© Universiti Tun Hussein Onn Malaysia Publisher's Office

JAITA

http://publisher.uthm.edu.my/ojs/index.php/jaita

e-ISSN : 2716-7097

Journal of Advanced Industrial Technology and Application

A Study on the Potential Pathways for Existing Drugs against COVID-19

Nor Aisyah Mohd Zain[1], Sity Aishah Mansur[1*], 'Aisyah Mohamed Rehan[1]

[1]Department of Chemical Engineering Technology, Faculty of Engineering Technology,
Universiti Tun Hussein Onn Malaysia, Pagoh Education Hub, KM1 Jalan Panchor, Pagoh, Johor, 86400, MALAYSIA

*Corresponding Author

DOI: https://doi.org/10.30880/jaita.2021.02.02.006
Received 11 March 2021; Accepted 01 June 2021; Available online 15 December 2021

Abstract: Coronavirus infectious disease 2019 (COVID-19) is a global pandemic declared by the World Health Organization (WHO) in March 2020. This emerging infectious disease is rapidly transmitted and does not only pose a global threat to public health but also badly affects the economy. At present, there is no effective drug to treat COVID-19, leading to a significant challenge upon current global attempts at restraining the outbreak. There are several currently available drugs, also considered as the repurposed drugs are in use for treatment against COVID-19. However, these drugs are not as efficient as it is hoped. Therefore, this study is conducted to further explore into other established antivirus that could function better for COVID-19 treatment. In addition, the pathways that associated with the drugs are identified and potential targeted proteins for the repurposed drugs are also pointed out. The articles for review were selected from several search engine databases, which are ScienceDirect, SpringerLink, PubMed, and Scopus including the keywords COVID-19, SARS, MERS, potential pathways for antiviral drugs as well as repurposed drugs, with more than 50 primary research articles identified. Findings and analysis have discovered potential repurposed drugs that could be used for COVID-19, namely bisoxatin, nitazoxanide and teicoplanin which could be involved in corona-related pathways. Meanwhile, the associated pathways are JAK-STAT, Neprilysin (NEP) and cGAS-STING that counteract excessive immune response and act as a medium for the drugs to access antiviral activities. The repurposed drugs target protein identification is also a critical significance, and it was found that S-protein, TMPRSS2, RdRp and RDB which are the signalling protein can be interrupted by the repurposed drugs, presenting a promising antivirus against SARS-CoV-2. It is concluded that this study will provide information to assist logical design of the repurposed drug for its effectiveness as antivirus against COVID-19

Keywords: COVID-19, SARS, MERS, potential pathways, antiviral, repurposed, drugs

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or widely known as coronavirus infectious disease 2019 (COVID- 19), originated from Wuhan in China. The World Health Organization (WHO) declared the series of COVID-19 as a pandemic exactly on 11th March 2020 as it was detected in all parts of the world. As of 8 January 2021, the number of confirmed cases and deaths are about 86,749,940 and 1,890,342 respectively [1]. Based on the database from the Ministry of Health (MOH), Malaysia country currently records the number of the confirmed cases which is 138 thousand and 555 deaths cases [2]. Increasing death toll corresponds to no available approved antiviral drug treatment to specifically treat COVID-19 [3] leading to extensive search in this area. Without effective treatment, the whole world is less-prepared for the sudden re-emergence of COVID-19 that also brings unstable economic and social life order [4]. As the previous outbreak by SARS-CoV and MERS-CoV have the same genus and only slightly change in structure with SARS-CoV-2 strain, studies are conducted in references to those corona-typed

*Corresponding author: aishah@uthm.edu.my

viruses. COVID-19 cases can be controlled and prevented by focusing on existing drugs which have antiviral activities and high efficacy against rapid infection of SARS-CoV-2 [5]. Globally, an alternative for immunization is focusing on existing drugs associated with passive immunization that might be safe and efficacious since those are established and already applied in viral disease outbreak before [6]. Even though several vaccines such as those from Pfizer, Moderna and AstraZeneca Oxford have been approved and administered into human, its side effects are still uncertain. Therefore, continuous search on repurposed drugs with known effects to human is warranted as a contingency plan for COVID-19 treatment.

Currently, potential drugs that are currently approved for clinical use have the abilities to block viral replication, modulate of immune function, control inflammatory response and reduce lung injury [6]. At the present, the most ideal strategy to treat COVID-19 is the reuse of established and licensed drugs for further use in clinical trials, however, repurposed drugs which are Bisoxatin, Nitazoxanide and Teicoplanin should be modified or re-designed to match pathomechanism of COVID-19 and target protein structure of SARS-CoV-2 [6]. At the present, the most ideal strategy to treat COVID-19 is the reuse of established and licensed drugs for further use in clinical trials, however, these drugs should be modified or re-designed to match pathomechanism of COVID-19 and target protein structure of SARS-CoV-2 [6]. Evaluation on the possible proteins that may be the target for the repurposed drugs is discussed followed by potential pathways, JAK-STATs, cGAS-STING and Neprilysin, proposed in this study. Apoptosis cells, cytokine storm and excess immune response are major causes to severe COVID-19 patient. The aforementioned pathways are mostly involved in multiple signaling proteins that could be used to relate with binding affinity of drugs-protein of Bisoxatin, Nitazoxanide and Teicoplanin [7], [8], [9]. Understanding the suitable pathways for drug actions becomes very crucial to modulate immune response that would support individuals with weak immune systems against COVID-19.

2. Materials and Methods

In this study, the potential of repurposed drugs and potential pathways are evaluated by applying the flow diagram of Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) that shows in Figure 1 and 2, which illustrate the flow for this critical review [10]. The objectives of this finding are assessed by recognizing the potential pathways of repurposed drugs and the binding affinity of the drugs with target protein by following the steps of Whittemore and Knalf study design as a scaffold for this study [10].

2.1 Data Collection

There are several literature databases searched in this study such as ScienceDirect, PubMed, Scopus, ChEMBL, the Cell and Google Scholar. In the search, we include integrative reviews in years ranging from 2019 to 2021. In addition, the keyword “repurposed drugs for COVID-19 with antiviral properties” is used to enclose the analyzing in searching journals as shown in Fig. 1.

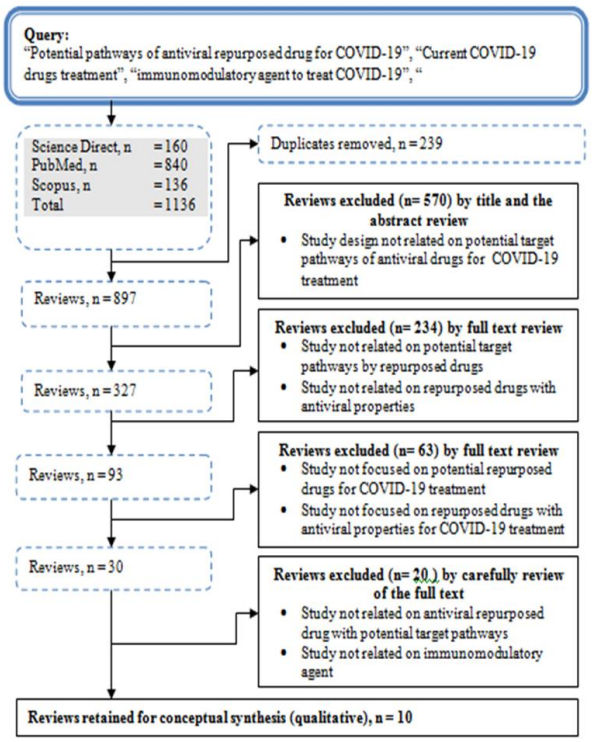

Fig. 1 - Excluded review for literature review [10]

In addition, the keyword of "binding affinity of targeted protein by repurposed drugs" is used to enclose the analyzing in searching journals as shown in Fig. 2 [10].

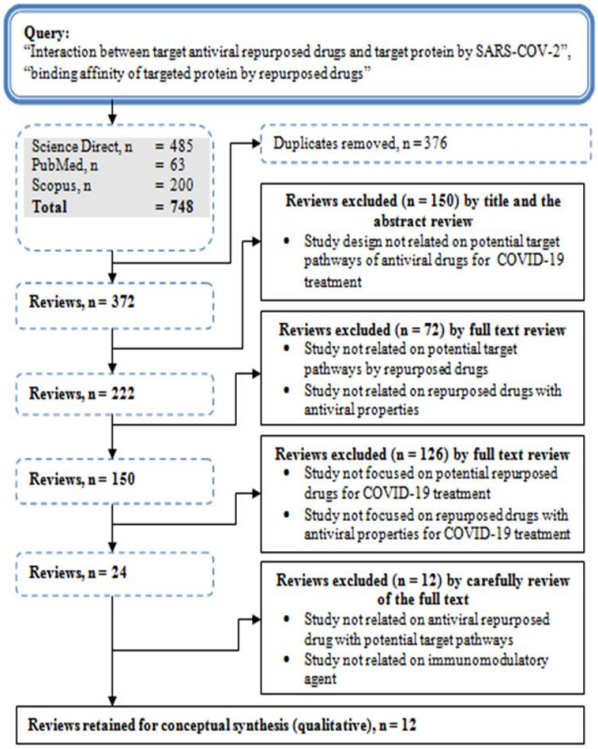

Fig. 2 - Excluded review for data analysis [10]

2.2 Selection of Data

The articles are retrieved from collection of data after the procedure of analyzing sources for literature review that tabulated by characterization of retrieved articles.

3. Results and Discussion

Target protein for the drugs is being analyzed from different papers and related with repurposed drugs. The binding affinity between the selected drugs repositioning and protein target is evaluated after targeted protein for repurposed drugs is identified.

3.1 Evaluation of the Potential Repurposed Drugs for COVID-19

For COVID-19 treatment, there are several existing drugs that are recommended to be used which are bisoxatin, nitazoxanide, and teicoplanin that have shown great results in the study of binding affinity with SARS-CoV-2 protein. The study of these drugs is described in three different articles. [11], [14]. Firstly, bisoxatin is known as a laxative drug that is used in constipation treatment and surgical procedure for colon preparation [11]. Fig. 3 shows the structure of bisoxatin, $C_{20}H_{15}NO_4$ which consists of 78.8 $Å^2$ of topological polar surface area with 333.3 g/mol of the molecular weight. It is considered as a safe drug as there is no acute effect reported with >7 gm/kg of bisoxatin dosage.

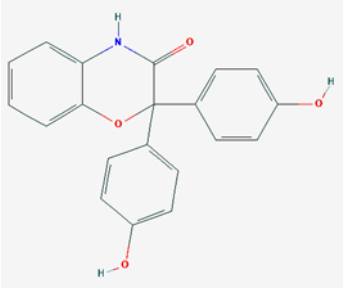

Fig. 3 - 2-D Structure of bisoxatin [12]

A review of insight to introduce Nitazoxanide, an anti-protozoal drug for repurposing in COVID-19 is assessed in the article by [21] A.S. Lokhande and P.V. Devarajan, (2020). In the preceding diseases, Nitazoxanide is being used in a wide range of diseases related to respiratory disease caused by various viruses such as HBV, HCV, HIV, and respiratory syncytial virus. In addition, the significant finding of this article reveals the antiviral properties of Nitazoxanide along with the potential to balance anti-inflammatory and pro-inflammatory responses in humans which promotes these drugs to hamper cytokine storms during COVID-19 infection [21]. Based on Fig. 4, the structure of the prodrug, Nitazoxanide is also known as nitrothiazolyl benzamide is shown with its moiety, tizoxanide which is responsible for multiple drug mechanisms of actions.

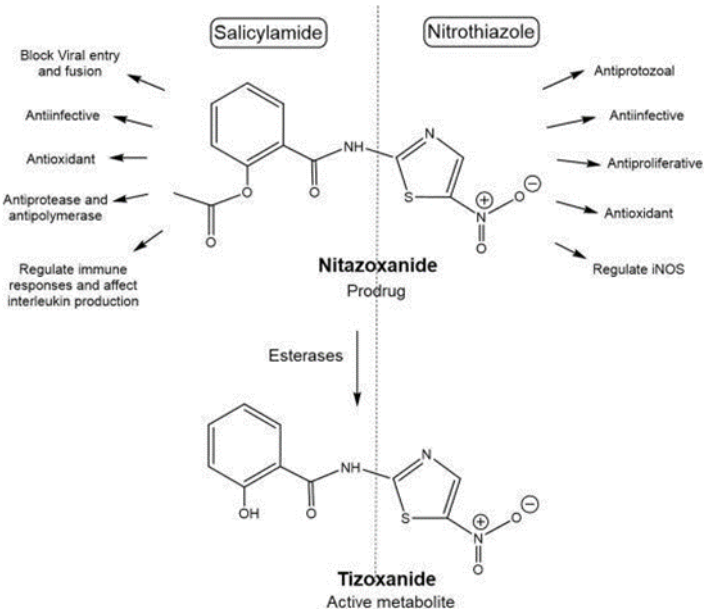

Fig. 4 - The structure of prodrug, Nitazoxinade and its active metabolite [20]

The other repurposed drug that has been identified to have the potential to be used for COVID-19 is Teicoplanin. The structure of 2-Dimensional of Teicoplanin, $C_{88}H_{97}Cl_2N_9O_{33}$ is shown in Fig. 5 which has 1879.7 g/mol and 662 $Å^2$ of molecular weight and topological polar surface area, respectively [19]. It is also known as a complex of glycopeptides antibiotics with the ability to hamper peptidoglycan polymerization. In this study, Teicoplanin is proposed as a potent inhibitor of main 3CL protease specifically to stop virus replication which further sustains its antiviral effects. Table 1 shows the summary of the repurposed drugs that have been identified in this study.

Table 1 - List of repurposed drugs that have potential for COVID-19 treatment [5]

Drugs	Mechanism	Primary indications
Currently being used for COVID-19		
Arbidol	Inhibit viral replication	Influenza A and Influenza B
Remdesivir	Inhibit viral replication	NA
Camostat mesylate	Inhibit viral entry	chronic pancreatitis and postoperative reflux esophagitis with acute symptoms
Favipiravir	Inhibit viral replication	Influenza A and Influenza B
Lopinavir/ritonavir	Inhibit cytochrome P450	HIV infection
Potential use for COVID-19		
Nitazoxanide	Interrupt viral entry and replication	Diarrhea
Bisoxatin	Inhibit viral fusion	Constipation and colon preparation in procedures of surgical
Teicoplanin	Inhibit viral genome release	Antibiotic

3.2 Discussion

In order to halt COVID-19, it is critical to search for alternative ways to block the spread of SARS-COV-2 as the study on the structure of SARS-COV-2 and its mechanism has successfully identify several potential drug targets that shown in Table 2 [15].

Table 2 - Current repurposed drugs used for COVID-19 with its targeted protein

Target protein of SARS-COV-2	The function of the protein	Interfering Stage	Drugs/inhibitors
RNA-dependent RNA polymerase (RdRp)	Inhibits the replication of RNA from an RNA template.	Replication Transcription Translation	Remdesivir Favipiravir Ribavirin Nitazoxanide
Transmembrane Protease Serine 2 (TMPRSS2)	Primes the viral spike protein to allow viral entry into the target cell	Binding fusion	Camostat mesylate Nitazoxanide
Main Protease	Release genomic material Cleavage of the peptide bond	Proteolysis (Virion assembly)	Lopinavir/Ritonavir Ribavirin Teicoplanin
Spike glycoprotein	Spike proteins latch the virus onto a cell	Binding fusion	Umifenovir Bisoxatin

3.3 Assessment on the Mechanisms of the Repurposed Drug

A receptor-binding domain (RBD) is a part of S-protein that functions to initiate the virus invasion by attaching to the ACE2. The main protease protein known as $3CL^{pro}$ plays a role for RNA replication that involves the cleavage of proteolytic. The spike protein of the virus entry can be inhibited by using camostat and Teicoplanin. Type II transmembrane serine protease (TMPRSS2) is a primer for S-protein that have an access for SARS-CoV-2 to enter the host cell. TMPRSS2 is idenfied that could be neutralized by utilizing camostat mesylate and Nitazoxanide [16]. Meanwhile, RNA dependent RNA polymerase (RdRp) is associated to modification and proofreading of the viral RNA. The drug that could use to inhibit the activity of RdRp is Nitazoxanide. In addition, host response can be improved against viral infection by the endothelial dysfunction as the ACE2/ACE ratio increases. Neprilysin pathway is commonly related with being able to convert angiotensin I to angiotensin II as mentioned in the previous chapter. However, the mechanism of several candidate drugs action remains vague, as well as the potential of a targeted drug that leads to further research on structural and biophysical to assess repurposed drugs mechanism binding and its impact on SARS-COV-2 [15].

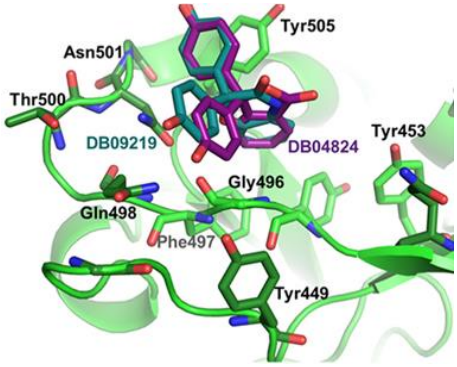

Fig. 5 - Bisoxatin docking pose [11]

3.4 Interaction of the Repurposed Drug and its Target Protein

The study applied the database from the library of DrugBank and PubChem upon the receptor-binding domain (RBD) of S-protein in order to identify sturdy drug repositioning molecules such as Bisoxatin. From an article by Sruthi Unni et al, (2020) the analysis methods engaged including docking, simulations of molecular dynamics, and virtual screening that also related with the study on the combination of molecular mechanics energies with Poisson-Boltzmann (MM-GBSA). From this paper, Bisoxatin is a drug that directly attaches to the domain of RBD during the interface RBD-ACE2. As a result, the S-protein cannot attach to the ACE2 and lead to no binding event. The structure of bisoxatin is observed in molecular docking for the intermolecular interactions between ACE2. The overlap of the bisoxatin can be found at the binding site with the S-protein. Fig. 6 shows the docking interaction of bisoxatin with intermolecular interactions of the drugs [11].

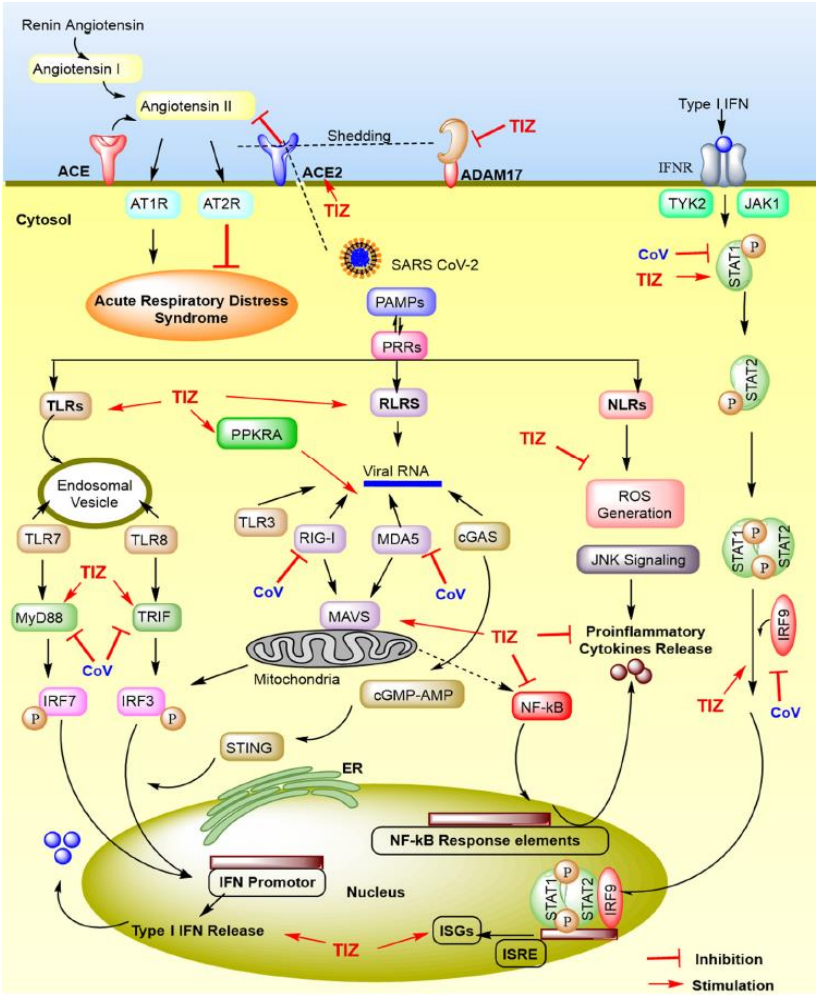

Fig. 6 - The overview of Tizoxanide actions in SARS-CoV-2 invasion [19]

The structure consists of moieties of twin hydroxyphenyl, the portion of benzofuranone which surrounds the Tyr505 through interactions of π-π stacking [11]. A bond that links Thr500 and ligand is a weak hydrogen bond. The interactions of π-π stacking between Tyr505 interrupt the binding site of S-protein on ACE2 which is at the 'hook 1' region [11]. Intriguingly, Bisoxatin appears to be steadier in the interactions of the binding pocket of the target. Throughout the simulation, Bisoxatin establishes both polar and nonpolar interactions in a comprehensive analysis which reveals the electrostatic interactions within the region of 'Site 1'. This is due to the interactions made by the precipitates Arg403, Asn501, Gly496, and Ser494 via the contacts of hydrogen bonds of the water-mediated directly equivalent to the contact by RBD-ACE2. It is significant to highlight on the analysis of cluster, contact, roots mean squared deviation (RMSD) that shows confrontational changes in the binding site that make differential contact analysis as well as two different cluster conformations.

In addition, the ligand is being speculated under constant interactions of hydrophobic that is caused by rigid complementarity in the pattern of the hydrophobic contact with the residues Tyr449 and Tyr 505 [11]. In addition, the ligand is being speculated under constant interactions of hydrophobic that is caused by rigid complementarity in the pattern of the hydrophobic contact with the residues Tyr449 and Tyr 505 [11]. As discussed earlier, the closeness of the ligand and hydrophobic cleft can be proved by the high energy component. In addition, van der Waals interactions may be assisted by the energy of lipophilic. Besides, hydrophobic contacts have an important function for the ligand to be stabilizes at the binding pocket.

The study of Nitazoxanide on binding affinity in molecular docking is insufficient. However, this drug tends to involve in the various pathways of the innate immune response. The article from A.S. Lokhande and P.V. Devarajan described the active metabolite of Nitazoxanide in an understanding manner. Figure 6 shows the overview pathways of the autoimmune system with tizoxanide (TIZ) associations [19]. SARS-CoV-2 passage through ACE2 is hampered by TIZ which manages the renin-angiotensin framework by impeding angiotensin II authoritative to its receptors (AT1R and AT2R), to give defensive reactions. ADAM-17 interceded ACE2 shedding is forestalled by TIZ because of PDI restraint, in this way controlling lung aggravation and therefore ARDS. TIZ actuates Type-I IFN discharge furthermore, control proinflammatory reactions. ACE2, Angiotensin changing over protein 2; ADAM-17, A disintegrin and

metallopeptidase space 17; ARDS, Acute respiratory trouble disorder; AT1R, Angiotensin II receptor type 1; AT2R, Angiotensin II receptor type 2; cGAS, cyclic GMP-AMP synthase; IFN, Interferon; IFNR, IFNα/β receptor; IRF3/7, Interferon administrative factor 3/7; JAK, Janus kinase; MAVS, Mitochondrial antiviral-flagging protein; MDA5, Melanoma separation-related quality 5; NF-κB, Nuclear factor-κB; NLRs, Nucleotide-restricting oligomerization area (NOD)- like receptors; PDI, protein disulfide isomerase; PPKRA, Phopsphorylated protein kinase receptor; RLRs, Retinoic corrosive inducible quality I protein (RIG-I) like receptors; ROS, Reactive oxygen species; STAT, signal transducer and activator of record; STING, the trigger of interferon qualities protein; TLRs, Toll-like receptors; TRIF, TIR-space containing connector protein including IFN-β; TYK2, Tyrosine kinase 2 [19].

In the study of bimolecular interaction from the same article is described Teicoplanin with great binding interaction to interrupt ACE2. Based on an article by P.K. Tripathi et al, the real-time interactions on the molecular $3CL^{pro}$ is monitored by using surface plasmon resonance (SPR) which also applied for identifying ligand molecules [14]. SPR is commonly employed for determining the binding of significant molecules such as interaction and detachment between drug molecules and target proteins [14]. In the case of Teicoplanin, SPR is used to evaluate its association with $3CL^{pro}$ with SPR type Biacore 3000. The study that applied in this article is SPR experiments which using 10mg/ml of $3CL^{pro}$ solution with PBS buffer pH 7.4 that immobilized to a chip made of CM5 gold by applying coupling of EDC-NHS with a range of Teicoplanin concentrations of the binding test. Additionally, the interaction between Teicoplanin and $3CL^{pro}$ is analyzed by using In-silico analysis. In fact, fluorescence quenching is necessary to use for agitating the overall structure of $3CL^{pro}$ with ligands. As a result, the Trp protein residues formed in the conformational dynamics are observed. Fig. 7 shows the 2-dimensional Teicoplanin that is able to block the active site of the protease [14].

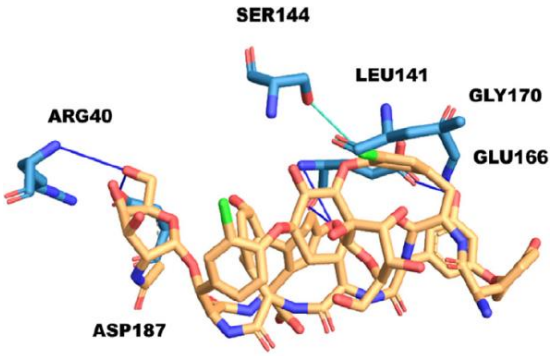

Fig. 7 - 2-Dimensional of Teicoplanin stick model [14]

The closeness of the binding Teicoplanin with histidine41 and cysteine145 is shown in Fig. 8. The intrinsic fluorescence is controlled as the fluorescence quenching indicates the interaction of drug-protein. In a docking investigation utilizing PARDock uncovered that the ligand drug Teicoplanin fits entirely in the dynamic site pocket and the coupling energy acquired for this coupling is about - 8 kcal/mol. The cavity is lined by the dynamic site amino acids for example histidine 41 and cysteine 14. The buildups His41 and Cys145 structure the reactant dyad, structure the substrate restricting area, and are situated at the split of space I and II in which His goes about as a proton acceptor while Cys carries on as a nucleophile [14].

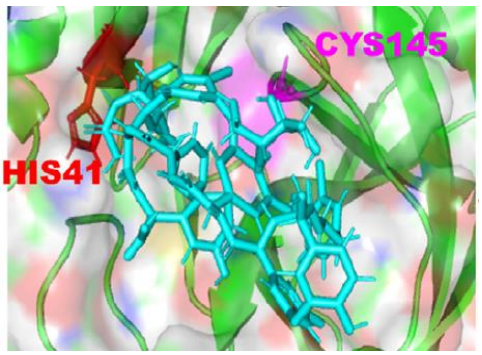

Fig. 8 - The binding of the Teicoplanin (cyan) is in proximity to the hsitidine41 (red) and cysteine145 (magenta) [14]

3.5 Proposing Potential Pathways as Amediated System for Drugs Development

The JAK-STAT is the main signaling pathway (Fig. 9) modulated by cytokines and prior to initiate the innate immune response and bring about the adaptive immune mechanisms, and lastly inhibiting the inflammatory and immune responses. This means JAK-1/JAK-2 inhibitors can treat an infectious disease that emerges unfounded given that the effects of antiviral from IFN are largely interceded by the JAK-STAT signaling pathway [8]. The critical stage of COVID-19 consists of high amounts of cytokine signaling, all of which signal via the JAK-STAT pathway. This finding recommends that when hospital care is required for patients with a pathogenic SARS-CoV-2 infection, utilizing inhibitors of the JAK-STAT pathway might be a potential strategy [8].

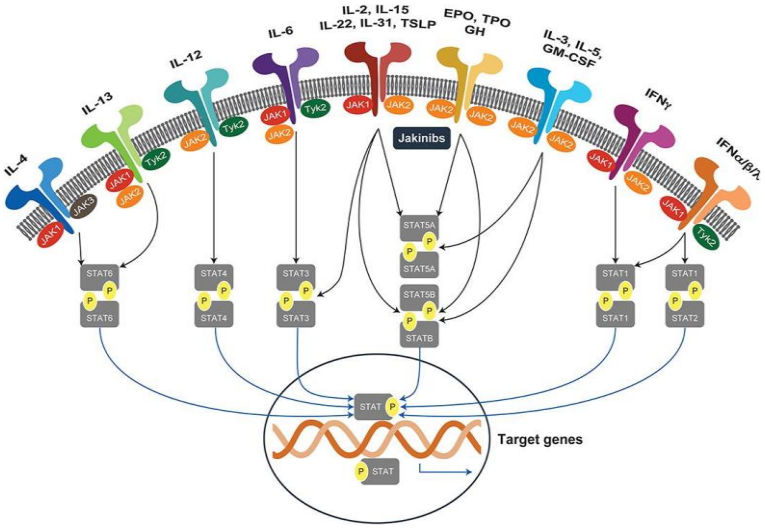

Fig. 9 - Overview for JAK-STATs signaling pathways [19]

The cGAS-STING pathway stands for cyclic-GMP-AMP synthase (cGAS) along with the downstream stimulator of interferon genes (STING) which is crucial to immune surveillance mediators [7]. This pathway assists type-I interferon (IFN) signaling responses and cellular processes, including cell survival, autophagy, and senescence [7]. The cGAS-STING pathway engages in inflammatory disease, cancer, and infection regulation as it interacts with innate immune pathways [7]. Previous studies have proven that cGAS-STING pathway provides particular responses control to the immune stimulatory DNA (ISD) different from other nucleotide-sensing pathways and demonstrated the role for mediating cellular immune sensing as illustrates in Fig. 10 [7]. B-type double stranded DNA (dsDNA) recognition can activate cGAS without sequence-specificity [7]. As a ligand of cGAS, mitochondrial DNA (mtDNA) can be produced in the cytosol under the stress of mitochondrial or dysfunction of proteins that lead to the maintain process by mitochondrial [7].

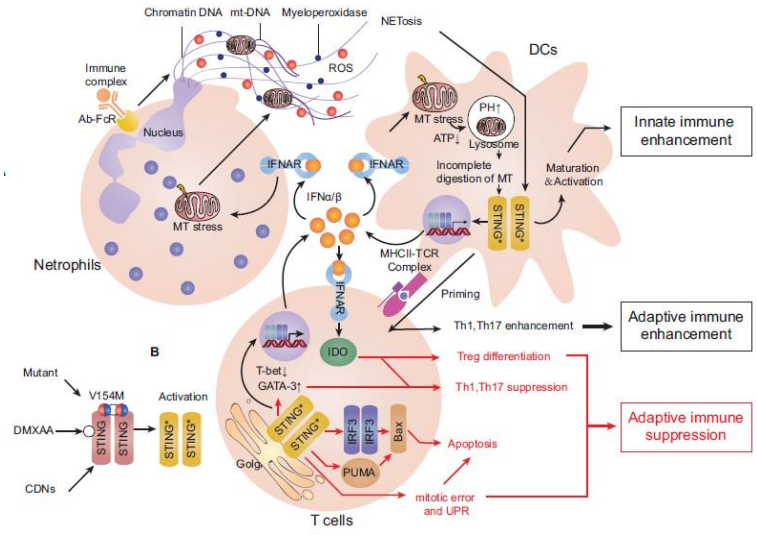

Fig. 10 - cGAS-STING signaling pathways for innate immunity [7]

Next, neutral endopeptidase or neprilysin (NEP) also known as CD10 is a type of transmembrane zinc-metalloendopeptidase that mostly found in lung and kidney as well as other tissues such as stomach, prostate and in the central nervous system [9]. NEP expresses a size-related specificity to hydrolyse peptides (Fig. 11) with a small molecular weight only at almost 3,000 Dalton [9]. Additionally, NEP has a function to protect the cells during the damage lung in the pathogenesis and reduce the enzymatic activity in the lung of mice with combination of inactivation of the tachykinins degradation pathway resulting uncontrolled inflammation reduction in ALI/ARDS and in other neurogenic respiratory diseases [9]. Presence of NEP in between a soluble circulating form (cNEP) and several body fluids such as cerebrospinal fluid, plasma and urine distinguish hydrolysing a wide range of physiologically suitable substrates and dominate substrate specificity.

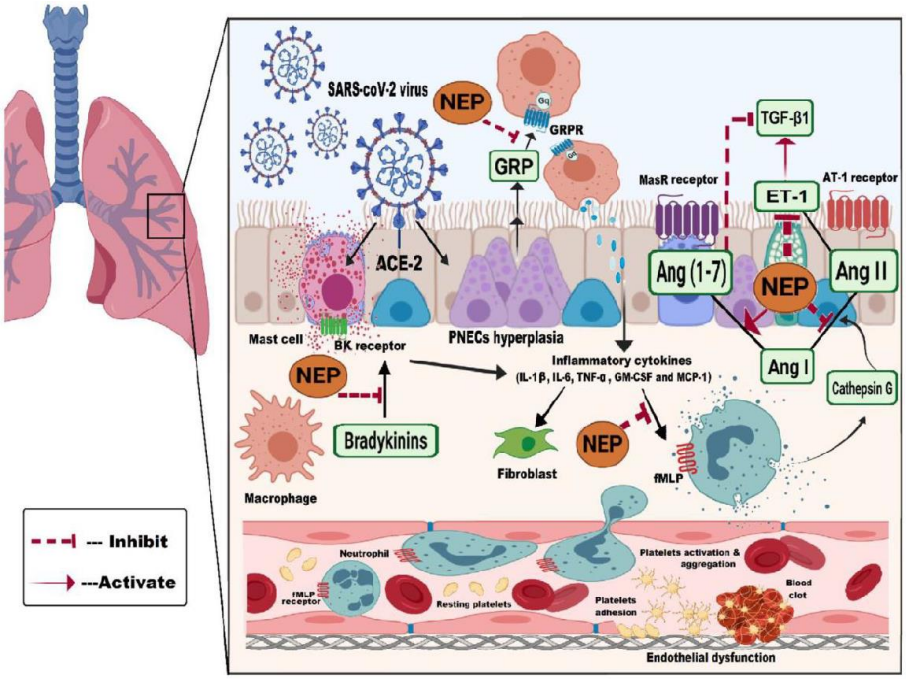

Fig. 11 - Represent the NEP-dependent therapeutic strategy for COVID-19 [9]

4. Conclusions

Even though new antiviral drugs development consumes a long period, potential repurposed drugs are recommended as a strategy to use in the treatment for COVID-19 patients. The best drugs repositioning that could be used for COVID-19 are Bisoxatin, Nitaxanide and Teicoplanin. Meanwhile, the best pathway for supporting the use of drugs including the cGAS-STING, JAK-STING and Neprilysin pathways. The potential pathways proposed in this study are evaluated and the target protein is being identified for each selected drug repositioning including spike protein and RdRp of the viral genome.

Acknowledgement

The authors would also like to thank the Faculty of Engineering Technology, Universiti Tun Hussein Onn Malaysia for its support.

References

[1] World Health Organization (WHO). (2020). Retrieved January 11, 2021, from: https://covid19.who.int
Ministry of Health (MOH). (2021). Home: Ministry of Health. Retrieved January 23, 2021, from http://covid-19.moh.gov.my/

[2] Dhama, K., Sharun, K., Tiwari, R., Dadar, M., Malik, Y. S., Singh, K. P., & Chaicumpa, W. (2020). COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. *Human vaccines & immunotherapeutics*, *16*(6), pp. 1232-1238

[3] Lu, S. (2020). Timely development of vaccines against SARS-CoV-2. *Emerging microbes & infections*, *9*(1), pp. 542-544

[4] Jin, Z., Liu, J. Y., Feng, R., Ji, L., Jin, Z. L., & Li, H. B. (2020). Drug treatment of coronavirus disease 2019 (COVID-19) in China. *European Journal of Pharmacology*, *883*, 173326

[5] Lisi, L., Lacal, P. M., Barbaccia, M. L., & Graziani, G. (2020). Approaching coronavirus disease 2019: Mechanisms of action of repurposed drugs with potential activity against SARS-CoV-2. *Biochemical pharmacology*, 114169
[6] Wan, D., Jiang, W., & Hao, J. (2020). Research advances in how the cGAS-STING pathway controls the cellular inflammatory response. *Frontiers in immunology*, *11*, pp. 615
[7] Zhang, X., Zhang, Y., Qiao, W., Zhang, J., & Qi, Z. (2020). Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. *International immunopharmacology*, *86*, 106749
[8] El Tabaa, M. M., & El Tabaa, M. M. (2020). Targeting Neprilysin (NEP) pathways: A potential new hope to defeat COVID-19 ghost. *Biochemical Pharmacology*, *178*, pp. 1-17
[9] Hopia, H., Latvala, E., & Liimatainen, L. (2016). Reviewing the methodology of an integrative review. *Scandinavian Journal of Caring Sciences*, *30*(4), pp. 662-669
[10] Unni, S., Aouti, S., Thiyagarajan, S., & Padmanabhan, B. (2020). Identification of a repurposed drug as an inhibitor of Spike protein of human coronavirus SARS-CoV-2 by computational methods. *Journal of Biosciences*, *45*(1), pp. 1-20
[11] NIH (2021). *Compound: National Center for Biotechnology Information*. Retrieved January 11, 2021, from https://pubchem.ncbi.nlm.nih.gov/compound/Bisoxatin#section=Structures
[12] Garrido-Trigo, A., & Salas, A. (2020). Molecular structure and function of Janus kinases: implications for the development of inhibitors. *Journal of Crohn's and Colitis*, *14*(2), pp. 713-724
[13] Tripathi, P. K., Upadhyay, S., Singh, M., Raghavendhar, S., Bhardwaj, M., Sharma, P., & Patel, A. K. (2020). Screening and evaluation of approved drugs as inhibitors of main protease of SARS-CoV-2. *International Journal of Biological Macromolecules*, *164*, pp.2622-2631
[14] Vlachakis, D., Papakonstantinou, E., Mitsis, T., Pierouli, K., Diakou, I., Chrousos, G., & Bacopoulou, F. (2020). Molecular mechanisms of the novel coronavirus SARS-CoV-2 and potential anti-COVID19 pharmacological targets since the outbreak of the pandemic. *Food and Chemical Toxicology*, *146*, 111805
[15] Poduri, R., Joshi, G., & Jagadeesh, G. (2020). Drugs targeting various stages of the SARS-CoV-2 life cycle: exploring promising drugs for the treatment of Covid-19. *Cellular Signalling*, *74*, 109721
[16] Vankadari, N. (2020). Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein. *International Journal of Antimicrobial Agents*, *56*(2), 10599
[17] Unni, S., Aouti, S., Thiyagarajan, S., & Padmanabhan, B. (2020). Identification of a repurposed drug as an inhibitor of Spike protein of human coronavirus SARS-CoV-2 by computational methods. *Journal of Biosciences*, *45*(1), 1-20
[18] Howell, M. D., Kuo, F. I., & Smith, P. A. (2019). Targeting the Janus kinase family in autoimmune skin diseases. *Frontiers in Immunology*, *10*, 2342
[19] Howell, M. D., Kuo, F. I., & Smith, P. A. (2019). Targeting the Janus kinase family in autoimmune skin diseases. *Frontiers in Immunology*, *10*, 2342
[20] National Center for Biotechnology Information (2021). *PubChem Compound Summary for CID 41684, Nitazoxanide*. Retrieved January 13, 2021, from https://pubchem.ncbi.nlm.nih.gov/compound/Nitazoxanide