## S7 Table I Literature-reported pharmacokinetically reductive drug combinations, in which reductive effect has been determined by established methods and its molecular mechanism has been revealed.

<table>
<thead>
<tr>
<th>Biochemical class of reductive effect</th>
<th>Drug A (therapeutic or toxic effects and mechanism of actions)</th>
<th>Drug B (mechanism of action related to reductive effect)</th>
<th>Reported reductive effect</th>
<th>Possible mechanism of reductive actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug transport and permeation</td>
<td>Amphotericin B (antileishmanial, formed aggregate with miltefosine)</td>
<td>Miltefosine (antileishmanial, formed aggregate with amphotericin B)</td>
<td>Reduced miltefosine-induced paracellular permeability enhancement in Caco-2 cell monolayers, inhibited uptake of both drugs, decreased transepithelial transport of both drugs</td>
<td>Reduced drug permeability and transport</td>
</tr>
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<td></td>
<td>Gamma-hydroxybutyrate (drug of abuse, increased dopamine concentration, MCT1 transporter mediated its disposition and renal reabsorption)</td>
<td>Luteolin (exhibited MCT1 transporter mediated uptake of gamma-hydroxybutyrate)</td>
<td>Significantly increased renal and total clearances of gamma-hydroxybutyrate</td>
<td>Enhanced drug excretion</td>
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<tr>
<td>Drug distribution and localization</td>
<td>Cisplatin (DNA inter- and intra- strand adduct)</td>
<td>Procainamide hydrochloride (formed cisplatin-procainamide complex)</td>
<td>Reduced cisplatin-induced hepatotoxicity via formation of less toxic platinum complex, leading to inactivation of cisplatin or its highly toxic metabolites and to a different subcellular distribution of platinum</td>
<td>Reduced level of toxic drug by formation of less toxic complex and rearrangement of its subcellular distribution</td>
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<tr>
<td>Drug metabolism</td>
<td>Warfarin (anticoagulant and antithrombotic, affected coagulation proteins that act sequentially to produce thrombin, metabolized by CYP3A4)</td>
<td>Quinidine (stimulated CYP3A4 mediated metabolism of warfarin)</td>
<td>Reduced anticoagulant effect of warfarin by stimulating its metabolism</td>
<td>Enhanced metabolism of active drug into inactive metabolite</td>
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<td></td>
<td>Diclofenac (anti-inflammatory, metabolized into 5-hydroxylated by cytochrome P450 CYP3A4)</td>
<td>Quinidine (stimulated CYP3A4 mediated metabolism of diclofenac)</td>
<td>Increased diclofenac clearance and reduced its plasma concentration by enhanced metabolism</td>
<td>Reduced level of drug by enhanced metabolism</td>
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<td>Mycophenolate mofetil (immunosuppressive, a prodrug whose metabolite mycophenolic acid is a potent and reversible uncompetitive inhibitor of inosine monophosphate dehydrogenase, metabolized by gastrointestinal uridine diphosphate-glucuronosyltransferases)</td>
<td>Rifampin (induced expression of gastrointestinal uridine diphosphate-glucuronosyltransferases)</td>
<td>Drug interaction leads to underexposure and loss of clinical efficacy of mycophenolate mofetil by induction of renal, hepatic, and gastrointestinal uridine diphosphate-glucuronosyltransferases and organic anion transporters</td>
<td>Reduced level of drug by enhanced metabolism</td>
</tr>
</tbody>
</table>
Valproic acid (antiepileptic, increased gabaaergic transmission, reduced release and/or effects of excitatory amino acids, blocked voltage-gated sodium channels, modulated dopaminergic and serotonergic transmission, metabolized into valproic acid glucuronide11)

Carbapenem antibiotics (inhibited the hydrolytic enzyme involved in the hydrolysis of valproic acid glucuronide to valproic acid, resulting in a decrease of plasma concentration of valproic acid12)

Caused seizures in epileptic patients due to lowered plasma levels of valproic acid12,13

Reduced level of drug in plasma by metabolism inhibition

References:

7 Ngui, J. S. et al., In vitro stimulation of warfarin metabolism by quinidine: increases in the formation of 4'- and 10-hydroxywarfarin. Drug Metab Dispos 29 (6), 877 (2001).
8 Ngui, J. S. et al., Cytochrome P450 3A4-mediated interaction of diclofenac and quinidine. Drug Metab Dispos 28 (9), 1043 (2000).