# Exploring the Inhibitory Potential of CoQ10 on Prenyl transferases through *in silico* Approach

**Battula Surender Reddy[1], Nalvothula Raju[2] and Gurram Shyam Prasad[1]***
1. Department of Microbiology, Chaitanya (Deemed to be University), Himayatnagar, Moinabad, Ranga Reddy (Telangana), INDIA
2. Department of Biochemistry, Chaitanya (Deemed to be University), Himayatnagar, Moinabad, Ranga Reddy (Telangana), INDIA
*shyamprasad1919@yahoo.com

***Abstract***
*Prenyltransferases including Farnesyltransferase (FTase) and Geranylgeranyl transferase-I (GGTase-I), play a crucial role in post-translational modifications by facilitating the attachment of isoprenoid groups to specific proteins, thereby influencing their localization and functionality. Dysregulation of these enzymes has been linked to various diseases such as cancer and neurodegenerative conditions. In this study, in order to identify novel anticancer targets, we employed in silico techniques to investigate the inhibitory effects of CoQ10, a naturally occurring compound, on FTase and GGTase-I. We performed molecular docking analyses to assess the binding affinity, stability and interaction profiles of CoQ10 with the active sites of these enzymes. Standard drugs recognized for their inhibitory effects were used as reference compounds for our comparative evaluation.*

*The findings revealed that CoQ10 shows a significant binding affinity and advantageous interaction characteristics with both FTase and GGTase-I, matching or surpassing those of conventional inhibitors. This underscores the potential of CoQ10 as a viable candidate for further exploration as a dual prenyl transferase inhibitor. Additional in vitro and in vivo research are necessary to confirm therapeutic efficacy.*

**Keywords:** CoQ10, Farnesyltransferase, Geranylgeranyl transferase-I, Prenyltransferases.

## Introduction

Cancer is a multifaceted disease marked by unregulated cell growth, evasion of programmed cell death and the ability to spread to other parts of the body. The World Health Organization (WHO) reports that cancer continues to be a major global health challenge, responsible for nearly 10 million fatalities in 2020[11]. This disease can manifest in various regions of the body with lung, breast, prostate and colorectal cancers being the most prevalent types[10]. A major challenge in cancer treatment is drug resistance which frequently develops due to changes in the drug targets found in cancer cells. Such alterations can reduce the effectiveness of therapies and facilitate the advancement of the disease[4]. This situation underscores the urgent need to discover new therapeutic targets to enhance patient outcomes. Prenyltransferases (PTs) represent a varied group of enzymes responsible for facilitating the transfer of prenyl groups such as farnesyl, geranyl, or geranylgeranyl from donor molecules, primarily isoprenoid pyrophosphates to acceptor molecules which include proteins, lipids and aromatic compounds. This post-translational modification influences hydrophobicity, membrane association and interactions between proteins, thereby playing a vital role in essential cellular functions such as signal transduction, protein localization and cell proliferation[8]. The inhibition of farnesyl transferase (FTase) and geranylgeranyl transferase (GGTase) has been widely investigated in relation to cancer therapy[5]. Nevertheless, the emergence of resistance to FTIs, attributed to alternative prenylation by GGTase, poses a significant obstacle. Therefore, future research should focus on identifying alternative inhibitors.

Coenzyme Q10 (CoQ10) is a naturally occurring antioxidant that plays a crucial role in the production of cellular energy. It is primarily located in the heart, liver, kidneys and pancreas which are organs with high energy requirements. As people age, the body's natural synthesis of CoQ10 diminishes, leading to increased interest in supplementation to address potential deficiencies and their related health consequences[6]. The protective function of antioxidants in cancer prevention and progression is well documented. They achieve this protective effect by diminishing oxidative activation, preventing DNA damage, regulating growth-related signaling pathways and promoting autophagy and apoptosis[3,9]. Coenzyme Q10 (CoQ10), a lipophilic compound synthesized in nearly all cells, is one of the key antioxidants involved in these protective mechanisms[2].

In this study, the anticancer properties of the natural antioxidant CoQ10, administered as a supplement, are examined through *in silico* analyses, specifically focusing on its effects on Prenyltransferases viz. Farnesyl transferase (FTase) and Geranylgeranyl transferase-I (GGTase-I).

## Material and Methods

**Preparation of ligand:** In this study, the natural antioxidant CoQ10, along with the standard medications Lonafarnib and GGTI-298, which acted as ligands, were depicted using Chem Draw software and saved in .mol format. Subsequently, these ligands were transformed into a 3D PDB format through Accelrys Discovery Studio 2.3.

Following this, water and hydrogen atoms were incorporated and energy minimization was performed, culminating in the final structure being saved as a pdbqt file using Autodock software.

**Preparation of Proteins:** Molecular docking analyses were performed to investigate the interactions of CoQ10 with the reference compounds Lonafarnib and GGTI-298, targeting the receptors Farnesyltransferase (FTase) and Geranylgeranyltransferase-I (GGTase-I). This was accomplished using AutoDock software, a molecular graphics tool designed to clarify protein-ligand interactions (available at http://viba.scripps.edu/). The crystal structures of FTase and GGTase-I were obtained from the Protein Data Bank (http://www.rcsb.org/pdb). Before initiating the docking process, the existing ligands, heteroatoms and water molecules were removed and polar hydrogen atoms were added. Furthermore, Kollman charges and solvation parameters were automatically assigned by the AutoDock software.

**Validation of the Software:** Before initiating the docking process, the AutoDock software was validated through the retrieval of the X-ray crystal structure of the receptor FTase (PDB ID: 1QBQ) and GGTase-I (PDB ID: 1N6H) from the Protein Data Bank. The co-crystallized ligand was then redocked to reproduce the original interactions of the reference protein-ligand complexes, with the root-mean square distance between the experimentally determined pose and the docked pose serving as the basis for comparison.

***In silico* studies:** The interaction of the ligands CoQ10 and the standard drugs Lonafarnib and GGTI-298 with the receptors FTase and GGTase-I was investigated through virtual screening utilizing molecular docking techniques. Following the preparation of both ligands and receptors, they were converted into pdbqt format via the automated docking software Auto Dock, which facilitated the docking process. A grid box was established for FTase to encompass the binding pocket and key residues of the protein, with dimensions set at X = 40, Y = 40 and Z = 40. The docking coordinates used were specified as X = 195.56, Y = 129.29 and Z = 26.64. A similar grid box was constructed for GGTase-I, maintaining the same dimensions. The coordinates for docking the ligands with GGTase-I were recorded as X = 14.44, Y = -3.09 and Z = 36.25.

The advanced molecular docking program AutoDock Vina, version 1.1.2, accessible at http://vina.scripps.edu/download.html, was employed to assess the binding affinities (kcal $mol^{-1}$) against the receptors. The ligands underwent *in silico* evaluation against the proteins in triplicate. Based on a comprehensive docking search comprising of ten runs, the average of the optimal conformation with the lowest docked energy was selected. The interactions between the three proteins and the ligands including hydrogen bonds, bond lengths and root mean square difference (RMSD), were analyzed using PyMOL software (http://pymol.sourceforge.net/).

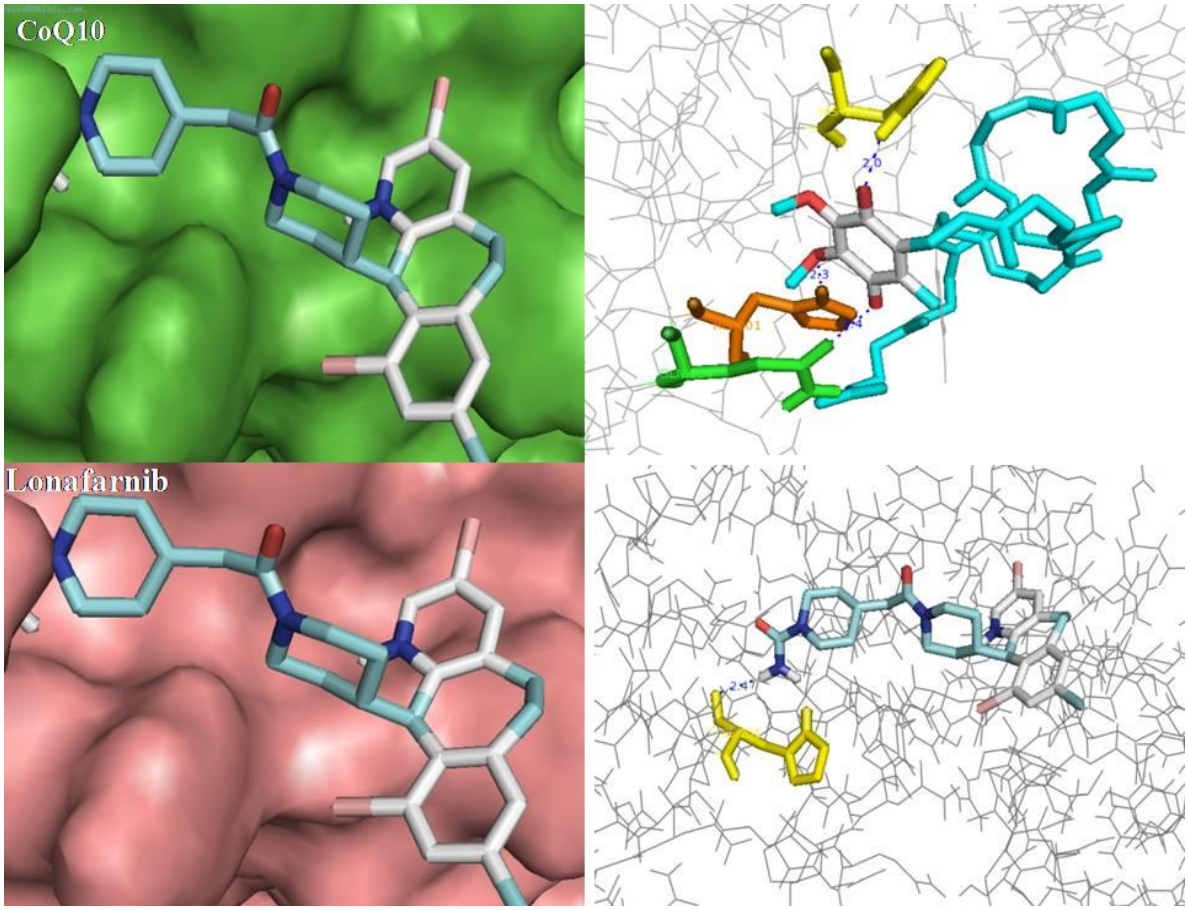



**Figure 1: Snapshot of docking of CoQ10 and standard drug Lonafarnib, with FTase (PDB ID: 1QBQ)**

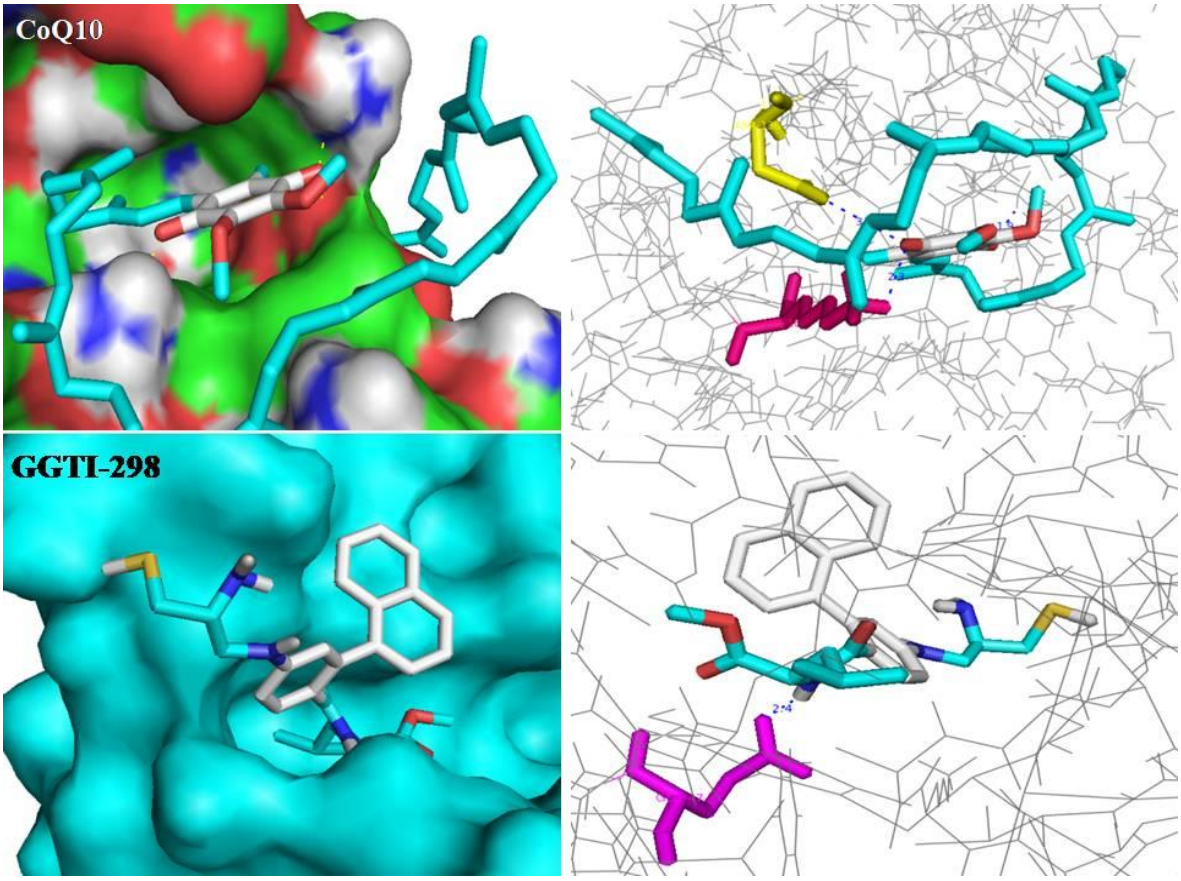
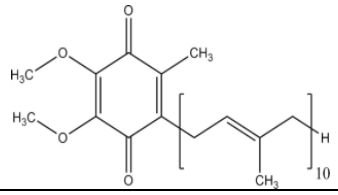
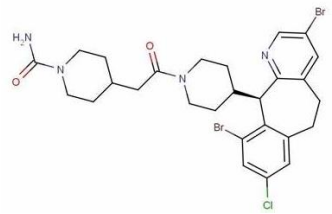
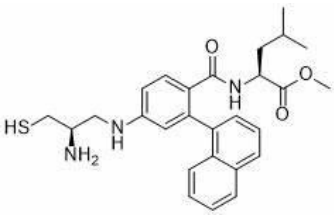



**Figure 2: Snapshot of docking of CoQ10 and standard drug GGTI-298, with GGTase-I (PDB ID: 1N6H)**

**Table 1**
**Structures and IUPAC names of Coenzyme Q10 and standard drugs**

| S.N. | Name of the Compound | IUPAC | Molecular Structure |
|---|---|---|---|
| 1. | Coenzyme Q10 | 2-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-3, 7, 11,15,19,23,27,31,35,39-Decamethyltetraconta-2, 6,10,14,18,22,26,30,34,38-decaen-1-yl]-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione |  |
| 2 | Lonafarnib | 4-(2-{4-[(11*R*)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]piperidin-1-yl}-2-oxoethyl)piperidine-1-carboxamide |  |
| 3 | GGTI-298 | Methyl (2*S*)-2-[[4-[[(2*R*)-2-amino-3-sulfanyl propyl]amino]-2-naphthalen-1-ylbenzoyl]amino]-4-methylpentanoate |  |

## Results and Discussion

The present study investigates the inhibitory effects of the natural antioxidant CoQ10 on Prenyltransferases (PTs) such as Farnesyltransferase (FTase) and Geranylgeranyltransferase-I (GGTase-I) using standard drugs Lonafarnib and GGTI-298 respectively as a

comparative reference (Table 1). This analysis was conducted *in silico* through computational methodologies which are instrumental in elucidating the interactions between organic compounds and their respective drug targets. The results obtained may offer essential insights for the development of ligands and the exploration of their interactions with target proteins prior to proceeding to experimental laboratory investigations. Docking simulations were performed using Auto dock software version 4.2.6.

***In silico* studies of COQ10 with Farnesyltransferase (FTase) and Geranyl transferase-I (GGTase-I):** The *in silico* investigation of CoQ10 in relation to FTase and GGTase-I revealed a successful molecular docking of the compound into the receptor's active site, evidenced by the formation of a stable complex between the proteins and the test compound CoQ10. Key parameters such as binding energy, hydrogen bond interactions, bond lengths, root mean square deviation (RMSD), active site residues and the orientation of the docked compounds were thoroughly analysed. The screened test compound exhibited an optimal RMSD value of 0.000, suggesting a statistically significant interaction. Notable interactions were observed with various amino acids of FTase and GGTase-I in comparison to the reference drugs. The receptor protein FTase formed three hydrogen bonds with the ligand CoQ10 with binding score of -6.3.

The interacting amino acids of the protein recorded were His-204, Gln-204 and with His-170 whereas the standard drug Lonafarnib showed the binding energy of -7.6 which is nearer to the binding energy of the test ligand CoQ10. The other receptor GGTase-I showed strong binding energy of -6.1 whereas the standard drug also showed the same binding energy of -7.4. A total of 3.0 hydrogen bonds were formed between CoQ10 and the receptor. The interacting amino acids recorded were Arg-102, Gln-19, Lys-16. The standard drug GGTI-298 showed 1.0 hydrogen bond with the receptor (Table 2). Coenzyme Q10 (CoQ10) has been the subject of research regarding its influence on the Bcl-2 protein family (Bcl-2, Bcl-xL, Mcl-1) which plays a crucial role in the regulation of apoptosis. CoQ10 treatment reduced anti-apoptotic proteins (Bcl-2, Bcl-xL, Mcl-1) and increased pro-apoptotic proteins (Bid, Bad, Bax, Bim, Bak), leading to caspase activation (3, 6, 9) and apoptosis (99th AACR Annual Meeting in 2008).

Similarly, a review published in 2024 underscores the potential of CoQ10 as both a preventive and therapeutic tool in cancer treatment. It notes that CoQ10 exhibits antitumor properties through mechanisms such as antioxidant activity, anti-inflammatory effects, induction of cell cycle arrest, promotion of apoptosis, decreased cell proliferation and inhibition of angiogenesis[1].

In the present study, in order to identify a novel target for cancer treatment, CoQ10 was studied against Farnesyl transferase (FTase) and Geranylgeranyl transferase-I (GGTase-I) inhibition potentials. The results showed potential binding of COQ10 Dwith Prenyl transferases (PTs) like FTase and GGTase-I. The natural antioxidant CoQ10, exhibited strong binding affinity to FTase which is a key enzyme in the post-translational modification of proteins, specifically catalyzing the transfer of a farnesyl group from farnesyl pyrophosphate (FPP) to the cysteine residue of target proteins, primarily those bearing a C-terminal CAAX motif (C: cysteine, A: aliphatic amino acid, X: any amino acid)[12].

This farnesylation is essential for the proper localization and function of several proteins including Ras and nuclear lamins[7]. Similarly, CoQ10 also showed strong binding with GGTase-I which is a key enzyme in modifying proteins by adding a geranylgeranyl group, enabling them to anchor to cell membranes and to participate in signaling pathways[12].

**Table 2**
**Interacting amino acids, H-bonds, distance and binding scores of Prenyltransferases, like Farnesyl transferase (FTase) PDB ID: 1QBQ and Geranylgeranyl transferase-I (PDB ID: 1N6H) with natural antioxidant UBQ10 and the standard drugs Lonafarnib and GGTI-298.**

| S.N. | Name of the Ligand | Name of the Protein | Affinity Kcal/mol | Number of Hydrogen Bonds | Interacting Amino acids |
|---|---|---|---|---|---|
| 1 | UBQ10 | Farnesyl transferase (FTase) PDB ID: 1QBQ | -6.3 | 03 | His-201<br>Gln-204<br>His-170 |
| 2 | Lonafarnib | | -7.6 | 01 | His-201 |
| 3 | UBQ10 | Geranyl geranyltransferase-I (PDB ID: 1N6H) | -6.0 | 03 | Asp-136<br>Lys-165<br>Lys-134 |
| 4 | GGTI-298 | | -7.5 | 01 | Glu-47 |

## Conclusion

CoQ10 demonstrates potent inhibitory activity against both Farnesyltransferase (FTase) and Geranylgeranyltransferase-I (GGTase-I), enzymes essential for protein prenylation, crucial for the proper functioning of various signaling proteins. By inhibiting both enzymes, CoQ10 effectively disrupts prenylation-dependent signaling pathways, leading to reduced proliferation and increased apoptosis in cancer cells. This dual inhibition mechanism makes CoQ10 a promising candidate for anticancer therapies. However, further investigation is required to assess its specificity, efficacy and safety in clinical applications.

## Acknowledgement

The authors are thankful to Dr. Snithik for helping in interpretation of data

## References

1. Dabaghi G.G., Mehrdad Rabiee Rad, Mahtab Mohammad-Zamani, Atieh Karimi Shervedani, Farnaz Bahrami-Samani and Kiyan Heshmat-Ghahdarijani, The role of coenzyme Q10 as a preventive and therapeutic agent for the treatment of cancers, *CPC*, **48**, 101063 **(2024)**

2. Garrido-Maraver J., Cordero M.D., Oropesa-Ávila M., Fernández Vega A., de la Mata M., Delgado Pavón A., de Miguel M., Pérez Calero C., Villanueva Paz M., Cotán D. and Sánchez-Alcázar J.A., Coenzyme q10 therapy, *Mol Syndromol.*, **5(3)**, 187-97, doi: 10.1159/000360101 **(2014)**

3. Gupta R.K., Patel A.K., Shah N., Chaudhary A.K., Jha U.K., Yadav U.C., Gupta P.K. and Mishra M., Oxidative stress and antioxidants in disease and cancer: A review, *APJ CP*, **15(11)**, 4405-4409 https://doi.org/10.7314/APJCP.2014.15.11.4405 **(2014)**

4. Housman G., Byler S., Heerboth S., Lapinska K., Longacre M., Snyder N. and Sarkar S., Drug Resistance in Cancer: An Overview, *Cancers*, **6(3)**, 1769-1792, https://doi.org/10.3390/cancers6031769 **(2014)**

5. James C., Zhang X., Fox M. and Gao H., Farnesyltransferase inhibitors in cancer therapy: Mechanisms, clinical applications and future perspectives, *Cancer Treat Rev*, **100**, 102284, https://doi.org/10.1016/j.ctrv.2021.102284 **(2021)**

6. Littarru G.P. and Tiano L., Bioenergetic and antioxidant properties of coenzyme Q10: Recent developments, *Mol. Biotechnol*, **37(1)**, https://doi.org/10.1007/s12033-007-0052-y, 31-37 **(2007)**

7. Maurer-Stroh S., Koranda M. and Eisenhaber F., Protein prenyltransferases, *Genome Biol*, **4(6)**, 212 **(2003)**

8. Park J., Lee J., Kim S. and Hong Y., Role of prenylation in protein-protein interactions and membrane localization: Implications in cancer, *Cell Signal*, **83**, 109981, https://doi.org/10.1016/j.cellsig.2021.109981 **(2021)**

9. Pizzino G., Irrera N., Cucinotta M., Pallio G., Mannino F., Arcoraci V., Squadrito F., Altavilla D. and Bitto A., Oxidative stress: Harms and benefits for human health, *Oxid. Med Cell Longev*, https://doi.org/10.1155/2017/8416763, 8416763 **(2017)**

10. Siegel R.L., Miller K.D. and Jemal A., Cancer statistics, *CA Cancer J Clin*, **73(1)**, https://doi.org/10.3322/caac.21763, 17-48 **(2023)**

11. Sung H., Ferlay J. and Siegel R.L., Global cancer statistics 2020: GLOBOCAN estimates, *CA Cancer J Clin*, **71(3)**, 209-249 **(2021)**

12. Zhang F.L. and Casey P.J., Protein prenylation: Molecular mechanisms and functional consequences, *Annu. Rev. Bioch*, **65(1)**, 241-269 **(1996)**.

(Received 28th March 2025, accepted 23rd May 2025)