



## Short Communication

# Targeting phosphoglycerate dehydrogenase enzyme using ginger compounds to suppress thyroid cancer progression

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## Abstract

Recent studies have recognized the potential of inhibiting phosphoglycerate dehydrogenase (PHGDH) enzyme as a therapeutic strategy for treating papillary thyroid cancer. However, research on the efficacy of herbal compounds in inhibiting the PHGDH enzyme that have been reported to possess anticancer activities, including those found in ginger (*Zingiber officinale*), remains limited. The aim of this study was to examine the potential of ginger compounds in inhibiting PHGDH enzyme and to identify its potential use in the treatment of papillary thyroid cancer. The study employed computational methods to identify ginger-derived compounds that inhibit the PHGDH and impede papillary thyroid cancer progression. Crystallized protein structures were obtained from the Protein Data Bank, and Discovery Studio software was utilized to remove water molecules, double chains, and ligands. The receptor was modified by adding polar hydrogen, and AutodockTools4 software was employed to establish an accurate binding site based on the position of the previous ligand. Molecular docking experiments were conducted with 125 ginger-derived phytochemicals retrieved from the PubChem database. The results revealed nine active compounds found in ginger (galanolactone, myricetin, quercetin, cyanin, kaempferol, chlorogenic acid, delphinidin, alpha-cadinol, and curcumin) with strong binding affinities to PHGDH (minimum score threshold <-7 kcal/mol), indicating their potential for drug development. Galanolactone, myricetin, and quercetin were the top three compounds with the strongest binding affinity (-8.2, -7.9, and -7.9 kcal/mol, respectively), involving multiple bonds in the ligand-protein complex interaction. Notably, myricetin and quercetin formed three hydrogen bonds each, contributing to strong and stable bonds with the pocket region of PHGDH. In conclusion, ginger-derived compounds show promise in inhibiting PHGDH for the treatment of papillary thyroid cancer. However, further research is needed to validate the efficacy of these compounds and their interactions with the PHGDH in the context of thyroid cancer therapy.

**Keywords:** Ginger, *in silico*, molecular docking, PHGDH enzyme, thyroid cancer

## Introduction

The global incidence of thyroid cancer has increased in the last three decades, with papillary thyroid carcinoma (PTC) being the most common type, accounting for 80–85% of the total cases



[1]. In 2020, there were approximately 586,202 new cases and 43,646 deaths worldwide associated with PTC [2]. Currently, thyroidectomy remains a definitive treatment of PTC, but the procedure carries potential complications [3]. The complexity of the surgical procedure and the surgeon's experience can influence the risk of complications, impacting the patient's quality of life and potentially leading to the need for lifelong medication or other complications such as hypoparathyroidism, dysphagia, and dysphonia. Therefore, developing alternative treatments is an urgent priority to expand clinical modalities and improve patient outcomes [4].

Phosphoglycerate dehydrogenase (PHGDH) is an enzyme that plays a role in the proliferation and tumorigenesis of thyroid cancer cells. Its expression is associated with stemness markers and metastases in PTC [5]. Based on a recent study, targeting this enzyme is suggested as a promising approach for treating PTC [5]. Unfortunately, literature investigating the use of herbal compounds in attenuating thyroid cancer via PHGDH inhibition is limited.

Drug development and discovery is a challenging, time-consuming, and costly process [6]. However, the use of computer-assisted drug design (CADD) tools in early investigations could accelerate drug discovery while reducing expenses and failures in the later stages [6,7]. CADD provides valuable insights into the binding affinity and molecular interactions between target proteins and ligands. Ginger compounds (*Zingiber officinale*), a widely recognized herbal medicine with anticancer activities [8,9], were chosen in this study. The aim of the study was to identify herbal compounds from ginger using computer-based methods and evaluate their potential as PHGDH inhibitors, offering potential therapeutic options for inhibiting the growth and progression of PTC.

## Methods

### Protein preparation

The study utilized a crystallized protein or receptor structure, specifically the D-3-phosphoglycerate dehydrogenase (6PLF) structure obtained from the Protein Data Bank (PDB). The structure was acquired in PDB format, bound by an inhibitor. The receptor was prepared for analysis using Discovery Studio software. This involved removing water molecules, double chains, and ligands from the receptor structure. Polar hydrogen was added, and the format was converted to pdbqt. An accurate binding site was established based on the previous ligand's position using AutodockTools4 software.

### Ligand preparation

The study utilized 125 phytochemicals derived from *Z. officinale* as the ligand. 3D conformations of the compounds were obtained from the PubChem database after referring to the knapsack database. The ligands were downloaded in .sdf format and converted to .pdbqt format using Open Babel 3.0.1, where energy minimization and the addition of polar hydrogen were performed afterward.

### Virtual screening and molecular docking

Molecular docking was performed using AutoDock Vina 1.2.3 with a docking grid box set at the position of the inhibitor active site. The size of the grid box was  $20 \text{ \AA} \times 20 \text{ \AA} \times 20 \text{ \AA}$ , placed in the following coordinates: 14.59 (x), 32.60 (y), and -3.91 (z). The ligands (n=126) were docked individually, and the results with the lowest affinity were observed and visualized using BIOVIA Discovery Studio Visualizer v19.1.0.18287.

## Results

### Binding affinity

Results from the molecular docking of ginger compounds exhibiting strong interactions with the PHGDH enzyme are presented in **Table 1**. Nine active compounds from ginger, including galanolactone, myricetin, quercetin, cyanin, kaempferol, chlorogenic acid, delphinidin, alpha-cadinol, and curcumin, demonstrated strong binding affinity to PHGDH enzyme (threshold  $< -7$  kcal/mol).

Table 1. Binding affinity of potential ligands docked to phosphoglycerate dehydrogenase (PHGDH)

Rank	Ligand	Binding affinity (kcal/mol)
1	Galanolactone	-8.2
2	Myricetin	-7.9
3	Quercetin	-7.9
4	Cyanin	-7.8
5	Kaempferol	-7.7
6	Chlorogenic-acid	-7.5
7	Delphinidin	-7.5
8	Alpha-cadinol	-7.1
9	Curcumin	-7

### Visualized interactions

The three compounds with the lowest binding affinity values: galanolactone, myricetin, and quercetin, were selected for further analysis to investigate the formed ligand-complex interactions. Visual representations of the three-dimensional and two-dimensional interactions are presented in **Figure 1** and **Figure 2**, respectively. The results revealed their respective lowest binding affinities of -8.2, -7.9, and -7.9 kcal/mol (for galanolactone, myricetin, and quercetin, respectively), with multiple bonds formed with the PHGDH enzyme (**Table 2**). Specifically, myricetin and quercetin formed three hydrogen bonds (**Table 2**). As galanolactone exhibited the highest binding affinity with PHGDH binding pocket, the interaction focusing on different surface conditions is visualized and presented in **Figure 3**.

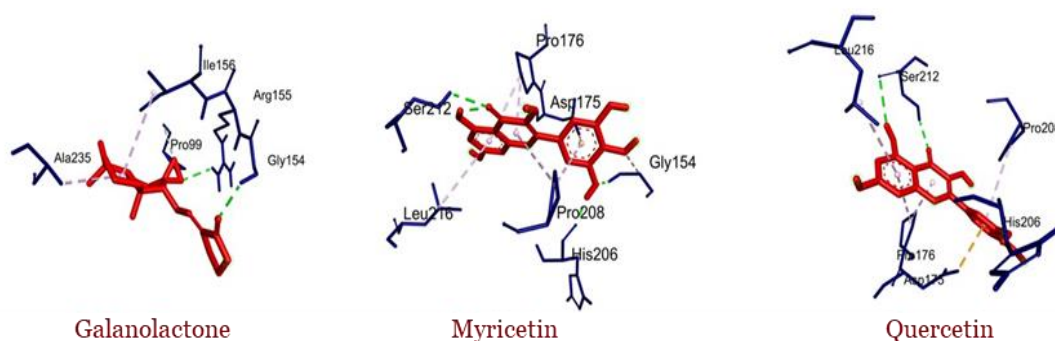


Figure 1. Three-dimensional interaction selected ligand with phosphoglycerate dehydrogenase (PHGDH) protein.

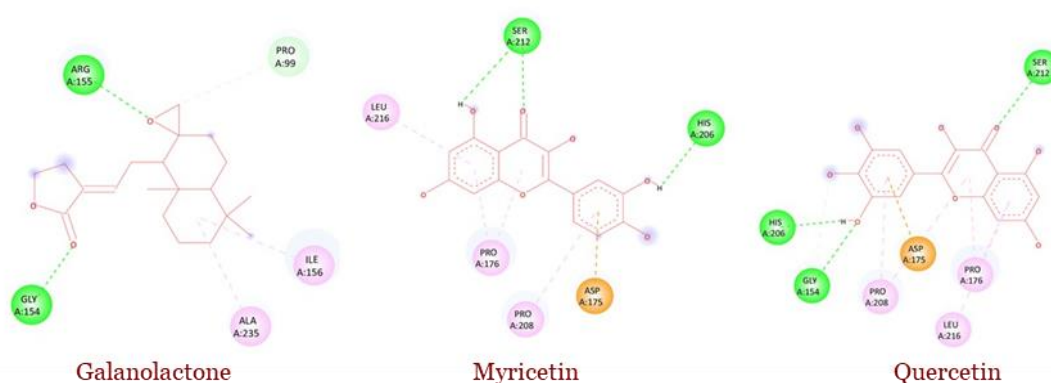
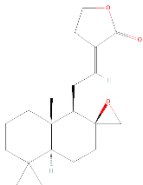
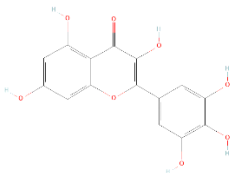
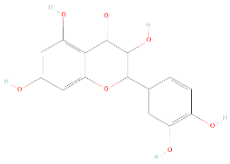


Figure 2. Two-dimensional interaction selected ligand with phosphoglycerate dehydrogenase (PHGDH) protein.

Table 2. Total interaction and residues of the top three ligands that are involved in the inhibition of phosphoglycerate dehydrogenase (PHGDH)

Rank	Ligand	2D structure	Total bond	Total hydrogen bond	Residues
1	Galanolactone		5	2	Pro:99, Arg:155, Gly:154, Ile:156, Ala:235
2	Myricetin		11	3	Gly:154, Asp:175, Pro:176, His:206, Pro:208, Ser:212, Leu:216
3	Quercetin		8	3	Asp:175, Pro:176, His:206, Pro:208, Ser:212, Leu:216

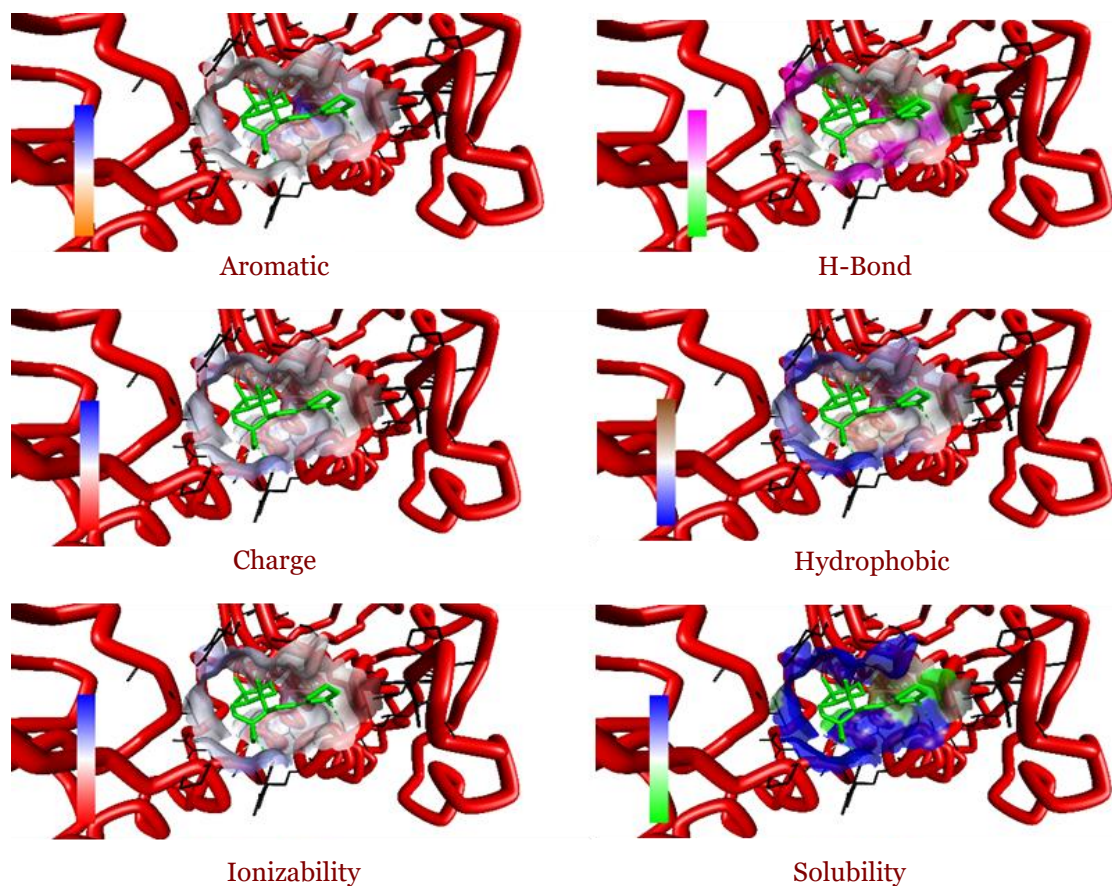


Figure 3. Phosphoglycerate dehydrogenase (PHGDH) receptor surface interacting with galanolactone.

## Discussion

Computational analysis in the present study revealed nine ginger compounds with potential inhibitory activities against PHGDH, with galanolactone, myricetin, and quercetin exhibiting the highest levels of interactions. In the protein complex, Asp175 is suggested to act as the active binding site with myricetin and quercetin forming pi-anion bonds at Asp175. These pi-anion bonds were arisen from the interaction between the pi moieties of ligand molecules and the negatively charged oxygen atom of Asp175. In accordance with a previous study, the complex formation also involved a hydrogen bond established through Asp175 [41]. Other interactions were observed between the active site bonds and neighboring amino acids, including Gly154, Ile156, Pro176, His206, Pro208, Ser212, and Leu216. Additionally, we observed that Arg155 was involved in establishing a hydrogen bond with the hydrogen moiety of galanolactone.

The quantity of hydrogen bonds indicates the strength of the intramolecular interaction, contributing to complex stability. Our study revealed that myricetin and quercetin established three hydrogen bonds with PHGDH, while galanolactone formed only two. This implies a more stable complex formation between myricetin and quercetin with PHGDH compared to galanolactone. Hydrogen bonds occur between a hydrogen atom with a partial positive charge and an electronegative atom with a partial negative charge. These interactions, though weaker than covalent or ionic bonds, can cumulatively enhance the overall bond strength. The formation of additional hydrogen bonds between a compound and an enzyme often results in a more stable complex, hence higher inhibitory activities. In the present study, myricetin and quercetin formed three hydrogen bonds formed with the protein, involving hydroxyl moieties of PHGDH active sites. Galanolactone also established two hydrogen bonds with PHGDH, involving similar hydroxyl moieties. However, only two hydrogen bonds formed between the galanolactone and PHGDH, suggesting the relatively instable complex.

Cancer cells frequently reprogram their metabolic behaviors to adapt to their rapid proliferation and altered tumor microenvironments [10]. This metabolic reprogramming is a hallmark of cancer with increased glucose uptake and redirection of glucose-derived metabolites into biosynthetic pathways, such as nucleotides, lipids, or protein synthesis [11]. Glucose and glutamine are two key energy sources for tumor cells, vital for their survival [12]. Compared to normal tissue, *in vitro* cancer tissue can use large amounts of glucose to produce lactate even in the presence of oxygen, a phenomenon known as aerobic glycolysis or the Warburg effect [13]. Current studies found that glucose metabolism plays an important role in the development and treatment of PTC [14,15]. PTC tissues present specific changes in glucose metabolism compared to benign or normal thyroid tissue [16,17]. Serine biosynthetic fluxes derived from glycolytic intermediates are driven by amplification of the gene coding for PHGDH [18,19]. The enzyme catalyzes the first step in the serine biosynthesis pathway, and it is a key enzyme in serine biosynthesis [20]. The serine biosynthetic pathway allows tumor cells to survive, proliferate and maintain redox homeostasis [21-26]. *In vivo*, synthesis by tumor cells of serine from 3-PG, an intermediate metabolite in the glycolytic pathway, involves several steps. The first step is to synthesize 3-phosphate hydroxy-pyruvate (pPYR) under the action of PHGDH and NAD<sup>+</sup>. Then, pPYR is transaminated by phosphoserine aminotransferase (PSAT) to form phosphoserine (pSER) and  $\alpha$ -ketoglutarate ( $\alpha$ -KG), providing nitrogen from glutamate. Finally, pSER is dephosphorylated to form serine under the action of phosphoserine phosphatase (PSPH) [27].

PHGDH expression is induced in thyroid cancer and is associated with stemness and aggressiveness of PTC [14]. In PTC, there is an observed upregulation of PHGDH [14,28]. The importance of PHGDH in cancer was first noted in 2011 by Sabatini *et al*, who revealed that PHGDH increased cancer proliferation by contributing to the increase in glutamine influx into the TCA cycle in estrogen receptor negative breast cancer [25]. Elevated PHGDH levels have been associated with enhanced proliferation and poor prognosis across various types of cancers [29-33]. PHGDH influences the prognosis of thyroid cancer by regulating stem cell marker expression. A study by Jeon *et al*. indicated that PHGDH may play a critical role in regulating the Sox2-Oct4 master complex of stemness in thyroid cancer thus serving as a potential prognostic and therapeutic target [34]. High expression of PHGDH is also strongly related to tumor resistance to chemotherapies; however, treatment with PHGDH inhibitors in conjunction with chemotherapy drugs may synergistically enhance overall patient survival [29].

PHGDH dominantly controls the serine and glycine synthesis pathway. PHGDH knockdown not only significantly reduced the colony numbers but also dramatically damaged the cell-cell tight junctions in a single colony. Knockdown of PHGDH significantly inhibited cell proliferation and tumorigenesis by disrupting the cell-cell tight junctions and the related proteins expression. PHGDH possesses the regulatory function in translation initiation through interacting with eIF4A1 and eIF4E to directly regulate the relevant proteins expression [35]. PHGDH may be of significance for the treatment of different types of cancer [36]. PHGDH inhibitors selectively slow down the proliferation of tumor cells with a high PHGDH expression [37]. Therefore, it may be utilized as a target for cancer treatment and the development of PHGDH inhibitors should be a priority [38].

Several PHGDH inhibitors have been reported. One type comprises allosteric inhibitors; another category comprises orthostatic inhibitors [36,39]. Despite substantial efforts, the search for therapeutic PHGDH inhibitors has yet to yield compounds with adequate potency or selectivity [40].

Findings from the present study provide valuable insights for the development of PHGDH inhibitors. Nevertheless, this study has limitations, particularly on pharmacokinetic and pharmacodynamic aspects. Firstly, molecular docking was only performed on a single software, whilst algorithms used across different software could exert different findings. Secondly, the complex stability was assessed qualitatively, where quantitative estimates based on molecular dynamics simulation were not performed. Thirdly, due to the nature of *in silico* studies, the binding affinity completely neglects the complex physiological response. Moreover, interactions between ginger compounds were not able to be observed through molecular docking alone. Therefore, *in vitro* and *in vivo* studies are warranted in the future to investigate the potential of ginger compounds as PHGDH inhibitors.

## Conclusion

Our study identified nine ginger-derived compounds with potential application in treating PTC via enzymatic inhibition of PHGDH. The nine compounds were galanolactone, myricetin, quercetin, cyanin, kaempferol, chlorogenic acid, delphinidin, alpha-cadinol, and curcumin. Among the identified compounds, galanolactone, myricetin, and quercetin exhibited the highest binding affinity with the protein due to the formation of hydrogen bonds. The computational analysis also suggests the significant role of partially positively charged ligand moieties that could form interaction with the partially negatively charged PHGDH moieties. However, further research is required to validate the efficacy of these compounds in treating thyroid cancer via PHGDH inhibition. It is also recommended to investigate the synergistic effect of ginger compounds on the available chemotherapies.

## Ethics approval

Not required.

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## Competing interests

The authors declare that there is no conflict of interest.

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## Underlying data

All underlying data have been presented.

## How to cite

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