Pharmacogenomics of genetic polymorphism within the genes responsible for SARS-CoV-2 susceptibility and the drug-metabolising genes used in treatment

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Summary
The ongoing outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents a significant challenge to international health. Pharmacogenomics aims to identify the different genetic variations that exist between individuals and populations in order to determine appropriate treatment protocols to enhance the efficacy of drugs and reduce their side-effects. This literature review provides an overview of recent studies of genetic polymorphisms in genes that mediate the SARS-CoV-2 infection mechanism (ACE1, ACE2, TMPRSS2 and CD26). In addition, genetic variations in the drug-metabolising enzyme genes of several selected drugs used in the treatment of COVID-19 are summarised. This may help construct an effective health protocol based on genetic biomarkers to optimise response to treatment. Potentially, pharmacogenomics could contribute to the development of effective high-throughput assays to improve patient evaluation, but their use will also create ethical, medical, regulatory, and legal issues, which should now be considered in the era of personalised medicine.

KEYWORDS
COVID-19, drug metabolising genes, pharmacogenomics, SARS-CoV-2, susceptibility to SARS-CoV-2

Abbreviations: 6-HB, six-helical bundle; ABCB1, ATP binding cassette subfamily B member 1; ABCG2, ATP binding cassette subfamily G member 2; ACE1, angiotensin-converting enzyme 1; ACE2, angiotensin-converting enzyme 2; ACS, acute coronary syndrome; AT1R, angiotensin II receptor type 1; CD26/DPP4, dipeptidyl peptidase 4; CETP, cholesteryl ester transfer protein; COVID-19, coronavirus disease 2019; CRHR1, corticotropin-releasing hormone receptor 1; CRP, C-reactive protein; CYP, cytochrome P450; E protein, envelope protein; FDA, Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase; HCoV-229E, human coronavirus 229E; HCoV-HKU1, human coronavirus HKU1; HCoV-OC43, human coronavirus OC43; HE, human coronavirus; HIV, human immunodeficiency virus; HR1, heptad repeat 1; HR2, heptad repeat 2; IFIT1, tetratricopeptide repeats 1; IFITM3, interferon-induced transmembrane protein 3; IL-10, Interleukin 10; IL-6, Interleukin 6; ITPA, inosine triphosphate pyrophosphatase; LEP, leptin; M protein, membrane protein; MCP-1, monocyte chemoattractant protein-1; MERS-CoV, middle east respiratory syndrome; N protein, nucleocapsid protein; NR3C1, nuclear receptor subfamily 3 group C member 1; NSTEMI, non-ST-segment elevation myocardial infarction; OAS1/2/3/L, 2'-5'-oligoadenylate synthetase 1/2/3/L; OATP1B1, organic anion transporting polypeptide 1B1; PD, peptidase domain; PHEIC, public health emergency of international concern; RAAS, renin-angiotensin-aldosterone system; RBD, receptor-binding domain; RBM, receptor-binding motif; S protein, spike glycoprotein; SARS-CoV-1, severe acute respiratory syndrome coronavirus 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLCO1B3, solute carrier organic anion transporter family member 1B3; SNV, single nucleotide polymorphism; STEMI, ST-segment elevation myocardial infarction; TMPRSS2, transmembrane protease/serine subfamily member 2; TNFα, tumour necrosis factor-alpha; VDR, vitamin D receptor; WHO, World Health Organization.
In December 2019, many cases of pneumonia stemming from an unknown aetiology were reported in Wuhan, Hubei Province, China. Throat swab samples were taken from patients in January 2020, which led to the identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus as the cause of coronavirus disease 2019 (COVID-19).\(^1\) SARS-CoV-2, has since infected and killed millions of people around the world, prompting the World Health Organization (WHO) to declare SARS-CoV-2 to be a global pandemic and a public health emergency of international concern (PHEIC) on March 11. Countries were quick to implement measures and restrictions to reduce the spread of the virus.\(^2\) As of November 13, more than 53,000,000 confirmed cases and 1,302,000 deaths have been reported around the world according to the WHO.\(^3\) Epidemiological studies have demonstrated a large disparity in the infection and mortality rates between men and women. This could be attributed to the difference between copies of the number of X-linked genes that play an important role in the immune response.\(^4,5\) Furthermore, more than 50% of fatalities were reported among elderly people (more than 60 years old) and those who have underlying medical conditions such as cardiovascular disease, diabetes, chronic respiratory disease and hypertension.\(^6\) In contrast, children and infants have shown low morbidity and mortality rates, and moderate symptoms regardless of gender.\(^6\) The symptoms that result from COVID-19 vary; some patients are asymptomatic, while others show mild or severe symptoms including fever, muscle pain, difficulty breathing and a loss of taste or smell.\(^7\)

Pharmacogenomics reveals the influence of genetic polymorphisms in drug response. These genetic variations are generally recognised as one of the major contributors to the individual or ethnic variations in the toxicity and efficacy of drugs. Pharmacogenomics gives new insights into the management, prevention and treatment of COVID-19 by analysing genetic variants and taking effective action for each patient based on these genetic differences.\(^8\) Research should focus on the genes (including receptors, transporters and enzymes) that facilitate entry and infection of SARS-CoV-2.

Furthermore, several drugs have been investigated for treating COVID-19. Studying the genetic variation of genes responsible for drug metabolism (pharmacodynamics and pharmacokinetics) assists in guiding personalised treatment programmes by examining the efficacy and toxicity levels of particular drugs. This review aims to summarise the pharmacogenomic studies available for the genetic biomarkers that could influence susceptibility to SARS-CoV-2 and the drug metabolism of several candidate drugs used in its treatment. At the time of writing, remdesivir and dexamethasone have been licensed based on the results of randomised controlled trials and another RCT of inhaled interferon-beta reports clinical benefit by inhibiting the cytokine storm that underlies severe COVID-19.\(^9,10\) All other drugs mentioned here are in early phase clinical trials.

Coronaviruses are a family of viruses enveloped with a positive-sense single-strand RNA and helical symmetry capsid.\(^11\) Coronaviruses are part of the family Coronaviridae, and subfamily Orthocoronavirinae, and comprise four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus.

Of the approximately 35 strains of coronaviruses, seven strains are known to infect humans: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1), Middle East Respiratory Syndrome (MERS-CoV), Human Coronavirus 229E (HCoV-229E), Human Coronavirus NL63 (HCoV-NL63), Human Coronavirus OC43 (HCoV-OC43) and Human Coronavirus HKU1 (HCoV-HKU1). All these strains can infect humans and can cause mild to severe respiratory infections (Table 1). However, several studies have shown that SARS-CoV-2 can also infect the nervous, circulatory, digestive and urinary systems, as well as the eyes.\(^12,13\) Both SARS-CoV-1 and MERS-CoV have caused outbreaks of severe acute respiratory syndrome (SARS) over the last two decades.\(^14\) The genetic material of SARS-CoV-2 constitutes approximately 29,811 nucleotides (between 26 and 32 kilobases) and possesses 14 open reading frames encoding 27 proteins.\(^15\) The SARS-CoV-2 genome has also shown a high homology with SARS-CoV-1 (79.5%) and moderate homology with MERS-CoV (50%).\(^16\) Structural proteins in SARS-CoV-2 particles, include spike glycoprotein (S), envelope protein (E), membrane protein (M), nucleocapsid protein (N) and hemagglutinin-esterase protein (HE) (Figures 1(a) and 2).\(^17\)

Additionally, there are eight accessory proteins 3a, 3b, p6, 7a, 7, 8, 9b, and orfl4, that play a role in the viral replication process (Figure 1(b)).\(^17\) The host protease, transmembrane protease/serine subfamily member 2 (TMPRSS2) mediates proteolytic cleavage of the S protein resulting in two subunits, receptor-binding S1 and membrane-fusion S2 that play an essential role in the virus-receptor binding and integration with the host plasma membrane. Within the S1 subunit, there are two functional domains: the receptor-binding domain (RBD) and the receptor-binding motif (RBM) (Figure 1(c)).\(^18,19\) The S2 subunit is structured from the cytoplasm domain, a transmembrane domain, the heptad repeat 1 (HR1) and 2 (HR2) regions and the fusion peptide region (Figure 1(c)).\(^18,19\)

Respiratory droplets generated by coughing and sneezing are the most common route of transmission for SARS-CoV-2.\(^20\) SARS-CoV-2 virions have also been detected in saliva, urine and faeces.\(^20\) Moreover, SARS-CoV-2 has been found in conjunctival secretions, gastrointestinal tissue, and in tear samples from COVID-19 patients.\(^21,22\) The angiotensin-converting enzyme 2 (ACE2) receptor—which is widely expressed in different organs such as the lungs, heart, intestines and kidneys—acts as the principal entry point for SARS-CoV-2 into cells. The virus entry process to the host cell begins when the RBD binds to a specific enzymatic domain in the ACE2 receptor, known as the peptidase domain (PD). At the same time, three HR1 are combined into a trimer-coiled structure,
followed by attachment of three HR2 subunits into the hydrophobic grooves of the trimeric-coiled structure results in the construction of the six-helical bundle (6-HB).24,25 This leads to fusion between the host and the viral membrane, allowing SARS-CoV-2 to enter the host cells via endocytosis.26 Inside infected cells, the virus genome is replicated and proliferated, resulting in the synthesis of chemokines and cytokines. T cells and macrophages are then drawn to the infected cells and stimulate adaptive immune responses.27–29

### 2.1 SARS-CoV-2 pharmacogenomics

Pharmacogenomic studies should be focused on the genetic variation found in the genes that relate to the entry and infection mechanisms of the virus. Moreover, many genes are implicated, both directly and indirectly, in the metabolism of selected drugs to treat COVID-19. The polymorphisms in these genes should therefore be analysed to ensure an effective response rate and a low level of toxicity.

**TABLE 1** Coronavirus strains that infect humans

| Coronaviridae genera | Coronavirus strains               | Year of discovery | Main receptor                                      | Intermediate host |
|----------------------|-----------------------------------|-------------------|----------------------------------------------------|-------------------|
| Alphacoronavirus     | Human coronavirus 229E (HCoV-229E) | 1966, Africa      | Aminopeptidase N                                   | Camelids          |
|                      | Human coronavirus NL63(HCoV-NL63)  | 2004, Netherlands  | Angiotensin-converting enzyme 2                    | Unknown           |
| Betacoronavirus      | Human coronavirus OC43 (HCoV-OC43) | 1967, unknown     | N-acetyl-9-O-acetylneuraminic acid                 | Cattle            |
|                      | Human coronavirus HKU1 (HCoV-HKU1)| 2004, Hong Kong   | N-acetyl-9-O-acetylneuraminic acid receptor        | Unknown           |
|                      | Severe acute respiratory syndrome coronavirus (SARS-CoV-1)| 2002, Foshan, China | Angiotensin-converting enzyme 2 | Palm civet        |
|                      | Middle East respiratory syndrome (MERS-CoV) | 2012, Jeddah, Saudi Arabia | Dipeptidyl peptidase 4 | Camel              |
|                      | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)| 2019, Wuhan, China | Angiotensin-converting enzyme 2 | Malayan Pangolins |

**FIGURE 1** (a) SARS-CoV-2 structure showing the structural proteins, S, M, E and HE. (b) The genome organisation of SARS-CoV-2. (c) TMPRSS2 cleaves the S protein into two subunits [S1 subunit, and S2 subunit] during the infection process.
3 | PHARMACOGENOMICS OF GENES RESPONSIBLE FOR SUSCEPTIBILITY TO SARS-CoV-2

3.1 | Angiotensin-converting enzyme 1 and 2

Angiotensin-converting enzyme 1 and ACE2 are both part of the renin-angiotensin-aldosterone system (RAAS) which is responsible for controlling blood pressure. In a healthy individual, both ACE1 and ACE2 regulate the RAAS system through levels of both enzymes. Studies in mice show the protective effect of ACE2, whereby severe lung failure is correlated with ACE2 downregulation. Interestingly, SARS-CoV-2 infection also downregulates ACE2. Deletion (D) or insertion (I) of a 287-bp Alu repeat sequence in intron 16 is an important polymorphism found in the ACE1 gene. The DD genotype has shown twice the ACE1 activity compared with the II genotype. Moreover, patients with the II genotype have a significantly greater chance of survival than patients with other genotypes. The prevalence of the DD genotype is higher in patients with severe lung infections and is significantly correlated with a high death rate. For example, African Americans in the United States are considered to have the highest D allele frequency (89%) compared with white Americans (69%). Additionally, populations in France, Italy and Spain have shown a high D allele frequency of between 82% and 87%. Conversely, populations in East Asian countries such as Japan, China, Taiwan and Korea have a high frequency of the II genotype. Accordingly, the high II genotype frequency and the low DD genotype frequency in the ACE1 gene seem to be correlated with the relatively low mortality rate of COVID-19 among these populations. On the other hand, European populations have shown a higher mortality rate, as in the case of black ethnicity in the United States.

It is clear that the ethnic variation of the ACE I/D genotype tends to correlate with the variations in outcomes where populations with a high D genotype frequency tend to experience higher mortality rates. Another study indicates that I/D polymorphism in the ACE1 gene is linked to the severity of the SARS-CoV-2 infection depending on the hypertensive condition of the patient. Moreover, ACE1 I/D polymorphism was also linked with the SARS-CoV-1 progression in China in 2003.

Polymorphisms present in ACE1 are just as important as those in ACE2. A point mutation in the ACE2 gene (Leu584Ala) facilitates entry of SARS-CoV-1 into host cells. Intriguingly, several amino acid variants can potentially affect the interaction between the viral
| Gene | Locus | Polymorphisms | Alleles | Variation type | Genetic susceptibility | References |
|------|-------|---------------|---------|---------------|------------------------|------------|
| ACE1 | Chromosome 17, 17q23.3 | rs1799752 | Insertion (I)/Deletion (D) | Indel<sup>a</sup> | Yes | 39,40 |
| ACE2 | Chromosome X, Xp22 | Enhance the ACE2/Viral S binding | A>G | SNV<sup>b</sup> | Yes | 45 |
| | | rs73635825 | A>G | SNV |
| | | rs1244687367 | T>C | SNV |
| | | rs778030746 | C>T | SNV |
| | | rs756231991 | C>T | SNV |
| | | rs1434130600 | T>C | SNV |
| | | rs4646116 | T>C | SNV |
| | | rs781255386 | T>A | SNV |
| | | rs778500138 | A>T | SNV |
| | | rs1199100713 | T>C | SNV |
| | | rs867318181 | G>A | SNV |
| | | rs763395248 | T>G | SNV |
| | | rs1395878099 | T>C | SNV |
| | | rs142984500 | C>T | SNV |
| | | Enhance the ACE2/Viral S binding | C>T | SNV |
| | | rs1348114695 | T>A | SNV |
| | | rs146676783 | T>C | SNV |
| | | rs1192192618 | T>C | SNV |
| | | rs760159085 | T>C | SNV |
| | | rs1569243690 | T>C | SNV |
| | | rs1325542104 | A>C | SNV |
| | | rs755691167 | C>A, T | SNV |
| | | rs1256007252 | C>T | SNV |
| | | rs766996587 | T>C | SNV |
| | | rs759579097 | C>A | SNV |
| | | rs143936283 | C>T | SNV |
| | | rs370610075 | T>A | SNV |
| | | rs961360700 | G>T | SNV |
| | | rs751572714 | T>C | SNV |
| | | rs762890235 | G>A, C | SNV |
| | | rs1016409802 | T>C | SNV |
| | | rs1352194082 | G>A, C | SNV |
| | | rs1263424292 | T>C | SNV |

(Continues)
S1 protein and ACE2 receptors and thus the level of infection. Different residues of amino acids expressed within the ACE2 receptor were observed to be very relevant either by promoting or preventing viral infection. A total of 13 polymorphisms (rs1434130600, rs1395878099, rs142984500, rs756231991, rs1244687367, rs73635825, rs778500138, rs867318181, rs763395248, rs4646116, rs778030746, rs1199100713 and rs781255386) enhanced ACE2/S1 recognition, thereby facilitating SARS-CoV-2 infection. In contrast, 18 SNPs (rs143936283, rs961360700, rs1569243690, rs751572714, rs1348114695, rs1263424292, rs766996587, rs760159085, rs1016409802, rs755979097, rs762890235, rs1192tnqh_9;192618, rs370610075 and rs1256007252) hindered interactions between ACE2 and S1, thereby reducing the infection rate (Tables 2 and 3).

Irham et al. reported that TMPRSS2 is highly expressed in the human respiratory system. The TMPRSS2 SNPs rs383510 and rs464397 showed the highest expression in the lung with homozygous TT genotypes. The heterozygous CT genotype showed an intermediate level of expression while the homozygous CC genotype had the lowest expression. Additionally, the GG genotype of the TMPRSS2 SNP rs2070788 showed the greatest expression in the lung, while AG and AA genotypes showed lower levels of expression. The TMPRSS2 SNP rs469390 has also shown a high expression level with the AA genotype, while the AG genotype has an intermediate expression level and the GG genotype has the lowest expression level (Table 2). Together, the genotypes with high expression levels in the lung may be correlated with higher susceptibility to SARS-CoV-2 infection.

The frequency of TMPRSS2 SNP alleles also differs among populations. For example, East Asian populations have a lower frequency of the high-expression genotypes compared with American and European populations which exhibit a higher frequency of the low-expression genotypes. Furthermore, four regulatory SNPs found in the TMPRSS2 gene (rs77675406, rs112657409, rs713400 and rs11910678) play an important role in the regulation of the expression of main regulatory genes that are involved in the infection process of SARS-CoV-2.

### 3.2 Transmembrane serine protease 2

Transmembrane serine protease 2 (TMPRSS2) primes S during the entry of SARS-CoV-2 into host cells. A previous study showed a deficiency of TMPRSS2 expression in the airways, which reduced the severity of lung pathology after SARS-CoV infection.

### 3.3 Dipeptidyl peptidase 4

Dipeptidyl peptidase 4 (DPP4), also identified as CD26, is a serine exopeptidase that is expressed in organs such as the lungs, stomach
and kidneys, as well as in the immune cells. DPP4 is the main receptor for MERS-CoV and plays a role in S glycoprotein priming during SARS-CoV-2 entry into host cells.\(^{47}\) One SNP found in the DPP4 gene (rs13015258) plays an important role in the regulation of expression of main regulatory genes that are involved in the infection process of SARS-CoV-2.\(^{50}\) Epigenetic modification at rs13015258-C

| Drug | Gene | Locus | Polymorphisms | Alleles | Variation Type | References |
|------|------|-------|---------------|---------|----------------|------------|
| Hydroxychloroquine and chloroquine | G6PD | Chromosome X, Xq28 | rs1050828 | C>T | SNV\(^a\) | 69,76 |
| | | | rs1050829 | T>C | SNV |
| | | | rs5030868 | G>A | SNV |
| | α-Interferon | IFIT1 | Chromosome 10, 10q23.31 | rs303218 | G>A, C | SNV | 82 |
| | | OAS1 | Chromosome 12, 12q24.13 | rs3177979 | G>A, C, T | SNV | 83 |
| | | OAS2 | Chromosome 12, 12q24.13 | rs1293747 | G>A | SNV | 83 |
| | | OAS3 | Chromosome 12, 12q24.13 | rs4767043 | C>A, G, T | SNV | 83 |
| | | OASL | Chromosome 12, 12q24.31 | rs10849829 | G>A, C, T | SNV | 83 |
| | | | rs12979860 | C>T | SNV |
| | | | rs8099917 | T>G | SNV |
| | | IL28B | Chromosome 19, 19q13.2 | rs12980275 | A>G | SNV | 83,84 |
| | | | rs1127354 | C>A, G | SNV |
| | | ITPA | Chromosome 20, 20p13 | rs1161447593 | delA/dupA | Indel\(^b\) | 76 |
| Ribavirin | ITPA | Chromosome 20, 20p13 | rs1127354 | C>A/C>G | SNV | 74,75 |
| | | | rs6051702 | A>C | SNV |
| | | | rs7270101 | A>C | SNV |
| | | | rs6139030 | T>C | SNV |
| | | VDR | Chromosome 12, 12q13.11 | rs2228570 | A>C, G, T | SNV | 76 |
| | | | rs1161447593 | delA/dupA | Indel |
| | Lopinavir | SLCO1B3 | Chromosome 12, 12p12.2 | rs4149117 | T>C, G | SNV | 89 |
| | | ABCC2 | Chromosome 10, 10q24.2 | rs3740066 | C>G, T | SNV | 89 |
| | | LEP | Chromosome 7, 7q32.1 | rs1137100 | A>G, T | SNV | 89 |
| | | CETP | Chromosome 16, 16q13 | rs11076174 | T>C | SNV | 89 |
| | | | rs11508026 | C>T | SNV |
| | | | rs7205804 | G>A | SNV |
| | | MCP-1 | Chromosome 17, 17q12 | rs13900 | C>A, G, T | SNV | 88 |
| | | | rs4586 | T>A, C | SNV |
| | Captopril | ACE | Chromosome 17, 17q23.3 | rs1799752 | Insertion (I)/Deletion (D) | Indel | 78,79 |
| | | AT1R | Chromosome 3, 3q24 | rs4343 | G>A | SNV | 79 |
| | Azithromycin | ABCB | Chromosome 7, 7q21.12 | rs1045642 | A>C, G, T | SNV | 86 |
| | | | rs2032582 | A>C, T | SNV |

\(^{a}\)Single nucleotide variant.
\(^{b}\)Insertion/deletion variant.
allele has associated with an overexpression of the CD26 gene, resulting in a high mortality rate in COVID-19 patients who also suffered from type-2 diabetes mellitus.50

3.4 | Cytokines signalling

Cytokines are small proteins, synthesized by various immune cells such as T lymphocytes, B lymphocytes and macrophages, as well as fibroblasts and endothelial cells.51 Cytokines are involved in the immune response against a wide range of viruses by implicating in the control of the inflammatory signals.52 Cytokine storm is defined as an activation signal of over cytokine releasing due to uncontrolled immune response to various stimuli.53 Among these stimuli, SARS-CoV-2 increases the release of cytokine storm during the infection process which results in lung inflammation and serious alveolar damage.54 Interleukin 6 (IL-6), a proinflammatory cytokine, is one of the cytokines released within the cytokine storm. Interleukin 1 beta (IL-1β), interleukin 10 (IL-10), tumour necrosis factor-alpha (TNFα) and others were also detected in COVID-19 patients.55 The cytokine levels are variable among the individuals based on the genetic polymorphisms found in cytokine genes, which affect the inflammatory response in a positive or negative way.56 Two mutations in the IL-6 gene (rs1800797 and rs1800795) have associated with the transcription levels of IL-6, and thus, affect the progression of many diseases.57-58 Moreover, polymorphisms located in the IL-6 gene (rs1800797), IL-10 gene (rs1800872) and C-reactive protein (CRP) gene (rs1205) have correlated with the severity and susceptibility of community-acquired pneumonia.59 Polymorphism in the interferon-induced transmembrane protein 3 (IFITM3) gene (rs12252), a protein involved in the immune response, has associated with the progression of influenza and COVID-19.60 Pharmacogenomics studies are needed to examine the impacts of the genetic variations located in the different cytokines genes that detected in the COVID-19 patients.

4 | PHARMACOGENOMICS OF DRUG METABOLISING GENES

4.1 | Hydroxychloroquine and chloroquine

Hydroxychloroquine and chloroquine are antiviral drugs used to treat and prevent malaria and are also used in the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and chronic discoid lupus erythematosus.61 Hydroxychloroquine is developed by adding a hydroxyl group to chloroquine to decrease its toxicological effects and to conserve its therapeutic potential. Although it was investigated against SARS-CoV-2 at the beginning of the pandemic, more recent studies suggest that the risks exceed its potential efficacy in treating COVID-19.62 The pharmacokinetics of hydroxychloroquine and chloroquine are complicated due to their long half-life and their large volume of distribution inside the body. Moreover, their toxicity thresholds and dose-response associations have not been fully investigated.63 These antimalarial medications have direct impacts on the autophagy process, cellular transduction pathways and lysosomal activity.64 Hydroxychloroquine accumulates inside cell vesicles such as endosomes and lysosomes, which generate a highly acidic environment leading to the suppression of vesicles that mediate SARS-CoV-2 entry.65 Moreover, hydroxychloroquine could directly affect the interactions between the SARS-CoV-2 and ACE2 by reducing ACE2 glycosylation.66

Cytochrome P450 (CYP) isomers, including CYP2D6, CYP2C8, CYP1A1 and CYP3A4, are involved in the metabolism of both hydroxychloroquine and chloroquine.67 Genetic polymorphisms among these isomers affect metabolism rate, and thus affect the potential response to both drugs. CYP2C8*4, CYP2C8*2 and CYP2C8*3 alleles reduce enzyme activity in vitro when compared with the wild-type allele CYP2C8*1A, thereby leading to a slow response to hydroxychloroquine and chloroquine treatment.68 Additionally, variants in the CYP2D6 (rs1135840 andrs1065852) gene increased hydroxychloroquine metabolism in a patient with systemic lupus erythematosus.69 SNPs in the glucose-6-phosphate dehydrogenase (G6PD) gene are associated with a greater risk of haemolysis. Three important SNPs—rs5030868, rs1050828 and rs1050829—reduce G6PD activity and increase the risk of haemolysis after treatment with chloroquine.70

4.2 | Ribavirin

Ribavirin is a synthetic guanosine nucleoside which is used to treat hepatitis C and a variety of viral haemorrhagic fevers and it used to treat SARS-CoV-2.70,71 It may also be used to treat rabies in combination with other drugs such as amantadine and midazolam.72 One of the possible mechanisms by which ribavirin works is the direct blocking of viral RNA replication and the capping of viral mRNA after metabolising into nucleoside analogues.73 Ribavirin is metabolised into ribavirin triphosphate by adenosine kinase. Ribavirin triphosphate then binds to the nucleotide-binding site of the viral polymerase which suppresses replication of the viral genome, thereby reducing the release of defective virions.72 Haemolytic anaemia is one of the side-effects of ribavirin.73 Genetic variations in the inosine triphosphate pyrophosphatase (ITPA) gene decrease the activity of ITPA. In addition, rs1127354, rs6051702 and rs7270101 correlate with low levels of haemoglobin inside the cells.74 On the other hand, rs6139030 SNP in the ITPA gene is a risk factor for the development of thrombocytopenia in hepatitis C patients treated with ribavirin and pegylated interferon.75 Moreover, polymorphism found in the vitamin D receptor (VDR) was shown to affect the efficacy of ribavirin. However, rs2228570 is a common nonsynonymous VDR gene polymorphism which could restrain the activity of the VDR gene, reducing overall efficacy.76
4.3 | Captopril

Captopril is an antihypertensive drug that inhibits the ACE receptors and has activity against SARS-CoV-2. A genetic SNP (rs2106809 T allele) in the ACE2 gene increases the risk of hypertension in women, and the DD genotype of the ACE gene further elevates the risk in response to captopril treatment. Two polymorphisms in the ACE gene (rs4343) and angiotensin II receptor type 1 (AT1R) (rs5182) were analysed to identify their impacts on acute coronary syndrome (ACS) in patients who received captopril. Both the GG rs4343 and GA rs5182 genotypes correlated with ST-segment elevation myocardial infarction (STEMI) (OR = [GG] 1.7, [GA] 1.5) and non-ST-segment elevation myocardial infarction (NSTEMI) (OR = [GG] 3, [GA] 3.8). Additionally, the CT rs5182 genotype was mildly related to STEMI (OR = 1.1).

4.4 | α-Interferon

α-Interferon is a cytokine synthesised from immune cells during viral infection and is mainly used to treat hepatitis B and C. The number of detectable SARS-CoV-2 virions was significantly reduced in the upper respiratory tract due to the effect of α-interferon. Genetic variations in different genes can affect the response to α-interferon. For example, an SNP (rs303218) found in the interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) can affect the α-interferon response in hepatitis B patients. The genotype rs303218 GG has a greater virological response rate (52%) when compared with the rs303218 GG genotype (27%). Moreover, a study investigated the effect of the polymorphisms found in the 2′-5′-oligoadenylate synthetase 1 (OAS1), 2 (OAS2), 3 (OAS3) and like (OASL) on the clinical outcomes of children with chronic hepatitis B who were being treated with α-interferon. The results showed a low level of responsiveness to α-interferon in the OAS1 rs3177979G, OAS2 rs1293747T, OAS3 rs4767043G and OASL rs10849829A genotypes. Additionally, chronic hepatitis B patients have different rates of serological and virological responses depending on the polymorphisms found in the ITPA gene. A significant serological and virological response was also observed in the rs12979860 CC genotype. Both rs12980275 AA and rs8099917 TT were mostly correlated with a virological response. Furthermore, rs1127354 is a genetic variant found in the ITPA gene that showed a reduction in the ITPA enzyme. This variant was more noticeable in Asian populations which means that the α-interferon/ribavirin combination can be responsible for a higher risk of anaemia in these populations.

4.5 | Azithromycin

Azithromycin is a macrolide commonly used to treat bacterial infections that, when used in conjunction with hydroxychloroquine, inhibited SARS-CoV-2. ATP binding cassette subfamily B member 1 (ABCB), a P-glycoprotein transporter, is also involved in azithromycin pharmacokinetics. Among 20 healthy Chinese subjects, two polymorphisms in the ABCB1 gene (rs2032582 and/ or rs1045642) showed a twofold lowering in peak azithromycin concentrations after receiving one dose of drug (rs2032582 TT and rs1045642 TT = 468.0 ng/mL; s2032582 GG and rs1045642 CC = 911.2 ng/mL).

4.6 | Lopinavir

Lopinavir is a protease inhibitor drug used to treat human immuno-deficiency virus (HIV). Polymorphisms in the solute carrier organic anion transporter family member 1B3 (SLCO1B3) [rs4149117], ATP binding cassette subfamily C member 2 (ABCC2) [rs3740066], leptin (LEP) [rs1137100] and cholesteryl ester transfer protein (CETP) [rs11076174] correlated with alterations in lipid content related to lipid toxicity among HIV patients treated with lopinavir. On the other hand, monocyte chemoattractant protein-1 (MCP-1) polymorphisms [rs13900 and rs4586], CETP rs11508026 and CETP rs7205804 protected against lipid toxicity.

4.7 | Remdesivir

Remdesivir is an antiviral drug used to treat several viral diseases such as SARS-CoV-1, MERS-CoV, Ebola virus, and recently, it is described to treat SARS-CoV-2. Remdesivir undergoes serial metabolized processes mediated by intracellular enzymes such as Esterase and phosphoamidase result in the formation of GS-441524, a main Remdesivir metabolite. The mode of administration of Remdesivir is mostly by direct injection into the vein. Remdesivir is approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19. The CYP isomers, CYP2D6, CYP3A4 and CYP2C8, are involved in the metabolism of Remdesivir. Furthermore, the transporters P-glycoprotein and Organic anion transporting polypeptide 1B1 (OATP1B1) are also implicated in the Remdesivir metabolism. There are no pharmacogenomics studies that illustrate the impacts of the genetic polymorphisms found in the drug-metabolizing genes of Remdesivir. There is a need to conduct more studies on the genetic biomarkers found in the metabolism-related genes of Remdesivir.

4.8 | Dexamethasone

Dexamethasone is a corticosteroid drug, a class of steroid hormones, used in the treatment of several diseases such as rheumatic, respiratory, gastrointestinal and dermatologic diseases, and recommended for treating COVID-19. Dexamethasone administration could be mediated either intramuscular or intravenous. Dexamethasone binds and activates the glucocorticoid receptors which mediate alterations in the gene expression. Genetic variation in genes
implicated in the metabolizing-related genes such as CYP3A7, CYP3A5 and CYP3A4 could affect the corticosteroids response.\textsuperscript{102} Moreover, receptor binding genes including Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1) and Corticotropin-Releasing Hormone Receptor 1 (CRHR1), and transporters such as ABCB1 are also involved in the corticosteroid’s response.\textsuperscript{102} Several studies are needed to determine the effect of the genetic variation in the genes related to Dexamethasone metabolism in the COVID-19 patients.

5 | CONCLUSION

Genetic variations among individuals and populations should be considered when drug protocols are being developed using healthy subjects. This article summarised some of the polymorphisms found in genes that have a direct role in SARS-CoV-2 infection, such as ACE1, ACE2, TMPRSS2 and DPP4. We also described some selected drugs currently used in the treatment of SARS-CoV-2. Future research should focus on more detailed analyses and studies of polymorphisms among genes that play a role in drug metabolism to help create effective therapy regimens and reduce adverse effects of these drugs. However, the genetic differences that affect the treatment of SARS-CoV-2 are still being studied and will require more research.

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CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

AUTHOR CONTRIBUTIONS

Laith N. AL-Eitan initiated the review. Laith N. AL-Eitan and Saif Z. Alahmad collected and reviewed the scientific literature resources. Laith N. AL-Eitan and Saif Z. Alahmad wrote the draft manuscript and contributed to the final version.

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