The Impact of Some Natural Phenolic Compounds on α-Glucosidase and Sorbitol Dehydrogenase Enzymes, and Anti-leukemia Cancer Potential, Spin Density Distributions, and in silico Studies

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Abstract: In this study, some phenolic compounds including 4-Hexylresorcinol, 5-Pentadecylresorcinol, 5-Tricosylresorcinol, Bilobol, and Urushiol were tested against α-glycosidase enzyme from Saccharomyces cerevisiae and sorbitol dehydrogenase enzymes from sheep liver. These compounds determined good inhibition properties against α-glycosidase and sorbitol dehydrogenase (SDH) enzymes. IC₅₀ values were record in the range of 1.45±0.20–24.532±3.83 μM for α-glycosidase and 6.20±0.96–108.22±18.02 μM for SDH. These inhibitor compounds can be selective drug candidates as anti-diabetic agents, because of they have inhibition properties against both enzymes. In this study, the anti-oxidant activities of the molecules were compared with density functional theory (DFT) calculations. Comparison was made with the experimental enzymes by molecular modeling calculations. In the cellular and molecular part of the recent study, the treated cells with some phenolic compounds were assessed by molecularly targeted therapy (MTT) assay for cytotoxicity and anti-acute lymphoblastic leukemia potentials on Clone 15 HL-60, HL-60, HL-60/MX1, and HL-60/MX2 cell lines. The IC₅₀ of these compounds were μg/mL level against these cell lines.

Key words: phenolic compounds, molecular modeling, anti-leukemia, enzyme inhibition

1 Introduction

Phenolic compounds have high antioxidant activity due to their ability to be easily oxidized. One of the important medicinal properties of phenolic compounds is their antidiabetic activity. Inhibition of α-glucosidase in the small intestine that convert complex carbohydrates into absorbable forms is an important approach in the treatment of Type 2 diabetes, which is characterized by high postprandial blood glucose levels¹,². Acarbose is an active compound used in the therapy of Type 2 diabetes and is also used as an active ingredient in many antidiabetic drugs. Type 2 diabetes is mostly seen in obese people. In this respect, it is quite natural to consider diabetes together with obesity. Oral anti-diabetics are very important in regulating the post-meal blood sugar level of type 2 diabetes patients. α-Amylase and α-glucosidase enzymes are involved in the digestion of starch taken with diabetes. Indeed, the inhibition of these enzymes, the postprandial blood sugar level can be regulated³,⁴. Sorbitol Dehydrogenase enzyme (E.C. 1.1.1.14) is the second and final enzyme of the polyol (sorbitol) pathway and catalyzes the reversible oxidation-reduction reaction between sorbitol and fructose in the presence of coenzyme NAD⁺. Sorbitol dehydrogenase (SDH) has approximately 20% amino acid sequence similarity with its distantly related alcohol dehydrogenases. It is a metalloenzyme containing a zinc ion in each subunit of the SDH enzyme, which has a tetrameric structure. In addition, studies conducted with SDH inhibitors in recent years suggest that inhibition of SDH may be beneficial in delaying the emer-
gence of diabetic complications by correcting redox disorders related to polyol metabolism. Leukemias are a group of neoplastic diseases that develop as a result of malignant transformation of hematopoietic (blood-forming) cells. Leukemia develops in the bone marrow; the bone marrow fills the inside of the large bones in the body and provides blood formation. As a result of a cell in the bone marrow undergoing a leukemic change, the cell multiplies uncontrollably. This is the beginning of the disease. Leukemic cells, which are abnormal cells, spread to the bone marrow and suppress the normal hematopoiesis process. There are many different types of leukemia, but they show similar characteristics to other types of cancer.

Theoretical calculations are developing day by day and new programs that will obtain more accurate results emerge. The most common of these programs is the Gaussian software program. Theoretical anti-oxidant activities calculations were made with this program. In the calculations, numerical values were calculated by analyzing a series of reactions. Molecular modeling calculations were made to theoretically support the results of the experimentally studied enzymes. The results of the calculations made were compared with the experimental results.

Finally, the activities of molecules against covid-19 (SARS-CoV-2) virus, one of the most contagious and effective diseases today, were compared. As a result of the interaction between the spike protein of the covid-19 virus and the ACE-2 protein in the cell wall, the covid-19 virus enters the cell. The schematic representation of the entry into this cell is given in Fig. 1. Therefore, the search for effective inhibitors to inhibit the spike protein of the covid-19 virus continues rapidly. The inhibitory activity of the molecules studied for the spike protein (pdb: 6M0J) of the SARCoV-2 virus was compared.

The aim of recent study, the enzyme inhibition, antioxidant, and in silico properties of prepared some phenolic compounds against acute lymphoblastic leukemia (Clone 15 HL-60, HL-60/MX1, HL-60, and HL-60/MX2) cell lines and diverse enzymes were evaluated.

2 Experimental

2.1 Enzymes assays

2.1.1 α-Glucosidase activity

*Saccharomyces cerevisiae* α-glucosidase (Sigma, G0660) was used as the model enzyme. The spectrophotometric method modified by Yılmazer-Musa et al., (2012) was used for α-glucosidase activity measurement. The phenolic compounds were dissolved with DMSO and the stock was prepared and diluted with 80% methanol from this stock. Serial dilutions were prepared from the samples and pre-incubated for 15 minutes at 37°C in 20 µL (20 mU) *S. cerevisiae* α-glucosidase and 135 µL 20 mM potassium phosphate buffer (pH 6.8) microplate. The reaction was initiated using 25 µL of 0.9 mM p-nitrophenyl α-D-glucopyranoside (p-NPG) as substrate. The amount of p-nitrophenol formed from pNPG as a result of α-glucosidase activity was measured at 400 nm with a multiplex reader (SpectraMax M5, Molecular Devices). Acarbose was used as inhibitor control. α-Glucosidase activity was expressed as a percentage compared with the inhibitor-free control. Each measurement was made in triplicate. The IC₅₀ values of the synthesized compounds were expressed as the concentration of the compounds prepared at different concentrations, which halved the maximum activity.

![Fig. 1 The entry of the SARS-CoV-2 virus into the cell.](image-url)
2.1.2 SDH activities

The SDH activity of these compounds was performed by spectrophotometrically that measured with 0.050 M Glycine/NaOH in alkaline medium (pH 10.0) with using substrate compounds of sorbitol (10 mM) and NAD$^+$ (470 mM). The SDH activity of these compounds was performed depending on the level of NAD$^+$ substrat, which did at 340 nm$^{16}$. 

2.1.3 α-Glycosidase and SDH inhibition assays

In order to find the impact of some phenolic compounds on SDH and α-glycosidase, various phenolic compounds concentrations were added into the reaction. The IC$_{50}$ was obtained from activity (%) versus some phenolic compounds concentration plots according to previous studies$^{17}$. 

2.2 Theoretical calculations

In order to compare the anti-oxidant properties of the molecules, it is made with the numerical value of the enthalpy energy of many reaction mechanisms$^{18}$. The different properties of the molecules in each reaction are calculated. For example, numerical values of many parameters like proton affinity (PA), proton dissociation enthalpy (PDE), electron transfer enthalpy (ETE), bond dissociation enthalpy (BDE), ionization potential (IP) and can be found$^{18,20}$:

$$R + AH \rightarrow RH + A^- \quad (1)$$

$$R^+ + AH \rightarrow R^- + AH^+ \quad (2)$$

$$AH^+ \rightarrow H^+ + A^- \quad (3)$$

In the anti-oxidant calculations, calculations were made for the three molecules with the highest experimental activity. For these calculations, the following five reactions are used. In the first (1) reaction, the energy value of the bond dissociation enthalpy (BDE) for the anti-oxidant molecules is calculated. In this reaction, the free radical molecule takes hydrogen from the anti-oxidant molecule$^{21}$. The following reactions (2, 3) are also called Single electron transfer-proton transfer (SET-PT). In these reactions, proton transfer occurs first, after which electrons are removed from $AH^+$. The last two reactions remaining are the SPLET mechanism. These two reactions are the proton dissociation enthalpy (PDE) and ionization potential (IP) mechanisms, respectively$^{22}$.

Gaussian software program was used to calculate the enthalpy energy values in these mechanisms. In the calculations, DFT calculations were used on the Hartree-Fock (HF) level 6-31 + + G(d,p)/basis set$^{23}$.

In addition, molecular modeling calculations were made to compare the biochemical activities of the studied complexes and their activities were compared. Indeed, for these calculations, many parameters were found from the calculations. The numerical value of these parameters gives a lot of important information for bioactivities of complexes$^{24}$. Calculations are made as a result of combining many modules. The first module used includes the preparation of the studied molecules for calculations. At first, optimized structures of the molecules were obtained from the Gaussian software program$^{25}$. It was then prepared for calculations using the LigPrep module$^{26}$ using optimized structures of the molecules. In another module, studied four proteins with the protein preparation module$^{27}$ were prepared for calculations. The Glide ligand docking module was used to interact with the molecules and protein prepared later. Finally, the Qik-prop module$^{28}$ of the Schrodinger software was used to predict the effects and responses on human metabolism as working molecules as drugs. With this calculation, the absorption of the molecules into the human body, their distribution in the body, their effects and reactions in the metabolism, their excretion from the metabolism and their toxic effects are examined by ADME/T analysis (distribution, absorption, excretion, metabolism, and toxicity).

2.3 Cancer assay

Replication of cells: In order to determine the cytotoxic activity of the compounds, human leukemia cancer cell lines were obtained from the American Type Culture Collection (ATCC) and used in the study. Cells were fed twice a week and cell flasks were incubated at 37°C (Thermo Forma II CO$_2$ Incubator, USA) in a 5% CO$_2$ environment throughout the experimental period. Confused cells were removed with trypsin-EDTA solution and counted under the microscope after staining with 0.4% trypan blue$^{29}$. For experimental studies, 96-well plates were seeded with approximately $15 \times 10^4$ cells per well. Treatment with test compounds: 1-100 μM concentrations of the compounds to be tested were added to the cell seeded wells, and then the plates were incubated for 24 hours at 37°C in a 5% CO$_2$ incubator. The possible effects of the applied compounds on cell viability at the end of the incubation were determined by the MTT method$^{30}$. MTT method: MTT solution at a concentration of 0.5 mg/ml was prepared for the analysis of viability levels in cells after compound administration. After the application, 50 μl of MTT solution was added to each well and incubated in a CO$_2$ incubator for 3 hours. After incubation, the solution in the well was withdrawn and 100 μl of DMSO was added to them. The optical density of the cells in the wells was read in an ELISA plate reader (Thermo MultiskanGo, USA) at a wavelength of 570 nm. The absorbance values obtained from the compound treated wells were proportioned to the control absorbance value and the percent viability values were calculated$^{31}$.
3 Results and Discussion

3.1 Enzymes results

We have obtained results for the SDH and AG enzymes were at the micromolar level (Table 1). We obtained $IC_{50}$ results for the SDH enzyme for 5-Pentadecylresorcinol, Bilobol, 4-Hexylresorcinol, 5-Tricosylresorcinol, and Urushiol compounds were 78.13, 108.22, 15.43, 6.20, and 24.50 µM. The 5-Tricosylresorcinol and 4-Hexylresorcinol were considered good inhibitors for SDH enzyme, and their $IC_{50}$ results were 6.20 and 15.43 µM, respectively. Additionally, we also obtained $IC_{50}$ result for the $\alpha$-glucosidase that control compound had $IC_{50}$ of 22.80 µM. 5-Tricosylresorcinol, Urushiol, Bilobol, and 4-Hexylresorcinol were recorded good inhibitors for enzyme when compared to control, and their $IC_{50}$ results of $\alpha$-glucosidase enzyme were 1.45 ± 0.20, 7.50 ± 0.93, 14.32 ± 2.46, and 21.38 ± 4.74 µM, respectively. 5-Pentadecylresorcinol was considered a weak inhibitor for the $\alpha$-glucosidase enzyme. The SDH enzyme belongs to the protein superfamily, which includes many alcohol dehydrogenases, and is found in many mammalian tissues. Functional mammalian SDH is a 38 kDa subunit homotetrameric enzyme. The crystal structures of rat, sheep and human SDH have been characterized in other studies. Each subunit of the enzyme contains an active site, and the catalytic zinc atom of each subunit coordinates with His68, Glu69, Cys43, and water. Recent studies suggest that SDH inhibitors may be beneficial in delaying the emergence of diabetic complications by correcting redox disorders related to polyol metabolism activated in case of hyperglycemia. This has encouraged studies to synthesize more potent SDH inhibitors. Therefore, many researchers today are working to develop potent and specific SDH inhibitors. The polyol pathway, which is activated in case of hyperglycemia, has a very important place in living metabolism. For this reason, studies on the sorbitol dehydrogenase enzyme show that inhibiting this enzyme is important in terms of preventing and/or delaying the diabetic complications they cause\textsuperscript{32, 33}. This clearly demonstrates the importance of our study.

$\alpha$-Glucosidase inhibitors are a group of drug compounds that are used in the therapy of type 2 diabetes mellitus. Also, these inhibitors may also be used in patients with delay the occurrence and impaired glucose tolerance of T2DM in these patients. Indeed, They are specialy useful for patients who are at risk of lactic acidosis or hypoglycemia\textsuperscript{34}.

3.2 DFT calculations

As a result of theoretical calculations, information about many chemical and biological properties of molecules has been obtained. Anti-oxidant properties of molecules were compared with DFT calculations. The labeling of the atoms of the three molecules studied is visualized in Figs. 2A, 2B, and 2C.

It is possible to comment on the activities of molecules with theoretical calculations. In this way, important information is obtained to synthesize molecules with higher activity. DFT calculations were made and anti-oxidant calculations were made for three molecules. The numerical value of the parameters obtained from these calculations is checked.

It was observed that there was more than one OH bond in the three molecules studied. Separate calculations are made for each OH bond. The bond dissociation enthalpy energy value of the OH bond in the molecules studied is related to the hydrogen atom transfer mechanism (HAT) of the molecule. When the bond dissociation enthalpy (BDE) energy values obtained from the calculations are examined, the molecule with higher BDE energy value has higher radical activity\textsuperscript{35}. For the three molecules studied, there is an ionization potential energy value in the SET - PT mechanism. It has been observed that if the ionization potential energy value of the molecules is lower, the molecule can give electrons more easily. In the second reaction of SET-PT, the proton dissociation enthalpy (PDE) value is calculated. This reaction is thought to progress faster when the PDE energy has a low numerical value\textsuperscript{36}. The last two reactions are SPLET reactions. The proton affinity (PA) energy value is calculated from the first reaction. If this energy value is low, the molecule has a higher proton affin-

Table 1  Inhibition effects of some naturel compounds on some metabolic enzymes studied in this work.

| NO | Compounds              | $\alpha$-Glucosidase $IC_{50}$ (nM) | Sorbitol dehydrogenase $IC_{50}$ (μM) |
|----|-----------------------|-----------------------------------|---------------------------------------|
| 1  | 5-Pentadecylresorcinol| 24.532 ± 3.83                      | 78.13 ± 15.63                         |
| 2  | Bilobol               | 14.32 ± 2.46                       | 108.22 ± 18.02                        |
| 3  | 4-Hexylresorcinol     | 21.38 ± 4.74                       | 15.43 ± 2.54                          |
| 4  | 5-Tricosylresorcinol  | 1.45 ± 0.20                        | 6.20 ± 0.96                           |
| 5  | Urushiol              | 7.50 ± 0.93                        | 24.50 ± 5.71                          |
|    | Acarbose              | 22.80 ± 4.07                       | –                                     |
ity. In the last reaction, electron transfer enthalpy (ETE) energy value is calculated. If this energy value is low, these SPLET reactions proceed faster\(^7\). All calculated parameters are given in Table 2.

For these three molecules studied, the spin densities of the atoms were found to obtain information about the charge densities of the molecules. In Figs. 2D, 2E, and 2F, the spin densities of the atoms in the molecules are given on the atoms. If the spin densities of the atoms are low, the molecule indicates higher delocalization. As a result of the calculations made, higher delocalization means easier radical formation. As a result of easier radical formation, more radicals are formed.

On the other hand, the activities of molecules against

### Table 2  Anti-oxidant properties of studies molecules.

| Molecule         | Atom | BDE  | IP   | PDE  | PA   | ETE |
|------------------|------|------|------|------|------|-----|
| 4-Hexylresorcinol| H31  | 42.50| 155.21| 201.79| 354.34| 2.66 |
|                  | H32  | 44.03| 155.21| 203.32| 360.39| -1.86 |
| 5-Tricosylresorcinol | H13 | 44.16| 158.12| 200.54| 357.34| 1.32 |
|                  | H11  | 44.83| 158.12| 201.21| 359.02| 0.31 |
| Urushiol         | H56  | 47.98| 156.76| 205.72| 366.90| -4.42 |
|                  | H57  | 42.28| 156.76| 200.02| 353.07| 3.72 |

Fig. 2  A) Atomic labeling of 4-Hexylresorcinol molecule, B) Atomic labeling of 5-Tricosylresorcinol molecule, C) Atomic labeling of Urushiol molecule, D) Spin density distributions of 4-Hexylresorcinol molecule, E) Spin density distributions of 5-Tricosylresorcinol molecule, F) Spin density distributions of Urushiol molecule.
enzymes in experimental studies were compared. The experimentally studied enzymes α-glucosidase from saccharomyces cerevisiae (pdb: 1VAD) and sorbitol dehydrogenase from Sinorhizobium (pdb: 6PEJ) were compared to the activities of molecules against crystal structures. The activities of the molecules are calculated with the docking score parameter from Maestro Molecular modeling calculations. Interactions between molecules and proteins change the numerical value of the docking score. It is seen that the more chemical interactions between them increase, the more the activity of the molecules.

Apart from that, the inhibitory activities of the molecules against the spike protein (pdb: 6M0J) of the SARS-CoV-2 virus were compared. Likewise, chemical interactions determine the inhibitory activity of molecules. Many FDA (U.S. Food and Drug Administration) approved drugs are used against the spike protein of the SARS-CoV-2 virus. Ribavirin (pub chem ID: 37542) is at the top of these drugs. However, drugs such as Clarithromycin (pub chem ID: 84029), Lopinavir (pub chem ID: 92727), and Arbidol (pub chem ID: 131411) are used. The numerical values of the inhibitory activities of these drugs against the spike protein
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Fig. 5 Presentation interactions of 5-Tricosylresorcinol with Sorbitol dehydrogenase.

Table 4 (A) Numerical values of the modeling parameters of compound against enzymes.

|                      | 4-Hexylresorcinol | 5-Pentadecylresorcinol | 5-Tricosylresorcinol | Bilobol  | Urushiol | Acarbose |
|----------------------|-------------------|------------------------|----------------------|----------|----------|----------|
|Docking Score         | -4.59             | -4.56                  | -6.74                | -5.84    | -4.77    | -7.34    |
|Glide ligand efficiency| -0.33             | -0.20                  | -0.29                | -0.25    | -0.21    | -0.17    |
|Glide hbond           | -0.44             | -0.30                  | -0.32                | -0.60    | 0.00     | -0.32    |
|Glide evdw            | -24.30            | -24.26                 | -31.46               | -31.47   | -31.55   | -32.97   |
|Glide ecol            | -3.17             | -11.92                 | -5.74                | -8.60    | -7.61    | -28.73   |
|Glide emodel          | -33.82            | -43.10                 | -53.75               | -50.92   | -47.73   | -86.79   |
|Glide energy          | -27.47            | -36.18                 | -39.71               | -40.07   | -39.16   | -61.69   |
|Glide einternal       | 2.72              | 8.32                   | 6.20                 | 5.73     | 7.18     | 17.15    |
|Glide posenum         | 173               | 291                    | 17                  | 384      | 209      | 266      |

Table 4 (B) Numerical values of the modeling parameters of compound against enzymes.

|                      | 4-Hexylresorcinol | 5-Pentadecylresorcinol | 5-Tricosylresorcinol | Bilobol  | Urushiol | Acarbose |
|----------------------|-------------------|------------------------|----------------------|----------|----------|----------|
|Docking Score         | -5.55             | -6.00                  | -4.63                | -5.56    | -5.49    |          |
|Glide ligand efficiency| -0.40             | -0.26                  | -0.15                | -0.24    | -0.24    |          |
|Glide hbond           | -0.57             | -0.32                  | -0.61                | -0.32    | 0.00     |          |
|Glide evdw            | -19.26            | -37.08                 | -38.40               | -38.68   | -40.03   |          |
|Glide ecol            | -11.50            | -6.52                  | -8.50                | -6.40    | -5.43    |          |
|Glide emodel          | -40.97            | -57.55                 | -55.46               | -58.23   | -57.26   |          |
|Glide energy          | -30.76            | -43.60                 | -46.89               | -45.09   | -45.47   |          |
|Glide einternal       | 2.48              | 3.77                   | 7.87                 | 4.28     | 6.48     |          |
|Glide posenum         | 340               | 37                     | 337                  | 190      | 372      |          |

Table 4 (C) Numerical values of the modeling parameters of compound against enzymes.

|                      | 4-Hexylresorcinol | 5-Pentadecylresorcinol | 5-Tricosylresorcinol | Bilobol  | Urushiol | Acarbose |
|----------------------|-------------------|------------------------|----------------------|----------|----------|----------|
|Docking Score         | -3.25             | -2.77                  | -4.06                | -2.34    | -3.03    |          |
|Glide ligand efficiency| -0.23             | -0.12                  | -0.27                | -0.10    | -0.13    |          |
|Glide hbond           | -0.14             | -0.61                  | -0.46                | -0.41    | 0.00     |          |
|Glide evdw            | -15.04            | -17.57                 | -23.61               | -26.29   | -22.04   |          |
|Glide ecol            | -7.53             | -12.78                 | -18.71               | -5.04    | -13.18   |          |
|Glide emodel          | -26.73            | -34.23                 | -39.73               | -33.22   | -39.42   |          |
|Glide energy          | -22.57            | -30.34                 | -32.32               | -31.33   | -35.22   |          |
|Glide einternal       | 2.44              | 4.09                   | 6.39                 | 6.42     | 6.49     |          |
|Glide posenum         | 84                | 307                    | 232                  | 226      | 311      |          |

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of the SARS-CoV-2 virus are given in Table 3.

Compounds with the highest bioactivity in the interaction among complexes and proteins in molecular docking calculations are visualized in Figs. 3, 4, and 5.

Many parameters in this part are recorded except for the docking score parameter. Parameters such as Glide ligand efficiency, Glide hbond, Glide evdw, and Glide ecoul are the numerical values of the chemical interactions that occur in the interaction between proteins and molecules.\(^4\)\(^0\). Apart from these, calculated parameters like Glide energy, Glide emodel, Glide posenum, and Glide einternal are numerical expressions about the interaction pose between molecules and protein.\(^4\)\(^1\)\(^)\(^ The numerical values of all the calculated parameters are visualized in Tables 4A and 4B.

Finally, considering the possibility of molecules being advanced drugs, ADME/T analysis was performed. With this analysis, the absorption of molecules in human metabolism, their distribution in metabolism, their effects on the metabolism, and finally, the stages from metabolism to excretion will be examined. It has been observed that the numerical values of most of the calculated parameters are in the desired range. It was observed that the QPPCaco and QPPMDCK parameters of the molecules were well above the desired range. These parameters show numerical ex-

| mol_MW         | 4-Hexylresorcinol | 5-Pentadecylresorcinol | 5-Tricosylresorcinol | Bilobol | Urushiol | Reference Range |
|----------------|-------------------|------------------------|----------------------|---------|---------|-----------------|
| dipole (D)     | 2.1               | 3.4                    | 544.9                | 3.5     | 2.7     | 1.0 – 12.5      |
| SASA           | 477               | 770                    | 1032                 | 759     | 753     | 300 – 1000      |
| FOSA           | 256               | 558                    | 934                  | 519     | 513     | 0 – 750         |
| FISA           | 96                | 109                    | 98                   | 109     | 87      | 7 – 330         |
| PISA           | 126               | 103                    | 0                    | 132     | 153     | 0 – 450         |
| WPSA           | 0                 | 0                      | 0                    | 0       | 0       | 0 – 175         |
| volume (Å\(^3\)) | 776               | 1318                   | 1664                 | 1299    | 1292    | 500 – 2000      |
| donorHB        | 2                 | 2                      | 2                    | 2       | 2       | 0 – 6           |
| accePHB        | 1.5               | 1.5                    | 1.5                  | 1.5     | 1.5     | 2.0 – 20.0      |
| glob (Sphere =1) | 0.9               | 0.8                    | 0.0                  | 0.0     | 0.0     | 0.75 – 0.95    |
| QPpolrz (Å\(^3\)) | 21.6              | 37.3                   | 59.2                 | 37.5    | 37.4    | 13.0 – 70.0     |
| QPlogPC16      | 7.3               | 12.7                   | 3.4                  | 2.6     | 2.7     | 4.0 – 18.0      |
| QPlogPct       | 10.1              | 15.1                   | 2467.6               | 15.2    | 15.1    | 8.0 – 35.0      |
| QPlogPw        | 5.2               | 3.9                    | 6.8                  | 4.3     | 4.3     | 4.0 – 45.0      |
| QPlogPo/w      | 2.7               | 6.1                    | 8.2                  | 6.0     | 6.1     | – 2.0 – 6.5     |
| QPLogS         | – 3.0             | – 6.9                   | – 14.1               | – 6.9   | – 6.7   | – 6.5 – 0.5     |
| CIQPLogg       | – 2.7             | – 5.3                   | – 5.4                | – 5.3   | – 5.3   | – 6.5 – 0.5     |
| QPlogHERG      | – 4.5             | – 6.0                   | – 17.7               | – 18.3  | – 18.4  | *               |
| QPPCaco (nm/sec) | 1231              | 918                    | 1158                 | 918     | 1478    | **              |
| QPlogBB        | – 0.7             | – 1.7                   | – 1.0                | – 1.0   | – 1.0   | – 3.0 – 1.2     |
| QPPMDCK (nm/sec) | 619               | 451                    | 580                  | 451     | 754     | **              |
| QPlogKp        | – 2.2             | – 1.6                   | – 3.1                | – 1.6   | – 1.1   | Kp in cm/hr     |
| IP (ev)        | 9.0               | 9.1                    | 38.8                 | 9.1     | 8.9     | 7.9 – 10.5      |
| EA (eV)        | – 0.3             | – 0.3                   | 38.7                 | – 0.3   | – 0.2   | – 0.9 – 1.7     |
| #metab         | 3                 | 3                      | 0                    | 5       | 5       | 1 – 8           |
| QPlogKhsa      | 0.0               | 1.1                    | 2.7                  | 1.1     | 1.1     | – 1.5 – 1.5     |
| Human Oral Absorption | 3 | 1 | 1 | 1 | 1 | – |
| Perc. Hum. Oral Absorp. | 100 | 100 | 100 | 100 | 100 | *** |
| PSA            | 43                | 45                     | 38                   | 45      | 42      | 7 – 200         |
| RuleOfFive     | 0                 | 1                      | 1                    | 1       | 1       | Maximum is 4    |
| RuleOfThree    | 0                 | 1                      | 1                    | 1       | 1       | Maximum is 3    |
| Jm             | 1.4               | 0.0                    | 0.0                  | 0.0     | 0.0     | –               |

*(corren below -5) ** < 25 is poor and > 500 is great, *** < 25% is poor and > 80% is high.

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pressions of the gut-blood and brain-blood barriers, respectively\(^2\). Other than that, the numerical values of the Percent Human-Oral Absorption parameter are 100, which is the highest value. Finally, RuleOfFive and RuleOfThree parameters are parameters that are formed by the combination of many parameters\(^3\).

### 3.3 Cancer results

The cytotoxic effect of test molecules on leukemia cancer cell lines is shown in Table 5. 100 µM concentration of all molecules significantly decreased viability in leukemia cells compared to standard compound. Indeed, it was recorded that the compound coded \(2\) and \(5\) had an effect on HL-60 and Clone 15 HL-60 cells starting from the low dose. All determined doses of Compounds \(1\) and \(3\) significantly decreased cell viability in HL-60/MX1 and HL-60/MX2 cells compared to control group. It was determined that \(1\), \(2\), \(3\) and \(5\) coded compounds applied to all cells exhibited cell viability-reducing impacts. Additionally, it was recorded that the molecule coded \(4\) applied to all cells did not have a significant effect on cell viability. These results generally show that all molecules exhibit cytotoxic impacts on diverse cell lines for leukemia. We can say that this is probably due to the molecular differences and physiological of cell lines.

### 4 Conclusions

As a result of theoretical calculations, the activities of the molecules are compared. Afterwards, the properties of molecules to become drugs in the future were examined. It will be an important guide for future in vitro and in vivo experiments. Among all compounds tested derivatives of Bilobol, Urushiol, and 5-Pentadecylresorcinol derivatives exerted the highest antileukemic activity. The compounds studied in this work as \(\alpha\)-glucosidase inhibitors may use for oral antihyperglycemic drugs, they inhibit upper gastrointestinal enzymes that break down complex carbohydrates into glucose. The numerical value of these parameters is desired to be zero, since the numerical values of these parameters are in the desired ranges, it is appropriate to use these molecules as drugs candidate. It was determined that \(1\), \(2\), \(3\), and \(5\) coded compounds applied to all cells exhibited cell viability-reducing effects.

### Authors Contributions

All of the authors contributed to the analysis of the results. QH and PM conceived the original idea. PM was in charge of overall direction and planning. QH participated in the study design and coordination, drafted the manuscript. QH and PM were responsible for bioactivity and anticancer effects. Molecular docking studies were carried out by RT. PM wrote the manuscript with support from QH and RT. All authors discussed the results and contributed to the final manuscript.

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### Conflict of Interest

There isn’t any conflict of Interest.

### References

1. Yang, C.S.; Landau, J.M.; Huang, M.T.; Newmark, H.L. Inhibition of carcinogenesis by dietary polyphenolic compounds. *Annu. Rev. Nutr.* **21**, 381-406 (2001).
2. Tomás-Barberán, F.; Espín, J.C. Phenolic compounds and related enzymes as determinants of quality of fruits and vegetables. *J. Sci. Food Agric.* **81**, 853-876 (2001).
3. Rosenstock, J.; Lorber, D.L.; Gnudi, L.; Howard, C.P.; Bielheimer, D.W. *et al.* Prandial inhaled insulin plus basal insulin glargine versus twice daily basal insulin insu-
lin for type 2 diabetes: A multicentre randomised trial. *Lancet* 375, 2244-2253 (2010).

4) Mayfield, J.A.; White, R.D. Insulin therapy for type 2 diabetes: Rescue, augmentation, and replacement of beta-cell function. *Am. Fam. Physician* 70, 489-500 (2004).

5) Pauly, T.A.; Ekstrom, J.L.; Beebe, D.A.; Chunyuk, B.; Rath, V.L. X-ray crystallographic and kinetic studies of human sorbitol dehydrogenase. *Structure* 11, 1071-1085 (2003).

6) Burnell, J.N.; Holmes, R.S. Purification and properties of sorbitol dehydrogenase. *Int. J. Biochem. 15*, 507-511 (1983).

7) Gupta, N.; Kavuru, S.; Patel, D.; Janson, D.; Driscoll, N. et al. Rituximab-based chemotherapy for steroid-refractory autoimmune hemolytic anemia of chronic lymphocytic leukemia. *Leukemia* 16, 2092-2095 (2002).

8) Zaja, F.; Vianelli, N.; Sperotto, A.; Patriarca, F.; Tani, M. et al. Anti-CD20 therapy for chronic lymphocytic leukemia-associated autoimmune diseases. *Leuk. Lymphoma 44*, 1951-1955 (2003).

9) Bauer, R.; Janowska, K.; Taylor, K.; Jordan, B.; Gann, S. et al. Structures of three polycystic kidney disease-like domains from *Clostridium histolyticum* collagenases CollI and CollH. *Acta Crystallogr. D 71*, 565-577 (2015).

10) Vijayalakshmi, J.; Meyer Jr, E.F.; Kam, C.M.; Powers, J.C. Structural study of porcine pancreatic elastase complexed with 7-amino-3-(2-bromoethoxy)-4-chloroisocoumarin as a nonreactivable doubly covalent enzyme-inhibitor complex. *Biochemistry 30*, 2175-2183 (1991).

11) Yurkovetskiy, L.; Wang, X.; Pascal, K.E.; Tomkintinch, C.; Nyalile, T.P. et al. Structural and functional analysis of the D614G SARS-CoV-2 spike protein variant. *Cell 183*, 739-751 (2020).

12) Lan, J.; Ge, J.; Yu, J.; Shan, S.; Zhou, H. et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature 581*, 215-220 (2020).

13) Yilmazer-Musa, M.; Griffith, A.M.; Michels, A.J.; Schneider, E.; Frei, B. Grape seed and tea extracts and catechin 3-gallates are potent inhibitors of α-amylase and α-glucosidase activity. *J. Agric. Food Chem. 12*, 8924-8929 (2012).

14) Fujita, H.; Yamagami, T.; Aishima, K. Long-term ingestion of a fermented soybean-derived Touchi-extract with alpha-glucosidase inhibitory activity is safe and effective in humans with borderline and mild type-2 diabetes. *J. Nutr. 131*, 2105-2108 (2001).

15) Van de Laar F.A.; Lucassen, P.L.B.; Akkermans, R.P.; Van de Lisdonk, E.H.; De Grauw, W.J.C. α-Glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose. *Cochrane Database Syst. Rev.* CD005061 (2006).

16) Dooley, J.F.; Turnquist, L.J.; Racich, L. Kinetic determination of serum sorbitol dehydrogenase activity with a centrifugal analyzer. *Clin. Chem. 25*, 2026-2029 (1979).

17) Van den Brock, L.A.; Kat-Van Den Nieuwenhof, M.W.; Butters, T.D.; Van Boeckel, C.A.A. Synthesis of alpha-glucosidase I inhibitors showing antiviral (HIV-1) and immunosuppressive activity. *J. Pharm. Pharmacol. 48*, 172-178 (1996).

18) Chigurupati, S.; Al-murikhi, A.; Almahmoud, S.A.; Almoshari, Y.; Ahmed, A.S. et al. Molecular docking of phenolic compounds and screening of antioxidant and antidiabetic potential of *Moringa oleifera* ethanolic leaves extract from Qassim region, Saudi Arabia. *Saudi J. Biol. Sci. 29*, 854-859 (2022).

19) Koç, E.; Üngördü, A.; Canadan, F. Antioxidant properties of methanolic extract of *Veronica multifida* and DFT and HF analyses of its the major flavonoid component. *J. Mol. Struct. 1197*, 436-442 (2019).

20) Urbaniak, A.; Szlag, M.; Molski, M. Theoretical investigation of stereochemistry and solvent influence on antioxidant activity of ferolic acid. *Comput. Theor. Chem. 1012*, 33-40 (2013).

21) Poladian, Q.; Şahin, O.; Karakurt, T.; İlhan-Ceylan, B.; Kurt, Y. A new zinc (II) complex with N202-tetradeinate Schiff-base derived from pyrido[1,2-a]pyrimidine: Synthesis, characterization, crystal structure, DFT, molecular docking and antioxidant activity studies. *Polyhedron 201*, 115164 (2021).

22) Marković, Z.; Jeremić, S.; Marković, J.D.; Pirković, M.S.; Amić, D. Influence of structural characteristics of substituents on the antioxidant activity of some anthraquinone derivatives. *Comput. Theor. Chem. 1077*, 25-31 (2016).

23) De Souza, G.L.; Peterson, K.A. Benchmarking antioxidant-related properties for gallic acid through the use of DFT, MP2, CCSD, and CCSD(T) approaches. *J. Phys. Chem. A 125*, 198-208 (2021).

24) Wright, J.S.; Johnson, E.R.; DiLabio, G.A. Predicting the activity of phenolic antioxidants: Theoretical method, analysis of substituent effects, and application to major families of antioxidants. *J. Am. Chem. Soc. 123*, 1173-1183 (2001).

25) Bartmess, J.E. Thermodynamics of the electron and the proton. *J. Phys. Chem. 98*, 6420-6424 (1994).

26) Schrodinger. L Small-Molecule Drug Discovery Suite 2019-4 (2019).

27) Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb M.A. et al. Gaussian 09, revision D.01. Gaussian Inc., Wallingford CT (2009).

28) Schrodinger Release 2019-4: LigPrep, Schrodinger, LLC, New York, NY (2019).
Anti-leukemia Cancer Potential, Spin Density Distributions, and in silico Studies

29) Rashood, S.T.A.; Aboldahab, I.A.; Nagi, M.N.; Abouzeid, L.A.; Aziz, A.A.M.A. et al. Synthesis, dihydrofolate reductase inhibition, antitumor testing, and molecular modeling study of some new 4(3H)-quinazolinone analogs. *Bioorg. Med. Chem.* 14, 8608-8621 (2006).

30) Asou, H.; Tashiro, S.; Hamamoto, K.; Otsuji, A.; Kita, K.; Kamada N. Establishment of a human acute myeloid leukemia cell line (Kasumi-1) with 8;21 chromosome translocation. *Blood* 77, 2031-2036 (1991).

31) Cho, S.H.; Chung, K.S.; Choi, J.H.; Kim, D.H.; Lee, K.T. Compound K, a metabolite of ginseng saponin, induces apoptosis via caspase-8-dependent pathway in HL-60 human leukemia cells. *BMC Cancer* 9, 449 (2009).

32) Ke, X.; Yu, P.H.; Hu, Z.C.; Chen, L.; Sun, X.Q.; Zheng, Y.G. Synergistic improvement of PQP-dependent D-sorbitol dehydrogenase activity from *Gluconobacter oxydans* for the biosynthesis of miglitol precursor 6-(N-hydroxyethyl)-amino-6-deoxy-α-L-sorbofuranose. *J. Biotecnol.* 300, 55-62 (2019).

33) Xu, S.; Wang, X.; Du, G.; Zhou, J.; Chen, J. Enhanced production of L-sorbose from D-sorbitol by improving the mRNA abundance of sorbitol dehydrogenase in *Gluconobacter oxydans* WSH-003. *Microb. Cell Fact.* 13, 146 (2014).

34) Rosenthal, J.H.; Mauersberger, H. Effects on blood pressure of the alpha-glucosidase inhibitor acarbose compared with the insulin enhancer glibenclamide in patients with hypertension and type 2 diabetes mellitus. *Clin. Drug Invest.* 22, 695-701 (2002).

35) Schrödinger Release 2019-4: Protein Preparation Wizard; Epik, Schrödinger, LLC, New York, NY, 2016; Impact, Schrödinger, LLC, New York, NY, 2016; Prime, Schrödinger, LLC, New York, NY (2019).

36) Schrödinger Release 2020-1: QikProp, Schrödinger, LLC, New York, NY (2020).

37) Matthew, R.; Freidel and Roger S. Armen. Modeling the structure–Activity relationship of arbidol derivatives and other SARS CoV-2 fusion inhibitors targeting the S2 segment of the spike protein. *J. Chem. Inf. Model.* 61, 5906-5922 (2021).

38) Bhardwaj, A.; Sharma, S.; Singh, S.K. Molecular docking studies to identify promising natural inhibitors targeting SARS-CoV-2 nsp10-nsp16 protein complex. *Turk. J. Pharm. Sci.* 19, 93-100 (2022).

39) Ma, Z.; Liu, J.; Pan, Q. Overwhelming COVID-19 clinical trials: Call for prospective meta-analyses. *Trends Pharmacol. Sci.* 41, 501-503 (2020).

40) Li, P.; Liu, J.; Ma, Z.; Bramer, W.M.; Peppelenbosch, M.P.; Pan, Q. Estimating global epidemiology of low-pathogenic human coronaviruses in relation to the COVID-19 context. *J. Infect. Dis.* 222, 695-696 (2020).

41) Wang, Y.; Li, P.; Rajpoot, S.; Saqib, U.; Yu, P. et al. Comparative assessment of favipiravir and remdesivir against human coronavirus NL63 in molecular docking and cell culture models. *Sci. Rep.* 11, 23465 (2021).

42) Tok, F.; Koçyiğit-Kaymakçioğlu, B.; Sağlık, B.N.; Levent, S.; Özkan, Y. et al. Synthesis and biological evaluation of new pyrazolone Schiff bases as monoamine oxidase and cholinesterase inhibitors. *Bioorg. Chem.* 84, 41-50 (2019).

43) Çevik, U.A.; Osmaniye, D.; Levent, S.; Sağlık, B.N.; Çavuşoğlu, B.K. et al. Synthesis and characterization of a new series of thiadiazole derivatives as potential anticancer agents. *Heterocycl. Comm.* 26, 6-13 (2020).

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