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Analgesics Candidates for JAK-STAT Pathway Inhibition as a Probable Treat for COVID-19, Bioinformatics Study

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ABSTRACT

The pandemic of COVID-19 with more than 160 million cases of which 5 percent being critical is characterized by cytokine storm and hyperinflammatory conditions. The disease leads more often to intensive care unit admission with a high rate mortality. Janus kinase enzymes of Jak-1, Jak-2, Jak-3, and Tyk2 seem to be good targets for inhibition and cytokine storm management in patients. In the present work, the binding ability and inhibitory potential of different analgesics were studied by molecular docking to assess their applicability for clinical trials from different points of view. As per our results, given their higher binding energy, lower variance in binding energy, and higher hydrophobicity, naproxen, methadone, and amitriptyline seemed to exert stronger inhibitory effects on Janus kinase enzymes than the approved inhibitors, *i.e.* baricitinib and ruxolitinib. Accordingly, we suggest a longer list of candidate analgesics including indomethacin, etodolac, buprenorphine, rofecoxib, duloxetine, valdecoxib, naproxen, methadone, and amitriptyline for clinical assessments to investigate their tentative usefulness for COVID-19 treatment.

Keywords: COVID-19, Janus kinase, Cytokine storm, Naproxen, Methadone, Amitriptyline

INTRODUCTION

Janus kinase (JAK) is a family of intracellular tyrosine kinase enzymes that participate in signal transduction through cytokine receptors in the JAK-STAT pathway. There are two types of cytokine receptors; type-1, and type-II; both have no kinase activities, thus depend on JAK enzymes for signal transduction. The family of JAK enzymes comprises tyrosine kinase-2 (Tyk2), JAK-1, JAK-2, and JAK-3 enzymes [1-2]. The enzyme of Tyk2 is the first described member of the family. It collaborates with cytoplasmic domains of cytokine receptors (type I and II) to mediate signals from IL-6, IL-11, IFN-α, IFN-β, and IFN-γ cytokines. The JAK-1 enzyme uses the gamma chain of cytokine receptor type-I, which participates in signal transduction from IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 cytokines. It also mediates signals through the type-II receptor induced by IFN-α, IFN-β, and IFN-γ. The JAK-2 enzyme transduces signals from IL-3, IL-5, IL-6, IL-11, GM-CSF, EPO, TPO, GH, G-CSF *via* cytokine type-I receptor as well as signals from IFN-α, IFN-β, and IFN-γ *via* type-II cytokine receptor [3-5]. Unlike other Janus kinase enzymes, JAK-3 mediates signals induced by IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 only via type-I receptor [6-11]. In contemporary medicine, Janus kinase inhibitors are used as medications to interfere with JAK-STAT signaling pathways to compensate hyperinflammatory (or cytokine storms), more especially in severe cases of cancer and autoimmune diseases [12-13]. Among well-known inhibitors of the JAK pathway, some are approved for clinical application, including ruxolitinib against JAK1/JAK2, oclacitinib, against JAK1, baricitinib against JAK1/JAK2, peficitinib against JAK3, fedratinib against JAK2 inhibitor, and upadacitinib against JAK1 pathways [14-17]. There are also some JAK inhibitors such as, filgotinib, cerdulatinib, gandotinib, lestaurtinib, momelotinib, pacritinib, and abrocitinib which are under clinical trials for future applications [18-21].

The newly emerging disease of COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease caused the ongoing pandemic with more than 160 million cases and 3.3 million deaths by May

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2021 [22-24]. It is well documented that COVID-19 patients experience a dramatic increase in plasma levels of different kinds of inflammatory cytokines that lead, in severe cases, to profound infiltration of immune cells in the lungs with ultimate alveolar damage and death [25-27].

Increasing the cytokines of IL-2, IL-6, IL-7, IL-10, G-CSF, GM-CSF, and IFN-γ in accordance with increasing different chemokines comprises the main cause for COVID-19 mortality, the state primarily mediated by JAK-STAT pathway [28-29].

There are increasing efforts to control hyperinflammatory state in COVID-19 by application of Janus kinase inhibitors. Ruxolitinib is one of the approved inhibitors used for clinical treatment of myelofibrosis. It selectively inhibits JAK-1 and JAK-2, showing capability in mitigating hyperinflammatory state of COVID-19 patients [30-31]. Baricitinib is the next example of JAK inhibitors prescribed as anti-rheumatic drug for rheumatoid arthritis. It significantly blocks both JAK1 and JAK2 and decreases fever, breathlessness, cough and improves pulmonary function in COVID-19 patients [32-33].

Molecular docking is a very useful computer-based drug screening method through which the three dimensional structure of a macromolecule like JAK enzymes are used as receptor and small molecules of analgesics as ligands (or candidate drugs) for docking. Docking gives a useful tool to predict the binding modes of ligands to enzyme active sites and to assess their inhibitory ability [34].

There are also miscellaneous reports indicating the benefits of JAK inhibitors in COVID-19 treatment [35-38]. These reports encouraged us to search for JAK-Stat inhibition candidates among old analgesics or pain relief drugs through molecular docking studies in a bid to suggest them for further clinical trials as probable and accessible treats for COVID-19.

METHODS AND MATERIALS

Obtaining Proteins Structures for JAK Enzymes

Protein chemical or coordinate structures of JAK-1, JAK-2, JAK-3, and TyK2 enzymes with PDB IDs' of 4I5C, 2W1I, 3LXK, and 4GVJ, respectively, were retrieved from the protein data bank (https://www.rcsb.org/). These structures were obtained by the X-ray diffraction methods and refined at the resolutions of 2.1 Å, 2.60 Å, 2 Å, and 2.03 Å, respectively. Since the given structures were prepared in dried and crystalline form, so that their conformations were far from hydrated and equilibrated states and did not represent the enzymes' native structures. Therefore, it was necessary to optimize structures by minimization of their structural energies in a native-like aqueous solution at the first step. All the structures were energy minimized in GROMACS 4.5.5 software using GROMOS force field for energy calculation as follows. The structures were placed in separate rectangular boxes with dimensions of 9.79×9.98×6.84 nm, 7.87×7.62×9.27 nm, 5.62×5.73×6.87 nm, and 5.67×7.18×6.18 nm dimensions, respectively. The boxes were filled with SPCE water. The algorithm of the steepest descent algorithm, neutral pH, 37 °C temperature, 1 atmosphere of pressure, and total energy of 200 kJ mol^{-1} was used as minimization criteria [39-40].

Chemical Structures of Analgesics

The structures of candidates, including almotriptan, amitriptyline, amlodipine, baricitinib, buprenorphine, celecoxib, diclofenac, duloxetine, ergotamine, esomeprazole, etodolac, famotidine, fentanyl, indomethacin, lansoprazole, lasmiditan, methadone, nalbuphine, naloxone, naproxen, naratriptan, oxycodone, piroxicam, remifentanil, rimegepant, rofecoxib, ruxolitinib, sufentanil, sulindac, tofacitinib, ubrogepant, and valdecoxib, in SDF format were retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and converted to PDB format with Open Babel software (http://openbabel.org/). The structures then were energy minimized in ArgusLab software (http://www.arguslab.com/) [41].

Enzymes active sites. The active sites of JAK enzymes were extracted using Computed Atlas of Surface Topography of proteins server (http://sts.bioe.uic.edu/castp/).

Docking experiments. In order to access the potential ability of the considered drugs to prefer JAK enzymes active sites for binding, in contrast to other potential sites, we have performed blind docking experiments in Hex 8.0.0 (http://www.loria.fr/~ritchied/hex/) software [42]. By setting the sahpe+electrostatic and macro sampling modes of docking, optimized structures of JAK enzymes were used

as receptors and the analgesics as ligands, we carried out separate docking experiments for each ligand and receptor. The best 100 docking poses and their binding energies were recorded for further analysis.

Drugs Hydrophobicity. Partition coefficient or logP is an acceptable index for drug hydrophobicity with the positive value showing hydrophobicity and negative ones hydrophilic properties. The server of the Virtual Computational Chemistry Laboratory (http://www.vcclab.org/) was used to calculated logP [43].

Data Handling and Analysis. All the numerical data were exploited in Excel and SPSS software. P-value under 0.05 was considered as the significance level.

RESULTS AND DISCUSSION

Figure 1a represents sequence alignment results for Janus kinase enzymes. As shown, there is a high degree of sequence similarity between these enzymes so as to make the overall shapes of the enzymes and the structure of their binding sites to be uniform (Fig. 1b). However, their complexes with ligands elucidate their diverse structures which are behind the different binding energies obtained from docking experiments.

Table 1 represents the docking results obtained for the analgesics used as ligands and Jak-1, Jak-2, Jak-3, and TyK2 as receptors. As expected, those drugs with higher binding energies, should exert better inhibition on the enzymes in case they are used *in vivo*. In fact, from an enzymology point of view, all uncleavable chemicals which compete with the substrate to bind enzyme active, behave as inhibitors. The more binding energy for a given drug leads to a more inhibitory effect. Statistical analysis of binding energies in the best 100 poses for each drug shows different variances from drug to drug. Apart from mean binding energy quantity, higher variance in binding energies

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Jak-1-4I5C      -G----------DIVSEKKP-------------ATE-VDPTHFEKRFLKRIRDLGEGHFG
Jak-2-2W1I      MSYYHHHHHHDYDI-----PTTENLYFQGAMGSAFEDRDPTQFEERHLKFLQQLGKGNFG
Jak-3-3LXK      MG--HHHHHH------------AQLY-------ACQ--DPTIFEERHLKYISQLGKGNFG
TyK-2-4GVJ      MG----------S------P------------AS---DPTVFHKRYLKKIRDLGEGHFG

Jak-1-4I5C      KVEL-CRYDPEGDNTGEQVAVKSLK---PESGGNHIADLKKEIEILRNLYHEN-IVKYKG
Jak-2-2W1I      SVEM-CRYDPLQDNTGEVVAVKKLQHS-TE---EHLRDFEREIEILKSLQHDN-IVKYKG
Jak-3-3LXK      SVEL-CRYDPLGDNTGALVAVKQLQHSGPD---QQ-RDFQREIQILKAL-HSDFIVKYRG
TyK-2-4GVJ      KVSLYC-YDPTNDGTGEMVAVKALK---ADAGPQHRSGWKQEIDILRTLYHEH-IIKYKG

Jak-1-4I5C      ICTEDGGNG-IKLIMEFLPSGSLKEYLPKNKNKINLKQQLKYAVQICKGMDYLGSRQYVH
Jak-2-2W1I      VCY-SAGRRNLKLIMEYLPYGSLRDYLQKHKERIDHIKLLQYTSQICKGMEYLGTKRYIH
Jak-3-3LXK      VSY-GPGRQSLRLVMEYLPSGCLRDFLQRHRARLDASRLLLYSSQICKGMEYLGSRRCVH
TyK-2-4GVJ      -CCEDAGAASLQLVMEYVPLGSLRDYLPR--HSIGLAQLLLFAQQICEGMAYLHAQHYIH

Jak-1-4I5C      RDLAARNVLVESEHQVKIGDFGLTKAIETDKEYYTVKDDRDSPVFWYAPECLMQSKFYIA
Jak-2-2W1I      RDLATRNILVENENRVKIGDFGLTKVLPQDKEYYKVKEPGESPIFWYAPESLTESKFSVA
Jak-3-3LXK      RDLAARNILVESEAHVKIADFGLAKLLPLDKDYYVVREPGQSPIFWYAPESLSDNIFSRQ
TyK-2-4GVJ      RDLAARNVLLDNDRLVKIGDFGLAKAVPEGHEYYRVREDGDSPVFWYAPECLKEYKFYYA

Jak-1-4I5C      SDVWSFGVTLHELLTYCDSDSSPMALFLKMIGPT-HGQMTV--T-RLVNTLK-EGKRLPC
Jak-2-2W1I      SDVWSFGVVLYELFTYIEKSKSPPAEFMRMIGNDKQGQMIV--F-HLIELLKNNG-RLPR
Jak-3-3LXK      SDVWSFGVVLYELFTYCDKSCSPSAEFLRMMGCERD----VPALSRLLELLE-EGQRLPA
TyK-2-4GVJ      SDVWSFGVTLYELLTHCDSSQSPPTKFLELIGIA-QGQMTV--L-RLTELLE-RGERLPR

Jak-1-4I5C      PPNCPDEVYQLMRKCW-----E----FQPSNRTSFQNL---IEGFEALL----K------
Jak-2-2W1I      PDGCPDEIYMIMTECWNNNVNQ-----RPS----FRDLALRVD----QI----R---DQM
Jak-3-3LXK      PPACPAEVHELMKLCWAPSPQD-----RPS----FSALGPQLD----MLWSGSRGC-ETH
TyK-2-4GVJ      PDKCPAEVYHLMKNCW-----ETEASFRPT----FENL---I----PIL----KTVHEKY

Jak-1-4I5C      ----------------
Jak-2-2W1I      A------G--------
Jak-3-3LXK      AFTAHPEGKHHSLSFS
TyK-2-4GVJ      RHHHH----HH-----
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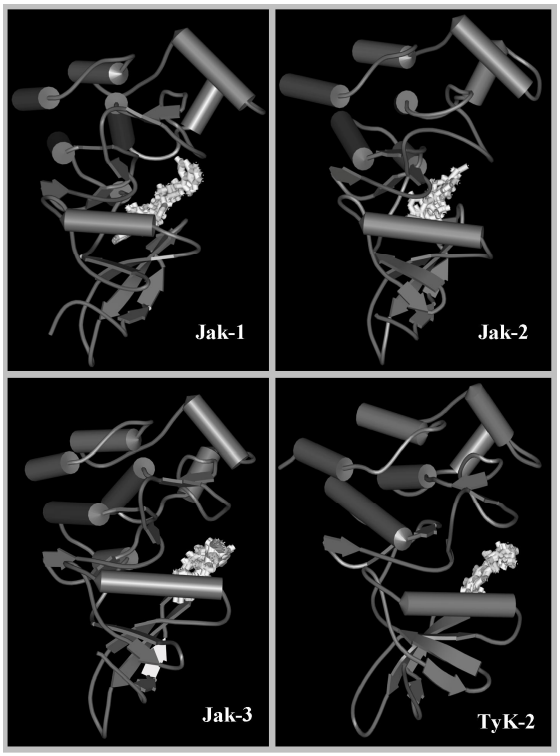

Fig. 1. a) Multiple sequence alignments for Jak-1, Jak-2, Jak-3, and TyK-2 was performed on CLUSTAL (www.ebi.ac.uk/Tools/msa/clustalo/). B) Binding sites predicted using Computed Atlas of Surface Topography of proteins server (http://sts.bioe.uic.edu/castp/) for Jak-1, Jak-2, Jak-3, and TyK-2 used for analysis of docking results.

Table 1. Average Binding Energy in kJ mol^{-1} (as Mean ± SD) as well as Variance in their Binding Energy Calculated for the Best 100 Poses for Janus Kinase Enzyme and the logP Values of the Drugs Calculated on (http://www.vcclab.org/) website

	JAK-1			JAK-2			JAK-3			TYK2			
	Mean	Variance	Occupancy	Mean	Variance	Occupancy	Mean	Variance	Occupancy	Mean	Variance	Occupancy	logP
Almotriptan	-344.5	67.81	100	-299.1	38.41	59	-323.44	92.07	100	-322.98	63.46	91	2.04
Amitriptyline	-312.29	77.97	100	-286.80	44.82	43	-296.33	37.98	100	-288.42	52.73	100	5.1
Amlodipine	-285.01	183.16	82	-324.08	78.87	41	-351.65	85.57	50	-327.91	132.51	49	2.22
Baricitinib	-340.86	74.59	100	-311.13	41.96	24	-309.04	74.49	97	-331.52	90.23	100	2.22
Buprenorphine	-389.48	206.8	100	-349.98	150.49	21	-319.16	51.84	68	-372.33	90.68	98	1.08
Buprenorphine	-389.48	206.8	100	-349.69	153.97	18	-319.16	51.84	58	-372.33	90.68	100	4.53
Celecoxib	-538.62	179.3	0	-444.11	68.44	47	-530.02	246.3	21	-426.53	211.48	25	4.53
Diclofenac	-391.72	82	0	-328.13	113.12	0	-392.19	74.11	39	-304.89	94.61	0	4.98
Duloxetine	-332.81	124.64	100	-310.25	71.65	60	-301.51	98.96	93	-299.41	70.77	87	4.72
Ergotamine	-414.33	178.31	0	-396.76	186.13	85	-368.09	122.89	80	-412.71	189.34	93	3.99
Esomeprazole	-363.94	103.22	100	-293.53	70.42	28	-307.21	74.64	94	-311.32	55.71	74	2.95
Etodolac	-304.10	70.5	100	-281.44	74.01	75	-273.05	60.78	92	-283.78	73.04	90	3.39
Famotidine	-299.92	28.37	100	-264.88	59.29	91	-266.55	74.12	86	-274.51	55.7	95	1.66
Fentanyl	-351.58	38.54	100	-314.62	78.45	68	-322.89	103.79	82	-347.59	68.84	72	-0.2
Indomethacin	-373.64	113.49	99	-346.31	178.68	80	-358.89	119.69	16	-322.96	71.17	96	4.25
Lansoprazole	-567.43	146.08	100	-452.15	100.09	25	-538.29	243.78	46	-431.28	135.44	11	2.84
Lasmiditan	-521.15	177.33	77	-431.78	149.32	4	-512.18	76.41	72	-385.99	267.03	40	2.76
Methadone	-320.14	99.74	100	-319.62	82.1	86	-272.80	52.53	95	-307.68	43.04	91	4.14
Nalbuphine	-336.72	46.67	100	-333.39	66.14	79	-288.05	67.86	63	-313.93	95.45	57	2
Naloxone	-319.80	115.51	100	-318.02	111.47	97	-286.58	95	95	-288.36	32.65	80	1.47
Naproxen	-276.41	57.86	100	-252.06	40.54	80	-250.64	38.96	80	-257.66	28.89	74	3.29
Naratriptan	-340.01	41.61	100	-308.16	50.56	30	-316.33	162.6	94	-330.94	108.44	100	2.16
Oxycodone	-301.71	26.67	100	-287.69	61.6	83	-274.92	47.76	63	-281.10	36.9	94	1.04
Piroxicam	-327.61	60.33	100	-291.07	68.25	75	-294.22	130.14	100	-298.19	41.28	74	2.2
Remifentanil	-368.40	136.09	100	-322.15	49.44	70	-305.59	64.79	94	-335.01	89.36	94	1.75
Rimegepant	-513.18	329.07	97	-437.91	168.09	24	-462.48	117.64	0	-448.28	104.52	100	2.68
Rofecoxib	-301.84	29.01	100	-275.29	38.81	58	-274.34	69.14	89	-285.52	34.76	95	2.32
Ruxolitinib	-331.57	79.9	100	-302.82	152.08	0	-287.14	77.19	0	-309.28	58.25	95	2.94
Sufentanil	-364.00	78.92	100	-336.96	133.74	39	-330.00	102.77	95	-350.91	146.58	100	3.4
Sulindac	-373.87	75.99	10	-332.61	105.94	0	-362.92	42.18	100	-315.03	56.63	67	2.96
Tofacitinib	-336.07	94.76	100	-300.26	34.57	41	-304.10	131.89	89	-307.66	39.09	92	1.58
Ubrogepant	-609.704	615.54	0	-509.55	216.56	60	-564.97	300.73	44	-472.12	574.14	4	3
Valdecoxib	-299.65	60.1	100	-275.96	39.86	40	-281.01	34.15	98	-288.52	55.06	95	3.32

conveys that the drug does not bind to the same binding site with similar energy throughout the 100 poses. Instead, it binds to distant sites with different energies that lead to higher variance. Therefore, we conclude that 1/variance could be considered as a stability index for ligand binding. Accordingly, the lower 1/variance could be used as a criterion for less stability and less inhibitory potency. Otherwise, logP or partition coefficient is a useful estimate for the drug distribution within the body. Hydrophobic drugs with higher logP are freely distributed to cell membranes and freely reach their targets for inhibition inside cells. The next important docking-based parameter in predicting drugs inhibitory potency is the percent of binding site occupation. A higher degree or frequency of binding site occupation means more probable inhibitory character for the drug.

To make sensible comparisons between our measured variables of Mean binding energy, 1/Variance, percent of binding site occupancy, and logP, we calculated the z-scores for each drug using the formula of Z = (X-Mean)/(SD). The z-score is a very useful statistical parameter that allows us to calculate the probability of a score occurring within our normal distribution. This enables us to compare two scores from different distributions, and obtain a cumulative index by adding different z-scores for our drugs [44].

In this manner we normalized the values of binding energies, 1/variances (as stability index), percent of binding site occupancies, and the logP values to normalize absolute values within 0 to 1 range, using the z-score formula and then sum up them in a total cumulative index for this purpose (Table 2). As indicated, indomethacin, etodolac, buprenorphine, rofecoxib, duloxetine, valdecoxib, naproxen, methadone, and amitriptyline show a total index higher than 10 contrasting the other studied drugs.

In this series, two drugs are from opioids including methadone and buprenorphine with 11.29 and 10.33 cumulative indices, respectively. There are reports showing their immunomodulatory effects on immune responses and controlling cytokine storm in COVID-19 in normal individuals, while they exert a worsening effect on drug abusers increasing the mortality rate of COVID-19 [45-46]. Two drugs are from antidepressants including amitriptyline and duloxetine with total indices of 12.21 and 10.89, respectively. Miscellaneous reports are indicating that these drugs may be useful in the treatment of peripheral neuropathic pain which may be encountered in COVID-19 [47-49]. It is also indicated that amitriptyline exerts

Table 2. The Total Cumulative Index for each Drug Calculated Based on Normalized Values for Binding Energies, 1/Variances, Binding Site Occupancies, and logP as Described in the Text

	Jak-1	Jak-2	Jak-3	Tyk2	Total
Fentanyl	2.23	1.72	1.68	1.84	7.47
Amlodipine	1.87	1.93	1.96	1.84	7.60
Buprenorphine	1.98	1.34	2.12	2.30	7.74
Ubrogepant	1.63	2.37	2.14	1.68	7.82
Nuxolitinib	2.45	1.40	1.53	2.68	8.06
Diclofenac	1.94	1.93	2.52	1.93	8.32
Lasmiditan	2.32	1.66	2.61	1.87	8.46
Lansoprazole	2.67	2.05	2.11	1.79	8.62
Rimegepant	2.42	1.84	1.63	2.75	8.64
Sulindac	1.64	1.56	3.03	2.43	8.66
Nalbuphine	2.52	2.38	2.04	1.93	8.86
Naloxone	2.04	2.22	2.10	2.58	8.96
Celecoxib	1.92	2.75	2.18	2.18	9.02
Tofacitinib	2.14	2.32	2.00	2.62	9.08
Naratriptan	2.62	2.02	2.13	2.39	9.17
Remifentanil	2.14	2.40	2.35	2.32	9.21
Baricitinib	2.35	2.12	2.41	2.46	9.34
Esomeprazole	2.43	1.93	2.52	2.50	9.38
piroxicam	2.41	2.28	2.21	2.50	9.41
Oxycodone	2.70	2.19	2.04	2.52	9.44
Ergotamine	1.61	2.62	2.51	2.74	9.49
Famotidine	2.76	2.37	2.12	2.38	9.62
Almotriptan	2.36	2.50	2.34	2.45	9.65
Sufentanil	2.60	1.99	2.53	2.61	9.73
Indomethacin	2.67	2.53	1.91	2.88	10.00
Etodolac	2.54	2.46	2.63	2.56	10.19
Buprenorphine	2.66	1.98	2.69	3.00	10.33
Rofecoxib	2.87	2.48	2.32	2.84	10.52
Duloxetine	2.69	2.64	2.73	2.84	10.89
Valdecoxib	2.59	2.47	3.13	2.74	10.92
Naproxen	2.56	2.82	2.77	2.93	11.07
Methadone	2.60	2.75	2.89	3.04	11.29
Amitriptyline	2.85	2.78	3.42	3.16	12.21

immunomodulatory effects through IL-10; IL-1β, IL-18, ICAM-1, MIP-2, MCP-1, TNF-α while duloxetine acts through IL-6, TNF-α [50-54]. Accordingly, these drugs seem to be useful for clinical trails. The rest of our candidate drugs including naproxen, valdecoxib, rofecoxib, etodolac, and indomethacin with a total index of 11.07, 10.92, 10.52, 10.19, and 10.00, respectively, belongs to non-steroidal anti-inflammatory drugs (NSAIDs). There are many investigations showing the potential benefits of NSAIDs for COVID-19 treatment. In a clinical trail, it was shown that naproxen in combination with clarithromycin and oseltamivir significantly decreases mortality in patients with H3N2 Influenza through modulating immunomodulatory effects [55-57]. According to WHO reports NSAIDs have no unwanted effects on survival or quality of life in patients with COVID-19 [58]. There is also a report indicating the benefits of indomethacin application as adjuvant besides standard treat helps faster relief of COVID-19 pneumonia [59-60].

CONCLUSIONS

Based on our findings and previous reports, the suggested drugs included indomethacin, etodolac, buprenorphine, rofecoxib, duloxetine, valdecoxib, naproxen, methadone, and amitriptyline seem to be good drug candidates for JAK-STAT pathway blockage and cytokine storm control in chronic and severe cases of cancer, autoimmune and COVID-19 diseases upon separate clinical trials assessments.

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