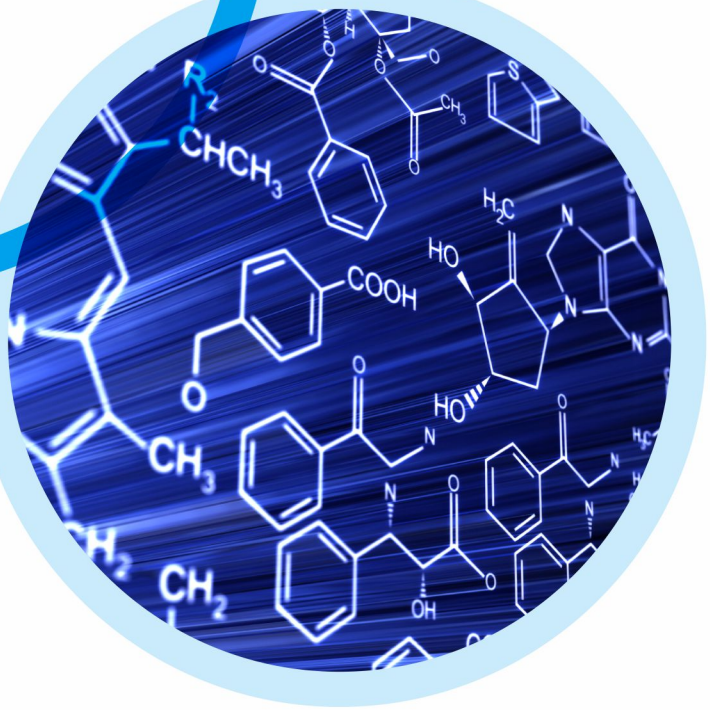

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Research Article
Inhibiting Effect of Medical Compounds for SARS-CoV-2 and Secretory Phospholipase A2

Faik Gökalp

Department of Mathematics and Science Education, Faculty of Education, Kirikkale University, Yahsihan/Kirikkale 71450, Turkey

Abstract

Background and Objective: New research about COVID-19 disease is emerging every day. The sPLA2 group IIA (sPLA2-IIA) enzyme, produced for the metabolic elimination of this virus is detected in the blood of COVID-19 patients. An excessive amount in the body will lead to multi-organ failure. The aim of this study was to investigate the inhibitory effect of the main natural active compounds found in medicinal plants on the sPLA2 group IIA (sPLA2-IIA) enzyme, COVID-19 and ACE2. **Materials and Methods:** The inhibition effects of active compounds (thymol, carvacrol, piperine, cucurbitacin-E and cucurbitacin-I) in some herbal products (oregano, black pepper and *Ecballium elaterium* L.) used medicinally in daily life on COVID-19 virus, ACE2-linked SARS-CoV-2 spike receptor and sPLA2 group IIA (sPLA2-IIA) enzyme will be calculated by using chemical calculation method and computational theoretical methods. **Results:** According to the data obtained from the docking energy scores of the chemical calculation method of piperine, one of the natural active substances investigated, it is seen that its inhibitory effect is quite good compared to other active compounds. It is understood that the natural active compounds determined as ligands here are quite effective on both SARS-CoV-2 and sPLA2 group IIA (sPLA2-IIA), according to the data obtained by the chemical calculation method. **Conclusion:** The data obtained in this study is of great importance in terms of guiding experimental studies. It will guide the experimental and clinical studies to be carried out in this field by preventing the loss of time and material.

Key words: ACE2, COVID-19, sPLA2 group IIA (sPLA2-IIA), carvacrol, cucurbitacin-E, cucurbitacin-I, thymol, piperine

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Corresponding Author: Faik Gökalp, Department of Mathematics and Science Education, Faculty of Education, Kirikkale University, Yahsihan/Kirikkale 71450, Turkey
Department of Nutrition and Dietetics, Faculty of Health Sciences, Igdir University, Igdir, Turkey
[https://livedna.org/90.41597, https://orcid.org/0000-0003-4363-3839]

Competing Interest: The author has declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Secretory Phospholipase A2 (sPLA2) is an interface enzyme protein. It is involved in the hydrolysis of lipids on the surface of a biological membrane and the selective degradation of fatty acid at the secondary position of a phospholipid[1]. It has been determined that the generation and replication of sPLA2-IIa for virus-exposed metabolism[2].

Recently, sPLA2-IIA levels have been found to be significantly elevated in the plasma of individuals exposed to this virus. Secretory Phospholipase 2 (sPLA2)[3] levels correlated with COVID-19 severity and may be a useful biomarker to reduce the risk for children with acute COVID-19[4]. The inhibitors of sPLA2-IIA have been used to reduce COVID-19 mortality[5].

The molecular mechanisms responsible for severe COVID-19 progressing to mortality have been identified by focused biochemistry plasma samples from patients with severe COVID-19 and higher metabolites indicating the relationship between Secretory Phospholipase A2 (sPLA2) activity detected in those samples and mitochondrial dysfunction, higher circulation in COVID-19 patients, catalytically active sPLA2 group IIA (sPLA2-IIA) is an indication that there are levels that caused kidney dysfunction, hypoxia, multiple organ dysfunction[5]. Morelloflavone, ochanflavone and several other biflavones were found to be groups IIA Secretory Phospholipase A2 (sPLA2-11A) inhibitors[6-8].

This study, aimed to investigate the inhibition effects of natural active substances by chemical calculation method and to determine the mechanism in order to prevent sPLA2-11A from being effective against the virus in patients with the COVID-19 epidemic and to prevent damage to healthy cells and to keep both the virus and the protective agents in balance.

MATERIALS AND METHODS

Study area: This study was carried out in the computer provided by the Kirikkale University project (grant number: BAP-2016/016,2017/019,2018/033) by using the chemical calculation method docking the ligand-receptor interactions at the molecular level.

In this study, the compounds (thymol, carvacrol, piperine, cucurbitacin-E and cucurbitacin-I) with inhibitory effects were investigated in the literature (17-20) and data were obtained in order to compare their effectiveness with the chemical calculation method. This method revealed the interaction of the target receptor and natural active compounds as ligands and what kind of intermolecular bonds are formed at which points during this interaction.

Main protease (Mpro) (PDB code: 6LU7) and spike (S) glycoprotein receptor binding domain (RBD) to ACE2 (PDB code: 6M0J) of SARS-CoV-2[9]. The structure of bovine pancreatic prophospholipase A2 (2BP2) is downloaded from Protein Databank[10]. A novel Secreted Phospholipase A2 (sPLA2) (5G3N) inhibitor is downloaded from Protein Databank[11]. The inhibition effects of active compounds in some medicinally used herbal products on COVID-19 virus, ACE2-bound SARS-CoV-2 spike receptor and sPLA2 group IIA (sPLA2-IIA) enzyme were calculated using docking[12,13] and compared.

RESULTS AND DISCUSSION

In Table 1, the inhibition values of some active substances that are effective on the group IIA-Secreted Phospholipase A2 (sPLA2-IIA) enzyme were given by comparing the values related to COVID-19 and ACE2.

As shown in Table 1, It is understood from the docking energy score values that the enzyme and the virus attach to ACE2 and that the active molecules selected on the Receptors of the virus are quite effective. The fact that the values for Piperine are quite close to each other means that it is effective on both the enzyme and the virus. The inhibition docking scores of some piperine, effective on the group IIA-Secreted Phospholipase A2 (sPLA2-IIA) enzyme were given in Table 2.

Table 1: Inhibition values of some active substances that are effective on the group IIA Secreted Phospholipase A2 (sPLA2-IIA) enzyme by comparing the values related to COVID-19 and ACE2

Receptors/Ligands (Est. Free energy of binding kcal mol^{-1})	2BP2	6LU7	6M0J
Thymol	-4.99	-4.41	-3.35
Carvacrol	-4.92	-4.46	-3.50
Piperine	-7.30	-4.86	-4.21
Cucurbitacin-E	+16.24	-4.81	-4.11
Cucurbitacin-I	-1.81	-4.82	-3.89

Table 2: Inhibition docking scores of some piperine, effective on the group IIA Secreted Phospholipase A2 (sPLA2-IIA) enzyme

Hydrogen bond	Polar	Hydrophobic	Other
TYR69 (-0.4562)	ASP49 (-0.5719)	TYR52 (-0.9933)	ASN23 (-0.9318)
PHE22 (-0.4014)		LEU19 (-0.7306)	LYS53 (-0.3361)
		HIS48 (-0.6094)	PHE106 (-0.2804)

Interactions of piperine with group IIA-Secreted Phospholipase A2 (sPLA2-IIA) enzyme were given in group IIA Secreted Phospholipase A2 (sPLA2-IIA) enzyme interaction points with piperine were 19: LEU22: PHE23: ASN48: HIS49: ASP52: TYR53: LYS69: TYR106: PHE

In thymol, on the other hand, it is understood that the energy value for the virus and the high binding affinity are more effective in the virus than the enzyme. The same conclusion can be reached as it is close to the carvacrol values.

Many experimental studies in this field and the results obtained from these studies have concluded that carvacrol has protective properties against inflammation, immune dysfunction and infection caused by COVID-19[14]. Carvacrol and thymol were found to show better potential in inhibiting COVID-19 S proteins[15].

It was concluded that piperine could have a promising function in developing anti-COVID-19 drug[16]. Cucurbitacin-E and I also show high inhibitory properties against COVID-19[17]. The use of clinically available sPLA2-IIA inhibitors to reduce COVID-19 mortality is an important therapeutic approach[6]. Phospholipase A2 (Lp-PLA 2) is an enzyme that can hydrolyze platelet-activating factor[18]. In this study, ligand-receptor interactions has been investigated by using docking[12,13,19].

The implications, applications, recommendations and limitations of this study, as it is a computational chemical method, help us to understand the interaction points and types that may occur, it does not replace experimental and clinical studies and guides them. The results obtained from this study will help to reveal the interaction mechanism of the active substances as ligands with the target receptors and therefore, it is important in terms of giving direction to experimental and clinical studies by preventing time and substance loss.

CONCLUSION

In one of the studies on the COVID-19 virus, which is an important health problem for all people in the world and can affect every individual, the effect of active substances in some traditional plants, which have an important role in inhibiting the sPLA2 group IIA (sPLA2-IIA) enzyme produced in human metabolism against the virus, affects the virus. The effect on ACE2-virus was compared and investigated and it was determined that the inhibition effect of piperine could be effective on the enzyme and the virus. It is an important study in terms of giving direction to experimental and clinical studies by preventing time and material loss.

SIGNIFICANCE STATEMENT

An increase in the amount of the sPLA2 group IIA (sPLA2-IIA) enzyme, which has the ability to damage healthy cells, has been observed in SARS-CoV-2 patients. For this reason, determining the inhibitory effect points on both this enzyme and SARS-CoV-2 receptors and the bonds that may form at the molecular level and knowing the mechanism of compounds effective in inhibiting SARS-CoV-2 and this enzyme as ligands will be used in experimental and clinical studies in new drug discoveries. will guide the work.

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