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BRIEF REPORT

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Predicting susceptibility for SARS-CoV-2 infection in domestic and wildlife animals using ACE2 protein sequence homology

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Abstract

The article is presenting a bioinformatics based method predicting susceptibility for SARS-CoV-2 infection in domestic and wildlife animals. Recently, there were reports of cats and ferrets, dogs, minks, golden hamster, rhesus monkeys, tigers, and lions testing for SARS-CoV-2 RNA which indicated for the possible interspecies viral transmission. Our method successfully predicted the susceptibility of these animals for contracting SARS-CoV-2 infection. This method can be used as a screening tool for guiding viral RNA testing for domestic and wildlife animals at risk of getting COVID-19. We provide a list of the animals at risk of developing COVID-19 based on the susceptibility score.

KEYWORDS

ACE2, COVID-19, pets, SARS-CoV-2, susceptibility, wildlife

1 | INTRODUCTION

The ongoing epidemic of COVID-19 is a global concern for human health, but its impact on domestic and wildlife animals is largely unevaluated. The epidemic was believed to have started from the wet wildlife market in Wuhan in the People's Republic of China, but until now, no study has located the actual source of the virus. Genomic analyses suggest that bat is the most likely origin of this virus (Zhou et al., 2020). The virus has been detected from the pangolins, but there is no concrete evidence that this animal can act as an intermediate host (Lam et al., 2020). Currently, very limited data is available that evaluates the susceptibility of the domestic and wildlife stocks for SARS-CoV-2 infection using laboratory testing. There have been reports for positive tests for SARS-CoV-2 RNA in cats and ferrets, dogs, minks, golden hamster, rhesus monkey, tigers, and lions (Imai et al., 2020; Kim et al., 2020; Shi et al., 2020; United States Department of Agriculture [USDA], 2020; Yu et al., 2020). Cats do show disease symptoms and transmit the infection to other animals of their species (Shi et al., 2020). In all the cases of pet or zoo animals testing positive, the source of infection was either confirmed or suspected to be a human (American Veterinary Medical Association, 2020).

SARS-CoV-2 infection in humans depends on the binding of its spike protein to a human cell receptor angiotensin-converting enzyme 2 (ACE2) which is expressed across the animal species as a cell surface receptor (Bibiana et al., 2020). Evolutionary conservation of protein sequence of ACE2 across vertebrate species, and more specifically, in hominids and primates, remains strong plausibility (Braun et al., 2020). Recent studies have decoded the receptor-binding domain (RBD) of SARS-CoV-2 spike protein and demonstrated its structural binding with the N-terminal peptidase domain of human ACE2 (*hACE2*). Receptor-binding motif (RBM) on SARS-CoV-2 RBD makes direct contacts with amino acid residues at *hACE2* (Lan et al., 2020; Wan et al., 2020). We assumed that a homology to *hACE2*, more particularly to viral RBD-binding interface, of ACE2 protein sequences of animal species could be used in predicting their susceptibility for contracting SARS-CoV-2 infection.

2 | MATERIALS AND METHODS

The complete protein sequence of *hACE2* (Q9BYF1.2) was retrieved from the open-access protein sequence data base Uniprot.org. Crystal structures of *hACE2* and SARS-CoV-2 RBD were created based on X-RAY diffraction data retrieved from RCSB protein data bank, PBD1D-6M0J (https://www.rcsb.org/structure/6m0j) using software: PyMOL built from Schrodinger, Inc. Amino acid residues at *hACE2*/RBD interface, and conserved RBD-binding hotspots at *hACE2*, were annotated in consultation with published literature (Lan et al., 2020; Othman et al., 2020; Wan et al., 2020).

Further, the NCBI protein blast tool (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastp) was used to analyze open-access protein sequence data of ACE2 for the species in animal kingdom available at NCBI databases. To minimize the prediction error, a two-step homology search was performed. First, we performed a comparative analysis of the variability of *hACE2* with that of wildlife and domestic animal species in complete protein sequences. The accession numbers of the species which showed significant homology (*E* value ≤ 0) for the complete sequence were selected for further analysis for the second step. In the second step, we narrowed down our homology search to a subrange of 36–53 amino acid residues of *hACE2* (<AEDLFYQSSLASWNYNTN>), which contain conserved hotspots for binding of SARS-CoV-2 RBD (Othman et al., 2020). A fixed query cover of 100% was applied for the sequence homology match in the second analysis. The final ACE2 sequence homology scores along with the statistical significance value (*E* value ≤ 1E−08) were used to determine the susceptibility ranking of the animal for contracting SARS-CoV-2 infection. A higher sequence homology score with *E*-value closure to zero signified higher susceptibility ranking for the species. Details of NCBI protein blast and statistical methods predicting significance can be consulted at https://www.ncbi.nlm.nih.gov/books/NBK20261/.

3 | RESULTS

Figure 1 presents crystal structures of *hACE2* and SARS-CoV-2 RBD (1a), and shows annotations for conserved RBD-binding hotspots (1b) and other interacting amino acids (1c) and at the ACE2/RBD interface. Significant alignments of the species-specific ACE2 orthologous to *hACE2* (Accession: Q9BYF1.2) for the complete sequence (Table S1) and a partial sequence at the RBD interface (a subrange of 36–53 amino acid residues) (Figure 1b and Table 1) were noted across the animal kingdom. In the search for complete sequence homology as well as a subrange of 36–53 amino acid residues at the RBD interface, hominids and other primates showed the highest homology (up to 100%) with *hACE2*, followed by

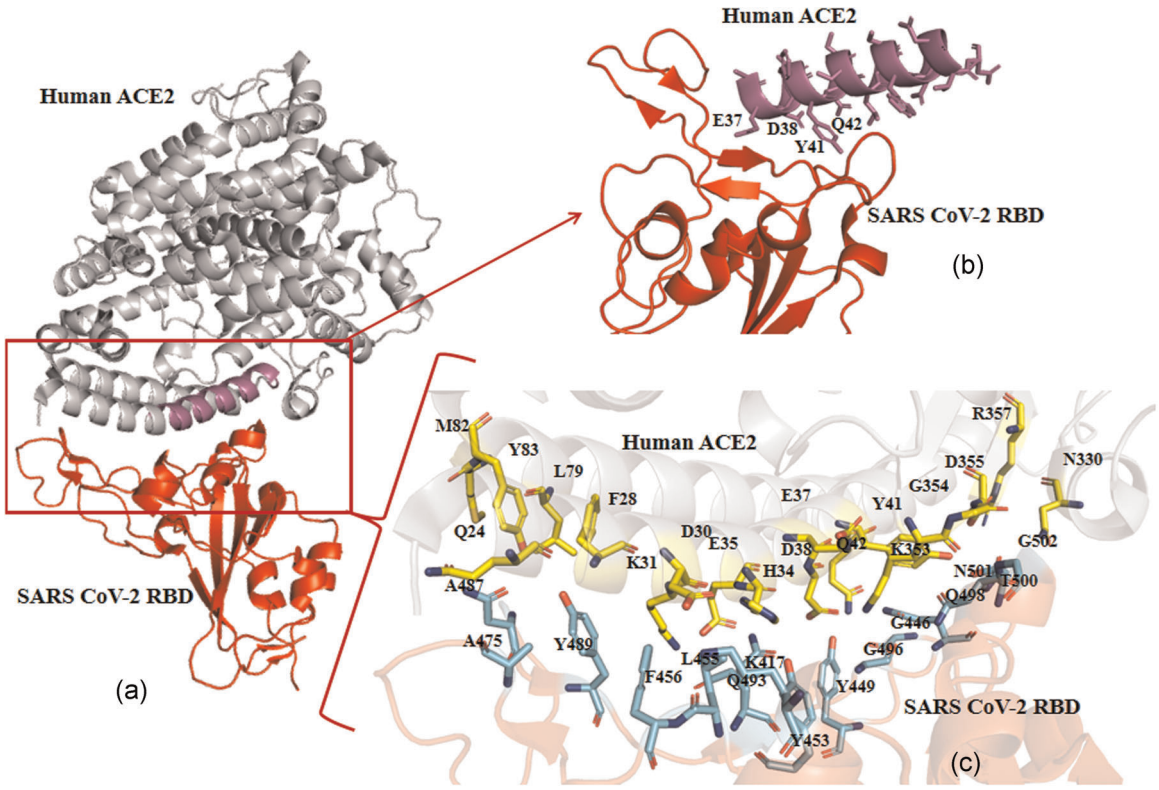

FIGURE 1 Interaction of SARS-CoV-2 receptor-binding domain RBD with Human ACE2. (a) Human ACE2 (*gray*)—RBD (red)-binding interface. (b) Segment of Human ACE2 (magenta) consisting of conserved RBD-binding hotspots (36–53 aa) at the RBD-binding interface. (c) Important residues participating in the interactions at Human ACE2 (yellow)-RBD (cyan) interface. *Source*: RCSB protein data bank, PBD1D-6M0J. Software used: PyMOL built by Schrodinger, Inc. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Species-specific ACE2 sequences producing significant alignments to human ACE2[a]

Description	Order/Family	Query cover (%)	*E* value	Percentage identity	Accession no.	Susceptibility ranking
ACE2 (*Gorilla gorilla* [Gorilla])	Primate/Hominidae	100	2E−16	100	XP_018874749.1	1
ACE2 isoform X1 (*Pan troglodytes* [Chimpanzee])	Primate/Hominidae	100	2E−16	100	XP_016798468.1	2
ACE2 isoform X1 (*Pan paniscus* [Bonobo])	Primate/Hominidae	100	2E−16	100	XP_008972428.1	3
ACE2 isoform X1 (*Pongoabelii* [Sumatran orangutan])	Primate/Hominidae	100	2E−16	100	XP_024096013.1	4
ACE2 (*Hylobatesmoloch* [Silvery gibbon])	Primate/Hylobatidae	100	2E−16	100	XP_032612508.1	5
ACE2 (*Nomascus leucogenys* [Northern white-cheeked gibbon])	Primate/Hylobatidae	100	2E−16	100	XP_003261132.2	6
ACE2 (*Piliocolobus tephrosceles* [Ugandan red colobus])	Primate/Cercopithecidae	100	2E−16	100	XP_023054821.1	7
ACE2 (*Rhinopithecus roxellana* [Golden snub-nosed monkey])	Primate/Cercopithecidae	100	2E−16	100	XP_010364367.2	8
ACE2 (*Theropithecus gelada* [Gelada])	Primate/Cercopithecidae	100	2E−16	100	XP_025227847.1	9
ACE2 (*Papioanubis* [Olive baboon])	Primate/Hominidae	100	2E−16	100	XP_021788732.1	10
ACE2 (*Macaca nemestrina* [Southern pig-tailed macaque])	Primate/Cercopithecidae	100	2E−16	100	XP_011733505.1	11
ACE2 (*Macaca mulatta* [Rhesus macaque])[b]	Primate/Cercopithecidae	100	2E−16	100	ACI04556.1	12
PREDICTED: ACE2 (*Macaca fascicularis* [Crab-eating macaque])	Primate/Cercopithecidae	100	2E−16	100	XP_005593094.1	13
PREDICTED: ACE2 (*Cercocebus atys* [Sooty mangabey])	Primate/Cercopithecidae	100	2E−16	100	XP_011891198.1	14
PREDICTED: ACE2 (*Mandrillus sphinx* [Mandrill])	Primate/Cercopithecidae	100	2E−16	100	XP_011850923.1	15
PREDICTED: ACE2 (*Chlorocebus sabaeus* [Green monkey])	Primate/Cercopithecidae	100	2E−16	100	XP_007989304.1	16
ACE2 (*Ursusarctos horribilis* [Grizzly bear])	Carnivora/Ursidae	100	2E−15	94.44	XP_026333865.1	17
PREDICTED: ACE2 (*Ailuropoda melanoleuca* (Giant panda])	Carnivora/Ursidae	100	2E−15	94.44	XP_002930657.1	18
PREDICTED: ACE2 (*Ursus maritimus* [Polar bear])	Carnivora/Ursidae	100	2E−15	94.44	XP_008694637.1	19
PREDICTED: ACE2 isoform X1 (*Chinchilla lanigera* [Long-tailed chinchilla])	Rodentia/Chinchillidae	100	3E−14	94.44	XP_013362428.1	20
ACE2 (*Heterocephalus glaber* [Naked mole-rat])	Rodentia/Heterocephalidae	100	3E−14	94.44	XP_004866157.1	21
ACE2 (*Camelusferus* [Wild Bactrian camel])	Artiodactyla/Camelidae	100	3E−14	94.44	XP_006194263.1	22
PREDICTED: ACE2 (*Jaculus jaculus* [Lesser Egyptian jerboa])	Rodentia/Dipodidae	100	3E−14	94.44	XP_004671523.1	23
PREDICTED: ACE2 isoform X1 X1 (*Dipodomys ordii* [Ord's kangaroo rat])	Rodentia/Heteromyidae	100	3E−14	94.44	XP_012887572.1	24
ACE2 (Physeter catodon [Sperm whale])	Artiodactyla/Physeteridae	100	3E−14	94.44	XP_023971279.1	25
ACE2 (Lipotes vexillifer [baiji])	Artiodactyla/Lipotidae	100	3E−14	94.44	XP_007466389.1	26
ACE2 (*Octodon degus* [Common degu])	Rodentia/Octodontidae	100	3E−13	88.89	XP_023575315.1	27

(Continues)

TABLE 1 (Continued)

Description	Order/Family	Query cover (%)	*E* value	Percentage identity	Accession no.	Susceptibility ranking
ACE2 (Eumetopias jubatus [Steller sea lion])	Carnivora/Otariidae	100	3E−13	88.89	XP_027970822.1	28
PREDICTED: ACE2 (*Fukomys damarensis* [Damara land Mole-rat])	Rodentia/Bathyergidae	100	3E−13	88.89	XP_010643477.1	29
ACE2 (*Puma concolor* [Cougar])	Carnivora/Felidae	100	3E−13	88.89	XP_025790417.1	30
PREDICTED: ACE2 isoform X1 (*Pantherapardus* [Leopard])	Carnivora/Felidae	100	3E−13	88.89	XP_019273508.1	31
ACE2 isoform X1 (*Acinonyx jubatus* [Cheetah])	Carnivora/Felidae	100	3E−13	88.89	XP_026910297.1	32
ACE2 precursor (*Felis catus* [Cat])[b]	Carnivora/Felidae	100	3E−13	88.89	NP_001034545.1	33
ACE2 (*Lynx pardinus* [Iberian lynx])	Carnivora/Felidae	100	3E−13	88.89	VFV30336.1	34
ACE2 (*Lynx canadensis* [Canada lynx])	Carnivora/Felidae	100	3E−13	88.89	XP_030160839.1	35
ACE2 (*Mesocricetus auratus* [Golden hamster])[b]	Rodentia/Cricetidae	100	3E−13	88.89	XP_005074266.1	36
ACE2 (*Cricetulus griseus* [Chinese hamster])	Rodentia/Cricetidae	100	3E−13	88.89	XP_003503283.1	37
ACE2 (Manis javanica [Sunda pangolin])	Pholidota/Manidae	100	3E−13	88.89	XP_017505746.1	38
ACE2 (Peromyscus bairdii [North American deer mouse])	Rodentia/Cricetidae	100	3E−13	88.89	XP_006973269.1	39
ACE2 (*Microtus ochrogaster* [Prairie vole])	Rodentia/Cricetidae	100	3E−3	88.89	XP_005358818.1	40
PREDICTED: ACE2 (*Panthera tigris* (Tiger])[b]	Carnivora/Felidae	100	3E−13	88.89	XP_007090142.1	41
PREDICTED: ACE2 (*Panthera leo* [lion])	Carnivora/Felidae	100	3E−13	88.89	Query_32935[c]	42
ACE2 (*Balaenoptera acutorostrata* [Minke whale])	Cetartiodactyla/ Balaenopteridae	100	1E−12	88.89	XP_028020351.1	43
PREDICTED: ACE2 (*Saimiri boliviensi* [Black-capped squirrel monkey])	Primate/Cebidae	100	1E−12	83.33	XP_010334925.1	44
ACE2 (*Sapajus apella* [Tufted capuchin])	Primate/Cebidae	100	1E−12	83.33	XP_032141854.1	45
PREDICTED: ACE2 (*Cebus capucinus* [Panamanian White-faced Capuchin])	Primate/Cebidae	100	1E−12	83.33	XP_017367865.1	46
ACE2 (*Aotusnancymaae* [Nancy Ma's night monkey])	Primate/Aotidae	100	1E−12	83.33	XP_012290105.1	47
ACE2 (*Callithrix jacchus* [Common marmoset])	Primate/Callitrichidae	100	1E−12	83.33	XP_008987241.1	48
ACE2 (*Carlito syrichta* [Philippine tarsier])	Primate/Tarsiidae	100	1E−12	83.33	XP_008062810.1	49
PREDICTED: ACE2 (*Propithecus coquereli* [Coquerel's sifaka])	Primate/Indriidae	100	2E−12	83.33	XP_012494185.1	50
PREDICTED: ACE2 (*Oryctolagus cuniculus* [European rabbit])	Lagomorpha/Leporidae	100	2E−12	83.33	XP_002719891.1	51
ACE2 (*Mustel aerminea* [Stoat])	Carnivora/Mustelidae	100	2E−12	83.33	XP_032187677.1	52
ACE2 (*Mustela putorius furo* [European domestic ferret])[b]	Carnivora/Mustelidae	100	2E−12	83.33	Q2WG88	53

TABLE 1 (Continued)

Description	Order/Family	Query cover (%)	*E* value	Percentage identity	Accession no.	Susceptibility ranking
PREDICTED: ACE2 (*Ceratotherium simum* [White rhinoceros])	Perissodactyla/Rhinocerotidae	100	4E−12	83.33	XP_004435206.1	54
ACE2 (*Vicugnapacos* [Alpaca])	Cetartiodactyla/Camelidae	100	6E−12	88.89	XP_006212709.1	55
ACE2 Isoform XI (*Canis lupus familiaris* [Dog])[b]	Carnivora/Canidae	100	6E−12	83.33	XP_005641049.1	56
PREDICTED: ACE2 (*Marmota marmota* [Alpine marmot])	Rodentia/Sciuridae	100	2E−11	88.89	XP_015343540.1	57
ACE2 (*Marmota flaviventris* [Yellow-bellied marmot])	Rodentia/Sciuridae	100	2E−11	88.89	XP_027802308.1	58
PREDICTED: ACE2 (*Ochotonaprinceps* [American pika])	Lagomorpha/Ochotonidae	100	2E−11	77.78	XP_004597549.2	59
ACE2 (*Paguma larvata* [Masked palm civet])	Carnivora/Viverridae	100	6E−11	77.78	Q56NL1.1	60
ACE2 (*Ictidomys tridecemlineatus* [Thirteen-lined ground squirrel])	Rodentia/Sciuridae	100	1E−10	83.33	XP_005316051.3	61
ACE2 isoform X1 (*Myotis lucifugus* (Little brown bat])	Chiroptera/Vespertilionidae	100	2E−10	77.78	XP_023609437.1	62
PREDICTED: ACE2 (*Equus przewalskii* [Przewalski's horse])	Perissodactyla/Equidae	100	3E−10	77.78	XP_008542995.1	63
ACE2 (*Equus caballus* [Horse])	Perissodactyla/Equidae	100	3E−10	77.78	XP_001490241.1	64
ACE2 enzyme (*Crocuta crocuta* [Spotted hyena])	Carnivora/Hyaenidae	100	6E−09	72.22	KAF0878287.1	65
ACE2 isoform X1 (*Urocitellus parryii* [Arctic ground squirrel])	Rodentia/Sciuridae	100	1E−08	77.78	XP_026252505.1	66

Note: *hACE2* Accession no.: Q9BYF1.2; query subrange: 36–53aa; subject subrange: 36–53aa.

[a]Species/Family compared: Primates (taxid: 9443), cat family (taxid: 9681), Equus (taxid: 9789), ferret (taxid: 9669), dog, coyote, wolf, fox (taxid: 9608), elephants (taxid: 9779), oxen, cattle (taxid: 9903), water buffalo (taxid: 89462), goats (taxid: 9925), pigs (taxid: 9821), deer (taxid: 9850), lion (taxid: 9689), Ursidae (taxid: 9632), Camelidae (taxid: 9835), carnivores (taxid: 33554), Mammalia (taxid: 40674), Rodents and rabbits (taxid: 314147), house mouse (taxid: 10090), birds (taxid: 8782), fishes (taxid: 7898), snakes (taxid: 8570), mouse (taxid: 10088), bats (taxid: 9397).

[b]SARS-CoV-2 RNA testing positive (Imai et al., 2020; Kim et al., 2020; Shi et al., 2020; United States Department of Agriculture [USDA], 2020; Yu et al., 2020).

[c]ACE2 protein sequence for *Panthera leo* (Lion) is not available in NCBI data base. A predicted ACE2 sequence has been referred from Alexander et al. (2020).

carnivores (up to 94.4%), rodents (up to 94.4%), and artiodactyles (even-toed ungulates) (up to 94.4%). Oxen, water buffaloes, goats, pigs, birds, fishes, and snakes showed no significant match in either of the searches. Sequence homology scores and susceptibility ranking (for contracting SARS-CoV-2 infection) for the animal species have been provided in the columns for "Percentage Identity" and "Susceptibility Ranking" in Table 1. The animals which have been described positive for the SARS-CoV-2 RNA in the recent literature have been marked (Table 1, footnote[b]). ACE2 sequence alignment data for the complete and partial sequences have been provided as Supporting Information, Files 2 and 3.

4 | DISCUSSION

Zoonotic spillover of human infectious diseases is not uncommon. Recent reports of SARS-CoV-2 infection and COVID-19 symptoms in selected wildlife and domestic animals warranted for caution that the epidemic can have possible spread in animal settings like zoos and wildlife sanctuaries, including a threat of viral transmission from domestic animals (CDC, 2020; Tiwari et al., 2020; Yoo & Yoo, 2020). The species-specific protein sequence homology to *hACE2* may be a valuable tool for predicting susceptibility for contracting SARS-CoV-2 infection. It can be used as a screening tool for guiding viral RNA-based laboratory testing to contain COVID-19 spread in wildlife and domestic animals during an epidemic outbreak.

Currently, polymerase chain reaction (PCR)-based laboratory testing for SARS-CoV-2 RNA is a standard practice for detecting viral infection and development of COVID-19 in humans. However, viral infectivity studies involving animals, especially wildlife, are very limited for now. We used open-access bioinformatics tools to predict susceptibility for SARS-CoV-2 infection in domestic and wildlife animals. For this purpose, we performed a comparative analysis of the variability of complete protein sequence and SARS-CoV-2 RBD-binding hotspots of *hACE2* with that of the animal species. On the basis of the sequence homology, we predicted the highest susceptibility for hominids and other primates, followed by carnivores, rodents, and artiodactyles (ungulates), however, sequence match varied widely among the species in any order of the animal kingdom. A similar pattern of susceptibility prediction was recently reported by Damas et al., (2020) who compared ACE2 sequence homology across species, however, their species list varied from us, which can be explained by differences of data sources. Damas et al., (2020) also noted conservation of ACE2 protein sequence among evolutionarily linked species; this has been reflected in our study also, as we find the highest sequence homology to *hACE2* in the members of order hominids and primate who are closest to humans, and further across mammalians, and other categories of vertebrates. A lesser sequence homology was found with the species which are remotely related to humans.

Our susceptibility predictions for cats, dogs, golden hamster, rhesus monkey, tigers, and lions get confirmation from the recent reports in literature which had performed PCR-based laboratory testing for SARS-CoV-2 RNA in the selective animals (Table 1, footnote[b]) (Imai et al., 2020; Kim et al., 2020; Shi et al., 2020; United States Department of Agriculture USDA, 2020; Yu et al., 2020). However, a viral RNA-based susceptibility information is currently highly limited, especially for the animals inhabiting in natural settings.

For certain species, such as American mink and ferret, which was recently reported to get SARS-CoV-2 infection (Shi et al., 2020; USDA, 2020); although we found their significant homology to *hACE2* (Table S1), we couldn't get homology score for SARS-CoV-2 RBD-binding hotspots in absence of complete protein sequence of ACE2 for these species. However, we found significant homology for SARS-CoV-2 RBD-binding hotspots for the species which are closely related to them, such as, European mink and stoat for which the complete protein sequences for ACE2 were available (Table 1).

Our two-step comparison for sequence homology (for complete sequence and SARS-CoV-2 RBD-binding hotspots, respectively) has reduced the chances of false inclusions and provides a susceptibility rank which may help to identify the most vulnerable animal species for contracting SARS-CoV-2 infection. Many of the wild animals noted in the list, such as giant panda, white rhinoceros, are endangered, which raises immediate concern to protect them from the reach of the COVID-19 pandemic. Laboratory testing of viral RNA for wildlife animals in zoos and sanctuaries is limited by many practical factors, in that sense software-based tool to predict COVID-19 susceptibility in the animals presents a very easy and cheap option for COVID-19 prevention and containment in these settings. However, there remains a need to further confirm their susceptibility through laboratory testing of viral RNA.

4.1 | Limitations

In the present study, we considered only viral host cell entry receptor ACE2 homology for predicting the susceptibility, however, SARS-CoV-2 host cell entry and replication, in addition, may also depend on many other factors like tissue proteases TMPRSS2 or CTSL, and ADAM-17 (Zhang et al., 2020), thus, a *hACE2* homology may not be sufficient, and a viral infectivity testing of the listed animals will be necessary to confirm their susceptibility for contracting SARS-CoV-2 infection. Also, some animals may not develop clinical symptoms or transmit the virus even after contracting SARS-CoV-2 infection, hence their identification through viral RNA testing accompanied by clinical observation will be necessary to understand their susceptibility risk.

Additionally, our susceptibility prediction list (Table 1) has only provided an assessment for the animal species for which ACE2 protein sequence (more particularly from amino acid residues 36–53) is available in the NCBI data base (except, Panthera leo, for which ACE2 sequence has been referred from Alexander et al., 2020). However, this tool can be suitably used to screen remaining animals if their ACE2 protein sequence is made available.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Sequence alignment data generated in this study have been provided as Supporting Information Files 2 and 3. ACE2 protein sequences used for this study can be retrieved from NCBI protein (https://www.ncbi.nlm.nih.gov/protein) and Uniprot.org (https://www.uniprot.org/) databases using species-specific accession numbers provided in Tables 1 and S1.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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