

## BRIEF REPORT

## Effect of Common Medications on the Expression of SARS-CoV-2 Entry Receptors in Kidney Tissue

Narjes Saheb Sharif-Askari<sup>1</sup>, Fatemeh Saheb Sharif-Askari<sup>1</sup>, Masha'al Alabed<sup>1</sup>, Ahmad Abou Tayoun<sup>2,3</sup>, Tom Loney<sup>3</sup>, Mohammed Uddin<sup>3</sup>, Abiola Senok<sup>3</sup>, Saba Al Heialy<sup>3,4</sup>, Rifat Hamoudi<sup>1,5</sup>, Tarek Kashour<sup>6</sup>, Alawi Alsheikh-Ali<sup>3</sup>, Qutayba Hamid<sup>1,4,5</sup> and Rabih Halwani<sup>1,5,7,\*</sup>

Besides the respiratory system, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection was shown to affect other essential organs such as the kidneys. Early kidney involvement during the course of infection was associated with worse outcomes, which could be attributed to the direct SARS-CoV-2 infection of kidney cells. In this study, the effect of commonly used medications on the expression of SARS-CoV-2 receptor, angiotensin-converting enzyme (ACE)2, and TMPRSS2 protein in kidney tissues was evaluated. This was done by *in silico* analyses of publicly available transcriptomic databases of kidney tissues of rats treated with multiple doses of commonly used medications. Of 59 tested medications, 56% modified ACE2 expression, whereas 24% modified TMPRSS2 expression. ACE2 was increased with only a few of the tested medication groups, namely the renin-angiotensin inhibitors, such as enalapril, antibacterial agents, such as nitrofurantoin, and the proton pump inhibitor, omeprazole. The majority of the other medications decreased ACE2 expression to variable degrees with allopurinol and cisplatin causing the most noticeable downregulation. The expression level of TMPRSS2 was increased with a number of medications, such as diclofenac, furosemide, and dexamethasone, whereas other medications, such as allopurinol, suppressed the expression of this gene. The prolonged exposure to combinations of these medications could regulate the expression of ACE2 and TMPRSS2 in a way that may affect kidney susceptibility to SARS-CoV-2 infection. Data presented here suggest that we should be vigilant about the potential effects of commonly used medications on kidney tissue expression of ACE2 and TMPRSS2.

## Study Highlights

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

✓ Angiotensin-converting enzyme (ACE)2 is the main severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) entry receptor. SARS-CoV-2 can directly infect and replicate in human kidney cells. Treatment of kidney organoid with human recombinant soluble ACE2 significantly reduced SARS-CoV-2 infection in a dose-dependent manner. It is not known how commonly used medications affect the expression of these receptors in kidney tissue.

**WHAT QUESTION DID THIS STUDY ADDRESS?**

✓ Whether commonly used medications regulate expression of SARS-CoV-2 receptors in kidney tissue.

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

✓ Through *in silico* analyses, we have shown that commonly used medications affect the expression of

SARS-CoV-2 entry receptors in kidney tissue. This may highlight how these medications would affect susceptibility of the kidney to coronavirus disease 2019 infection.

**HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**

✓ Our data suggested that many of the tested medications, or their combinations, may regulate SARS-CoV-2 receptors expression in kidney tissue and may hence modulate its susceptibility to infection. This may suggest that the effect of the medication on SARS-CoV-2 receptors expression may be considered when selecting drug combinations especially for chronic conditions.

Besides the respiratory system, other organs have been shown to be affected by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection, such as the

gastrointestinal tract,<sup>1</sup> the liver,<sup>2</sup> and the kidneys.<sup>3</sup> Renal impairment has been observed by several studies as a major secondary outcome of coronavirus disease 2019

<sup>1</sup>Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates; <sup>2</sup>Al Jalila Genomics Center, Al Jalila Children's Hospital, Dubai, United Arab Emirates; <sup>3</sup>College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates; <sup>4</sup>Meakins-Christie Laboratories, Research Institute of the McGill University Health Center, McGill University, Montreal, Quebec, Canada; <sup>5</sup>Department of Clinical Sciences, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates; <sup>6</sup>Department of Cardiology, King Fahad Cardiac Center, King Saud University Medical City, Riyadh, Saudi Arabia; <sup>7</sup>Prince Abdullah Ben Khaled Celiac Disease Research Chair, Department of Pediatrics, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia. \*Correspondence: Rabih Halwani (rhalwani@sharjah.ac.ae)

Received: May 8, 2020; accepted: July 17, 2020. doi:10.1111/cts.12862

(COVID-19) infection, following respiratory dysfunction.<sup>4</sup> Acute kidney injury during COVID-19 infection could be due to several factors, including the direct infection of renal cells with SARS-CoV-2, cytokine storm, inflammation, and drug-induced toxicity. The progression of renal injury needs to be correlated clinically with the course of COVID-19 to further understand its underlying mechanisms. In a recent observation by Cheng and colleagues,<sup>3</sup> renal impairment on admission correlated with poor outcomes among patients with COVID-19. The level of renal impairment and elevated baseline serum creatinine were associated with a more severe course of SARS-CoV-2 infection, and with higher likelihood of intensive care unit admission, and mechanical ventilation. This reported increase in serum creatinine early during the infection suggests that it could be attributed to early infection of the kidneys by SARS-CoV-2. On the other hand, late impairments could be a manifestation of systemic inflammation and multi-organ failure or secondary to late infection of the kidneys.

Both SARS-CoV-1<sup>5</sup> and SARS-CoV-2<sup>2</sup> were detected in urine samples. Angiotensin-converting enzyme 2 (ACE2) is the main receptor of SARS-CoV-1 and 2, whereas the transmembrane serine protease, TMPRSS2, is needed to prime the viral spike protein, an essential step for virus binding to ACE2<sup>6</sup> but the binding affinity of SARS-CoV-2 spike protein to ACE2 is much higher than that of SARS-CoV-1.<sup>7</sup> CD147 has also been described as an alternative receptor of SARS-CoV-2 entry to the cell.<sup>8</sup>

ACE2 was previously shown to be strongly expressed in kidney tubules.<sup>9</sup> Recently, Monteil and colleagues found that SARS-CoV-2 can directly infect human tubular kidney cells and has the ability to replicate in the kidney organoid postinfection.<sup>10</sup> They further demonstrated that treatment of kidney organoid with human recombinant soluble ACE2 significantly reduced SARS-CoV-2 infection in a dose-dependent manner.<sup>10</sup> By binding to SARS-CoV-2 spike protein, the recombinant ACE2 is expected to neutralize the viral particles and prevent them from binding to cell surface receptors, and hence lowers infectivity and viral load. That said, the levels of ACE2 expression in the kidney tissues could influence renal susceptibility to SARS-CoV-2 infection. In this study, we set to examine the effect of commonly used medications on the expression of ACE2, TMPRSS2, and CD147 in kidney tissues. By applying bioinformatic analyses of publicly available data, we have determined the ability of 59 commonly used medications to regulate the expression of SARS-CoV-2 receptors in kidney tissues.

## METHODS

Bioinformatic analyses were conducted to evaluate the effect of different groups of medications on mRNA expression levels of ACE2, TMPRSS2, and CD147 gene signatures in rat kidney tissues. Publicly available gene expression datasets on Open Toxicogenomic Project-Genomics Assisted Toxicity Evaluation System<sup>11</sup> and DrugMatrix toxicogenomic database were used. In these two toxicogenomic projects, rats were treated with different medication groups in biological triplicates for different time points. For the purpose of this study, we selected the longest exposure time available

for each medication. From the Toxicogenomic Project-Genomics Assisted Toxicity Evaluation System study, we used the data of *in vivo* daily treatments with moderate and high doses for a duration of 29 days. From the DrugMatrix database, we had chosen the daily *in vivo* treatments that were mainly administered in a single dose manner with the longest post-treatment time points ranging from 1 day to 7 days. Hybridization to the whole genome was performed for all included samples using the RG230\_2.0 rat GeneChip (Affymetrix, CA).

Before data preprocessing, all mRNA expression data were evaluated for quality control, and all poor-quality data were removed. The raw Affymetrix data were normalized and log transformed. Microarray data (CEL files) were preprocessed with the Robust Multi-Array Average technique using R software.<sup>12</sup> Log-transformed normalized intensities were used in the final analyses; and differentially expressed genes between treated and control samples were carried out using Linear Models for MicroArray data (LIMMA) analyses.<sup>13,14</sup> Statistical analysis was performed using R (version 3.0.2) and Prism (version 8; GraphPad Software) softwares. For all analyses, *P* values < 0.05 were considered significant.

## RESULTS AND DISCUSSION

In this study, bioinformatic analyses of publicly available drug databases were conducted to evaluate the effect of commonly used medications on kidney tissue expression of SARS-CoV-2 receptors (**Figure 1**). Kidney tissue is known to express ACE2 at higher levels and TMPRSS2 and CD147 at comparable levels to bronchial lung tissue (**Figure 1a**). Among the viral entry genes, renal expression of ACE2 was affected with a larger number of medications and to a greater extent. Of 59 tested medications, 56% affected ACE2 (15% increased and 41% decreased expression), 27% affected CD147 (19% increased and 8% decreased expression), whereas 24% affected TMPRSS2 (16% increased and 8% decreased expression).

Besides acting as the main receptor for SARS-CoV-1 and SARS-CoV-2, ACE2 enzyme plays an essential role in protecting multiple organs against injury, including the lungs,<sup>15</sup> the heart,<sup>16</sup> and the kidneys.<sup>17</sup> Therefore, although upregulation of ACE2 may increase susceptibility to COVID-19 infection in the early phase of the disease, its suppression could lead to an extensive acute kidney injury at later stages.<sup>17</sup> In our study, ACE2 was increased with some of the tested medication groups, namely the renin-angiotensin inhibitors, such as enalapril, antibacterial agents, such as nitrofurantoin, and proton pump inhibitor medication, including omeprazole. The majority of the other medications decreased ACE2 expression to variable degrees. The most pronounced downregulation was observed with allopurinol (gout medication) and cisplatin (antineoplastic agent; **Figure 1b,c**). The average ACE2 fold change caused by each medication class was calculated and displayed in **Figure 1b**. Interestingly, among the tested analgesics, acetaminophen did not change the ACE2 expression level; whereas multiple nonsteroidal anti-inflammatory drug medications, such as indomethacin and ibuprofen, significantly lowered the mRNA levels of this gene.

The expression level of TMPRSS2 was increased with a number of medications, such as diclofenac, furosemide, and dexamethasone (**Figure 1d**). Other medications, such as allopurinol, cisplatin, and acetaminophen, downregulated this membrane-associated enzyme. To our knowledge, this effect of commonly used medications on the renal expression of TMPRSS2 was not reported before. The observed increase in expression of TMPRSS2 will lead to an increase in priming of the virus spike protein and, hence, may enhance the level of SARS-CoV-2 infectivity within this tissue.<sup>18</sup>

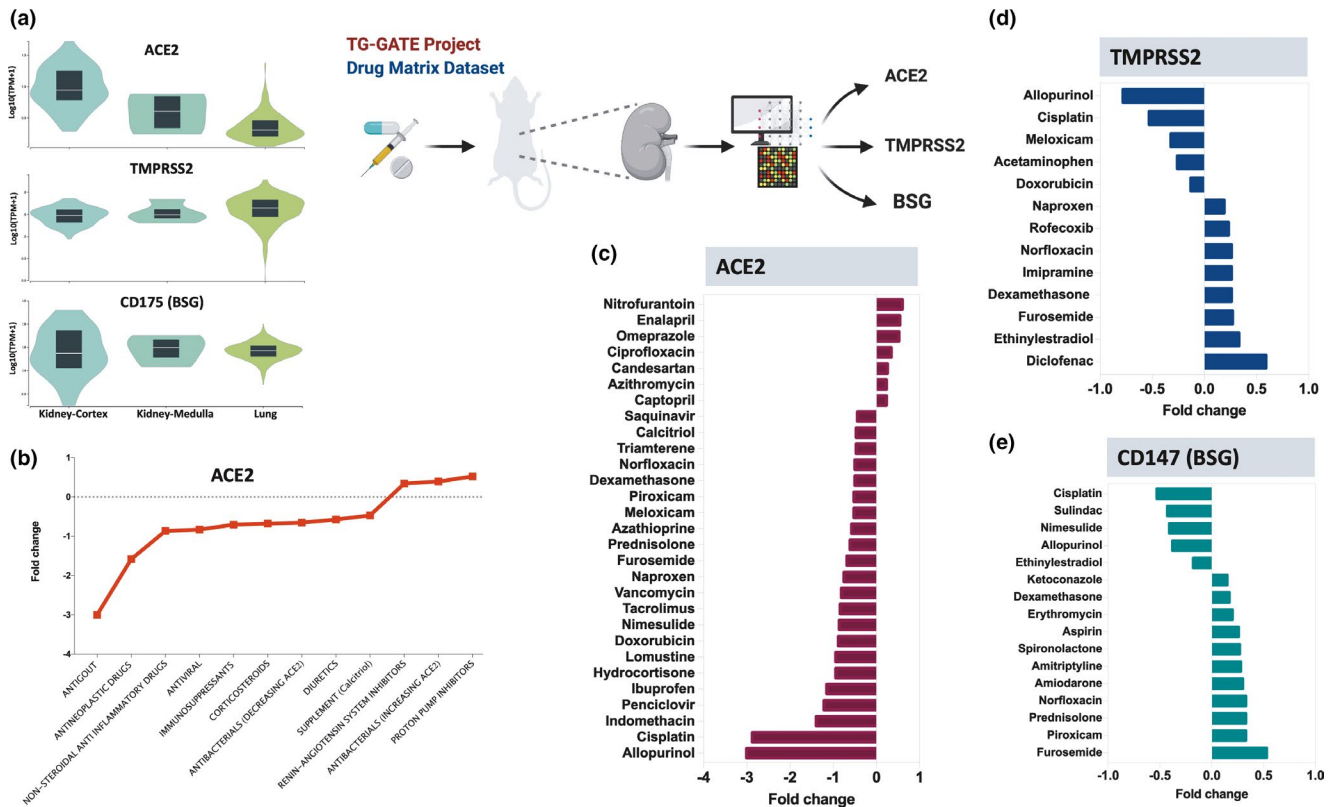
We have also tested the effect of these medications on CD147 (Basigin).<sup>19</sup> Furosemide, piroxicam, prednisolone, and norfloxacin were among the top upregulating medications for CD147 expression, whereas cisplatin, sulindac, and nimesulide were among the top suppressors of its expression (**Figure 1e**). The regulatory effect of all the different medications on the expression of SARS-CoV-2 receptors is presented in **Table 1**.

Treatment of common comorbidities, such as hypertension, often requires the chronic use of multiple medications; which may result in an additive regulatory effect on the expression of ACE2 and TMPRSS2.

Given the fact that SARS-CoV-2 infection does not increase the expression of ACE2 and TMPRSS2,<sup>6,20,21</sup> the combined effect of these chronically used medications may modulate the susceptibility of kidney tissue to SARS-CoV-2

infection. For example, captopril and omeprazole, if used in combination, both increase ACE2 levels. Furosemide increases TMPRSS2 expression, despite lowering the ACE2 level, which may enhance viral priming. On the other hand, a single or combined treatment with penciclovir and acetaminophen, both of which lowers expression of entry receptors, is expected to decrease the availability of receptors for SARS-CoV-2 entry to the cells. Nonetheless, ACE2 plays a protective role against lung and kidney injury<sup>22,23</sup> and, therefore, the net biological effects of the single or combination drug therapy on the expression of these receptors is still to be elucidated.

Data presented here provides evidence that medications may regulate the expression of SARS-CoV-2 receptors in the kidney tissues and hence may modulate the susceptibility of the kidneys to SARS-CoV-2 infection. The mechanisms regulating drug-induced receptor expression are unknown and requires further investigations. Previous *in vitro* studies of gene expression changes in response to drugs like cisplatin and ochratoxin A in rat and human kidney cell lines and rat kidney tissue slices mirror the observed *in vivo* gene expression changes in rats.<sup>24–26</sup> However, this does not provide proof that those *in vivo* drug-induced expression changes of SARS-CoV-2 receptors we observed in this bioinformatics-based study would reflect similar changes in humans. Moreover, our results are based on public gene expression



**Figure 1** Effect of common medications on the expression levels of severe acute respiratory syndrome-coronavirus 2 entry receptors in kidney. (a) Shows the baseline expression of angiotensin-converting enzyme (ACE)2 and TMPRSS2 in healthy lung and kidney tissues extracted from the Genotype-Tissue Expression project. (b) Represents the main medication classes that affected the expression levels of ACE2. (c–e) Shows medications causing the highest and lowest fold change for ACE2 TMPRSS2, and CD147 expression levels.

**Table 1** Effect of common medications treatments on expression levels of renal SARS-Cov-2 receptors of *ACE2* and *TMPRSS2*

Medication	Classifications	Repeat dose mg/kg	ACE2 mRNA fold change ( <i>P</i> value)	TMPRSS2 mRNA fold change ( <i>P</i> value)	BSG (CD147) mRNA fold change ( <i>P</i> value)
Acetaminophen, 29 days, oral	Analgesics	600	Nonsignificant	<b>-0.26 (<i>P</i> = 0.002)**</b>	Nonsignificant
	Analgesics	1,000	Nonsignificant	Nonsignificant	Nonsignificant
Captopril, 29 days, oral	Renin-angiotensin system inhibitors	100	Nonsignificant	Nonsignificant	Nonsignificant
	Renin-angiotensin system inhibitors	300	<b>0.23 (<i>P</i> = 0.045)*</b>	Nonsignificant	Nonsignificant
	Renin-angiotensin system inhibitors	1,000	Nonsignificant	Nonsignificant	Nonsignificant
Captopril, 5 days, oral	Renin-angiotensin system inhibitors	1,750	Nonsignificant	Nonsignificant	Nonsignificant
Candesartan, 3 days, oral	Renin-angiotensin system inhibitors	1,300	<b>0.25 (<i>P</i> = 0.021)*</b>	Nonsignificant	Nonsignificant
Enalapril, 29 days, oral	Renin-angiotensin system inhibitors	300	Nonsignificant	Nonsignificant	Nonsignificant
	Renin-angiotensin system inhibitors	600	<b>0.54 (<i>P</i> &lt; 0.0001)****</b>	Nonsignificant	Nonsignificant
Ramipril, 3 days, oral	Renin-angiotensin system inhibitors	1,500	Nonsignificant	Nonsignificant	Nonsignificant
Spironolactone, 5 days	Diuretics	300	Nonsignificant	Nonsignificant	<b>0.27 (<i>P</i> = 0.002)**</b>
Triamterene, 29 days, oral	Diuretics	50	Nonsignificant	Nonsignificant	Nonsignificant
	Diuretics	150	<b>-0.47 (<i>P</i> = 0.002)**</b>	Nonsignificant	Nonsignificant
Furosemide, 5 days, oral	Diuretics	375	<b>-0.68 (<i>P</i> = 0.006)**</b>	<b>0.27 (<i>P</i> = 0.01)*</b>	<b>0.53 (<i>P</i> = 0.0001)***</b>
Diclofenac, 5 days, oral	Analgesics › nonsteroidal anti-inflammatory drugs	3.5	Nonsignificant	<b>0.59 (<i>P</i> = 0.0003)***</b>	Nonsignificant
Ibuprofen, 5 days, oral	Analgesics › nonsteroidal anti-inflammatory drugs	263	<b>-1.15 (<i>P</i> = 0.048)**</b>	Nonsignificant	Nonsignificant
Indomethacin, 29 days, oral	Analgesics › nonsteroidal anti-inflammatory drugs	1.6	Nonsignificant	Nonsignificant	Nonsignificant
	Analgesics › nonsteroidal anti-inflammatory drugs	5	<b>-1.39 (<i>P</i> = 0.048)**</b>	Nonsignificant	Nonsignificant
Mefenamic acid, 5 days, oral	Analgesics › nonsteroidal anti-inflammatory drugs	93	Nonsignificant	Nonsignificant	Nonsignificant
Meloxicam, 1 day, oral	Analgesics › nonsteroidal anti-inflammatory drugs	33	<b>-0.52 (<i>P</i> = 0.0009)***</b>	<b>-0.32 (<i>P</i> = 0.006)**</b>	Nonsignificant
Piroxicam, 5 days, oral	Analgesics › nonsteroidal anti-inflammatory drugs	14	<b>-0.52 (<i>P</i> = 0.01)*</b>	Nonsignificant	<b>0.33 (<i>P</i> = 0.0008)</b>
Naproxen, 1 day, oral	Analgesics › nonsteroidal anti-inflammatory drugs	134	<b>-0.75 (<i>P</i> = 0.002)**</b>	<b>0.19 (<i>P</i> = 0.022)*</b>	Nonsignificant
Nimesulide, 5 days, oral	Analgesics › nonsteroidal anti-inflammatory drugs	162	<b>-0.86 (<i>P</i> = 0.02)**</b>	Nonsignificant	<b>-0.41 (<i>P</i> = 0.001)**</b>
Sulindac, 1 day, oral	Analgesics › nonsteroidal anti-inflammatory drugs	23	Nonsignificant	Nonsignificant	Nonsignificant
	Analgesics › nonsteroidal anti-inflammatory drugs	64	Nonsignificant	Nonsignificant	<b>-0.43 (<i>P</i> = 0.002)**</b>
Rofecoxib, 1 day, oral	Selective nonsteroidal anti-inflammatory drugs	755	Nonsignificant	<b>0.23 (<i>P</i> = 0.006)**</b>	Nonsignificant
Dexamethasone, 3 days, oral	Corticosteroids	300	<b>-0.50 (<i>P</i> = 0.022)*</b>	<b>0.26 (<i>P</i> = 0.013)*</b>	<b>0.17 (<i>P</i> = 0.032)*</b>
Hydrocortisone, 5 days, s.c.	Corticosteroids	65	<b>-0.94 (<i>P</i> = 0.002)**</b>	Nonsignificant	Nonsignificant
Prednisolone, 1 day, oral	Corticosteroids	184	<b>-0.61 (<i>P</i> &lt; 0.0001)****</b>	Nonsignificant	<b>0.33 (<i>P</i> = 0.005)**</b>
Methyltestosterone, 29 days, oral	Androgens	100	<b>0.42 (<i>P</i> = 0.0007)***</b>	Nonsignificant	Nonsignificant
	Androgens	300	<b>0.37 (<i>P</i> = 0.006)**</b>	Nonsignificant	Nonsignificant
Ethinylestradiol, 29 days, oral	Contraceptives	3	Nonsignificant	<b>0.33 (<i>P</i> = 0.0004)***</b>	<b>-0.18 (<i>P</i> = 0.03)*</b>
	Contraceptives	10	Nonsignificant	<b>0.32 (<i>P</i> = 0.002)**</b>	Nonsignificant

(Continues)

Table 1 (Continued)

Medication	Classifications	Repeat dose mg/kg	ACE2 mRNA fold change (P value)	TMPRSS2 mRNA fold change (P value)	BSG (CD147) mRNA fold change (P value)
Omeprazole, 29 days, oral	Proton pump inhibitors	300	<b>0.52 (P = 0.001)**</b>	Nonsignificant	Nonsignificant
	Proton pump inhibitors	1,000	Nonsignificant	Nonsignificant	Nonsignificant
Penciclovir, 5 days, s.c.	Antiviral	1,200	<b>-1.21 (P = 0.013)*</b>	Nonsignificant	Nonsignificant
Saquinavir_1d_Oral	Antiviral	1,200	<b>-0.44 (P = 0.0002)*</b>	Nonsignificant	Nonsignificant
Ritonavir, 1 d, Oral	Antiviral	1,200	Nonsignificant	Nonsignificant	Nonsignificant
Gentamicin, 29d, oral	Antibacterials	30, 100	Nonsignificant	Nonsignificant	Nonsignificant
Vancomycin, 5 days, i.v.	Antibacterials	160	<b>-0.81 (P = 0.002)**</b>	Nonsignificant	Nonsignificant
Amikacin, 5 days, i.p.	Antibacterials	160	Nonsignificant	Nonsignificant	Nonsignificant
Ciprofloxacin, 29 days, oral	Antibacterials	300	<b>0.34 (P = 0.008)**</b>	Nonsignificant	Nonsignificant
	Antibacterials	1,000	<b>0.24 (P = 0.04)*</b>	Nonsignificant	Nonsignificant
Norfloxacin, 5 days, oral	Antibacterials	1,500	<b>-0.5 (P = 0.004)**</b>	<b>0.26 (P = 0.007)**</b>	<b>0.33 (P = 0.0007)***</b>
Cephalexin, 3 days, oral	Antibacterials	2,500	Nonsignificant	Nonsignificant	Nonsignificant
Azithromycin, 5 days	Antibacterials	225	<b>0.23 (P = 0.04)*</b>	Nonsignificant	Nonsignificant
Erythromycin ethylsuccinate, 29 days, oral	Antibacterials	300	Nonsignificant	Nonsignificant	<b>0.11 (P = 0.024)*</b>
	Antibacterials	1,000	Nonsignificant	Nonsignificant	<b>0.2 (P = 0.003)**</b>
Nitrofurantoin, 29 days, oral	Antibacterials	30	Nonsignificant	Nonsignificant	Nonsignificant
	Antibacterials	100	<b>0.6 (P = 0.02)*</b>	Nonsignificant	Nonsignificant
Ketoconazole, 29 days, oral	Antifungals	30	Nonsignificant	Nonsignificant	Nonsignificant
	Antifungals	100	Nonsignificant	Nonsignificant	<b>0.15 (P = 0.04)*</b>
Ethambutol, 3 days, oral	Antimycobacterials	998	Nonsignificant	Nonsignificant	Nonsignificant
Rifampicin, 29 days, oral	Antimycobacterials	60, 200	Nonsignificant	Nonsignificant	Nonsignificant
Cyclophosphamide, 29 days, oral	Antineoplastic drugs	5, 15	Nonsignificant	Nonsignificant	Nonsignificant
Cisplatin, 29 days, oral	Antineoplastic drugs	0.1	Nonsignificant	Nonsignificant	Nonsignificant
	Antineoplastic drugs	0.3	<b>-0.83 (P = 0.0005)***</b>	Nonsignificant	Nonsignificant
	Antineoplastic drugs	1	<b>-2.87 (P &lt; 0.0001)****</b>	<b>-0.53 (P &lt; 0.0001)****</b>	<b>-0.53 (P &lt; 0.0001)****</b>
Lomustine, 29 days, oral	Antineoplastic drugs	2	Nonsignificant	Nonsignificant	Nonsignificant
	Antineoplastic drugs	6	<b>-0.94 (P &lt; 0.0001)****</b>	Nonsignificant	Nonsignificant
Doxorubicin, 29 days, oral	Antineoplastic drugs	0.3	Nonsignificant	-0.13(P = 0.038)*	Nonsignificant
	Antineoplastic drugs	1	<b>-0.88 (P = 0.026)***</b>	Nonsignificant	Nonsignificant
Imipramine, 29 days, oral	Antidepressants	30	<b>-0.30 (P = 0.002)**</b>	Nonsignificant	Nonsignificant
	Antidepressants	100	Nonsignificant	0.26 (P = 0.009)**	Nonsignificant
Amitriptyline, 1 day, oral	Antidepressants	160	Nonsignificant	Nonsignificant	<b>0.28 (P = 0.04)**</b>
Valproic acid, 29 days, oral	Antiepileptics	150	Nonsignificant	Nonsignificant	Nonsignificant
	Antiepileptics	450	<b>-0.3 (P = 0.042)**</b>	Nonsignificant	Nonsignificant
Allopurinol, 29 days, oral	Antigout	50	Nonsignificant	Nonsignificant	Nonsignificant
	Antigout	150	<b>-3 (P &lt; 0.0001)****</b>	<b>-0.78 (P = 0.004)**</b>	<b>-0.38 (P = 0.018)*</b>
Azathioprine, 5 days, oral	Immunosuppressants	54	<b>-0.57 (P = 0.003)**</b>	Nonsignificant	Nonsignificant
Methotrexate, 3 days, oral	Immunosuppressants	27	Nonsignificant	Nonsignificant	Nonsignificant
Tacrolimus, 5 days, oral	Immunosuppressants	134	<b>-0.84 (P &lt; 0.0001)****</b>	Nonsignificant	Nonsignificant
Cyclosporin, 29 days, oral	Immunosuppressants	30, 100	Nonsignificant	Nonsignificant	Nonsignificant
Aspirin, 1 day, oral	Antiplatelet drugs	375	Nonsignificant	Nonsignificant	<b>0.26 (P = 0.01)*</b>

(Continues)



Table 1 (Continued)

Medication	Classifications	Repeat dose mg/kg	ACE2 mRNA fold change (P value)	TMPRSS2 mRNA fold change (P value)	BSG (CD147) mRNA fold change (P value)
Amiodarone, 5 days, oral	Antiarrhythmics	147	Nonsignificant	Nonsignificant	<b>0.3 (P = 0.006)*</b>
Fenofibrate, 5 days, oral	Lipid modifying drugs	215	Nonsignificant	Nonsignificant	Nonsignificant
Gemfibrozil, 7 days, oral	Lipid modifying drugs	700	Nonsignificant	Nonsignificant	Nonsignificant
Clofibrate, 29 days, oral	Lipid modifying drugs	100, 300	Nonsignificant	Nonsignificant	Nonsignificant
Atorvastatin, 3 days, oral	Lipid modifying drugs	300	Nonsignificant	Nonsignificant	Nonsignificant
Calcitriol, 5 days, oral	Supplement	0.04	<b>-0.47 (P = 0.009)**</b>	Nonsignificant	Nonsignificant

Effect of medications on expression of ACE2 and TMPRSS2 was measured with two controls vs. two treatments per dose. For all analyses,  $p < 0.05$  was considered significant, presented as bold value. \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ , \*\*\*\*  $P < 0.0001$ .

ACE2, angiotensin-converting enzyme; BSG, Basigin; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

For all analyses,  $P < 0.05$  was considered significant, presented as bold value.

\* $P < 0.05$ ;

\*\* $P < 0.01$ ;

\*\*\* $P < 0.001$ ;

\*\*\*\* $P < 0.0001$ .

datasets and thus they may or may not reflect changes in protein expression. Therefore, confirmatory experiments at the mRNA and protein levels are needed to support our findings. Additionally, population studies are necessary to ultimately understand the clinical implications of these findings and further guide the proper use of these medications or identify safer alternatives.

#### Acknowledgments.

None.

**Conflict of Interest.** The authors declared no competing interests for this work.

**Funding.** This research has been financially supported by Tissue Injury and Repair (TIR) group operational grant (Grant code: 150317); COVID-19 research grant; seed grant (Grant code: 2001090275); and by collaborative research grant (Grant code: 2001090278) to RH, University of Sharjah, UAE; and by a Sandoq Al Watan Applied Research & Development grant to RH; and by Prince Abdullah Ben Khalid Celiac Disease Research Chair, under the Vice Deanship of Research Chairs, King Saud University, Riyadh, Kingdom of Saudi Arabia.

**Author Contributions.** N.S.A., A.A.T., R.H., A.A., and R.H. wrote the manuscript. R.H., N.S.A., F.S.A., Q.H., A.A.T., T.L., M.U., and T.K. designed the research. N.S.A., F.S.A., M.A., and R.H. performed the research. N.S.A., F.S.A., M.A., A.S., and S.A. analyzed the data.

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