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

Biomedicine & Pharmacotherapy 143 (2021) 112095

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Factors regulating dynamics of angiotensin-converting enzyme-2 (ACE2), the gateway of SARS-CoV-2: Epigenetic modifications and therapeutic interventions by epidrugs

Suvasmita Rath [a], Venkateswarlu Perikala [a], Atala Bihari Jena [b], Jagneshwar Dandapat [b,c,*]

[a] Centre of Environment, Climate Change and Public Health, Utkal University, Vani Vihar, Bhubaneswar 751004, Odisha, India
[b] Centre of Excellence in Integrated Omics and Computational Biology, Utkal University, Bhubaneswar 751004, Odisha, India
[c] Post-Graduate Department of Biotechnology, Utkal University, Bhubaneswar 751004, Odisha, India

ARTICLE INFO

Keywords:
SARS-CoV-2
Environmental toxicants
Drugs
Hypoxia
Endocrine disruptors
Epidrugs

ABSTRACT

Angiotensin-converting enzyme-2 (ACE2) is one of the major components of the renin-angiotensin system (RAS) and participates in the physiological functions of the cardiovascular system and lungs. Recent studies identified ACE2 as the receptor for the S-protein of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and thus acts as the gateway for viral entry into the human body. Virus infection causes an imbalance in the RAS axis and induces acute lungs injury and fibrosis. Various factors regulate ACE2 expression patterns as well as control its epigenetic status at both transcription and translational levels. This review is mainly focused on the impact of environmental toxicants, drugs, endocrine disruptors, and hypoxia as controlling parameters for ACE2 expression and its possible modulation by epigenetic changes which are marked by DNA methylation, histone modifications, and micro-RNAs (miRNAs) profile. Furthermore, we have emphasized on interventions of various phytochemicals and bioactive compounds as epidrugs that regulate ACE2-S-protein interaction and thereby curb viral infection. Since ACE2 is an important component of the RAAS axis and a crucial entry point of SARS-CoV-2, the dynamics of ACE2 expression in response to various extrinsic and intrinsic factors are of contemporary relevance. We have collated updated information on ACE2 expression modulated by epidrugs, and urge to take over further studies on these important physiological regulators to unravel many more systemic linkages related to both metabolic and infectious diseases, in general and SARS-CoV-2 in particular for further development of targeted interventions.

1. Introduction

The renin-angiotensin system (RAS) is a complex homeostatic regulator of vascular function and plays a key role in regulating blood pressure, fluid and salt balance in blood [1]. This system has three major components, renin, angiotensin II and aldosterone, which collectively command the dynamic control over the vascular function in both healthy and diseased conditions [2]. The renin-angiotensin system is critically regulated by the angiotensin-converting enzyme (ACE) which drives the conversion of angiotensin I to angiotensin II [3]. Angiotensin II binds to Angiotensin II receptors 1 and 2 and exerts various systemic and local effects in the cardiovascular system. Angiotensin-converting enzyme-2 (ACE2), the homolog of the ACE, is involved in the metabolic conversion of angiotensin II into the vasodilatory

Abbreviations: ACE2, Angiotensin-converting enzyme-2; ACEIs, Angiotensin-converting enzyme inhibitors; ACEi, ACE inhibitors; AICAR, 5-amino-4-imidazole-carboxamide riboside; ARBs, Angiotensin receptor blockers; BPA, Bisphenol A; CTD, C-terminal domain; CQ, Chloroquine phosphate; DNMTs, DNA methyltransferases; ER, Estrogen receptors; EGCG, Epigallocatechin-3-gallate; GPR, G protein-coupled receptor; GRAVY, Grand average of Hydrophobicity; HDAC, Histone deacetylase; 8-HDS, Hydroxydihydrosanguinarine; HRE, Hypoxia-responsive elements; HIF, Hypoxia-inducible factor; Mas R, Mas receptor; MERS-CoV, Middle East respiratory syndrome coronavirus; NO_2, Nitrogen dioxide; NRF2, Nuclear factor erythroid 2-related factor 2; NTD, N-terminal domain; PM, Particulate matter; PRR, Prorenin receptor; RBM, Receptor-binding motif; RBD, Receptor-binding domain; RAAS, Renin-angiotensin-aldosterone system; SARS-CoV-2, Severe acute respiratory syndrome coronavirus-2; SIRT1, Silent information regulator; S-protein, Spike protein.

* Correspondence to: Centre of Excellence in Integrated Omics and Computational Biology and Post Graduate Department of Biotechnology, Utkal University, Bhubaneswar, Odisha 751004, India.
E-mail addresses: jd.biotech@utkaluniversity.ac.in, jdandapat.nou@gmail.com (J. Dandapat).

https://doi.org/10.1016/j.biopha.2021.112095
Received 2 August 2021; Accepted 20 August 2021
Available online 30 August 2021

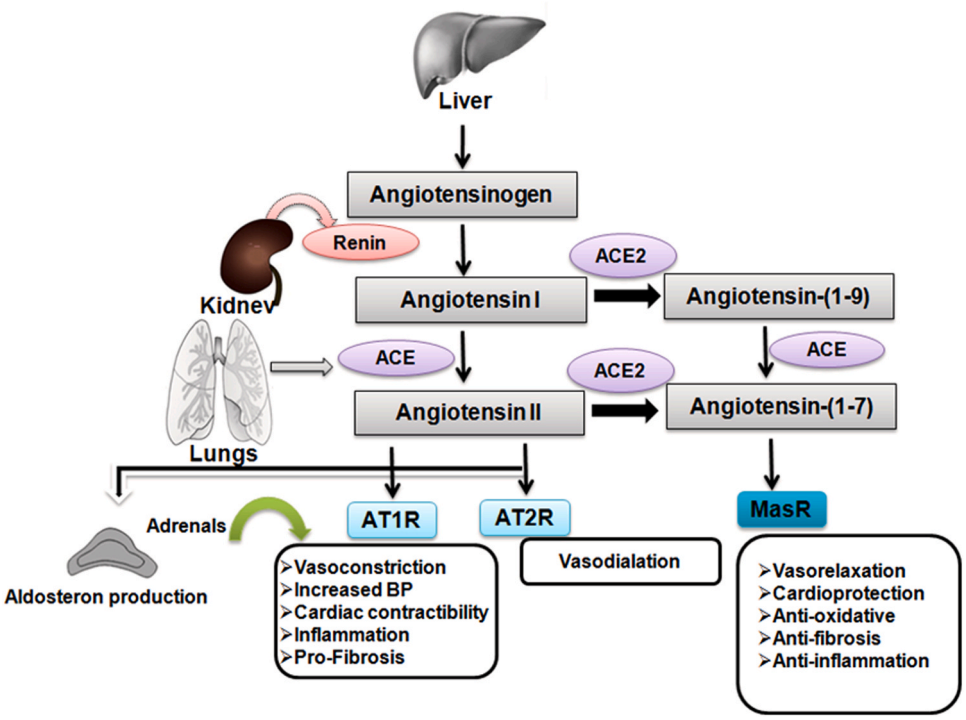

Fig. 1. The renin-angiotensin-aldosterone system (RAAS).

Angiotensin-(1–7) and counterbalances the effects of angiotensin II after binding to G-protein coupled mas receptor [4,5]. The detailed mechanism of the RAS pathway is explained in Fig. 1. Apart from its angiotensinase activity, ACE2 has also been associated with integrin functions [6]. The degree of expression of ACE2 is maximum in the epithelial cells of the lungs, intestine, kidney, brain, and blood vessels [7].

Conversion of liver angiotensinogen to angiotensin I is catalyzed by renin secreted from the kidney which is further converted into angiotensin II by the action of angiotensin-converting enzyme (ACE) secreted from the lungs. Angiotensin II binds to AT1R and AT2R (angiotensin II receptor type 1 and 2); leading to aldosterone production by stimulating adrenals which have a systemic effect on the cardiovascular system. Further the homolog of ACE, ACE2 (angiotensin-converting enzyme-2) catalyzes the conversion of angiotensin I to angiotensin (1–9) and angiotensin II to angiotensin (1–7). ACE also converts Angiotensin-(1–9) to Angiotensin-(1–7). Angiotensin-(1–7) further acts on the Mas receptor (MasR) and counterbalances angiotensin II effect.

Table 1
Role of various drugs in ACE2 regulation.

Types of drugs	Effect on ACE2 expression	Ref.
Beta-Antiadrenergic blockers (Propranolol)	Downregulation	[58]
Diuretics (Olmaesartan)	Upregulation	[59]
ARBs (Losartan, Valsartan, Telmisartan)	Downregulation	[60]
Tricyclic antidepressant (Clomipramine)	Downregulation	[60]
Topoisomerase inhibitor (camptothecin, SN-38, Genz-644282)	Downregulation	[61]
PI3K/Mtor inhibitor (PF-04691502, GDC-0980(RG7422), Taselisib)	Downregulation	[61]
HDAC inhibitor (Sodium butyrate and panobinostat)	Downregulation	[62]
Dopamine receptor antagonist (clozapine)	Downregulation	[63, 64]
Rho kinase inhibitor	Upregulation	[65]
Androgenic/hypertensive antagonist (Spironolactone)	Upregulation of circulating ACE2	[66]
Muscle relaxant	Downregulation	[67]
Cholesterol lowering agents (Statins)	Upregulation	[68, 69]
Antineoplastic agents (Allopurinol and Cisplatin)	Downregulation	[70]

Recently, ACE2 has gained additional importance to the current COVID-19 pandemic situation which is a prodigious global health emergency for the scientific community caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [9,10]. It has been reported that ACE2 acts as the medium of entry for SARS-CoV-2. ACE2 on the cell surface acts as a receptor for the SARS-CoV-2 viral spike protein and facilitates its entry to the host cell [8]. Biophysical analysis including surface plasmon resonance, X-ray crystallography, cryo-EM analysis, and *in silico* studies confirmed an interaction between the ACE2 receptor and SARS-CoV-2 S-protein with a greater affinity as compared to SARS-CoV-S-protein [11]. A few recent studies support a strong correlation between ACE2 expression profile and a higher rate of infectivity of SARS-CoV-2 [12,13]. The membrane-bound form of ACE2 (mACE2) provides anchorage for SARS-CoV-2 binding while the rate of mutation in ACE2 accumulates variations in a population-specific manner that supports its differential infectivity in different groups of population [14]. So, regulating ACE2 expression might have reasonable control over SARS-CoV-2 infection by controlling viral entry into the host cell. Several factors might influence ACE2 expression level and its epigenetic modifications, creating life-threatening conditions after SARS-CoV-2 infection [15]. These contributing factors include environmental factors, drugs, endocrine disruptors, and hypoxia. This review mainly focuses on various factors regulating ACE2 expression including epigenetic factors, thereby establishing a correlation between SARS-CoV-2 infection, and associated comorbidities along with other factors which potentially contribute towards fatal consequences. ACE2 is ubiquitously expressed in a wide range of cells and increased ACE2 expression may potentially result in the invasion of SARS-CoV-2 to the multiple organ systems. As such considerably higher levels of ACE2 expression has been observed in the gastrointestinal tract (small intestine), lungs, kidney, testis, and heart [16–20]. ACE2 expression is tightly regulated both at transcriptional and translational levels in different tissues. The gene expression of ACE2 and protein can also be modulated by epigenetic factors like DNA methylation, histone modifications, and micro-RNAs (miRNAs) that control gene function [21]. For example, ACE2 transcript levels are controlled by micro-RNAs (hsa-miR-125a-5p,

Table 2
Binding affinity of drugs-ACE2.

Ligand types	Protein-ligand	Binding Affinity (kcal/mol)
Anti-diabetic drugs	ACE2-Metformin	-4.5
	ACE2-Sulfonylureas	-3.7
	ACE2-Pioglitazone	-6.3
	ACE2-Liraglutide	-2.7
Anti-thyroid drugs	ACE2-Carbimazole	-4.2
Anti-hypertensive	ACE2-Losartan	-5.4
	ACE2-Valsartan	-5.5
	ACE2-Telmisartan	-6.4
Anti-neoplastic	ACE2-Erlotinib	-7.3
	ACE2-Bleomycin	-3.6
Anti-allergic and Anti-asthmatic	ACE2-Dexamethasone	-7.8
Anti-nephric drugs	ACE2-Probenecid	-5.7
Antibiotics	ACE2-Vancomycin	-7.8

miR-200 family) targeting the 30 untranslated regions of ACE2. Another report linked histone demethylase to the ACE2 transcript. This paper showed H3K4me3 demethylation is controlled by KDM5B and down-regulated mir-125a expression [22]. Enhanced ACE2 gene expression is linked with promoter hypomethylation of specific sites in ACE2 promoter in human cells. Hence, the epigenetic regulation of the ACE2 promoters is very crucial in disease pathogenesis. A detailed study is required to evaluate which epigenetic factors or epigenetic marks control ACE2 gene expression. Various advanced techniques like formaldehyde-assisted isolation of regulatory elements (FAIRE)-Seq and DNase-Seq are used to identify the binding sites of transcription factors in the ACE2 gene [23]. Several active ingredients or epidrugs from various food sources have been reported to exhibit anti-SARS-CoV-2 properties by modulating epigenetic processes [24,25]. This review, therefore, summarizes the recent studies dealing with various factors that modulate host ACE2 expression and its epigenetic modifications, which can be extrapolated for the development of targeted intervention against SARS-CoV-2 infection. We have further analyzed the biophysical attributes of ACE2 protein in relation to its stability and functional activities. Besides the role of different drugs in SARS-CoV-2 infection, which has been described in this communication (Table 1), we have also calculated the binding energy of some of these common drugs with ACE2 receptors by computational approaches (Table 2).

1.1. Brief overview of SARS-CoV-2 and its protein

Coronavirus particles are spherical in shape measuring about 80–120 nm diameter. Morphologically this group of viruses has four structural proteins such as an envelope (E), membrane (M), nucleocapsid (N), and spike (S) proteins. The S protein forms large protrusions from the virus surface, giving a crown-like appearance, and therefore, the virus is named coronavirus [26]. The S and HE (transmembrane protein) proteins facilitate the release of progeny virions into the host cells. The M and E protein forms homopenta/dimers and allows the process of virion release. The N protein enables viral genome replication, RNA packing, and evasion of the immune response of the host cell. This overall mechanism undergoes various modifications including glycosylation, palmitoylation, phosphorylation, and many other processes [27]. The coronavirus strain rapidly mutates and is transmitted from one person to the other. The genome is a single-stranded positive-sense RNA containing around 27–32 kb. Some of the important strains include A2A, A3, A3I, B1, B4, and A1A. Among these, A2A and A3I strains are seen in the majority of Indian patients infected with the coronavirus. Besides, A2A strain is also found across the globe. SARS-CoV-2 virus affects the upper respiratory tract and spreads to the lungs. Due to genetic variability and the occurrence of mutations in the strains, the pathogen is also responsible for causing the common cold, oral/nasopharyngeal disorders, hypoxia, and neurological inflammation [28].

2. Structure and biophysical parameters of ACE2 protein

ACE2 is 805 amino acid long type 1 integral membrane glycoprotein with a molecular weight of 120 kDa and predominantly expressed in the lung, heart, kidney, testis, and gastrointestinal tract [29]. The ACE2 gene is located in the human X-chromosome (Xp22) and has a similar number of exons (18) as that of the ACE gene [30]. ACE2 is composed of the amino-terminal catalytic domain and the carboxy-terminal non--catalytic domain (Fig. 2A). The extracellular catalytic N-terminal domain (NTD) of ACE2 enzyme functions as a carboxypeptidase and shares a sequence identity of 42% and sequence similarity of 61% with the ACE gene catalytic domain [31]. NTD has an active site containing zinc metallopeptidase domain (HEMGH) which is involved in the formation of the vasodilator peptide Ang (1–7) and binding between SARS-CoV-2 and S-protein. The short intracellular C-terminal domain (CTD) mainly functions as an interacting partner of neutral amino acid transporters and shares 48% homology with collectrin. The domain structure of ACE2 protein is described in Fig. 2A. ACE2 expression is mainly restricted to the endothelium and renal tubular epithelium. Sometimes its expression is evident in vascular smooth muscle cells [32]. Shedding of the catalytic ectodomain of ACE2 protein is controlled by a calmodulin-binding site towards its cytoplasmic tail. ACE2 is an endothelium-bound carboxypeptidase cleaved by various metalloproteases and shows its soluble form activity [12]. So the altered mRNA and protein expression pattern of ACE2 contributes to the severity of SARS-CoV-2 infection and acts as a potential therapeutic target in patients with comorbidities like hypertension and cardiac dysfunctions [33].

Different biophysical parameters act as determining factors for ACE2 function. We have analyzed the different parameters like half-life, aliphatic index, instability index, and grand average of hydrophobicity (GRAVY) value of ACE2 protein by using the ExPASyProtParam tool. The half-life of ACE2 protein is estimated to be 30 h in mammalian reticulocytes and in vitro systems, whereas it is greater than 20 h in yeast. This came out to be greater than 10 h in *E. coli* and in vivo systems. Secondly, the stability of a protein depends on its instability index, with the value exceeding 40 indicates to be more unstable as compared to the value which is less than 40 indicates its stability [34]. As our data predicted the instability index of ACE2 protein as 47.36, it is considered to be unstable in nature. Further, we focused on the aliphatic index of the protein which measures thermal stability. Proteins with a higher aliphatic index are considered to be thermostable in nature. As the aliphatic amino acids are hydrophobic in nature, the number of hydrophobic proteins present determines their aliphatic property. For example, the aliphatic index of cytotoxins in the range of 66.5–84.33 indicated its thermostability and higher amounts of hydrophobic amino acids. We predicted the aliphatic index of ACE2 protein as 78.71 which falls within the thermostable range, indicating ACE2 protein is thermostable in nature. One of the important biophysical parameters of the ACE2 protein is determining its GRAVY value calculated as the sum of hydropathy values of all of the amino acids divided by the number of residues in the sequence. The GRAVY index ranges from −0.66 to 0.855. The lower GRAVY value indicates the possibility of globular or hydrophilic protein whereas the higher GRAVY value indicates membranous or hydrophobic protein. We observed a GRAVY index of −0.451 for ACE2 protein which supports its membranous nature [35,36].

3. Linkage between ACE2 expression and SARS-CoV-2 infection

Recent findings have established a correlation between the viral spike (S) protein and the expression profile of the host ACE2 receptor. The tissue-specific expression of ACE2 enhances the vulnerability of specific organs for SARS-CoV-2 infection. For example, heightened expression of ACE2 protein in the lungs and heart increased their

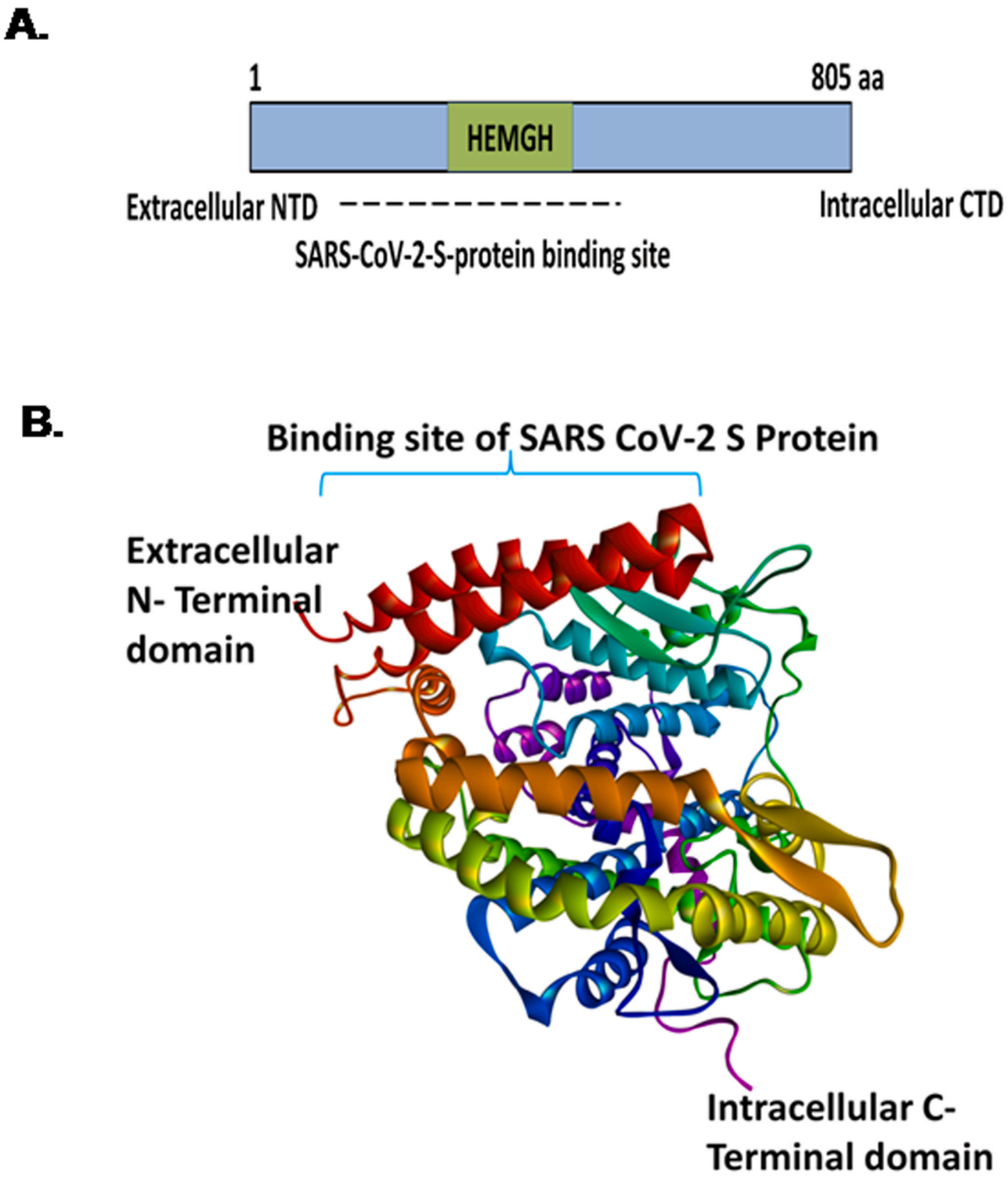

Fig. 2. Domain structure of ACE2 protein. (A) ACE2 is 805 amino acid long type 1 transmembrane protein that contains N-terminal extracellular domain and C-terminal intracellular domain. The zinc-binding motif (HEMGH) is depicted in yellow (B) structure of human ACE2 protein showing N-terminal domain (red color) containing binding site for SARS-CoV-2 protein. The intracellular C-terminal domain is in purple color. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

vulnerability for SARS-CoV-2 infection [37]. Apart from those various other parameters are taken into consideration while discussing the viral entry into the host cells [38]. Binding between the receptor-binding motif (RBM) of the receptor-binding domain (RBD) of the S-protein and ACE2 is evident in several research articles [10]. The trans-membrane domain of ACE2 proteins act as a receptor for the S-protein of SARS-CoV-2 in the extracellular domain of the plasma membrane [39] as depicted in Fig. 3. The SARS-CoV-2 RBM contains a four-residue motif (Gly-Val-Glu-Gly) at 482–485 which furnishes a better contact with the ACE2. ACE2 has two lysine residues which create positive charges that are neutralized after the viral infection. The two amino acid residues in the viral RBM, Gln493, and Leu455 have a very high affinity to the ACE2

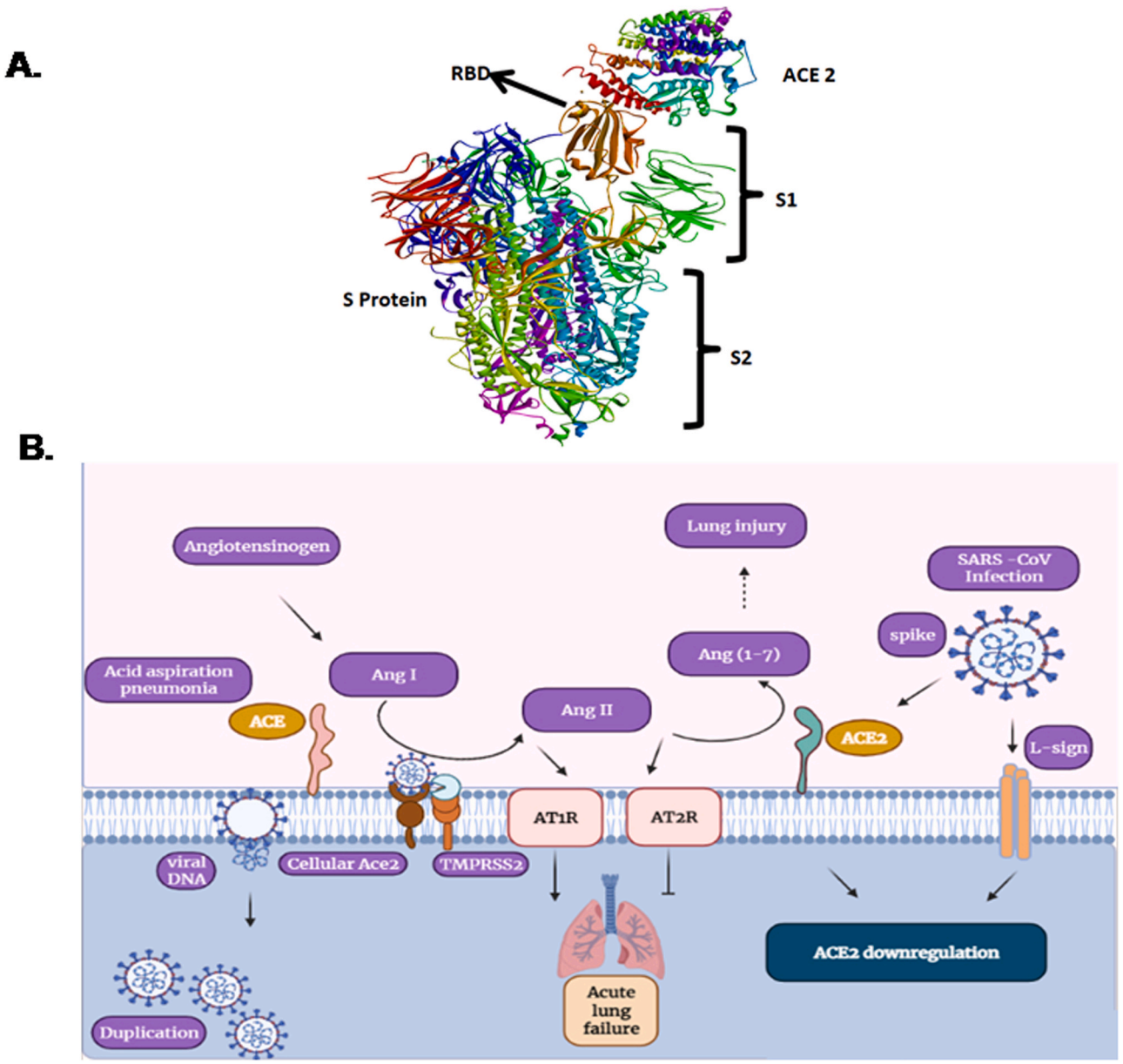

Fig. 3. ACE2-SARS-CoV-2 interaction and downstream effect. (A) Representative structure showing interaction between SARS-CoV-2 and ACE2 receptor. The receptor binding domain (RBD) of SARS-CoV-2 shown in cyan color interacts with the N-terminal helix of ACE2 receptor shown in red color. (B) Schematics of deregulation in the RAS pathway and its downstream effect after SARS-CoV-2 infection. The viral S-protein interacts with the membrane-bound ACE2 receptor of the host lungs. The viral entry is initiated by the proteolytic cleavage of viral S-protein by host proteases like cathepsins, transmembrane serine protease (TMPRSS)2 which is followed by fusion between viral and host cell membrane. This induces shedding of ACE2 receptors and downregulates Angiotensin 1–7 production that acts on the MAS receptor. This leads to loss of protective function by MASR and induces vasoconstriction and acute lungs injury. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

hotspot site and lead to a stabilized conformation. ACE2 receptor protein is expressed as a full-length surface-bound form or a circulating soluble form detected primarily in plasma and urine [40]. This soluble form acts as a competitive inhibitor for S1 unit of the viral S-protein and blocks its binding with full-length ACE2 receptor. The entry for SARS-CoV-2 is mainly facilitated by two mechanisms: endocytosis and membrane fusion. Endocytosis is either initiated through clathrin-dependent and/or non-caveolae lipid raft-dependent endocytosis to enter the host cell. But the detailed mechanism of action needs to be validated. In addition to ACE2-mediated virus endocytosis, TMPRSS2-mediated direct membrane fusion is another important way for SARS-CoV-2 entry. After the viruses are attached, TMPRSS2 induces direct membrane fusion between the virus and the host cells [8]. This process leads to the shedding of host ACE2 receptors and loss of its protective function which further downregulates Ang 1–9 and Ang 1–7 production. Unavailability of Ang1–7 deregulates the activity of the MAS receptor and hence is unable to perform its protective functions like vasorelaxation, cardioprotection, antioxidative and anti-fibrotic function. So there is upregulation of the RAS/Ang II pathway and accumulation of angiotensin II which further leads to vasoconstriction, thrombophilia, micro-thrombosis, alveolar epithelial injury, and respiratory failure [40]. Hence, it is a hot field of research to develop new tools that limit viral attachment and entry into the host cells [41]. New generation techniques are used to elucidate SARS-CoV-2 and ACE2 interaction at the atomic level, which showed its higher binding affinity than SARS-CoV [42]. Co-crystal structure analysis revealed an interaction between RBM of viral S-protein and ACE2 in mammalian species at specific residues [43].

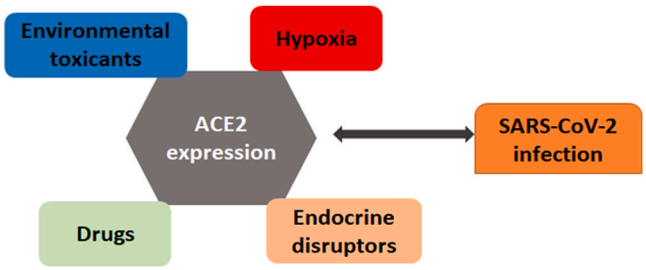

Fig. 4. Figure summarizing the various factors regulating ACE2 expression pattern which mainly includes environmental toxicants, drugs, endocrine disruptors and hypoxia. These factors further influence SARS-CoV-2 infection.

4. Factors regulating ACE2 expression

Various factors are regulating ACE2 expression in a tissue-specific manner. Few of them are discussed here (Fig. 4).

4.1. Environmental toxicants

Exposure to various environmental toxicants can affect ACE2 expression, and this might increase the severity of infection. Studies revealed enhanced ACE2 expression in polluted air having ultrafine particulate matter (PM 2.5). A novel finding correlated a higher rate of air pollution with an increased fatality rate in COVID-19 patients in the northern part of Italy [44]. A correlation between air pollution and ACE2 expression is recently reviewed by Paital et al. This review summarized nitrogen dioxide (NO_2) and particulate matter (PM) enhances ACE2 expression after chronic exposure to these pollutants [45]. The degree of air pollution has a different effect on different COVID-19 patients. For example, the pattern of infection is different in infants and lactating mothers in aerosol-mediated air pollution [46]. Another study also established a correlation between cigarette smoke and ACE2 expression pattern. The authors showed a dose-dependent up-regulation of ACE2 expression in rodents as well as human lungs. The exponential increase in ACE2 expression is evident in highly multiplying cells after chronic smoke exposure, which is reversed after restraining from the smoking habit. This paper also demonstrated enhanced ACE2 expression after inflammatory signaling subsequent to viral infection and interferon treatment. Furthermore, this work identified the interferon-stimulated effect of the ACE2 gene in the lungs, which stimulates positive feedback loops directed to more SARS-CoV-2 infection and viral dissemination. The single-cell sequencing approach used by Smith et al. demonstrated induced ACE2 expression in the respiratory epithelial cells including goblet cells, club cells, and alveolar type 2 cells after exposure to cigarette smoke. Chronic smoke exposure triggers a protective expansion of mucus-secreting goblet cells and a concomitant increase in ACE2 expression which is reversed after quitting smoking habit [47]. Induced expression of ACE2 mRNA is reported in the airway brushings from the smoking population as compared to the non-smoking population from both Asian and Caucasian origin [48].

4.2. Drugs

Drugs involved in ACE2 activation and suppression are in the limelight against COVID-19 infection [49]. A very recent study showed down-regulation of ACE2 expression after nicotine exposure in neurons and glial cells [50]. Drugs like ACE inhibitors and angiotensin II type I receptor blockers (ABRs) such as losartan and Olmesartan have a positive role in maintaining ACE2 expression levels in humans and other animal models. ACE2 expression levels are also enhanced after treatment with a non-steroidal anti-inflammatory drug (NSAID), Ibuprofen [51]. Various laboratories use a combination of drugs against COVID-19 infection. For example, the combination of Ibuprofen with ARBS or ACE inhibitors exacerbates SARS-CoV-2 infection. A positive link between SARS-CoV-2 patients and NSAIDs administration is recently reported in France [52]. Treatment with various drugs can alter ACE2 expression, leading to a possible increase or decrease in ACE2 expression [53]. Work done by Sinha et al. identified various clinically approved ACE2 modifying drugs using in vitro and in vivo model systems [54]. ACE2 regulators including corticosteroid (Dexamethasone), antineoplastic drugs (erlotinib, bleomycin, cisplatin), antibiotic (vancomycin), and an uricosuric agent (probenecid) need further verification to study their effect on ACE2 expression. Another study explains currently prescribed drugs in the UK that might affect ACE2 expression [55]. This study includes 21 different types of drugs to which they have been exposed for 30 min in vitro study and 15 weeks for in vivo study.

Another group of drugs showing a similar effect as that of ACE inhibitors is angiotensin receptor blockers (ARBs), which inhibit angiotensin II binding to muscles on blood vessels. Various angiotensin receptor blockers, namely losartan, valsartan, telmisartan, etc, are used to treat high blood pressure, cardiac dysfunction, and nephrological disorders in diabetes patients. These can be used as a novel therapeutic approach that restricts the binding of SARS-CoV-2 RBD and host cell ACE2 expressing cells. Acetaminophen down-regulates ACE2 expression in a dose-dependent fashion, while non-steroid anti-inflammatory drugs have mixed effects on ACE2 expression [56]. The detailed mechanism of the mode of action of these drugs, might open up new avenues in COVID-19 therapy.

Studies revealed a correlation between hypertension and COVID-19 manifestation. Patients taking drugs like ACEIs or ARBs against hypertension are more prone to covid-19 infection by increasing the availability of ACE2 to S-protein of SARS-CoV-2 [57]. Distinctly, ARBs increase angiotensin II availability since this class blocks its coupling with the AT2 receptor, leading to compensatory up-regulation of ACE-2 in the membrane. The role of different drugs in SARS-CoV-2 infection is described in detail in Table 1.

Further, we have analyzed the binding energy of these drugs with ACE2 receptor (Table 2). The molecular docking software AutoDock Tools 1.5.6 [71] is used to assess the binding affinities of ACE2 with various drugs. The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) is used to obtain the canonical SMILES ids of various drugs. CHIMERA 1.11.2 programm is used for the conversion of 3D structures [38]. To identify the binding site of ACE2, various parameters such as binding affinity, receptor-interacting atom, receptor pocket atom, receptor-ligand interaction site, atomic contact energy (ACE), and side amino acid residues have been studied. Pictorial depiction of docking results is analyzed by Discovery Studio 2017 R2 Client.

4.3. Endocrine disruptors

Chemicals interfering with the endocrine system are known as endocrine disruptors and these are reported to have control over ACE2 expression which includes ACE inhibitors (ACEi), angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA) [72]. Steroid hormone receptors regulate multiple components of the RAAS pathway and significantly contributed to COVID-19 infection in patients with the pre-existing endocrine-related disease [73]. Dexamethasone, a synthetic glucocorticoid and endocrine disruptor is gaining importance in COVID-19 treatment [74]. Endocrine disruptors like insulin and dipeptidyl peptidase 4 inhibitors are safe for COVID-19 patients with diabetes. But studies indicated the adverse effect of metformin and sodium-glucose co-transporter 2 inhibitors in COVID-19 patients with severe comorbidity [75].

Several studies revealed an indirect link between angiotensin-converting enzyme inhibitors (ACEIs) and ACE2 expression level as compared to angiotensin receptor blockers (ARBs) [76]. Those reports suggested the role of ACEIs or ARBs as an inhibitory factor for COVID-19 S-protein and ACE2 interaction [77]. Exposure to these endocrine disruptors increases cardio-metabolic diseases, endocrine cancers, and

immune dysfunctions positively and can be linked with COVID-19 infection. For example, Bisphenol A (BPA) is the most commonly used EDCs and associated with COVID-19 infection by enhancing the co-morbidity parameters. BPA receptors are widely distributed in human tissues, including nuclear estrogen receptors (ERα and ERβ), membrane-bound estrogen receptors (G protein-coupled receptor 30; GPR30), and human nuclear receptor estrogen-related receptor gamma. Data showed a positive correlation between BPA exposure and SARS-CoV-2 infection [78].

4.4. Hypoxia

Hypoxia is a physiological condition that is triggered by an insufficient supply of oxygen to the body [79]. Hypoxic condition is the contributing factor for several diseases, including cancer, myocardial ischemia, metabolic diseases, chronic heart and kidney diseases, and reproductive diseases such as preeclampsia and endometriosis [80]. Hypoxia-inducible factor (HIF) is a transcription factor upregulated in hypoxia, and it consists of two subunits, alpha, and beta. HIF-1α is upregulated upon hypoxia exposure, and beta is constitutively expressed in the nucleus. HIF-1α binding to hypoxia-responsive elements (HREs) determines the induction of at least 100 target genes to restore tissue homeostasis [81]. A recent finding established a correlation between HIF-1α and ACE protein expression under normoxia, whereas knock-down of HIF-1α expression in pulmonary artery smooth muscle cells (PASMCs) inhibited hypoxia-induced ACE up-regulation [82,83]. Another report showed direct interaction between HIF-1α and ACE promoters, which transactivate its function. Hence, it is considered as a target of HIF-1α [59]. Unlike ACE, ACE2 mRNA and protein levels increased to acute response against hypoxia, further decreasing after chronic exposure. Increased cell migration and proliferation are correlated with reduced ACE2 expression in PASMCs by RNA interference mechanism in hypoxia exposed cells which showed a bi-directional regulation of ACE2 as compared to the direct regulation of ACE [83]. One recent finding strongly supports the positive upregulation of hypoxia for angiotensin II, angiotensin-converting enzyme (ACE), angiotensin II type 1 receptor (AT1R), and negative regulation for ACE2 and angiotensin II type 2 receptor in mouse lewis lung carcinoma (LLC) cells. This paper showed Captopril (ACE inhibitor), losartan (AT1R blocker) decreased ACE and AT1R, and increased expression of ACE2 angiotensin II type 2 receptor in LLC cells in a hypoxic environment. Further, this work demonstrated expression of vascular endothelial growth factor-A in LLC cells is suppressed by captopril and losartan treatment under hypoxic conditions which supports the role of hypoxia in RAS dysregulation. RAS inhibitors as a potential therapeutic agent against hypoxia-induced tumors in COVID-19 infected patients need to be properly evaluated [84]. Up-regulation of hypoxia-induced genes and severe impairment of cardiac contractility are reported to be associated with ACE2 deficiency [85]. Another paper explained the hypoxia-mediated increase in ACE2 expression in human hepatocellular carcinoma-derived cells Huh7, which similarly responds to AMP mimic AICAR (5-amino-4-imidazolecarboxamide riboside) [86]. Another study emphasizes on the accumulation of Nox2 engaged in the production of reactive oxygen species (ROS) and hence creates a hypoxic environment in covid-19 patients that triggered thrombotic complexities [87].

Table 3
Epigenetic regulation of ACE2.

Cells/tissue types	Epigenetic marks	Effect on ACE2 expression	Ref.
Airway epithelial cells	Decreased DNA methylation of CpG (cg085599149) near the ACE2 transcription start site (TSS200 region)	Increased ACE2 expression	[93]
Lung tissue/ Elder/Smoker	Hypomethylation of ACE2 gene	Increased ACE2 expression	[99]
Lung tissue (E096)	Histone modifications (H3K4me1, H3K4me3, H3K27Ac) in ACE2 gene	Increased ACE2 expression	[97]
Lung/Children	Hypermethylation of ACE2 gene	Decreased ACE2	[88]
Lungs systemic lupus erythematous	Hypomethylation of ACE2 promoter	Increased ACE2	[81]
Uterine Corpus Endometrial carcinoma	Hypomethylation of ACE2 promoter	Increased ACE2	[89]
Breast Carcinoma	Increased KDM5B histone demethylase	Increased ACE2 expression	[85]
Kidney Renal Papillary Cell Carcinoma	Hypomethylation of ACE2 promoter	Increased ACE2 expression	[100]
Lung's tissue	*HAT1, HDAC2*, and *KDM5B*control over ACE2 expression	Increased ACE2 expression	[97]
Mammary tissue	Activation of histone enhancer marks through JAK-STAT pathway	Induced ACE2 expression	[78]
Cardiovascular tissues	miR-143, miR-421	Inhibition of ACE2 expression	[101]
Lung tissue	miR-200b, hsa-miR-200c and hsa-miR-429, miR-141 are repressed by KDM5B and induced H3K4Me3 methylation mark	Induced ACE2 expression	[77]
Lung tissue	upregulation of miR-200c-3p	Downregulation of ACE2 expression by targeting 3′-UTR	[97]

5. ACE2-associated epigenetic modifications and impact on SARS-CoV-2 infection

Epigenetic modifications are DNA, histone, and miRNA levels changes without altering the DNA sequence and play a crucial role in the onset of many diseases [88]. Here we mainly focused on the epigenetic modifications associated with ACE2 expression. Epigenetic modifications of the ACE2 gene mainly regulate the entry of coronavirus into the host cell and thus affect the disease pathogenesis. For example, viral infection-mediated oxidative stress-induced hypomethylation of the ACE2 gene leads to its overexpression on the X-chromosome in systemic lupus erythematous patients independent of immune-suppressed condition. So epigenetic regulation of the ACE2 gene might have greater importance in COVID-19 treatment [89]. Several findings correlate DNA methylation with ACE2 regulation which indicates host epigenome as a risk factor in COVID-19 infection [90]. Work done by Chlamydas et al. extensively focused on DNA methylation (5mC) in the ACE2 promoter region which is further linked with SARS-CoV-2 infection [91]. Another interesting finding stated DNA methylation profile in ACE2 and TMPRSS2 promoter region and their role in COVID-19 progression [92]. Further, studies conducted by using Illumina DNA methylation array which identified three CpGs (cg04013915, cg08559914, cg03536816) at the ACE2 promoter region with a lower expression in lung epithelial cells compared to the other tissue cell types (e.g. hepatocytes, colon epithelial, pancreatic, vascular endothelial cells). Interestingly, data revealed a correlation between smoking habits and gender-specific ACE2 methylation status. In female smokers who are likely to be infected by SARS-CoV-2 have hypomethylation of two CpG sites (cg23232263, cg16734967) for ACE2 in lung tissue compared to males [93]. Patients with essential hypertension have greater CpG methylation in the ACE2 promoter region as compared to the healthy control [94]. Further, lower CpG methylation is observed in the promoter region of the ACE2 gene which enhances its expression in patients with lupus compared to healthy controls [89]. Yang et al. studied ACE2 promoter methylation status in uterine corpus endometrial carcinoma and kidney renal papillary cell carcinoma from the UALCAN database used to analyze cancer omics data [95]. This study revealed hypomethylation of

the ACE2 promoter in cancer tissue and induced its upregulation compared to the normal tissue. Hence this study correlates the susceptibility of the cancer patients to SARS-CoV-2 infection. Epigenetic regulation of ACE2 is also controlled by histone modifications. Open chromatin confirmation increased the accessibility to transcription factors while the closed chromatin confirmations are involved in transcriptional repression. For example, H3K27me3 is acting as a repressive mark and regulated by the action of histone methyltransferase EZH2. Loss of function of this enzyme enhances ACE2 expression by downregulating the H3K27me3 repressive mark in mouse germline cells [96]. Transcriptomic and system biology approach revealed a close association between induced ACE2 expression with RAB1A, HAT1, HDAC2, and KDM5B in COVID-19 patients having comorbidities like hypertension, diabetes and chronic obstructive lung disease [97]. Several histone deacetylases have also been reported regulating ACE2 function. For example, silent information regulator T1 (SIRT1), a histone deacetylase (HDAC) class III, affects ACE2 expression after interacting with its promoter. Hence, SIRT1 has an impact on viral entry over the host cells [86]. Apart from histone modification machinery, microRNA (miRNA)-mediated ACE2 regulation is also reported in the literature. miRNAs are non-coding RNAs with nearly 30 nucleotide long sequences and regulate the expression of genes in post-transcriptional and translational levels by complementary binding to the 3′ UTR of the target mRNA [98]. These miRNAs are regulating ACE2 expression in a tissue-specific manner. For example, hsa-miR-125a-5p is involved in ACE2 regulation in various tissues like lung, kidney, and esophagus. Transcription of these miRNA is also regulated by some factors. This report explained the involvement of lysine-specific demethylase 5B (JARID1B) in transcription repression machinery of hsa-let-7e/hsa-mir-125a miRNAs, and miR-200 family (including miR-141, miR-200a, miR-200b, miR-200c, and miR-429) by inducing H3K4me3 histone repressive mark in the regulatory regions of miRNAs, and hence downregulates their transcription. This finally triggered an induced ACE2 expression as these miRNA target 3′ UTR of ACE2 mRNA [22]. A few more epigenetic regulations of ACE2 are listed in Table 3.

These studies suggested promoter methylation and acetylation status of ACE2, also acting as a biomarker in COVID-19 therapeutics.

6. Role of epidrugs in ACE2 regulation

Epidrug concept is the blooming field and these drugs have a significant impact on epigenetic modifications and target the epigenetic marks, which is a primary therapeutic approach against diseases associated with epigenetic modifications [102]. Various epidrugs are used alone or in combination against several viral infections [103]. For example, resveratrol induces SIRT-1 activation and decreases NP protein expression, thereby decreasing viral replication and hyper-inflammation [104]. Recently, a few epidrugs have been identified against covid-19 infection. One such epidrug is Chloroquine phosphate (CQ) which blocks viral entry into the host cells by elevating the endosomal pH necessary for entry, replication, and maturation. This compound is also effective against MERS-CoV and SARS-CoV by affecting cellular proteases and glycosylation of ACE2, respectively [105,106]. Now, these days, antiviral therapies are being merged with epidrugs to enhance their effect. For example, various antiviral drugs such as remdesivir, ribavirin, favipiravir, and galidesivir could be combined with DNMT inhibitors such as decitabine, azacitidine or HDAC inhibitors, including vorinostat, belinostat, panobinostat, TSA. But further preclinical and clinical trials are needed for validation of this type of combinational therapy [107]. Combinational treatment by using different epidrugs is also gaining importance now these days. *In silico* study on the combination of vitamin C, curcumin and glycyrrhizic acid (VCG Plus) revealed strong immunoprotection against SARS-CoV-2 infection by inhibiting the inflammatory response and cytokine storm [108]. As the epigenetic data strongly support most elderly persons are the host for SARS-CoV-2 as compared to the young generations, there might be a strong connection between aging and SARS-CoV-2 infection. Anti-aging drugs targeting epigenetics (Resveratrol), other anti-aging drugs (CQ, rapamycin, and doxycycline), and senolytics (azithromycin and Quercetin) could decrease substantial morbidity and mortality [109,110]. There are many FDA-approved therapies available that are used against the COVID-19 pandemic [111]. A very recent work by Jena et al. showed intervention of curcumin and catechin in S-protein binding to the ACE2 via *in silico* system [112]. This group also studied the inhibitory effect of 8-Hydroxydihydrosanguinarine (8-HDS), a pyridone containing an analog of sanguinarine against S-protein and M protease of SARS-CoV-2, *in silico* models [113]. Several other *in silico* studies revealed the anti-SARS-CoV-2 activity of epidrugs from various Indian medicinal plants and their pathophysiological importance to treat SARS-CoV-2 infection [114]. A few other bioactive compounds, including curcumin, deferasirox, and 8-hydroxyquinoline (8HQ) are also involved in the epigenetic regulation of the ACE2 gene [99]. Quercetin is mainly

Table 4
Role of epidrugs in ACE2 regulation.

Bioactive compounds	Sources	Effects	Ref.
Resveratrol	Grape, nuts, red wine, berries, chocolate	1. Increased ACE2 protein expression 2. Affects methyltransferase (DNMT) and histone deacetylase (HDAC) activity	1. [125] 2. [104]
Urso-deoxycholic	Ipomoea obscura	Competitive inhibitor of ACE2 protein	[126]
Curcumin	Rhizome of turmeric (*Curcuma longa)*	1. Targets epigenetic silencing of ACE2 protein 2. Anti-viral activity	1. [99] 2. [119]
Quercetin	apples, berries, onions, dill, lovage, cilantro (coriander) or capers	Reduces interaction between ACE2 and viral spike protein	[111]
Ascorbic Acid	Green and red peppers Tomatoes Broccoli, Brussels sprouts, and cauliflower Leafy greens (Spinach, cabbage, turnip greens) Sweet and white potatoes Winter squash	Lowers ACE2 expression in RNA and protein level	[127]
Vitamin D	Dairy products Eggs Fish	Decreases ACE2 expression pattern	[128]
EGCG (epigallocatechin-3-gallate)	Green tea	DNA methyltransferases (DNMTs), ACE2, and helicase interaction	[120]
Hydroxytyrosol	Virgin olive oil Leaves of the olive tree (*Olea europaea*)	Inhibits ACE2 and S-protein interaction	[129]
Emodin	*Aloe vera*	Competitive inhibitor of S-protein and binds with ACE-2	[130]
Isothymol, Thymol, Limonene, P-Cymene and c-Terpinene	*Ammoides verticillata* plant	Inhibits ACE2 function	[131]

available in oranges, green leafy vegetables, buckwheat, peanuts, a variety of flowers, bark, broccoli, olive oil, apples, onions, green tea, red wine, cherries, blueberries, and cranberries. A recent study demonstrated quercetin-mediated ACE2 suppression [115]. Another phytochemical involved in anti-SARS-CoV-2 therapy is Luteolin found in oranges and juniper fruit with antiviral activity against SARS-CoV infection [116]. Hesperidin is a bioflavonoid compound commonly found in citrus fruits such as lemons, sweet oranges (*Citrus sinensis*), sour oranges, ponderosa lemons, and other citrus fruits is effective against SARS-CoV-2 infection [117]. This compound can bind ACE2 at TYR-613, SER-611, ARG-482, and GLU-479 residues [118]. Chen and colleagues also carried out molecular docking of hesperidin by using AutoDockVina and Gibss binding free energy value of -10.1 kcal mol^{-1} was obtained. Molecular docking studies reveal that these compounds can be complexed with ACE2, furin, 3CLpro, and S protein viruses [118,119]. EGCG (epigallocatechin-3-gallate) is a specific flavanol derivative that can be found in green tea. A molecular docking study shows that DNA methyltransferases (DNMTs), ACE2, and helicase may interact well with EGCG [120]. Resveratrol is another epidrug as well as SART1 activator naturally available in peanuts, mulberries, cranberries, blueberries, and grape and regulates ACE2 modifications. This compound increases the ACE2/angiotensin 1–7 (Ang1–7)/Mas receptor (MasR) axis parallel to the downregulation of the Angiotensin II receptor type 1 (AT1R) expression belonging to the prorenin receptor (PRR)/ACE/angiotensin II (Ang II)/AT1R axis. Nevertheless, the clear evidence between SIRT1 and ACE2 needs to be correctly evaluated [107]. A few other reports support the anti-MERS-CoV infection property of resveratrol by modulating the epigenetic enzymes DNA methyltransferase (DNMT) and histone deacetylase (HDAC) [92]. This is primarily related to some enzymes such as DNA methyltransferase (DNMT) and histone deacetylase (HDAC). Hence more intense study needs to be done to explore the anti-SARS-CoV-2 properties of resveratrol. *Nigella sativa* (black seed) is a well-known worldwide herb and is associated with the reduction of viral load associated with oxidative stress and inflammation reduction [121]. Thymoquinone, one of its components, has been reported to activate the nuclear factor erythroid 2–related factor 2 (Nrf2) transcription factor that reduces the expression of ACE2 receptor in respiratory epithelial cells [122]. Statin is another epidrug used for the treatment of viral pneumonia. But the clinical evidences are not well established and its role in covid-19 is needs to be studied in detail [123].

Another nutrient factor is selenium (Se) which is abundantly present in tomato, beet, potato, cucumber, garlic, and brassica is indirectly linked with COVID-19 infection. It has been reported that the recovery rate from COVID-19 infection is higher in the Enshi city of Hubei province, where the selenium concentration is higher in the landmass as compared to the Heilongjiang Province, which contains the lowest percentage of selenium in the world [124]. Various clinical trials are undergoing which will be the future medicine to treat respiratory disorders like SARS-CoV2 infection. The role of various epidrugs in ACE2 regulation is summarized in Table 4.

7. Conclusion

The role of ACE2 in COVID-19 infection is a hot topic of research, and concrete information on its exact mechanism is still under investigation. As ACE2 counterbalances the deleterious effect of angiotensin II and protects cells from lung injury, its status during and after SARS-CoV-2 infection is a matter of public health concern. This review discusses the effects of various drugs, natural bioactive compounds, environmental factors, endocrine disruptors, and hypoxia as a regulatory factors for ACE2 expression, which is a crucial determining factor for the viral entry to the host cell. The role of various ACEIs, ARBs is under debate in COVID-19 infection, and far more studies are required to draw a conclusion on SARS-CoV-2 infection as a function of ACE2. However, this review for the first time provides an insight into the expression profile of ACE2 and its epigenetic regulation in response to various intrinsic and extrinsic factors as a putative cause and mechanism of SARS-CoV-2 entry to the host cell. We hope this review will brace up the conceptual framework for inter-dependence of ACE2 profile, SARS-CoV-2 attachment and subsequent entry to the target cell, as an important step for the onset of pathogenesis. Still, there is a need for concrete information to explain the global and promoter-specific gene regulation of ACE2 and the involvement of transcription factors therein. This article recapitulates our knowledge about the epigenetic regulation of ACE2 and opens up a new strategy and epidrug based therapies. Therefore, this study will enhance the existing epigenomic landscape for ACE2 and therapeutic intervention can be achieved by introducing novel pharmacological tools. We urge that future studies should be carried out with an integrated approach for a comprehensive understanding of the above crucial interactions and crosstalk for effective management of covid-19 pandemic and other communicable and non-communicable diseases associated with altered renin-angiotensin-aldosterone system (RAAS), in general, and RAAS-SARS-CoV-2 axis, in particular.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Jagneshwar Dandapat: conceptualized, discussed, drafted and revised the manuscript. **Suvasmita Rath:** conceptualized, discussed, drafted and revised the manuscript. **Venkateswarlu Perikala:** participated in manuscript writing. **Atala Bihari Jena:** participated in manuscript writing and performed *in silico* analysis. All authors have read and agreed to the published version of the manuscript.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgments

Authors are thankful to the RUSA Centre of Excellence (CoE) in Environment, Climate Change and Public Health (ECCPH), Utkal University supported by MHRD, Govt of India for financial assistance. Support from DBT, Government of India, New Delhi to Department of Biotechnology, Utkal University is also gratefully acknowledged.

References

[1] U. Eriksson, U. Danilczyk, J.M. Penninger, Just the beginning: novel functions for angiotensin-converting enzymes, Curr. Biol. 12 (2002) 745–752, https://doi.org/10.1016/S0960-9822(02)01255-1.
[2] K. Zenonos, RAS signaling pathways, mutations and their role in colorectal cancer, World J. Gastrointest. Oncol. 5 (2013) 97–101, https://doi.org/10.4251/wjgo.v5.i5.97.
[3] M.J. Peach, Renin-angiotensin system: biochemistry and mechanisms of action, Physiol. Rev. 57 (1977) 313–370, https://doi.org/10.1152/physrev.1977.57.2.313.
[4] M. Donoghue, F. Hsieh, E. Baronas, K. Godbout, M. Gosselin, N. Stagliano, M. Donovan, B. Woolf, K. Robison, R. Jeyaseelan, R.E. Breitbart, S. Acton, A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9, Circ. Res. 87 (2000) 1–9, https://doi.org/10.1161/01.RES.87.5.e1.
[5] M.A. Crackower, R. Sarao, G.Y. Oudit, C. Yagil, I. Kozieradzki, S.E. Scanga, A. J. Oliveira-dos-Santos, J. da Costa, L. Zhang, Y. Pei, J. Scholey, C.M. Ferrario, A. S. Manoukian, M.C. Chappell, P.H. Backx, Y. Yagil, J.M. Penninger, Angiotensin-converting enzyme 2 is an essential regulator of heart function, Nature 417 (2002) 822–828, https://doi.org/10.1038/nature00786.
[6] C. Tikellis, M.C. Thomas, Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease, Int. J. Pept. 2012 (2012) 1–8, https://doi.org/10.1155/2012/256294.
[7] I. Hamming, W. Timens, M.L.C. Bulthuis, A.T. Lely, G.J. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, J. Pathol. 203 (2004) 631–637, https://doi.org/10.1002/path.1570.

[8] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.H. Wu, A. Nitsche, M.A. Müller, C. Drosten, S. Pöhlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2020) 271–280, https://doi.org/10.1016/j.cell.2020.02.052, e8.

[9] M. Liu, T. Wang, Y. Zhou, Y. Zhao, Y. Zhang, J. Li, Potential role of ACE2 in coronavirus disease 2019 (COVID-19) prevention and management, J. Transl. Intern. Med. 8 (2020) 9–19, https://doi.org/10.2478/jtim-2020-0003.

[10] S. Beyerstedt, E.B. Casaro, É.B. Rangel, COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection, Eur. J. Clin. Microbiol. Infect. Dis. 2 (2021), https://doi.org/10.1007/s10096-020-04138-6.

[11] I. Mercurio, V. Tragni, F. Busto, A. De Grassi, C.L. Pierri, Protein structure analysis of the interactions between SARS - CoV - 2 spike protein and the human ACE2 receptor: from conformational changes to novel neutralizing antibodies, Cell. Mol. Life Sci. 78 (2021) 1501–1522, https://doi.org/10.1007/s00018-020-03580-1.

[12] W. Ni, X. Yang, D. Yang, J. Bao, R. Li, Y. Xiao, C. Hou, H. Wang, J. Liu, D. Yang, Y. Xu, Z. Cao, Z. Gao, Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19, Crit. Care 24 (2020) 1–10, https://doi.org/10.1186/s13054-020-03120-0.

[13] V. Bhalla, C.A. Blish, A.M. South, A historical perspective on ACE2 in the COVID-19 era, J. Hum. Hypertens. (2020), https://doi.org/10.1038/s41371-020-00459-3.

[14] F. Scialo, A. Daniele, F. Amato, L. Pastore, M.G. Matera, M. Cazzola, G. Castaldo, A. Bianco, ACE2: the major cell entry receptor for SARS-CoV-2, Lung 198 (2020) 867–877, https://doi.org/10.1007/s00408-020-00408-4.

[15] T.H. Beacon, G.P. Delcuve, J.R. Davie, Epigenetic regulation of ACE2, the receptor of the SARS-CoV-2 virus 1, Genome 14 (2020) 1–14, https://doi.org/10.1139/gen-2020-0124.

[16] J. Fu, B. Zhou, L. Zhang, K.S. Balaji, C. Wei, X. Liu, H. Chen, J. Peng, J. Fu, Expressions and significances of the angiotensin-converting enzyme 2 gene, the receptor of SARS-CoV-2 for COVID-19, Mol. Biol. Rep. 47 (2020) 4383–4392, https://doi.org/10.1007/s11033-020-05478-4.

[17] X. An, W. Lin, H. Liu, W. Zhong, X. Zhang, Y. Zhu, X. Wang, J. Li, Q. Sheng, SARS-CoV-2 host receptor ACE2 protein expression atlas in human gastrointestinal tract, Front. Cell Dev. Biol. 9 (2021) 1–12, https://doi.org/10.3389/fcell.2021.659809.

[18] A.B. Goulter, M.J. Goddard, J.C. Allen, K.L. Clark, ACE2 gene expression is up-regulated in the human failing heart, BMC Med. 2 (2004) 1–7, https://doi.org/10.1186/1741-7015-2-19.

[19] F. Hikmet, L. Méar, Å. Edvinsson, P. Micke, M. Uhlén, C. Lindskog, The protein expression profile of ACE2 in human tissues, Mol. Syst. Biol. 16 (2020) 1–16, https://doi.org/10.15252/msb.20209610.

[20] C.G.K. Ziegler, S.J. Allon, S.K. Nyquist, I.M. Mbano, V.N. Miao, C.N. Tzouanas, Y. Cao, A.S. Yousif, J. Bals, B.M. Hauser, J. Feldman, C. Muus, M.H. Wadsworth, S.W. Kazer, T.K. Hughes, B. Doran, G.J. Gatter, M. Vukovic, F. Taliaferro, B. E. Mead, Z. Guo, J.P. Wang, D. Gras, M. Plaisant, M. Ansari, I. Angelidis, H. Adler, J.M.S. Sucre, C.J. Taylor, B. Lin, A. Waghray, V. Mitsialis, D.F. Dwyer, K. M. Buchheit, J.A. Boyce, N.A. Barrett, T.M. Laidlaw, S.L. Carroll, L. Colonna, V. Tkachev, C.W. Peterson, A. Yu, H.B. Zheng, H.P. Gideon, C.G. Winchell, P. L. Lin, C.D. Bingle, S.B. Snapper, J.A. Kropski, F.J. Theis, H.B. Schiller, L. E. Zaragosi, P. Barbry, A. Leslie, H.P. Kiem, J.A.L. Flynn, S.M. Fortune, B. Berger, R.W. Finberg, L.S. Kean, M. Garber, A.G. Schmidt, I.M. Lingwood, A.K. Shalek, J. Ordovas-Montanes, N. Banovich, A. Brazma, T. Desai, T.E. Duong, O. Eickelberg, C. Falk, M. Farzan, I. Glass, M. Haniffa, P. Horvath, D. Hung, N. Kaminski, M. Krasnow, M. Kuhnemund, R. Lafyatis, H. Lee, S. Leroy, S. Linnarson, J. Lundeberg, K. Meyer, A. Misharin, M. Nawijn, M.Z. Nikolic, D. Pe'er, J. Powell, S. Quake, J. Rajagopal, P.R. Tata, E.L. Rawlins, A. Regev, P. A. Reyfman, M. Rojas, O. Rosen, K. Saeb-Parsy, C. Pe'er, H. Schiller, J.L. Schultze, M.A. Seibold, D. Shepherd, J. Spence, A. Spira, X. Sun, S. Teichmann, F. Theis, A. Tsankov, M. van den Berge, M. von Papen, J. Whitsett, R. Xavier, Y. Xu, K. Zhang, SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues, Cell 181 (2020) 1016–1035, https://doi.org/10.1016/j.cell.2020.04.035, e19.

[21] T.H. Beacon, G.P. Delcuve, J.R. Davie, Epigenetic regulation of ACE2, the receptor of the SARS-CoV-2 virus 1, Genome (2020) 1–14, https://doi.org/10.1139/gen-2020-0124.

[22] S. Nersisyan, M. Shkurnikov, A. Turchinovich, E. Knyazev, A. Tonevitsky, Integrative analysis of miRNA and mRNA sequencing data reveals potential regulatory mechanisms of ACE2 and TMPRSS2, PLOS One 15 (2020) 1–12, https://doi.org/10.1371/journal.pone.0235987.

[23] S. Jahan, T.H. Beacon, W. Xu, J.R. Davie, Atypical chromatin structure of immune-related genes expressed in chicken erythrocytes, Biochem. Cell Biol. 98 (2020) 171–177, https://doi.org/10.1139/bcb-2019-0107.

[24] C.M. Galanakis, T.M.S. Aldawoud, M. Rizou, N.J. Rowan, S.A. Ibrahim, Food ingredients and active compounds against the coronavirus disease (COVID-19) pandemic: a comprehensive review, Foods 9 (2020) 1701, https://doi.org/10.3390/foods9111701.

[25] J. Remali, W.M. Aizat, A review on plant bioactive compounds and their modes of action against coronavirus infection, Front. Pharmacol. 11 (2021) 1–13, https://doi.org/10.3389/fphar.2020.589044.

[26] H. Yao, Y. Song, H. Yao, Y. Song, Y. Chen, N. Wu, J. Xu, C. Sun, J. Zhang, Article molecular architecture of the SARS-CoV-2 virus ll ll article molecular architecture of the SARS-CoV-2 virus, Cell 183 (2020) 730–738, https://doi.org/10.1016/j.cell.2020.09.018, e13.

[27] A.C. Walls, Y.J. Park, M.A. Tortorici, A. Wall, A.T. McGuire, D. Veesler, Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein, Cell 181 (2020) 281–292, https://doi.org/10.1016/j.cell.2020.02.058, e6.

[28] S. Kumar, R. Nyodu, V.K. Maurya, S.K. Saxena, Morphology, Genome Organization, Replication, and Pathogenesis of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), 2, 2020, pp. 23–31. ⟨https://doi.org/10.1007/978-981-15-4814-7_3⟩.

[29] M. Gheblawi, K. Wang, A. Viveiros, Q. Nguyen, J.C. Zhong, A.J. Turner, M. K. Raizada, M.B. Grant, G.Y. Oudit, Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2, Circ. Res. 126 (2020) 1456–1474, https://doi.org/10.1161/CIRCRESAHA.120.317015.

[30] M.J. Soler, C. Barrios, R. Oliva, D. Batlle, Pharmacologic modulation of ACE2 expression, Curr. Hypertens. Rep. 10 (2008) 410–414, https://doi.org/10.1007/s11906-008-0076-0.

[31] C. Tikellis, M.C. Thomas, Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease, Int. J. Pept. 2012 (2012), 256294, https://doi.org/10.1155/2012/256294.

[32] M.A.R. Chamsi-Pasha, Z. Shao, W.H.W. Tang, Angiotensin-converting enzyme 2 as a therapeutic target for heart failure, Curr. Heart Fail. Rep. 11 (2014) 58–63, https://doi.org/10.1007/s11897-013-0178-0.

[33] K. Kuba, Y. Imai, T. Ohto-Nakanishi, J.M. Penninger, Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters, Pharmacol. Ther. 128 (2010) 119–128, https://doi.org/10.1016/j.pharmthera.2010.06.003.

[34] M. Wink, Allelochemical properties or the raison d'être of alkaloids, Alkaloids Chem. Pharmacol. 43 (1993) 1–118, https://doi.org/10.1016/S0099-9598(08)60134-0.

[35] R.L. Graham, R.S. Baric, Recombination, reservoirs, and the modular spike: mechanisms of coronavirus cross-species transmission, J. Virol. 84 (2010) 3134–3146, https://doi.org/10.1128/jvi.01394-09.

[36] J.F. Riordan, Angiotensin-I-converting enzyme and its relatives, Genome Biol. 4 (2003) 225, https://doi.org/10.1186/gb-2003-4-8-225.

[37] F. Chaudhry, S. Lavandero, X. Xie, B. Sabharwal, Y.Y. Zheng, A. Correa, J. Narula, P. Levy, Manipulation of ACE2 expression in COVID-19, Open Heart 7 (2020), https://doi.org/10.1136/openhrt-2020-001424.

[38] E.F. Pettersen, T.D. Goddard, C.C. Huang, G.S. Couch, D.M. Greenblatt, E. C. Meng, T.E. Ferrin, UCSF Chimera – a visualization system for exploratory research and analysis, J. Comput. Chem. 25 (2004) 1605–1612, https://doi.org/10.1002/jcc.20084.

[39] D. Batlle, J. Wysocki, K. Satchell, Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? Clin. Sci. 134 (2020) 543–545, https://doi.org/10.1042/CS20200163.

[40] H. Zhang, J.M. Penninger, Y. Li, N. Zhong, A.S. Slutsky, Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target, Intensive Care Med. 46 (2020) 586–590, https://doi.org/10.1007/s00134-020-05985-9.

[41] P.S. Masters, The molecular biology of coronaviruses, Adv. Virus Res. 65 (2006) 193–292, https://doi.org/10.1016/S0065-3527(06)66005-3.

[42] P. V'kovski, A. Kratzel, S. Steiner, H. Stalder, V. Thiel, Coronavirus biology and replication: implications for SARS-CoV-2, Nat. Rev. Microbiol. 19 (2021) 155–170, https://doi.org/10.1038/s41579-020-00468-6.

[43] T.S. Pillay, T.S. Pillay, Gene of the month: the 2019-nCoV/SARS-CoV-2 novel coronavirus spike protein, J. Clin. Pathol. 73 (2020) 366–369, https://doi.org/10.1136/jclinpath-2020-206658.

[44] S.X. Naughton, U. Raval, J.M. Harary, G.M. Pasinetti, The role of the exposome in promoting resilience or susceptibility after SARS-CoV-2 infection, J. Expo. Sci. Environ. Epidemiol. 30 (2020) 776–777, https://doi.org/10.1038/s41370-020-0232-4.

[45] B. Paital, Nurture to nature via COVID-19, a self-regenerating environmental strategy of environment in global context, Sci. Total Environ. 729 (2020), 139088, https://doi.org/10.1016/j.scitotenv.2020.139088.

[46] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA J. Am. Med. Assoc. 323 (2020) 1061–1069, https://doi.org/10.1001/jama.2020.1585.

[47] J.C. Smith, E.L. Sausville, V. Girish, M. Lou Yuan, A. Vasudevan, K.M. John, J. M. Sheltzer, Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract, Dev. Cell 53 (2020) 514–529, https://doi.org/10.1016/j.devcel.2020.05.012, e3.

[48] N. Zamorano Cuervo, N. Grandvaux, ACE2: evidence of role as entry receptor for SARS-CoV-2 and implications in comorbidities, Elife 9 (2020), https://doi.org/10.7554/eLife.61390.

[49] H. Dambha-Miller, A. Albasri, S. Hodgson, C. Wilcox, N. Islam, S. Khan, P. Little, S. Griffin, Drug treatments affecting ACE2 in COVID-19 infection: a systematic review protocol, BJGP Open 4 (2020) 1–6, https://doi.org/10.3399/bjgpopen20X101115.

[50] G. Cai, Y. Bossé, F. Xiao, F. Kheradmand, C.I. Amos, Tobacco smoking increases the lung gene expression of ACE2, the receptor of SARS-CoV-2, Am. J. Respir. Crit. Care Med. 201 (2020) 1557–1559, https://doi.org/10.1164/rccm.202003-0693LE.

[51] G. Kutti Sridharan, R. Kotagiri, V.H. Chandiramani, B.P. Mohan, R. Vegunta, R. Vegunta, V.R.P. Rokkam, COVID-19 and avoiding ibuprofen. How good is the evidence? Am. J. Ther. 27 (2019) E400–E402, https://doi.org/10.1097/MJT.0000000000001196.

[52] B. Russell, C. Moss, A. Rigg, M. Van Hemelrijck, COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? Ecancermedicalscience 14 (2020) 1–3, https://doi.org/10.3332/ecancer.2020.1023.
[53] S. Sinha, K. Cheng, K. Aldape, E. Schiff, E. Ruppin, Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del), Cochrane Database Syst. Rev. 12 (2020), 010966, https://doi.org/10.20944/preprints202003.0446.v1.
[54] S. Sinha, K. Cheng, A.A. Schäffer, K. Aldape, E. Schiff, E. Ruppin, In vitro and in vivo identification of clinically approved drugs that modify ACE 2 expression, Mol. Syst. Biol. 16 (2020) 1–9, https://doi.org/10.15252/msb.20209628.
[55] H. Dambha-Miller, A. Albasri, S. Hodgson, C.R. Wilcox, S. Khan, N. Islam, P. Little, S.J. Griffin, Currently prescribed drugs in the UK that could upregulate or downregulate ACE2 in COVID-19 disease: a systematic review, BMJ Open 10 (2020) 1–10, https://doi.org/10.1136/bmjopen-2020-040644.
[56] N. Saheb Sharif-Askari, F. Saheb Sharif-Askari, B. Mdkhana, S. Al Heialy, E. Ratemi, M. Alghamdi, S. Abusnana, T. Kashour, Q. Hamid, R. Halwani, Effect of common medications on the expression of SARS-CoV-2 entry receptors in liver tissue, Arch. Toxicol. 94 (2020) 4037–4041, https://doi.org/10.1007/s00204-020-02869-1.
[57] A.S. Yehualashet, T.F. Belachew, Aceis and arbs and their correlation with covid-19: a review, Infect. Drug Resist. 13 (2020) 3217–3224, https://doi.org/10.2147/IDR.S264882.
[58] N. Vasanthakumar, Beta-adrenergic blockers as a potential treatment for COVID-19 patients, BioEssays 42 (2020) 1–9, https://doi.org/10.1002/bies.202000094.
[59] M. Furuhashi, N. Moniwa, T. Mita, T. Fuseya, S. Ishimura, K. Ohno, S. Shibata, M. Tanaka, Y. Watanabe, H. Akasaka, H. Ohnishi, H. Yoshida, H. Takizawa, S. Saitoh, N. Ura, K. Shimamoto, T. Miura, Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker, Am. J. Hypertens. 28 (2015) 15–21, https://doi.org/10.1093/ajh/hpu086.
[60] J. Hippisley-Cox, D. Young, C. Coupland, K.M. Channon, P.S. Tan, D.A. Harrison, K. Rowan, P. Aveyard, I.D. Pavord, P.J. Watkinson, Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people, Heart 106 (2020) 1503–1511, https://doi.org/10.1136/heartjnl-2020-317393.
[61] J.R. White, M.B. Foote, J. Jee, G. Argilés, J.C.M. Wan, L.A. Diaz, PI3K/mTOR and topoisomerase inhibitors with potential activity against SARS-CoV-2 infection, medRxiv (2020) 1–15, https://doi.org/10.1101/2020.09.02.20186783.
[62] Y. Takahashi, A. Hayakawa, R. Sano, H. Fukuda, M. Harada, R. Kubo, T. Okawa, Y. Kominato, Histone deacetylase inhibitors suppress ACE2 and ABO simultaneously, suggesting a preventive potential against COVID-19, Sci. Rep. 11 (2021) 1–9, https://doi.org/10.1038/s41598-021-82970-2.
[63] J. Lu, Y. Hou, S. Ge, X. Wang, J. Wang, T. Hu, Y. Lv, H. He, C. Wang, Screened antipsychotic drugs inhibit SARS-CoV-2 binding with ACE2 in vitro, Life Sci. 266 (2021), 118889, https://doi.org/10.1016/j.lfs.2020.118889.
[64] N.H. Gonsai, V.H. Amin, C.G. Mendpara, R. Speth, G.M. Hale, Effects of dopamine receptor antagonist antipsychotic therapy on blood pressure, J. Clin. Pharm. Ther. 43 (2018) 1–7, https://doi.org/10.1111/jcpt.12649.
[65] G. Bertoldi, L. Gianesello, L.A. Calò, Letter: ACE2, Rho kinase inhibition and the potential role of vitamin D against COVID-19, Aliment. Pharmacol. Ther. 52 (2020) 577–578, https://doi.org/10.1111/apt.15895.
[66] F.A. Cadegiani, C.G. Wambier, A. Goren, Spironolactone: an anti-androgenic and anti-hypertensive drug that may provide protection against the novel coronavirus (SARS-CoV-2) induced acute respiratory distress syndrome (ARDS) in COVID-19, Front. Med. 7 (2020) 1–5, https://doi.org/10.3389/fmed.2020.00453.
[67] K. Yamamoto, H. Takeshita, H. Rakugi, ACE2, angiotensin 1-7 and skeletal muscle: review in the era of COVID-19, Clin. Sci. 134 (2020) 3047–3062, https://doi.org/10.1042/CS20200486.
[68] N. Katsiki, M. Banach, D.P. Mikhailidis, Lipid-lowering therapy and renin-angiotensin-aldosterone system inhibitors in the era of the COVID-19 pandemic, Arch. Med. Sci. 16 (2020) 485–489, https://doi.org/10.5114/aoms.2020.94503.
[69] N.M. Schmidt, P.A.C. Wing, J.A. McKeating, M.K. Maini, Cholesterol-modifying drugs in COVID-19, Oxf. Open Immunol. 1 (2020) 1–6, https://doi.org/10.1093/oxfimm/iqaa001.
[70] N. Saheb Sharif-Askari, F. Saheb Sharif-Askari, M. Alabed, A.A. Tayoun, T. Loney, M. Uddin, A. Senok, S. Al Heialy, R. Hamoudi, T. Kashour, A. Alsheikh-Ali, Q. Hamid, R. Halwani, Effect of common medications on the expression of SARS-CoV-2 entry receptors in kidney tissue, Clin. Transl. Sci. 13 (2020) 1048–1054, https://doi.org/10.1111/cts.12862.
[71] A. Allouche, Software news and updates gabedit — a graphical user interface for computational chemistry softwares, J. Comput. Chem. 32 (2012) 174–182, https://doi.org/10.1002/jcc.
[72] V. Michaud, M. Deodhar, M. Arwood, S.B. Al Rihani, P. Dow, J. Turgeon, ACE2 as a therapeutic target for COVID-19; its role in infectious processes and regulation by modulators of the RAAS system, JCM 9 (2020) 2096, https://doi.org/10.3390/jcm9072096.
[73] M.J. Young, C.D. Clyne, K.E. Chapman, Endocrine aspects of ACE2 regulation: RAAS, steroid hormones and SARS-CoV-2, J. Endocrinol. 247 (2020) R45–R62, https://doi.org/10.1530/JOE-20-0260.
[74] M.H. Ahmed, A. Hassan, Dexamethasone for the treatment of coronavirus disease (COVID-19): a review, SN Compr. Clin. Med. 2 (2020) 2637–2646, https://doi.org/10.1007/s42399-020-00610-8.
[75] S. Lim, J.H. Bae, H.S. Kwon, M.A. Nauck, COVID-19 and diabetes mellitus: from pathophysiology to clinical management, Nat. Rev. Endocrinol. 17 (2021) 11–30, https://doi.org/10.1038/s41574-020-00435-4.
[76] K. Kuba, Y. Imai, S. Rao, H. Gao, F. Guo, B. Guan, Y. Huan, P. Yang, Y. Zhang, W. Deng, L. Bao, B. Zhang, G. Liu, Z. Wang, M. Chappell, Y. Liu, D. Zheng, A. Leibbrandt, T. Wada, A.S. Slutsky, D. Liu, C. Qin, C. Jiang, J.M. Penninger, A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury, Nat. Med. 11 (2005) 875–879, https://doi.org/10.1038/nm1267.
[77] A.S. Yehualashet, T.F. Belachew, ACEIs and ARBs and their correlation with COVID-19: a review, Infect. Drug Resist. 13 (2020) 3217–3224, https://doi.org/10.2147/IDR.S264882.
[78] A. Zahra, C. Sisu, E. Silva, S.-C. De Aguiar Greca, H.S. Randeva, K. Chatha, I. Kyrou, E. Karteris, Is there a link between bisphenol A (BPA), a key endocrine disruptor, and the risk for SARS-CoV-2 infection and severe COVID-19? JCM 9 (2020) 3296, https://doi.org/10.3390/jcm9103296.
[79] J.W. Lee, J. Ko, C. Ju, H.K. Eltzschig, Hypoxia signaling in human diseases and therapeutic targets, Exp. Mol. Med. 51 (2019) 1–13, https://doi.org/10.1038/s12276-019-0235-1.
[80] P.S. Chen, W.T. Chiu, P.L. Hsu, S.C. Lin, I.C. Peng, C.Y. Wang, S.J. Tsai, Pathophysiological implications of hypoxia in human diseases, J. Biomed. Sci. 27 (2020) 1–19, https://doi.org/10.1186/s12929-020-00658-7.
[81] C. Corrado, S. Fontana, Hypoxia and HIF signaling: one axis with divergent effects, Int. J. Mol. Sci. 21 (2020) 1–17, https://doi.org/10.3390/ijms21165611.
[82] H.H. Hu, R.F. Zhang, L.L. Dong, E.G. Chen, K.J. Ying, Overexpression of ACE2 prevents hypoxia-induced pulmonary hypertension in rats by inhibiting proliferation and immigration of PASMCs, Eur. Rev. Med. Pharmacol. Sci. 24 (2020) 3968–3980, https://doi.org/10.26355/eurrev_202004_20867.
[83] R. Zhang, Y. Wu, M. Zhao, C. Liu, L. Zhou, S. Shen, S. Liao, K. Yang, Q. Li, H. Wan, Role of HIF-1α in the regulation ACE and ACE2 expression in hypoxic human pulmonary artery smooth muscle cells, Am. J. Physiol. Lung Cell. Mol. Physiol. 297 (2009) 631–640, https://doi.org/10.1152/ajplung.90415.2008.
[84] L. Fan, Y. Feng, H.Y. Wan, L. Ni, Y.R. Qian, Y. Guo, Y. Xiang, Q.Y. Li, Hypoxia induces dysregulation of local renin-angiotensin system in mouse Lewis lung carcinoma cells, Genet. Mol. Res. 13 (2014) 10562–10573, https://doi.org/10.4238/2014.December.12.19.
[85] M.A. Crackower, R. Sarao, A.J. Oliveira-dos-Santos, J. Da Costa, L. Zhang, Angiotensin-converting enzyme 2 is an essential regulator of heart function, Nature 417 (2002) 822–828, https://doi.org/10.1038/nature00786.
[86] N.E. Clarke, N.D. Belyaev, D.W. Lambert, A.J. Turner, Epigenetic regulation of angiotensin-converting enzyme 2 (ACE2) by SIRT1 under conditions of cell energy stress, Clin. Sci. 126 (2014) 507–516, https://doi.org/10.1042/CS20130291.
[87] F. Violi, A. Oliva, R. Cangemi, G. Ceccarelli, P. Pignatelli, R. Carnevale, V. Cammisotto, M. Lichtner, F. Alessandri, M. De Angelis, M. Claudia, G. D. Ettorre, F. Ruberto, M. Venditti, F. Pugliese, C. Maria, Nox2 activation in Covid-19, Redox Biol. 36 (2020), 101655, https://doi.org/10.1016/j.redox.2020.101655.
[88] H.Y. Zoghbi, A.L. Beaudet, Epigenetics and human disease, Cold Spring Harb. Perspect. Biol. 8 (2016), 019497, https://doi.org/10.1101/cshperspect.a019497.
[89] A.H. Sawalha, M. Zhao, P. Coit, Q. Lu, Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients, Clin. Immunol. 215 (2020), 108410, https://doi.org/10.1016/j.clim.2020.108410.
[90] L. Holmes, A. Lim, C.R. Comeaux, K.W. Dabney, O. Okundaye, DNA methylation of candidate genes (ACE II, IFN-Γ, AGTR 1, CKG, ADD1, SCNN1B and TLR2) in essential hypertension: a systematic review and quantitative evidence synthesis, IJERPH 16 (2019) 4829, https://doi.org/10.3390/ijerph16234829.
[91] S. Chlamydas, A.G. Papavassiliou, C. Piperi, Epigenetic mechanisms regulating COVID-19 infection, Epigenetics 00 (2020) 1–8, https://doi.org/10.1080/15592294.2020.1796896.
[92] K. Subbarayan, K. Ulagappan, C. Wickenhauser, B. Seliger, Expression and clinical significance of SARS-CoV-2 human targets in neoplastic and non-neoplastic lung tissues, Curr. Cancer Drug Targets 21 (2021) 428–442, https://doi.org/10.2174/1568009620666201207145019.
[93] M. Corley, L. Ndhlovu, DNA methylation analysis of the COVID-19 host cell receptor, angiotensin I converting enzyme 2 gene (ACE2) in the respiratory system reveal age and gender differences, Med. Pharmacol. (2020) 1–29, https://doi.org/10.20944/preprints202003.0295.v1.
[94] R. Fan, S.Q. Mao, T.L. Gu, F. De Zhong, M.L. Gong, L.M. Hao, F.Y. Yin, C.Z. Dong, L.N. Zhang, Preliminary analysis of the association between methylation of the ACE2 promoter and essential hypertension, Mol. Med. Rep. 15 (2017) 3905–3911, https://doi.org/10.3892/mmr.2017.6460.
[95] J. Yang, Y. Zheng, X. Gou, K. Pu, Z. Chen, Q. Guo, R. Ji, H. Wang, Y. Wang, Y. Zhou, Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: a systematic review and meta-analysis, Int. J. Infect. Dis. 94 (2020) 91–95, https://doi.org/10.1016/j.ijid.2020.03.017.
[96] R. Sen, M. Garbati, K. Bryant, Y. Lu, Epigenetic Mechanisms Influencing COVID-19, 1, 385, 2021, pp. 372–385.
[97] B.G.G. Pinto, A.E.R. Oliveira, Y. Singh, L. Jimenez, A.N.A. Gonçalves, R.L. T. Ogava, R. Creighton, J.P.S. Peron, H.I. Nakaya, ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19, J. Infect. Dis. 222 (2020) 556–563, https://doi.org/10.1093/infdis/jiaa332.
[98] T.W. Nilsen, Mechanisms of microRNA-mediated gene regulation in animal cells, Trends Genet. 23 (2007) 243–249, https://doi.org/10.1016/j.tig.2007.02.011.
[99] L. Pruimboom, Methylation pathways and SARS-CoV-2 lung infiltration and cell membrane-virus fusion are both subject to epigenetics, Front. Cell. Infect. Microbiol. 10 (2020) 1–5, https://doi.org/10.3389/fcimb.2020.00290.
[100] J. Yang, H. Li, S. Hu, Y. Zhou, NSfMQRDyZ3r4ijG6S, 12, 2020, pp. 6518–6535.

[101] L.-J. Chen, R. Xu, H.-M. Yu, Q. Chang, J.-C. Zhong, The ACE2/apelin signaling, microRNAs, and hypertension, Int. J. Hypertens. 2015 (2015) 1–6, https://doi.org/10.1155/2015/896861.
[102] M. Ghorbaninejad, M. Khademi-Shirvan, S. Hosseini, M. Baghaban Eslaminejad, Epidrugs: novel epigenetic regulators that open a new window for targeting osteoblast differentiation, Stem Cell Res. Ther. 11 (2020) 1–14, https://doi.org/10.1186/s13287-020-01966-3.
[103] E. Sobarzo-sánchez, S. Fakhri, Z. Nouri, S.Z. Moradi, E.K. Akkol, S. Piri, E.S. Sánchez, M.H. Farzaei, J. Echeverría, Targeting Multiple Signal Transduction Pathways of SARS-CoV-2: Approaches to COVID-19 Therapeutic Candidates, 2021. ⟨https://doi.org/10.3390/molecules26102917⟩.
[104] S.C. Lin, C.T. Ho, W.H. Chuo, S. Li, T.T. Wang, C.C. Lin, Effective inhibition of MERS-CoV infection by resveratrol, BMC Infect. Dis. 17 (2017) 1–10, https://doi.org/10.1186/s12879-017-2253-8.
[105] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res. 30 (2020) 269–271, https://doi.org/10.1038/s41422-020-0282-0.
[106] C.A. Omolo, N. Soni, V.O. Fasiku, I. Mackraj, T. Govender, Update on therapeutic approaches and emerging therapies for SARS-CoV-2 virus, Eur. J. Pharmacol. 883 (2020), 173348, https://doi.org/10.1016/j.ejphar.2020.173348.
[107] R. El Baba, G. Herbein, Management of epigenomic networks entailed in coronavirus infections and COVID-19, Clin. Epigenet. 12 (2020) 1–12, https://doi.org/10.1186/s13148-020-00912-7.
[108] L. Chen, C. Hu, M. Hood, X. Zhang, L. Zhang, J. Kan, J. Du, A novel combination of vitamin c, curcumin and glycyrrhizic acid potentially regulates immune and inflammatory response associated with coronavirus infections: a perspective from system biology analysis, Nutrients 12 (2020) 1–17, https://doi.org/10.3390/nu12041193.
[109] R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, W. Wang, H. Song, B. Huang, N. Zhu, Y. Bi, X. Ma, F. Zhan, L. Wang, T. Hu, H. Zhou, Z. Hu, W. Zhou, L. Zhao, J. Chen, Y. Meng, J. Wang, Y. Lin, J. Yuan, Z. Xie, J. Ma, W.J. Liu, D. Wang, W. Xu, E. C. Holmes, G.F. Gao, G. Wu, W. Chen, W. Shi, W. Tan, Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet 395 (2020) 565–574, https://doi.org/10.1016/S0140-6736(20)30251-8.
[110] J.G. Bartlett, The severe acute respiratory syndrome, Infect. Dis. Clin. Pract. 12 (2004) 218–219, https://doi.org/10.1097/01.idc.0000129853.80250.2c.
[111] C. Sargiacomo, F. Sotgia, M.P. Lisanti, COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection? Aging 12 (2020) 6511–6517, https://doi.org/10.18632/AGING.103001 (Albany NY).
[112] A.B. Jena, N. Kanungo, V. Nayak, G.B.N. Chainy, J. Dandapat, Catechin and curcumin interact with S protein of SARS-CoV2 and ACE2 of human cell membrane: insights from computational studies, Sci. Rep. 11 (2021) 1–14, https://doi.org/10.1038/s41598-021-81462-7.
[113] A.B. Jena, N. Kanungo, G.B.N. Chainy, V. Devaraji, J. Dandapat, 8-Hydroxydihydrosanguinarine (8-HDS), a pyridone containing analogue of sanguinarine, can be a potential inhibitor of S protein and M protease of SARS CoV2: insights from computational studies, Research Square. ⟨https://doi.org/10.21203/rs.3.rs-153786/v1⟩.
[114] V. Umashankar, S.H. Deshpande, H.V. Hegde, I. Singh, D. Chattopadhyay, Phytochemical moieties from Indian traditional medicine for targeting dual hotspots on SARS-CoV-2 spike protein: an integrative in-silico approach, Front. Med. 8 (2021) 1–20, https://doi.org/10.3389/fmed.2021.672629.
[115] M. Saakre, D. Mathew, V. Ravisankar, Perspectives on plant flavonoid quercetin-based drugs for novel SARS-CoV-2, Beni-Suef Univ. J. Basic Appl. Sci. 10 (2021), https://doi.org/10.1186/s43088-021-00107-w.
[116] S. Lalani, C.L. Poh, Flavonoids as antiviral agents for enterovirus A71 (EV-A71), Viruses 12 (2020) 184, https://doi.org/10.3390/v12020184.
[117] P. Bellavite, A. Donzelli, Hesperidin and SARS-CoV-2: new light on the healthy function of citrus fruits, Antioxidants 9 (2020) 1–18, https://doi.org/10.3390/antiox9080742.
[118] Y.W. Chen, C.P.B. Yiu, K.Y. Wong, Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CLpro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates, F1000Research 9 (2020) 1–17, https://doi.org/10.12688/f1000research.22457.2.
[119] R. Yudi Utomo, E. Meiyanto, Revealing the Potency of Citrus and Galangal Constituents to Halt SARS-CoV-2 Infection, 2, 2020, pp. 1–8. ⟨https://doi.org/10.20944/preprints202003.0214.v1⟩.
[120] S. Jo, S. Kim, D.H. Shin, M.S. Kim, Inhibition of SARS-CoV 3CL protease by flavonoids, J. Enzym. Inhib. Med. Chem. 35 (2020) 145–151, https://doi.org/10.1080/14756366.2019.1690480.
[121] G. Alexander Haslberger, U. Jacob, B. Hippe, H. Karlic, Mechanisms of selected functional foods against viral infections with a view on COVID-19: Mini review, Funct. Foods Health Dis. 10 (2020) 195–209, https://doi.org/10.31989/ffhd.v10i5.707.
[122] P. Mendonca, K.F.A. Soliman, Flavonoids activation of the transcription factor NRF2 as a hypothesis approach for the prevention and modulation of SARS-CoV-2 infection severity, Antioxidants 9 (2020) 1–28, https://doi.org/10.3390/antiox9080659.
[123] E. Crimi, G. Benincasa, N. Figueroa-Marrero, M. Galdiero, C. Napoli, Epigenetic susceptibility to severe respiratory viral infections and its therapeutic implications: a narrative review, Br. J. Anaesth. 125 (2020) 1002–1017, https://doi.org/10.1016/j.bja.2020.06.060.
[124] A. Andika, R. Ahdyani, L. Erlina, A. Azminah, A. Yanuar, Epigenetic diet to modulate immune response against SARS-CoV-2, Pharm. Sci. Res. 7 (2020) 114–122, https://doi.org/10.7454/psr.v7i2.1087.
[125] J.L. Quiles, L. Rivas-García, A. Varela-López, J. Llopis, M. Battino, C. Sánchez-González, Do nutrients and other bioactive molecules from foods have anything to say in the treatment against COVID-19? Environ. Res. 191 (2020), 110053 https://doi.org/10.1016/j.envres.2020.110053.
[126] S.P. Poochi, M. Easwaran, B. Balasubramanian, M. Anbuselvam, A. Meyyazhagan, S. Park, H.K. Bhotla, J. Anbuselvam, V.A. Arumugam, S. Keshavarao, G. V. Kanniyappan, M. Pappusamy, T. Kaul, Employing bioactive compounds derived from Ipomoea obscura (L.) to evaluate potential inhibitor for SARS-CoV-2 main protease and ACE2 protein, Food Front. 1 (2020) 168–179, https://doi.org/10.1002/fft2.29.
[127] V. Ivanov, A. Goc, S. Ivanova, A. Niedzwiecki, M. Rath, Inhibition of ACE2 expression by ascorbic acid alone and its combinations with other natural compounds, Infect. Dis. Res. Treat. 14 (2021), 117863372199460, https://doi.org/10.1177/1178633721994605.
[128] J. Xu, J. Yang, J. Chen, Q. Luo, Q. Zhang, H. Zhang, Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system, Mol. Med. Rep. 16 (2017) 7432–7438, https://doi.org/10.3892/mmr.2017.7546.
[129] M.C. Ergoren, S. Paolacci, E. Manara, A. Dautaj, K. Dhuli, K. Anpilogov, G. Camilleri, H.K. Suer, M. Sayan, G. Tuncel, N. Sultanoglu, M. Farronato, G. M. Tartaglia, M. Dundar, G. Farronato, I.S. Gunsel, M. Bertelli, T. Sanlidag, A pilot study on the preventative potential of alpha-cyclodextrin and hydroxytyrosol against SARS-CoV-2 transmission, Acta Biomed. 91 (2020) 1–7, https://doi.org/10.23750/abm.v91i13-S.10817.
[130] Y. Yan, X. Shen, Y. Cao, J. Zhang, Y. Wang, Preprints202002.0254.V2, 2020. ⟨https://doi.org/10.20944/preprints202002.0254.v2⟩.
[131] I. Abdelli, F. Hassani, S. Bekkel Brikci, S. Ghalem, In silico study the inhibition of angiotensin converting enzyme 2 receptor of COVID-19 by Ammoides verticillata components harvested from Western Algeria, J. Biomol. Struct. Dyn. (2020) 1–14, https://doi.org/10.1080/07391102.2020.1763199.