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Research Article

A Study On The İnteraction of Aspirin and Some Effective Compounds with Covid-19, Prostaglandins and Thromboxane Receptors

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ABSTRACT

In the studies of Hippocrates, it was stated that the leaves of the willow tree were used as a painkiller. In the discovery of salicylic acid, it was converted into acetylsalicylic acid and used as aspirin. In this study, the inhibitory effect of aspirin, which is effective in many diseases, on the mechanism of action on Covid-19 has been investigated. In addition, the interaction of prostaglandins and thromboxane, which increased in amount with this virus, with other effective compounds (Pitavastatin, Rosoxacin, Ridogrel) has tried to be determined comparatively. In addition to the effect of aspirin on this virus, many diagnostic and treatment methods have been developed in its treatment and it is known to be effective on diseases whose mortality is a serious health problem. Chemical calculation method has been used to clarify, understand and examine the interactions of the metabolic events mentioned here. Recently, scientists have been studying on targeted treatments. A drug that will be formed from an active molecule to be developed for the target will provide more effective results by suppressing the proliferation, growth and spread of the target unit.

Keywords: Aspirin, pitavastatin, rosoxacin, ridogrel, prostaglandins,thromboxane, SARS-CoV-2.

1. INTRODUCTION

The usage of aspirin in SARS-CoV-2 positive patients has been associated with good outcomes.[1] Aspirin is a non-steroidal anti-inflammatory. There are studies on its use as a drug that reduces the incidence and mortality of colorectal cancer.[2] Prostaglandin (PG) D 2 is the predominant COX product, an effector of aspirin-induced respiratory reactions in patients.[3]

The main antithrombotic effect of aspirin is its tendency towards inhibition of thromboxane A2 (TXA2) synthesis by acetylating cyclooxygenase-1 (COX-1) in platelets.[4] Aspirin irreversibly inhibits the cyclooxygenase-1 (COX-1) enzyme in platelets by acetylating the serine residues, thereby inhibiting the production of Thromboxan-A2 and other eicosanoids synthesized from arachidonic acid [5].

Cyclooxygenase-1 (COX-1) and its isozyme COX-2 are important key enzymes in the synthesis of prostanoids however, Cyclooxygenase-1 (COSX-1) is a prostaglandin-endoperoxide synthase.[6] Prostaglandin endoperoxide synthase-1 (PGHS-1) is also known as cyclooxygenase-1 (COX-1).[7] The role of cyclooxygenase-1 (COX-1), a key enzyme It can be defined as the conversion of arachidonic acid to proinflammatory prostaglandins.[8]

In this study, the inhibition effect of Aspirin on Covid-19,human ACE2 (hACE2) and prostaglandins and thromboxane, which are detected in high amounts in these patients, was investigated by comparing Aspirin, which is effective on many diseases, especially Pitavastatin, Rosoxacin and Ridogrel, which are effective on Covid-19.

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2.MATERIALS and METHOD

The crystal structure of hematopoietic prostaglandin D synthase apo form (5YWE) was downloaded from Protein Data Bank. [9] The crystal structure of the human thromboxane A2 receptor (6IIU) was downloaded from Protein Data Bank .[10,11]

In a study, it was determined that only cilostazol as anti-CoVID-19 had the most favorable binding interaction on Mpro (PDB ID: 6LU7) and higher binding affinity on spike glycoprotein (S) (PDB ID: 6VYB).[12] The pdb file (6LU7) that makes up the main protease of SARS-CoV-2 3C-like protease or SARS-CoV-2 3CLpro (monomeric form)[13].Superiority of cilostazol over others among antiplatelets It is an FDA-approved drug against COVID 19 M(pro) and spike protein .[14]

The spike glycoprotein (S protein) receptors in both the closed state (6VXX) and the open state (6VYB) form [15,16] are receptors associated with human ACE2 (hACE2) receptors. [17]

3.RESULTS and DISCUSSIONS

The comparison of the inhibition effects of effectively used active substances with cancer and SARS-CoV-2 receptors is given in Table 1. [34,35]

Table 1. The inhibition effects of effectively used active substances with cancer and covid-19 receptors.

Receptors/Ligands (Docking score) kcal/mol	Prostaglandin D synthase apo form(5YWE)	Human thromboxane A2 receptor(6IIU)	SARS-CoV-2-Receptor (6LU7)	Spike glycoprotein (6VYB)
Aspirin	-4.40	-4.50	-4.04	-3.37
Ridogrel	-6.23	-8.59	-4.51	-4.68
Pitavastatin	-7.99	-6.38	-6.47	-5.86
Rosoxacin	-6.31	-7.56	-4.88	-4.64

The inhibition order from high to low as the binding energy

For prostaglandin D synthase apo form (5YWE)

Pitavastatin > Rosoxacin > Ridogrel > Aspirin

For human thromboxane A2 receptor(6IIU)

Ridogrel > Rosoxacin > Pitavastatin > Aspirin

For CoVID-19 Receptor (6LU7)

Pitavastatin > Rosoxacin > Ridogrel > Aspirin

For spike glycoprotein (6VYB)

Pitavastatin > Ridogrel > Rosoxacin > Aspirin

The interaction of human thromboxane A2 receptor with aspirin is given Table 2. [34,35]

Table 2. The interaction of human thromboxane A2 receptor with aspirin.

Hydrogen bonds	Hydrophobic	Other
ARG295 (-2.1359)	PHE34 (-1.5465)	LEU294 (-0.335)
THR298 (-0.4638)	PHE30 (-0.6901)	ALA31 (-0.2862)
TRP299 (-0.5582)		

The interaction of human thromboxane A2 receptor with Pitavastatin is given Table 3. [34,35]

Table 3. The interaction of human thromboxane A2 receptor with Pitavastatin.

Hydrogenbonds	Polar	Cation-pi	Hydrophobic	Other
THR298 (-2.6965)	THR81(-0.3271)	TRP258(-0.2424)	ALA31 (-0.9929)	ARG295(-0.8893)
			VAL85 (-0.8208)	SER181(-0.383)
			CYS35 (-0.7148)	PHE115(-0.2386)
			PHE34 (-0.5524)	
			TRP182(-0.4844)	
			LEU294(-0.1941)	
			MET112(-0.1341)	
			PHE30 (0.3592)	
			LEU78 (0.4862)	
			LEU291 (0.938)	

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The interaction of prostaglandin D synthase apo form with Pitavastatin is given Table 4. [34,35]

Table 4. The interaction of prostaglandin D synthase apo form with Pitavastatin.

Halogen-bond	Polar	Cation-pi	Hydrophobic	Other
ILE51 (-0.3297)	TRP39(-0.9707)	PHE9(-0.8047)	TRP104(-2.5529)	ARG14 (-1.5534)
			TYR8 (-0.6637)	LEU199(-0.8074)
				LYS50 (-0.6842

The interaction of human thromboxane A2 receptor with Ridogrel is given Table 5.

Table 5. The interaction of human thromboxane A2 receptor with Ridogrel.

Hydrogenbonds	Halogen-bond	Polar	Hydrophobic	Other
ARG295 (-2.5199)	SER181(-0.2682)	TRP299(-0.8904)	PHE34 (-0.829)	THR298(-0.8161)
THR81 (-0.2304)				VAL85(-0.8361)
			PHE30 (-0.7751)	LEU291(-0.4764)
				PRO179(-0.2734)
			HIS89 (-0.256)	
			ALA31 (-0.3167)	LEU78(-0.5015)

The interaction of prostaglandin D synthase apo form receptor with Ridogrel is given Table 6. [34,35]

Table 6. The interaction of prostaglandin D synthase apo form receptor with Ridogrel.

Hydrogen Bonds	Halogen-Bond	Polar	Other
HIS62 (-1.2203)	SER64 (-0.5555)	ARG14 (-1.7704)	LYS50 (-0.7867)
ILE51 (1.0318)	ASP96 (-.3121)		LEU65 (-0.6967)
	GLN63 (0.4813)		

Pitavastatin, ridogrel and rosoxacin can be further optimized in preclinical and clinical studies to determine their possible role in COVID-19 treatment and Ridogrel is replaced by aspirin in treatment because it is clinically superior. [18]

In molecular dynamics simulations, it was concluded that pitavastatin, ridogrel and rosoxacin have superior binding properties and can be further optimized in preclinical and clinical studies to determine their possible roles in COVID-19. [19]

The 6VYB ligand has the most hydrogen bonds with the receptors and bonds due to the binding energy and the presence of hydrogen, the most stable interacting ligand is between the spike ectodomain structure. [20]Aspirin has the effect of irreversibly blocking prostaglandin (PG) and thromboxane (TXA) production. [21] In patients with COVID-19, a significant increase in the amount of thromboxane has been observed. [22] The emphasis in this study is that aspirin has inhibitory effects on thromboxane and prostaglandins.[23] It is important to control chemical mediators such as prostaglandin that act on the central nervous system causing fever [25], pain thromboxane to regulate their anti-inflammatory effects. [24]

Aspirin, especially in high doses, can cause significant reductions in the production of rostanoids in other tissues, such as prostaglandins. [26] The selective effect of oral aspirin on thromboxane compared to prostacyclin biosynthesis may be explained by the pharmacokinetics of aspirin [27]. One study highlighted that aspirin can reduce the mortality rate from COVID-19.[28]

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) to enter host cells to target COVID-19.[29] It has been stated that aspirin may prevent severe COVID-19 by reducing the prostaglandins/thromboxane storm in the lungs and is probably safe and beneficial for patients severely affected by COVID-19. [30] It was emphasized in a study that macrovesicular steatosis, mild necroinflammation and portal inflammation were observed in COVID-19 patients.[31] It was emphasized that aspirin is widely accepted as a chemopreventive.[32] This effect was expressed in another study as Aspirin, by inhibiting the AKT/mTOR pathway and suppressing SREBP-1 expression, increased the sensitivity of CRC cells with oncogenic PIK3CA activation to ferroptosis induction. [33]

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4. CONCLUSIONS

Based on this study, the inhibitory effects of aspirin on SARS-CoV-2 and human ACE2 (hACE-2) was quite good when compared to Covid-19 referrence active ingredients Pitavstatin, Rosoxacin and Ridogrel. Aspirin seems to be very close when compared to both Covid-19 and human ACE2 (hACE2) reference drugs. In addition, the inhibitory capacity of prostaglandins and thromboxane, whose amount increases in those infected with this virus, is effective when looking at the bonds and interaction points formed at the molecular level. The study conducted here and the data obtained is an important study in terms of preventing time, substance loss, and guiding experimental and clinical studies.

Declaration of Competing Interest

The author declares that there is no competing interest.

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