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Highlights

Don't sugar coat the COVID (only the vasculature)

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ABSTRACT

This issue of the *Biomedical Journal* acquaints us with the compelling hypothesis that the vascular glycocalyx lies at the intersection of severe COVID-19 risk factors and damages, and the ways used by artificial intelligence to predict interactions between SARS-CoV-2 and human proteins. Furthermore, we explore the antiviral potential of valinomycin and the long list of COVID-19-related clinical trials, and learn how (not) to fix a broken femoral head. Last but not least, we get to enjoy the tale of the cellular oxygen-sensing system as well as the role of the host complement system during *Leptospira* infection, and learn that SARS-CoV-2 can sometimes come with a pathogenic plus one.

Spotlight on reviews

Don't Sugar Coat the COVID (only the vasculature)

On September 27th, the COVID-19 pandemic crossed the ominous threshold of one million deaths worldwide over the last ten months, beating the other big bullies in the infectious diseases field, such as HIV, malaria, influenza and cholera combined.[1] The extremely large spectrum of disease severity, ranging from a fully asymptomatic course to multiple organ failure, initially left both health professionals and scientists struggling in the dark - just as much as the diversity of non-specific symptoms and ensuing sequelae.

Rapidly, as reports on myocardial damage and kidney failures started to accumulate [1], it became clear that the havoc caused by SARS-CoV-2 was not restricted to the respiratory tract, but affects numerous other organs. These damages revealed themselves to be more tenacious than expected from other influenza-like variants. Indeed, many COVID-19 patients seem to experience a range of disconcerting residual symptoms, ranging from fatigue and shortness of breath to, most worryingly, cognitive issues.[2]

While we still await reliable therapeutics and a safe vaccine, it is of utmost importance to determine which COVID-19 patients should be considered at high risk, and how to recognise early signs of disease worsening in time. Advanced

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[1] https://www.nytimes.com/2020/09/28/world/covid-1-million-deaths.html?utm_source=Nature+Briefing&utm_campaign=bd09922789-briefing-dy-20200929&utm_medium=email&utm_term=0_c9dfd39373-bd09922789-44226293.

[2] https://www.nytimes.com/2020/07/01/health/coronavirus-recovery-survivors.html.

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age was the first obvious risk factor emerging from the initial statistics [2]. By now, it has become evident that a long list of comorbidities increases mortality rates and the likelihood to develop severe COVID-19. Figuring among these are a substantial number of conditions related to the cardiovascular system - hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and acute coronary syndrome (ACS) – rendering cardiovascular disease (CVD) the most common comorbidity correlated with COVID-19 [3].

Reciprocally, the serious to lethal forms of COVID-19 comprise many syndromes involving defects of the blood supply apparatus, such as acute respiratory disease syndrome (ARDS), coagulation defects, sepsis, myocardial injury, and heart failure.

In this featured review of this *Biomedical Journal* issue, Minako Yamaoka-Toji points out that both the above-mentioned COVID-19 risk factors and disease complications share one crucial common denominator: the pathophysiology of a damaged vascular endothelial glycocalyx [4].

This literal "sugar coat" is a dense, negatively charged, gelatinous mesh of glycolipids and glycoproteins surrounding the cell membrane of bacteria, epithelial, and many other cells. On the shoulders of glycans lie a vast amount of vital duties, starting with adhesion, cell–cell communication, and recognition of "self" *versus* intruders or renegade cells. In addition, the molecular jungle serves as storage for enzymes and signalling molecules, notably involved in cytoskeleton regulation, cell migration, and proliferation.

Unsurprisingly, its roles in mechanotransduction and growth factor storage confer the glycocalyx an essential role in tumorigenesis and metastasis [5]. Moreover, cancer cells frequently tend to camouflage themselves from the immune system under a thick layer of sialic acid. Notably, Natural Killer (NK) cytotoxicity is dampened by the binding of the sugar to two Siglec receptors, but immunotherapy has recently decided to strike back by targeting the latter [6].

As for the vascular epithelium, the luminal side of all blood vessels is fully coated by a voluminous polysaccharide layer, ensuring its impermeability and protection from mechanical stress caused by the blood flow. Countless signalling factors, including chemokines and cytokines, nested in the vascular glycocalyx regulate blood volume, angiogenesis, coagulation, and inflammation [7]. This essential barrier is all too easily disrupted by a profusion of stresses, such as inflammation, hypoxia, hyperglycemia, or reactive oxygen species (ROS), which trigger shedding of glycocalyx components into the blood stream. The ensuing damage has disastrous consequences in the form of disseminated intravascular coagulation (DIC) and leakage into the extravascular space, leading respectively to systemic thrombosis and oedema, altogether culminating in multiple organ failure. Yet multiple conditions, like diabetes, infections, or atherosclerosis, as well as mechanical trauma or burns induce exactly these types of stress.

Here, Yamaoka-Toji convincingly argues that on the one hand, SARS-CoV-2 infection-caused damages to the vascular endothelial glycocalyx might account for many features of critically ill COVID-19 patients, and on the other, that pre-existing defects of the sugar coating due to comorbidities facilitate infection and are exacerbated by the disease (Fig. 1).

As a matter of fact, the intimate relationship of the novel coronavirus with the vascular system is strongly suggested by its entry strategy, consisting in the binding of the viral spike protein to the host angiotensin-converting enzyme 2 (ACE2), present notably on vascular endothelial cells and several heart cells. Along these lines, the author elaborates on possible ways how SARS-CoV-2 could damage specifically vascular epithelial and myocardial cells, and interfere with the functions of ACE2 and neighbouring complexes on the cellular surface, leading among others to cardiac arrhythmia [4].

Conversely, an already impaired glycocalyx offers easier access and dissemination possibilities for the virus, rendering damaged vessels easier to infect. Besides this being the consequence of many comorbidities, the author speculates that it could also partially explain the bias towards elderly and male subjects, as well as patients with high ACE2 expression.

Be it cause or consequence of SARS-CoV-2 infection, the damage of the vascular endothelial glycoclayx is either triggered or aggravated mainly by excessive inflammation. Severe COVID-19 has been observed to be frequently paralleled by a "cytokine storm", similar to sepsis or Kawasaki disease shock syndrome, and infiltration of the myocardium by mononuclear cells [3]. Massive inflammatory cytokine and ROS production activate sheddases that drastically reduce the glycocalyx volume, causing vascular hyperpermeability and its previously mentioned consequences.

Of note, an association of endothelial glycocalyx damage and inflammation has been described for other infectious diseases. Yamaoka-Toji notably quotes dengue fever and the observation of DIC in victims of the previous coronavirus epidemics SARS and MERS [4]. In addition, glycocalyx shedding during ARDS caused by bacterial sepsis or influenza viruses has been observed [8].

Helpful suggestions on how taking into account the vascular glycocalyx in the COVID-19 context are scattered throughout the review. For instance, circulating glycocalyx components, like D-dimers, could serve as early biomarkers alongside regular electrocardiograms for disease worsening, and upon detection, preventive treatment for coagulation should be undertaken. Furthermore, validated therapeutic approaches from other diseases affecting vascular endothelial cells could be repurposed for COVID-19 treatment, just as much as drugs directed against known causes of glycocalyx damage, such as the anti-hyperglycaemic "drug for everything" metformin [9].

Spotlight on original articles

It's a match!

Pathogens know no borders, as proven by SARS-CoV-2 spreading over the entire planet in no time, but neither does scientific progress. Over the past half century, the boundaries between the different fields of Science have gradually eroded, giving rise at their interfaces to new fusion domains, such as biophysics. Moreover, completely new fields emerged - the prime example being informatics, which has by now become an indispensable component of data analysis for any scientific discipline, especially with the democratisation of high-

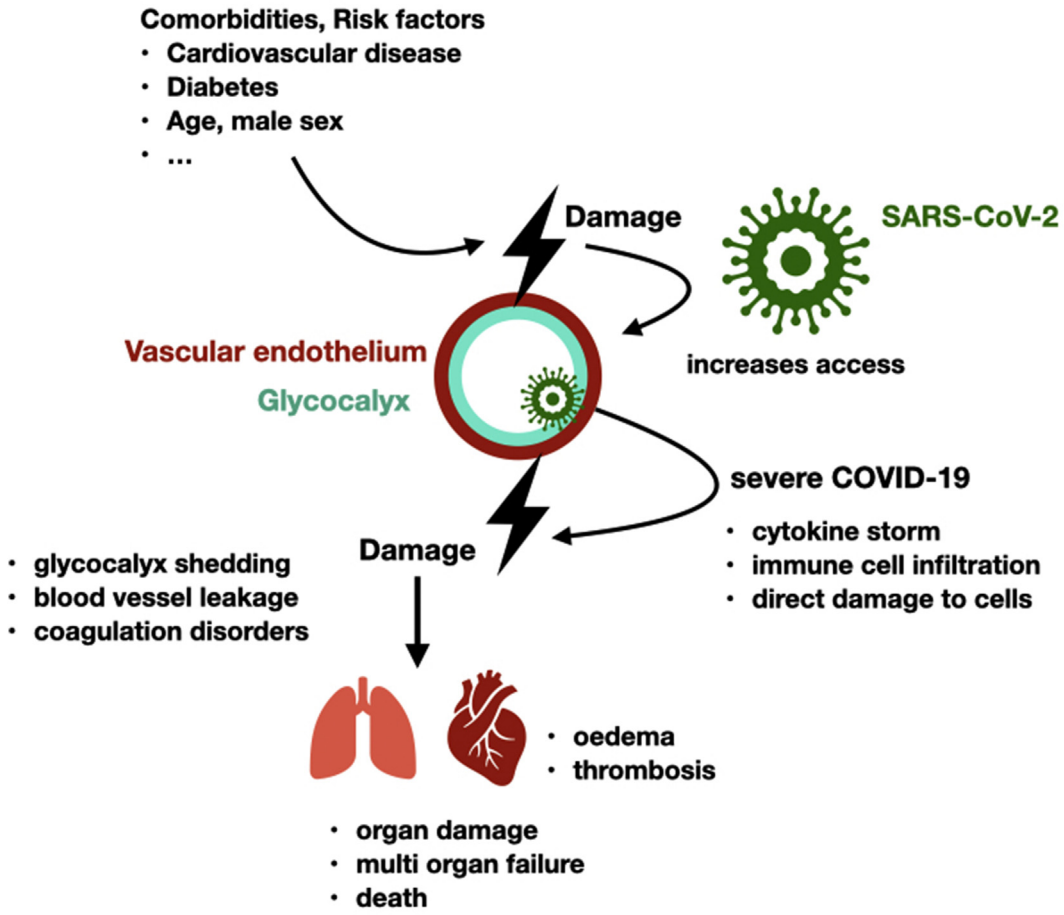

Fig. 1 The glycocalyx at the intersection of risk factors and damage caused by severe COVID-19. The vascular endothelial glycocalyx ensures vascular impermeability, protection of the endothelium, and the homeostasis of many processes, including coagulation. Damage to the glycocalyx through comorbidities prior to infection by SARS-CoV-2 could increase the infection risk and be exacerbated by damage caused either directly by the virus or induced *via* excessive inflammation. The ensuing loss of blood vessel integrity can lead to oedema and thrombosis formation, ultimately causing irreversible organ damage.

throughput sequencing techniques and the analysis of all kinds of −omics.

As a consequence, research teams with original names like *Aleatory Science Group* sprouted, proudly announcing that "The Future Is Uncertain" on their homepage.[3] Ironically though, the process generated new communication barriers, as the common mortal is rapidly lost in "random forests", "hyperplanes", or "gradient boosted decision trees". Those are the jargon of the latest buzzword sparking science-fiction worthy hopes and fears: machine learning. The basic idea behind the concept is to train an algorithm on a large dataset to recognise specific features and to identify them subsequently in another, unknown dataset. However, this is pretty much where the explanatory power of common language comes to an end, because the ways of code are pretty much impenetrable, notably due to the fact that – not unlike evolution of organic creatures – they don't proceed in a way that would seem logic to the human mind, as the mathematician Grant Sanderson explains in his highly recommendable (and surprisingly understandable) videos.[4]

COVID-19 has been, if one can say so, the correct timing to supply the artificial intelligence field with a concrete training ground. In the introduction to their own study highlighted in this issue, Dey et al. provide several examples of the application of machine learning for diagnosis and treatment design, including the classification of medical images, vaccine candidate prediction, and the search for drug candidates [10]. For that matter, the special issue of the *Biomedical Journal* has previously featured additional examples of neural network-based screens mining for known drugs and molecules that could be repurposed [11,12], and molecular docking simulations for inhibitors of SARS-CoV-2 [13]. At the edge of the technologically possible is a voice-analysis company that already developed a smartphone application apparently able to detect acute episode of chronic obstructive pulmonary disease.[5]

[3] https://aleatory.science/.

[4] https://www.youtube.com/watch?v=aircAruvnKk&list=PLZHQObOWTQDNU6R1_67000Dx_ZCJB-3pi.

[5] https://www.nature.com/articles/d41586-020-02732-4?utm_source=Nature+Briefing&utm_campaign=2acca733e7-briefing-dy-20200930&utm_medium=email&utm_term=0_c9dfd39373-2acca733e7-44226293.

Here, Dey et al. set out to predict potential interactions between the human proteome and SARS-CoV-2 viral proteins [10].

Indeed, one of the first cornerstones in decoding the SARS-CoV-2 attack strategy was the confirmation of the binding between the viral spike protein (SP) to the host angiotensin-converting enzyme 2 (ACE2), present on alveolar epithelial cells, macrophages, vascular endothelial cells, and myocardial cells, similar to SARS-CoV [14,15]. This interaction provided both information on the primary target organs and possible ways to inhibit the virus [16]. As it turns out, it is not exclusive – *in silico* modelling predicted the ability of the spike protein to bind to the Neuropilin-1 (NRP-1) receptor, involved in axonal growth and angiogenesis, instead of the vascular endothelial growth factor (VEGF-A) [17]. Follow-up studies speculated that this could explain the observed neurologic features and central nervous system involvement of COVID-19 by facilitating the access of SARS-CoV-2 to the brain *via* the olfactory epithelium [18], and the frequent absence of symptoms in infected subjects by inducing analgesia [19]. Another recent preprint claims that the Kidney Injury Molecule-1/T cell immunoglobulin mucin domain 1 (KIM-1/TIM-1) expressed in lung and kidney epithelial cells could function as an alternative receptor for SARS-CoV-2 [20].

Without doubt, the current list of protein–protein interactions (PPI) between SARS-CoV-2 and the human host is far from complete yet. The Human Immunodeficiency Virus 1 (HIV-1) for instance has about 1000 direct protein–protein interactions with the human proteome [10].

In order to capture the maximal amount of potential contacts, Dey et al. compare human and viral proteins using three different approaches to describe a peptide: the brute amino acid composition, the pseudo amino acid composition – which integrates information on sequence order [21], and conjoint triad features, which encodes protein sequences using the frequency distribution of three consecutive amino acids [22]. The protein interactome layman might be initially puzzled by the fact that none of these methods resorts to three-dimensional peptide models, however such an approach would massively increase the required computing power, and sequence only-based strategies have been proven remarkably efficient in the prediction of protein–protein and protein-RNA interactions, as well as of nuclear receptors [23]. Similarly, the authors employ and compare five of the most popular machine learning algorithms. Without doubt aware of the arcane nature of their field, they take great care to detail the *modus operandi* of each algorithm used in the study, and the choice of positive and negative control datasets.

After some optimisation regarding the required amount of significant features and the classification accuracy, a total of 3603 potential protein interactions with a probability of over 70% is predicted.

Subsequently, the authors examine the gene ontology (GO) term enrichment of the candidate list, in order to verify the likelihood of the hypothesised interactions to occur. The subcellular localisations comprise both nucleus and cytoplasm, as expected. As for the predominant molecular functions, they are mainly energy-, cell cycle-, and cell adhesion-related, fitting previous reports and the typical interference of intracellular pathogens with the host metabolism. In addition, relevant pathways are analysed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) and pointed towards the proteasome and endocytosis, both known to be hijacked by viruses. Further corroboration for the hits to represent realistic candidates stems from a substantial overlap with interactions between the human proteome and other human RNA viruses.

Finally, the authors run their dataset against known drugs, in the above described attempt to repurpose some of them for COVID-19 treatment. The identification 30 targets among the human proteins for which FDA-approved drugs exist concludes the extensive tour of possibilities created by artificial intelligence.

Also in this issue

Review articles

Send in the K^+

As we have passed the one million casualties due to the ongoing COVID-19 pandemic, there is considerable pressure to track down an efficient treatment against SARS-CoV-2, and probably similar viruses, given the worrying increase in frequency of threatening coronaviruses over the past two decades. The safest and fastest route to an efficient therapy relies on the repurposing of already known and studied compounds [12]. With this intent, Zhang et al. plead the case of valinomycin, a fungal potassium ion transporter [24]. Despite being still categorised as an extremely hazardous substance in the United States, this ion channel has been recently coveted for applications ranging from anti-malarial [25] to DNA logic gates in molecular robots [26], and ranked first in a screen for small molecules targeting SARS-CoV [27]. In their review, the authors exhaustively compile existing experimental evidence for valinomycin's antiviral activity against a long list of viruses, including human coronaviruses, specifying for each case the required doses, and the likely mechanism of action. Overall, the data points indeed towards a compelling potential as a broad-spectrum antiviral agent for valinomycin.

Trials and tribulations

According to the latest headlines, a number of ongoing coronavirus-vaccine trials may report "game-changing" results next months, including the current top vaccine candidate in development by the University of Oxford and the pharmaceutical company AstraZeneca.[6]

Worldwide, public and private scientific organisms are concentrating their effort and resources into the search for an efficient treatment of COVID-19, as well as for a vaccine against SARS-CoV-2. Updates regarding various trials make the news on a daily basis, but keeping track of hundreds of programmes at different stages gets more and more complicated. Here, Verma et al. have created a comprehensive list of 60 clinical trials and their main characteristics by the World

[6] https://www.nature.com/articles/d41586-020-02706-6?utm_source=Nature+Briefing&utm_campaign=08df647e03-briefing-dy-20200925&utm_medium=email&utm_term=0_c9dfd39373-08df647e03-44226293.

Health Organisation (WHO) and European institutes [28]. In addition, on the current background of intensifying fears of political meddling with the approval of vaccines and therapies, the authors rightfully appeal to the strict respect of universal safety guidelines.

Original articles

Break a leg!
Although the idiom means "good luck", it should better not happen the at any bone extremity. The femoral head corresponds to the half-spherical upper femur part forming the hip articulation together with the pelvis. Fractures of this bone typically occur in young subjects as a consequence of car or motorcycle accidents, and through falls in the elderly, in association with hip dislocations. Depending on the severity of the fracture, treatments consists either in closed reduction of the hip or surgery by fixation with screws. While healing of the fracture is usually achieved, ensuing complications are frequent, including bone death following damage to the surrounding blood vessels, cartilage deterioration, or excessive ossification [29]. Peng et al. performed a retrospective study on 35 patients having received surgical treatment [30]. Although healing of the fracture was observed in all patients, the rate of above-mentioned complications was indeed high and prompts the authors to call for therapeutic improvement measures.

News and perspectives

Life is in the air
In September 2020, astronomers reported the apparent presence of phosphine gas in Venus's atmosphere, which does not fit any currently known abiotic production route under the given conditions. However, biological production is only one of several possible explanations and eager claims of alien life should be taken with a big pinch of salt [31]. Back down to Earth, it is time to remember one of the molecules essential to most life – oxygen. Lee et al. dedicate their editorial note to the three scientists who unravelled the cellular oxygen-sensing mechanism, earning them the 2019 Nobel Prize in Physiology or Medicine [32]. They acquaint the reader with the fascinating system of cellular oxygen level gauging *via* the hypoxia-inducible factor (HIF), historical milestones of its discovery, as well as the implication in numerous diseases.

Letter to editor

Complementary complement
The ongoing COVID-19 pandemic is one massive reminder of the tremendous threat posed by zoonotic diseases, infections transmitted from animal hosts to humans. Their number is on a steady rise, due to climate change, increasing word population and mobility, as well as animal farming and trade [33]. Coronaviruses in particular are present worldwide in a large range of animal species, resistant to many conditions, and characterised by a high mutation and recombination rate [34]. This year's first issue of the *Biomedical Journal* featured an exhaustive review by Sun et al. about another tenacious zoonotic pathogen, the bacterium *Leptospira*, and its ability to rapidly invade the entire host organism, evade the immune system, and cause systemic inflammation [35,36]. In this regard, Johnson et al. here provide some additional ideas regarding the susceptibility of the host complement system to *Leptospira* virulence factors. The authors briefly outline three strategies the bacterium uses to circumvent the complement apparatus, by either opposing its activation, redirecting it into non-specific systemic inflammation, or *via* the targeted destruction of complement proteins with proteases [37].

Brief communication

Two for one
The incidence of COVID-19 cases has been on the rise again in many countries,[7] however other factors than SARS-CoV-2 are likely to influence the numbers. Notably, it is the start of flu season in many parts of the Northern hemisphere, boosting the request for testing, while tropical and sub-tropical regions experience annual outbreaks of respiratory infections such as dengue or chikungunya. Indeed, the diagnosis of COVID-19 is hampered by a wide variety of presentations that overlap with other common viral infections, such as fever, cough, and diarrhoea. Into the bargain, simultaneous infection with other pathogens leading to similar symptoms is quite possible and susceptible to influence the disease outcomes [38]. By way of illustration, Huang et al. from the Chang Gung Memorial Hospital in Taiwan describe here the case of an elderly COVID-19 patient presenting a co-infection with *Mycoplasma pneumoniae* that recovered after treatment [39].

Conflicts of interest

The author declares no conflict of interests.

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REFERENCES

[1] Zhu Y, Du Z, Zhu Y, Li W, Miao H, Li Z. Evaluation of organ function in patients with severe COVID-19 infections. Med Clin 2020;155:191–6.
[2] Kashnitsky I, Aburto JM. COVID-19 in unequally ageing European regions. World Dev 2020;136:105170.
[3] Unudurthi SD, Luthra P, Bose RJC, McCarthy J, Kontaridis MI. Cardiac inflammation in COVID-19: lessons from heart failure. Life Sci 2020;260:118482.
[4] Yamaoka-Tojo M. Endothelial glycocalyx damage as a systemic inflammatory microvascular endotheliopoathy in COVID-19. Biomed J 2020;43:399–413.
[5] Kang H, Wu Q, Sun A, Liu X, Fan Y, Deng X. Cancer cell glycocalyx and its significance in cancer progression. Int J Mol Sci 2018;19:2484.

[7] https://www.worldometers.info/coronavirus/.

[6] Daly J, Carlsten M, O'Dwyer M. Sugar free: novel immunotherapeutic approaches targeting siglecs and sialic acids to enhance natural killer cell cytotoxicity against cancer. Front Immunol 2019;10:1047.
[7] VanTeeffelen JW, Brands J, Stroes ES, Vink H. Endothelial glycocalyx: sweet shield of blood vessels. Trends Cardiovasc Med 2007;17:101–5.
[8] Benatti MN, Fabro AT, Miranda CH. Endothelial glycocalyx shedding in the acute respiratory distress syndrome after flu syndrome. J Intensive Care 2020;8. 72–10.
[9] Hafner S. One drug to cure them all. Microb Infect 2020;22:290–3.
[10] Dey L, Chakraborty S, Mukhopadhyay A. Machine learning techniques for sequence-based prediction of viral-host interactions between SARS-CoV-2 and human proteins. Biomed J 2020;43:438–50.
[11] Häfner SJ. Pandemic number five - latest insights into the COVID-19 crisis. Biomed J 2020;43:305–410.
[12] Ke YY, Peng TT, Yeh TK, Huang WZ, Chang SE, Wu SH, et al. Artificial intelligence approach fighting COVID-19 with repurposing drugs. Biomed J 2020;43:355–62.
[13] Dubey K, Dubey R. Computation screening of narcissoside a glycosyloxyflavone for potential novel coronavirus 2019 (COVID-19) inhibitor. Biomed J 2020;43:363–7.
[14] Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450–4.
[15] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–8.
[16] Iacob S, Iacob DG. SARS-CoV-2 treatment approaches: numerous options, No certainty for a versatile virus. Front Pharmacol 2020;11:1224.
[17] Perez-Miller S, Patek M, Moutal A, Cabel CR, Thorne CA, Campos SK, et al. In silico identification and validation of inhibitors of the interaction between neuropilin receptor 1 and SARS-CoV-2 Spike protein. bioRxiv [Preprint]. 2020.09.22.308783 Available from: www.biorxiv.org/content/10.1101/2020.09.22.308783v1.
[18] Davies J, Randeva HS, Chatha K, Hall M, Spandidos DA, Karteris E, et al. Neuropilin-1 as a new potential SARS-CoV-2 infection mediator implicated in the neurologic features and central nervous system involvement of COVID-19. Mol Med Rep 2020;22:4221–6.
[19] Moutal A, Martin LF, Boinon L, Gomez K, Ran D, Zhou Y, et al. SARS-CoV-2 Spike protein co-opts VEGF-A/Neuropilin-1 receptor signaling to induce analgesia. Pain 2020 [Ahead of Print].
[20] Ichimura T, Mori Y, Aschauer P, Padmanabha Das KM, Padera RF, Weins A, et al. KIM-1/TIM-1 is a receptor for SARS-CoV-2 in lung and kidney. medRxiv [Preprint] 2020. 2020.09.16.20190694 Available from: www.medrxiv.org/content/10.1101/2020.09.16.20190694v1.
[21] Chou KC. Pseudo amino acid composition and its applications in bioinformatics, proteomics and system biology. Curr Proteomics 2009;6:262–74.
[22] Shen J, Zhang J, Luo X, Zhu W, Yu K, Chen K, et al. Predicting protein-protein interactions based only on sequences information. Proc Natl Acad Sci Unit States Am 2007;104:4337–41.
[23] Wang H, Hu X. Accurate prediction of nuclear receptors with conjoint triad feature. BMC Bioinf 2015;16:402–13.
[24] Zhang D, Ma Z, Chen H, Lu Y, Chen X. Valinomycin as a potential antiviral agent against coronaviruses: a review. Biomed J 2020;43:414–23.
[25] Bharti H, Singal A, Raza M, Ghosh PC, Nag A. Ionophores as potent anti-malarials: a miracle in the making. Curr Top Med Chem 2019;18:2029–41.
[26] Kawano R. Synthetic ion channels and DNA logic gates as components of molecular robots. ChemPhysChem 2018;19:359–66.
[27] Wu CY, Jan JT, Ma SH, Kuo CJ, Juan HF, Cheng YSE, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci Unit States Am 2004;101:10012–7.
[28] Verma HK, Merchant N, Verma MK, Kuru CI, Singh AN, Ulucan F, et al. Current updates on the European and WHO registered clinical trials of coronavirus disease 2019 (COVID-19). Biomed J 2020;43:424–33.
[29] Barney J, Piuzzi NS, Akhondi H. Femoral head avascular necrosis Treasure Island (FL): StatPearls Publishing; 2020.
[30] Peng SH, Wu CC, Yu YH, Lee PC, Chou YC, Yeh WL. Surgical treatment of femoral head fractures. Biomed J 2020;43:451–7.
[31] Greaves JS, Richards AMS, Bains W, Rimmer PB, Sagawa H, Clements DL, et al. Phosphine gas in the cloud decks of Venus. Nat Astron 2020;850:1–10.
[32] Lee CC, Wu CY, Yang HY. Discoveries of how cells sense oxygen win the 2019 Nobel Prize in Physiology or medicine. Biomed J 2020;43:434–7.
[33] Rahman MT, Sobur MA, Islam MS, Ievy S, Hossain MJ, Zowalaty El ME, et al. Zoonotic diseases: etiology, impact, and control. Microorganisms 2020;8:E1405.
[34] Khamassi Khbou M, Daaloul Jedidi M, Bouaicha Zaafouri F, Benzarti M. Coronaviruses in farm animals: epidemiology and public health implications. Vet Med Sci 2020;50:1937.
[35] Sun AH, Liu XX, Yan J. Leptospirosis is an invasive infectious and systemic inflammatory disease. Biomed J 2020;43:24–31.
[36] Häfner SJ. Tumour travel tours - why circulating cancer cells value company. Biomed J 2020;43:1–7.
[37] Johnson PA, Johnson JC. Role of the complement in *Leptospira* virulence and infection. Biomed J 2020;43:462–3.
[38] Agarwal A, Chaurasia D, Dash PK. Concerns and public health challenges for arboviral and other respiratory infections amidst SARS-CoV-2 pandemic. Pathog Glob Health 2020;7:1–2.
[39] Huang ACC, Huang CG, Yang CT, Hu HC. Concomitant infection with COVID-19 and *Mycoplasma pneumoniae*. Biomed J 2020;43:458–61.