATP, organic anion transporting protein; RPTC, renal proximal tubule epithelial cells; URAT1, urate transporter 1.

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