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ACE2 and Covid-19 Spike Protein Docking in Family Pets

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Abstract

COVID-19 infection is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). COVID-19 infection has resulted in hundreds of thousands of human deaths since the announcement of the Coronavirus pandemic in 2020. Emerging evidence supports the fact that SARS-CoV-2 infection happened not only in humans but in animals as well. Given the high frequency f of pets in family homes in many countries, COVID-19 infection in pets poses a potential threat to other domestic and wild animals, and humans. In this paper, we review the infection cases in pets world-wide and investigate the possible infection chain by an in-silico docking analysis of the SARS-CoV-2 spike protein with ACE2 proteins amongst 27 species including many pet animals. High docking scores indicate high interacting affinities between the SARS-CoV-2 spike protein and the cellular ACE2 receptor from these pet species. The phylogenetic analysis of human and pet ACE2 receptors show high sequence identities, especially for several functional sequence regions. These results suggest that the SARS-Cov-2 may have similar ability to penetrate cells from these different species and use similar molecular interactions to initiate infection of pet and human cells. Considering the high occupancy rates of pets in American and world-wide, the results suggest that pets should be considered in strategies to control COVID-19.

Keywords: SARS-CoV-2; Family pets; Human ACE2 receptor; Protein–protein docking

Abbreviations: WHO: World Health Organization; COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TEMPRSS2: Transmembrane Serine Protease 2; ACE2: Angiotensin I Converting Enzyme 2; RT-PCR: Reverse Transcription-Polymerase Chain Reaction; NCBI: National Center for Biotechnology Information

Introduction

Early in 2020, the World Health Organization (WHO) announced Coronavirus Disease (COVID-19) a pandemic [1]. This infection is caused by a pathogen named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This existing pandemic has currently been reported in 215 countries and territories with about 250 million proven cases and more than 5 million deaths globally [2]. It is now proven that SARS-CoV-2 is able to infect not only in humans but also in pets as well as other domestic and wild animals [3]. Various published scientific evidence revealed a strong homology between SARS-CoV-2 and bat coronaviruses, suggesting that the COVID19 pandemic is a zoonotic pandemic caused by a virus originating in bats. Additionally, pangolins have been counted as one of the possible intermediate hosts (Figure 1) [4,5].

Coronaviruses are one type of protein enveloped RNA viruses, which measure 80–220 nm in diameter. Their genome is the largest among RNA viruses and comprises a non-segmented, single-stranded positive-sense genome of approximately 26–32 kilobases (kb) in size [6]. Structurally, the viral particle comprises four main proteins; 1) spike (S) glycoprotein, 2) small envelope (E) glycoprotein, 3) membrane (M) glycoprotein, and 4) nucleocapsid (N) protein (Figure 1) [7]. The M protein is the most abundant structural protein, specifies the shape of the viral particle and plays a major role in viral assembly [8]. The N protein is an RNA binding protein involved in the binding and packaging of the viral RNA genome into a long helical nucleocapsid structure. The S glycoprotein facilitates viral binding to a specific receptor on the animal and human host cells, and promotes fusion between the viral envelope and a cellular membrane [9].

The attachment of SARS-CoV-2 S glycoprotein to the ACE2 receptor starts the process of entry into target cells [10]. The SARS-CoV-2 can enter cells using either endosomal or non-endosomal pathways [11]. In the endosomal pathway, the binding of the S glycoprotein to ACE2 triggers receptor-mediated endocytosis which is followed by fusion between the viral envelope and an

endosomal membrane to release the viral genome in the cytosol. In the non-endosomal pathway, cleavage of the viral S glycoprotein by transmembrane serine protease 2 (TMPRSS2) at the surface of the host cell allows the S glycoprotein to mediate fusion of the viral envelope directly with the cell plasma membrane. Both entry pathways lead to the release and uncoating of the viral genome in the cytosol of the host cell allowing it to be subsequently translated and replicated [12].

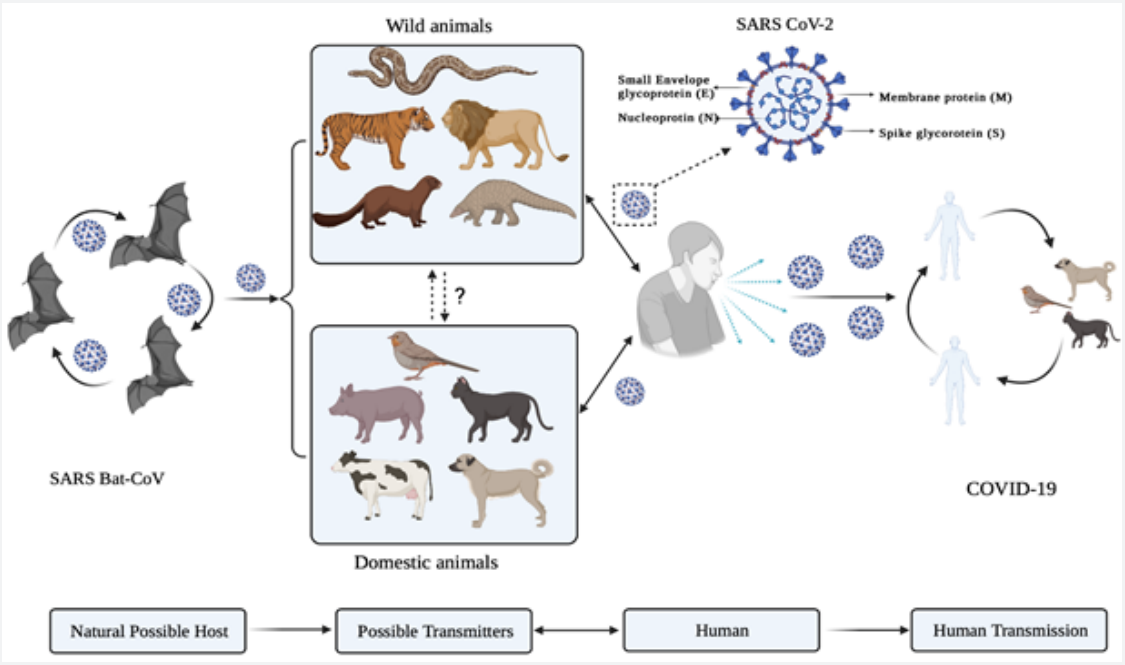

Figure 1: Origin and transmission of SARS-CoV-2 along with the potential role of pets and other animals in disease transmission. This figure illustrates the putative origin of CoVs and disease transmission to humans with a special focus on SARS-CoV-2.

The human ACE2 receptor, also termed as ACEH (ACE homologue), is a dimeric, zinc-dependent metalloproteinase of the ACE family that comprises germinal and somatic ACE [13,14]. ACE2 mRNA is highly detected in testes, heart and kidneys, however, it is found at lower levels in an extensive variety of tissues [13,15]. As part of its natural function, ACE2 acts as a carboxypeptidase which cleaves various substrates including angiotensin I and II [10]. It is also involved in the function of the B0AT1-family of amino acid transporters [13]. Due to these physiological functions, ACE2 has been linked to various diseases including, heart disease [16] as well as liver and lung fibrosis [17], although it has been shown to have a protective effect in acute lung injury [18]. ACE 2 is a major factor in COVID-19, due to its key role as a receptor for SARS-CoV-2.

Structurally, the ACE2 protein comprises three main regions: 1) the N-terminal part of the extracellular region that contains the catalytic domain of the peptidase; 2) the C-terminal part of the extracellular region contains a collectrin-like domain (CLD) which extends through the transmembrane region; and 3) a short cytoplasmic tail [19]. The N-terminal region is essential for attachment to the SARS-CoV and SARS-CoV-2 spike proteins, while the CLD contains a region that allows dimerization and interaction with amino acid transporters [14]. The peptidase domain comprises a long deep cleft that undergoes a large hinge-bending movement at inhibitor and substrate attachment [19].

Pets as targets of SARS-CoV-2 infection

The first COVID-19 case in a domestic animal was reported in a Pomeranian dog from China in February 2020 [20]. Afterwards, in March 2020, COVID-19 was observed in a cat in the same country [21]. These cases were detected after their owners were positively diagnosed for COVID-19 [20,21]. The persistent positive reverse transcription-polymerase chain reaction (RT-PCR) test results of the Pomeranian dog was considered as a true positive for an infection of the animal [22]. This conclusion was further supported by the absence of contamination when the dog was kept in quarantine at government kennels [22]. Genetic sequence similarities of the SARS-CoV-2 genomes isolated from the pet and the owners suggested the possibility of human-to-animal transmission [23]. Additionally, both serological tests and viral culture were performed to evaluate if the dog was contagious or not. The negative results of these tests and the absence of any symptom, led to the conclusion that the dog was not contagious to humans and another animal [22].

After the first reported case of COVID-19 in a cat in China [21], other COVID-19 cases were reported from Belgium [24],

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France [25], Germany [26], Russia [27], and the United States [28]. According to these reports, it is currently accepted that cats and dogs are two companion animals susceptible to SARS-CoV-2. Cats are more susceptible than dogs and may have the potential to transmit the illness to other naive cats [29]. In addition, in laboratory experiments golden Syrian hamsters have been shown to be susceptible to SARS-CoV-2 and effectively transmit infection to naïve hamsters via aerosols or direct contact [30].

According to Dodds et al. [31] animals that are susceptible to SARS-CoV-2 under experimental conditions, include cats, dogs, and ferrets, but not horses, pigs, or poultry [31]. The results of experimental studies in cattle are conflicting, however it does not appear that cattle can easily be infected [31]. Additionally, another study of caged cats demonstrates that transmission between cats is possible with prolonged close contact. It does claim how likely this is to occur in natural settings [32]. Under natural conditions, dogs and cats are not considered easily infected, and infected cats or dogs are not easily to spread the virus to other animals or humans. However, according to the Ohio State University College of Veterinary Medicine, dogs appear to be more resistant than cats, and ferrets in a laboratory setting [33]. In summary, pets living in the household of COVID-19 diagnosed people are in danger of contracting the disease and can spread the virus to the nearby naive pets. Therefore, owners need to strictly protect their companion animals from getting infected. Understanding how COVID-19 affects companion animals is essential given that 84.9 millions of U.S households' own pets (Figure 2A) [34]. Notably, as of July 2021, the USDA reports that the highest number of positively tested animals in the USA are in Texas (Figure 2B) [35]. Although, the numbers of infected pets remain low overall, these pets may have the potential to transmit the virus and potentially generate variants which may adapt to better use animal ACE2 receptors and spread through new species [30].

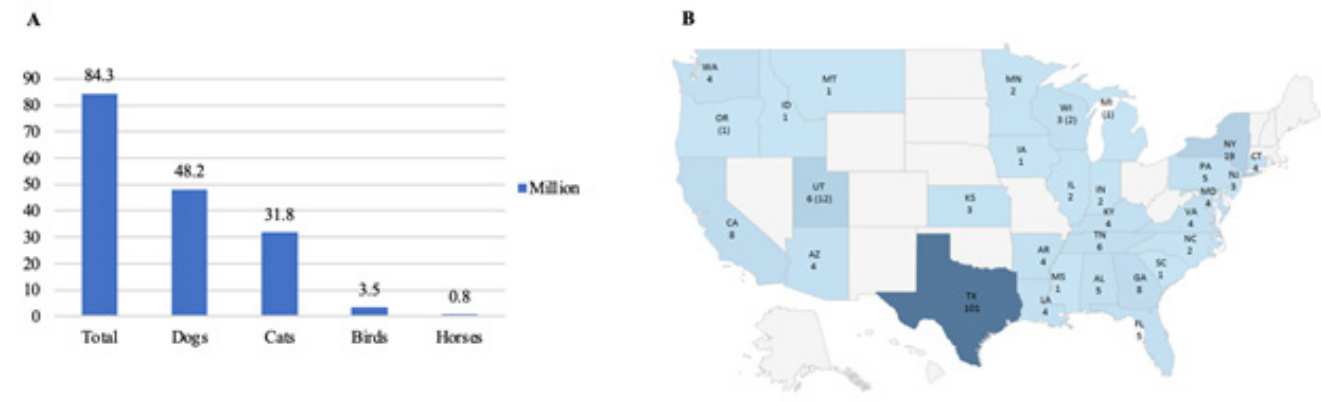

Figure 2: Epidemiology of pets in USA households and prevalence of COVID-19 in the USA animals. A. This chart represents the number of USA households' own pet. B. This map represents the cases of SARS-CoV-2 in animals in the USA (the updated to July 2021).

High sequence similarity among human and pets ACE2 proteins

To understand the properties that allow SARS-CoV-2 infection of pets, we considered primarily the interaction of SARS CoV-2 S glycoprotein with the cellular receptor ACE2. Although species specificity of viral infections is defined by numerous factors that may affect multiple stages of the replication cycle of a virus, effective interaction with a receptor that allows entry is an essential, albeit not sufficient, step to ensure infection. Thus, we modelled and analysed the interaction of the S glycoprotein with ACE2 proteins from different species by phylogenetic analysis and protein docking method [36]. We first compared the amino acid sequences of ACE2 proteins from human and 27 animal species, including major household animals (Table 1). The sequences were retrieved from the National Center for Biotechnology Information (NCBI) protein sequence database and the Sequence Alignment was performed using the online tool "Clustal Omega" (https://www.ebi.ac.uk/Tools/msa/clustalo/) [37]. Noticeably, pair-wise alignments showed that all 27 ACE2 receptor sequences displayed high similarities with human ACE2 protein, ranging from 99% (chimpanzee) to 66.38% (white-ruffed manakin). We observed that 5 species, chimpanzee, Sumatran orangutan, Macaca nemestrina, sooty mangabey and rat, have an overall amino-acid identity larger than 90%, suggesting that ACE2 is highly conserved in structure and function between these species. We conducted multiple sequence alignment for the 28 species sequences by using the ClustalX method [38]. Results show that all these sequences have either high amino acid sequence similarity or high physical/structural features (Figure 3). As shown in figure 3B, 3C and 3D, these regions are highly conserved [39]. In particular, the 362-366 region has been annotated to be important for natural substrate binding and for interaction with SARS-CoV spike glycoprotein (Protein Data Bank, https://www.rcsb.org), (Figure 3C).

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Table 1: Sequence identity between the human ACE2 receptor and 27 other species.

S. No	Species Name	NCBI ID	Sequence Identity (%)
1	*Homo sapiens*	NP_001358344.1	100%
2	*Chimpanzee*	XP_016798468.1	99%
3	*Sumatran orangutan*	NP_001124604.1	98.14%
4	*Macaca nemestrina*	XP_024647450.1	95.34%
5	*Sooty mangabey*	XP_011891201.1	95.21%
6	*Rattus norvegicus (brown rat)*	NP_001012006.1	90.43%
7	*Acinonyx Jubatus (cheetah)*	XP_026910301.1	86.53%
8	*Oryctolagus cuniculus (european rabbit)*	XP_002719891.1	85.14%
9	*Felis catus (domestic cat)*	XP_023104564.1	84.67%
10	*Chinchilla lanigera*	XP_013362429.1	84.38%
11	*Canis lupus dingo*	XP_025292925.2	84.01%
12	*Nyctereutes procyonoides (raccoon dog)*	ABW16956.1	83.88%
13	*Canis lupus familiaris (domestic dog)*	NP_001158732.1	83.25%
14	*Vicugna pacos*	XP_006212709.1	83.25%
15	*Mustela erminea*	XP_032187679.1	83%
16	*Capra hircus (goat)*	NP_001277036.1	81.86%
17	*Mustela putorius furo (ferret)*	NP_001297119.1	81.49%
18	*Sus scrofa (wild boar)*	NP_001116542.1	81.23%
19	*Rhinolophus affinis (bat)*	QMQ39244.1	80.60%
20	*Monodelphis domestica*	XP_007500942.1	72.80%
21	*Charadrius vociferus*	XP_009887332.1	70.43%
22	*Falco rusticolus*	XP_037233643.1	67.29%
23	*Falco cherrug*	XP_027666699.1	66.92%
24	*Pipra filicauda (manakin)*	XP_027593975.1	66.75%
25	*Gallus gallus (red junglefowl)*	XP_416822.3	66.67%
26	*Neopelma chrysocephalum*	XP_027544865.1	66.50%
27	*Lonchura striata domestica (society finch)*	XP_021388026.1	66.46%
28	*Corapipo altera (manakin)*	XP_027494828.1	66.38%

Additionally, phylogenetic and molecular evolutionary analyses were conducted using neighbour-joining method by MEGA software [40]. A rooted phylogenetic tree was then created by using the amino acid sequences to demonstrate the evolutionary relationships between the 28 species (Figure 4). The branching pattern of the phylogenetic tree reflects evolutionary relationships. The phylogenetic analysis (Figure 4) shows that the human ACE2 protein is most closely related to the orangutan and chimpanzee proteins, but much less related to ACE2 from the 8 bird species analysed, which is consistent with general taxonomic analysis. Overall, these sequence-based analyses demonstrate a high genetic and structural conservation of ACE2 proteins among the major pet species and humans. This suggests that ACE2 from numerous species may be functional receptors for SARS-CoV-2 S glycoprotein and allow entry of the virus into cells from these species.

High docking affinity of SARS-CoV-2 spike protein with pet ACE2 protein

The interaction between ACE2 and SARS-CoV-2 S glycoprotein is of utmost importance for SARS CoV-2 infection and spread in humans [41]. To determine the potential binding affinity of the S glycoprotein for ACE2 proteins from pet species, we performed a protein–protein docking analysis using the HDOCK server [36]. This approach generates docking scores to represent the binding free energy of two interacting proteins. Smaller negative docking scores suggest higher docking affinity strength. For each of the 28 ACE2 proteins, the top ten models and their docking scores were outputted and then the smallest negative docking scores were selected (Figure 5). In surprise, we found there are 7 species (Chimpanzee, Canis Lupus, Canis Lupus Dingo, Nyctereutes Procyonoides, Oryctolagus Cuniculus, Sus Scrofa and Mustela Putorius Furo) whose docking scores are smaller than human's

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score. Among them, Chimpanzee achieves a smallest docking score of -665.81 kcal/mol, indicating it may be the most suspectable to Covid-19 infection. Meanwhile, humans and cats (Felis Catus) have similar docking scores (-527.72 kcal/mol vs -523.15 kcal/mol), which is in agreement with the published data suggests cats can spread the infection among animals and humans [31]. Shen et al. [42] also assessed the receptor utilization capacity of ACE2 from different species and noticed that cats were most susceptible to infection by SARS-CoV-2 [42].

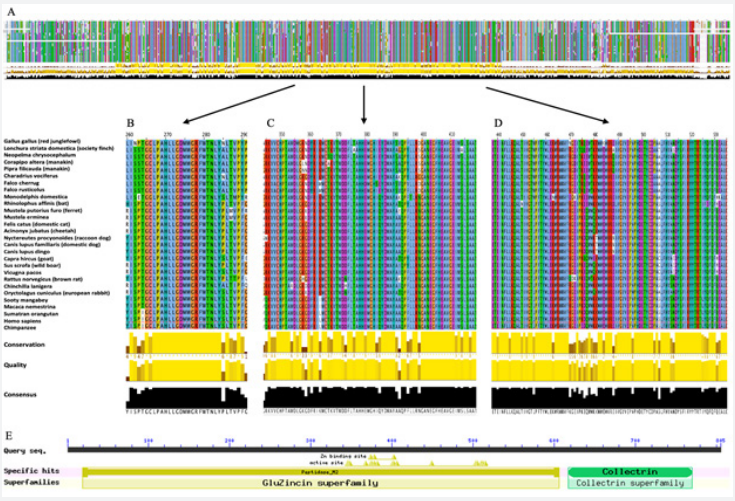

Figure 3: Multiple Sequence alignment of the human ACE2 receptor in adding to 27 selected species. Hydrophobic residues are coloured in blue, positive charges in red, negative charges in magenta, polar in green, cysteines in pink, glycines in orange, prolines in yellow, aromatics in cyan and uncovered in white.
A. This figure represents the whole multiple Sequence alignment of all 28 species. These figures represent the highly conserved regions in amino acids located in 260-290, 350-410 and 440-530 sites, respectively. Conservation measures the number of conserved physico-chemical properties conserved for each column of the alignment. Quality measures the likelihood of observing the mutations (if any) in a particular column of the alignment. Consensus measures the percentage of the modal residue per column. E. This figure represents the conserved domains of ACE2 protein by NCBI CDD database.

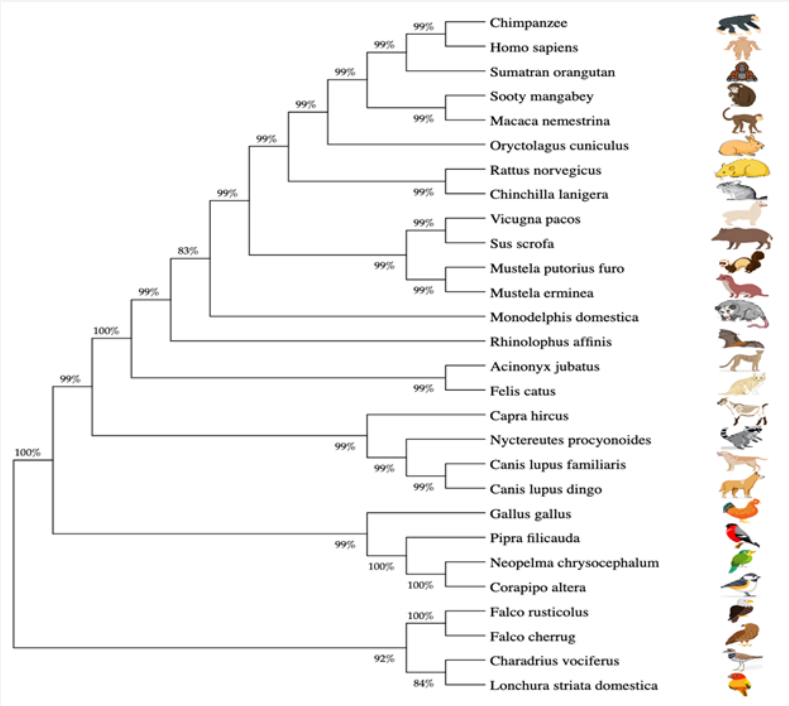

Figure 4: Phylogenetic tree inclusive of human and 27 selected animal species. The percentage numbers represent a measure of support for each node.

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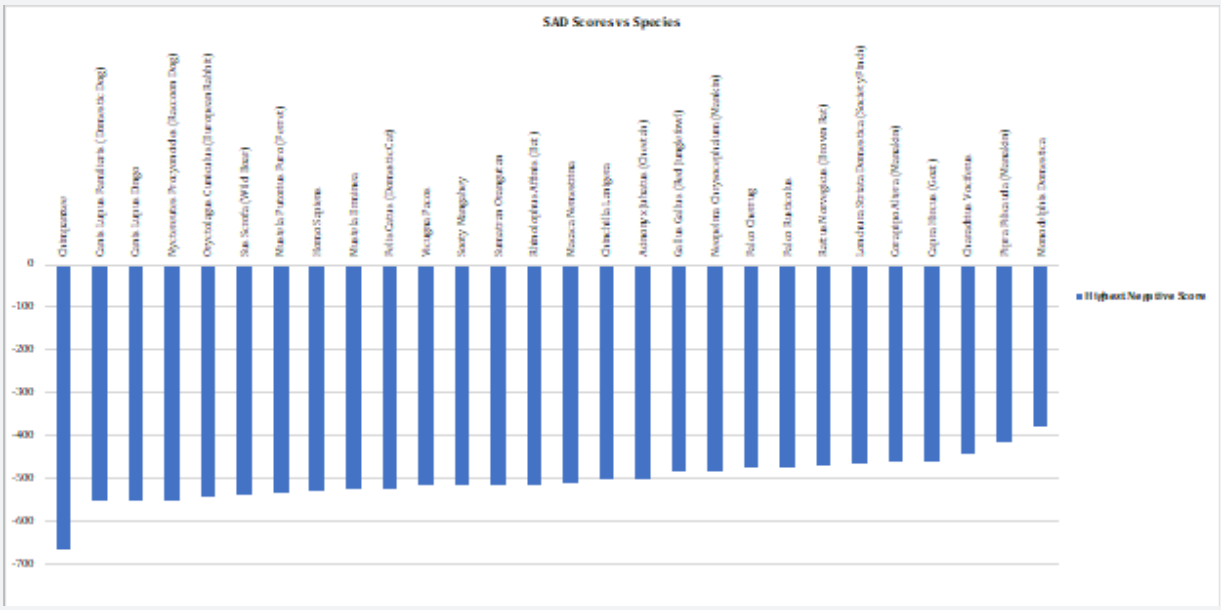

Figure 5: Plot of protein-protein docking scores vs species, ranked by most-least negative docking scores. (Y axis represents docking scores with the unit of kcal/mol).

Pets as players in COVID-19 transmission

The protein-protein docking data and phylogenetic analysis of ACE2 indicate that certain animal species express cellular ACE2 receptors that are highly similar to the human protein and are likely to be used by SARS-CoV-2 with similar efficiency to penetrate cells. Despite this similarity, infections of animals by SARS-CoV-2 remain very limited in number and severity, due to other species-specific restriction to infection. Nevertheless, the data suggest that if the essential step that initiate infection of e cell is conserved between humans and several animal species, the virus may target such animals and possibly evolve into variants more adapted to infect those new species. This is relevant since 53% of US families own dogs, 35.7% own cats, and 4.8% own birds (Figure 2B) [34]. Quarantine has affected many pets throughout the pandemic, similarly to humans, pets can be stressed by change to their daily lives. The Ohio State College of Veterinary Medicine has also pointed out that there is no reason to harm wildlife or abandon family pets out of fear [33]. Many families have actually opted to adopt a pet during quarantine, increasing the percentage of U.S. families who own pets. The risk of COVID-19 infection in pets can be contained by treating pets as if they were a human member of the family, keeping them away from people and animals who are ill [33].

The phylogenetic analysis (Figure 4) shows a high degree of conservation between orangutan and human ACE2 proteins. This suggests that the SARS-CoV-2 S glycoprotein interacts with both receptors in a very similar fashion and that the same region of the S glycoprotein is involved in the binding to both receptors. This supports the idea that a SARS-CoV-2 vaccine would be effective to protect orangutans and human equally well, despite minor differences in ACE2 proteins. The phylogenetic comparisons are supportive of the fact that pets can also be infected by and spread SARS-CoV-2. Indeed, infection has been confirmed in various species, including 115 cats, 81 dogs, 27 big cats, 3 gorillas, 1 domestic ferret and 1 mink [7]. Our phylogenetic and sequence alignment analysis (Figures 3 and 4) further demonstrates that ACE2 proteins have highly conserved functional domains which may be responsible for the docking process of the S-glycoprotein. Vaccination of zoo animals has been undertaken in various zoos. For instance, four orangutans at the San Diego Zoo received an experimental COVID-19 vaccine, receiving two doses each [43]. The vaccines developed to protect animals uses the same approaches as human COVID-19 vaccines. As of July 2021, Zoetis has donated approximately 11,000 doses of the experimental veterinary use COVID-19 vaccine with hopes of protecting the animals residing in nearly 70 zoos [44]. According to the Oakland Zoo in Northern California, their veterinary team has started early to vaccinate the animals deemed most at risk by their team, including tigers, black bears, grizzly bears, mountain lions, ferrets and chimpanzees [44]. The vaccines used in these studies were safe and efficient in eliciting an immune response as judged by the generation of serum neutralizing antibodies in-vitro.

Conclusion

The main purpose of this review is to contribute to our understanding of how COVID-19 affects various family pets. This is a relevant issue since humans have frequently maintained close contacts with household pets and other animal species during the current pandemic. To understand how pets and other

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animals may become infected by SARS-CoV-2, we investigated the binding of the viral S glycoproteins to the cellular ACE2 receptor, since this interaction is necessary to initiate infection of host cells. In particular, we performed a protein-protein molecular docking analysis of SARS-CoV-2 S glycoprotein with the ACE2 receptor from different species to better understand the potential of those species to serve as intermediate hosts or simply to be susceptible to SARS-CoV-2 infection. Our modeling data on ACE2 and S-glycoprotein docking provides a molecular and structural basis for comparing how the virus infects animals to humans. This approach provides an important tool to understand fundamental aspects of SARS-CoV-2 infection that can translate to better prevention and treatment and advance the fields of veterinary medicine and public health. Functional studies have emerged to address testing animals and reporting cases, case management for minimizing exposure and handling recommendations for equine species, food animals and other farm animals [45]. People are primarily contracting COVID-19 from close contact with infected individuals. Based on limited data available, the risk of animals contributing to the spread of COVID-19 to humans remains very low [45]. We learn more about the biology of SARS-CoV-2 every day, but obviously more research must be conducted assess how animals contribute to and suffer from the spread of this virus. In addition, structural and functional analyses of SARS-CoV-2 infection, epidemiological studies will provide remarkable information about outbreaks in humans and animals. For instance, compartmental models have been applied in several countries to analyses the compound transmission pattern of the COVID-19 pandemic, using delay differential equations, ordinary differential equations, fractional order Caputo derivative and stochastic differential equations [46-51]. Such mathematical model with pets added as contributors may help understanding SARS-CoV-2 transmission patterns that include family pets and humans. As the contribution of animals, especially pets, to viral spread in households remains undetermined, it is important to have a plan of care in place if a family pet tests positive for COVID-19.

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