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Original Research Article

In silico Evaluation of the Antileukemia Activities of Thymoquinone by Targeting FLT3-ITD and BCR-ABL Signaling in Myeloid leukemia

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ABSTRACT

The FMS-like tyrosine kinase-3 internal tandem duplication (*FLT3*-ITD) represents a distinct genetic mutation that characterizes acute myeloid leukaemia (AML). The breakpoint cluster region (BCR)-Abelson murine leukaemia (ABL) (*BCR-ABL*) is a key initiator of chronic myeloid leukaemia (CML) Hyperactivation of phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) signalling is crucial in AML and CML pathogenesis. The recent development of tyrosine kinase inhibitors (TKIs) contributed to substantial improvements in leukaemia therapy. However, most leukaemia patients fail to completely recover and develop drug resistance after prolonged TKI therapy. Thymoquinone (TQ), a major ingredient of *Nigella sativa* seeds, has anti-tumour properties in a variety of cancers. However, the anti-leukemia effect of TQ was not extensively studied. Thus, the current research aims to identify TQ's ability to bind on the active sites inFLT3-ITD, BCR-ABL, PI3K, Akt, and mTOR tyrosine kinases. The molecular docking of TQ toFLT3-ITD, BCR-ABL, PI3K, Akt, and mTOR was evaluated. Midostaurin; FLT3-ITD inhibitor, imatinib; BCR-ABL inhibitor, wortmannin; PI3K inhibitor, AZD5363; Akt inhibitor, and rapamycin; mTOR inhibitor were selected as positive controls. The findings revealed that TQ interacts with high affinities with the active site of PI3K(-7.02Kcal/mol), Akt(-6.4Kcal/mol), mTOR(-6.58Kcal/mol), FLT3-ITD(-6.35Kcal/mol), and BCR-ABL(-6.31Kcal/mol) and with low free binding energy to inhibit their enzymatic activities. In conclusion, TQ could potentially act as a TKI for FLT3-ITD, BCR-ABL, PI3K, Akt, and mTOR tyrosine kinases suggesting that TQ could act as a promising multi-targeted TKI for several tyrosine kinases for AML and CML treatment.

Keywords: *Signaling pathways; Tyrosine kinase inhibitors; Myeloid leukaemia; Thymoquinone; Molecular docking.*

Introduction

Leukaemia is a blood malignancy that arises from genetic mutations that accumulate in the hematopoietic stem cell (HSC) leading to unregulated differentiation and proliferation.[1, 2]The FMS-like tyrosine kinase 3 with internal tandem duplication (*FLT3*-ITD) represents a distinct genetic mutation that characterizes acute myeloid leukaemia (AML).[3] *FLT3*-ITD mutation induces hyperactivation of tumorigenic signaling including the Phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway.[4, 5]*BCR-ABL* fusion gene formed by t(9; 22) chromosome translocation initiates chronic myeloid leukaemia (CML) pathogeneses.[6, 7]The BCR-ABL oncoprotein enhances the hematopoietic cell's ability to proliferate and survive by hyperactivating several signalling including PI3K/Akt/mTOR signalling.[8]

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Chemotherapy remains the first-line therapy for leukaemia patients with poor outcomes and unsatisfactory survival rates.[9]Tyrosine kinase inhibitors (TKIs) development recently contributed to substantial improvements in leukaemia therapy.[8]However, most leukaemia patients receiving TKIs treatment fail to completely recover and develop drug resistance after prolonged therapy.[10]Additionally, TKIs treatment is associated with several unfavourable side effects.[11]Therefore, developing alternate therapies obtained from natural compounds could substantially enhance the treatment of leukaemia. Natural phytochemical substances are safe and efficient alternatives in the treatment of cancers.[12-14] The phytochemical substance, thymoquinone (TQ) is a principal bioactive component in *Nigella sativa* seeds (black seeds).[15]TQ has anticancer activities in a variety of tumour cells.[15-21]However, the impact of TQin leukaemia cells remains incompletely evaluated. Molecular docking is commonly used in silico method for ligand-protein interaction which is used to find new inhibitors of tyrosine kinases involved in several signalling pathways and to reveal the possible mechanisms of action of both previously identified compounds and new drugs for cancer therapies.[22, 23]TKIs represent innovative therapy for various types of cancers. Therefore, identifying TKIs from natural sources is a promising approach for the identification of new TKIs. To overcome resistance to the current TKIs treatment and unfavourable side effects, the current study aims to investigate the ability of TQ to bind to the active sites and inhibit the enzymatic activities ofFLT3-ITD, BCR-ABL, PI3K, Akt, and mTOR tyrosine kinases. For this purpose, the

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molecular docking of TQ toFLT3-ITD, BCR-ABL, PI3K, Akt, and mTOR oncoproteins was evaluated.

Materials and Methods

Software for the molecular docking study

The www.python.comwas accessed to download Python language (accessed on 15 March 2022), the http://mgltools.scripps.edu was accessed to download the Molecular graphics laboratory (MGL) tools (accessed on 15 March 2022), the http://autodock. scripps.edu was accessed to download AutoDock4.2 (accessed on 15 March 2022), the http://accelrys. com was accessed to download Bio Via Draw (accessed on 15 March 2022), the http://accelrys.com was accessed to download the Discovery studio visualizer 2017 (accessed on 15 March 2022), and the https://acms.ucsd.edu was accessed to download the Chem3D (accessed on 15 March 2022).[24]

Protein preparation for the molecular docking study

The three-dimensional crystal structure from RCSB protein data bank for the molecular target proteins; PI3K protein (3APC), AKT protein (3E8D), mTOR protein (5GPG), BCR-ABL protein (5OC7), FLT3-ITD protein (6JQR) were selected then downloaded from the Protein Data Bank (www.rvcsb.org/pdb).[25]Using Argus Lab, the complexes bonded to the receptor molecules, all the unessential heteroatoms and water molecules were deleted, and hydrogen atoms were ultimately added to the target receptor molecules.[26]

Ligand preparation for the molecular docking study

In this study, Midostaurin; an inhibitor of FLT3-ITD, imatinib; an inhibitor of BCR-ABL, wortmannin; an inhibitor of PI3K, AZD5363; an inhibitor of Akt, and rapamycin; an inhibitor of mTOR were selected as positive controls.

Thymoquinone and the positive controls with the identified crystallography structure were available. The sdf format was prepared using Pubchem and then converted to PDB format using Pymol which was further utilized to perform the docking studies.

The AutoDock tools were used to prepare the proteins' starting structures.[27] Water molecules were deleted from the proteins' starting structures, and the Kollman charges and polar hydrogen were added to the proteins' starting structures. The grid box with the size of 126×126×126Å was set with 0.375 Å grid spacing at the binding site. BioVia draw was used to construct the starting structure of TQ. The Pubchem website was used to provide the structures of TQ and the positive controls, and the Autodock Tools were used to assign Gasteiger charges into an optimized ligand. A hundred docking runs with 0.8 crossover rate and 0.02 mutation rate were carried out. A randomly 250 placed individuals were used to set the population size. Lamarckian Genetic algorithm with 0.2 Å translational step, 5 Å quaternion step, and 5 Å torsion step was utilized as the searching algorithm. As a final result, the lowest and most populated free binding energies were selected.[27]

Results and Discussion

Tyrosine kinase inhibitors (TKIs) resistance and chemotherapy side effects remain the primary obstacles to leukaemia patients' treatment, despite the notable advancements in the treatment of leukaemia.[10]Therefore, developing novel medicinal alternatives may bear substantial consequences for the treatment of leukaemia. From our previous published data, the findings have demonstrated TQ-induced anti-leukemia effects in AML and CML cells.[19-21, 26, 28]Moreover, in our previous study, we demonstrated that TQ caused inhibition ofPI3K/Akt/mTOR pathway by reducing the gene, protein, and phosphorylation levels of PI3K, Akt, and mTOR in both MV4-11 AML and K562 CML cells.[20]We also demonstrated that TQ inhibited JAK/STAT pathway and could potentially act as a TKI of JAK2, STAT3, and STAT5.[19-21, 26]In the current research, we further assessed TQ's ability to act as a TKI which potentially inhibits the enzymatic activities of FLT3-ITD, BCR-ABL PI3K, Akt, and mTOR tyrosine kinases for AML and CML treatment by molecular docking study.

FLT3 is considered a potential drug target for AML treatment, particularly for patients with *FLT3*-ITD gene mutation. Therefore, targeting FLT3-ITD could provide promising candidates to treat AML patients. In our previous published findings, we demonstrated the effect of TQ on the expression of *FLT3*-ITD in MV4-11 AML cells, and the results showed down regulation of *FLT3*-ITD in MV4-11 cells after treatment with TQ.[26]In the present study, FLT3-ITD oncoprotein was targeted by TQ using molecular docking study.

The docked conformation of FLT3-ITD protein clearly showed numerous potential interactions with the active conformation of TQ (Figures 1). The results of the free binding energy and Ki value for each compound after the interaction with the studied protein are demonstrated in Table 1.

The chemical interaction between FLT3-ITD protein and TQ involved one hydrogen bond with MET645, pi sigma bond with TYR572, Van der waals bond formed with LYS623, amide pi stacked bond with GLY622, and five alkyl bonds with PHE830, VAL624, LYS644, LEU646 and LEU658 with -6.35 Kcal/mol free binding energy (Figure 1A).

Table 1: Free binding energy (FBE) and Ki values of the interactions between TQ and positive controls with the studied target proteins

	FBE (Kcal/mol)		Ki	
PI3K	**TQ**	**Wortmannin**	**TQ**	**Wortmannin**
	-7.02	-10.05	7.16 µM	43.05 nM
Akt	**TQ**	**Capivasertib**	**TQ**	**Capivasertib**
	-6.4	-9.71	9.01 µM	75.72 nM
mTOR	**TQ**	**Rapamycin**	**TQ**	**Rapamycin**
	-6.58	-20.04	14.93 µM	2.06 fM
FLT3-ITD	**TQ**	**Midostaurin**	**TQ**	**Midostaurin**
	-6.35	-9.79	21.98 µM	67.14 nM
BCR-ABL	**TQ**	**Imatinib**	**TQ**	**Imatinib**
	-6.31	-9.11	23.88 µM	211.64 nM

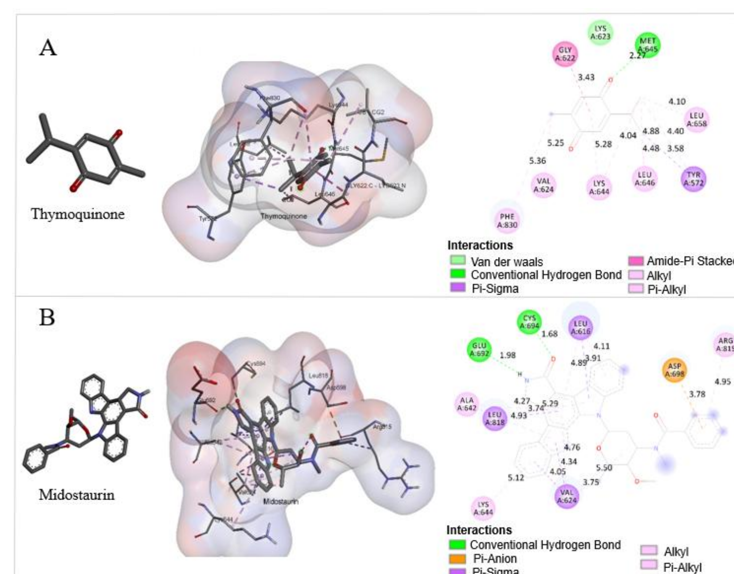

Figure 1: The 3D and 2D configuration of the interactions between FLT3-ITD protein and the studied compounds **(A)** TQ's crystallographic structure and the 3D and 2D configuration of FLT3-ITD protein and TQ interactions **(B)** Crystallography structure of midostaurinand the 3D and 2D configuration of midostaurin and FLT3-ITD protein interactions.

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The chemical interactions between Midostaurin (positive control) and FLT3-ITD protein involved two hydrogen bonds with GLU692 and CYS694, a Pi anion bond with ASP698, three pi sigma bonds with LEU616, LEU818, and VAL624, and three alkyl bonds with ARG815, ALA642, and LYS644 with -9.79 Kcal/molfree binding energy (Figure 1B). The interaction of midostaurin with the active site of FLT3-ITD showed higher affinity and lower free binding energy than TQ. The results agree with previous findings that revealed that several phytochemical compounds such as glabridin and ellipticine showed good binding affinities to FLT3-ITD.[29]

Although treatment with the imatinib, BCR-ABL TKI, enhanced the remission and survival rate of CML patients, point mutations in the BCR-ABL kinase domain confer imatinib resistance. Therefore, in the current study, the BCR-ABL pleckstrin homology (PH) domain was targeted to overcome imatinib resistance.[30]In our previous published findings, we evaluated the effect of TQ on the expression of *BCR-ABL* in K562 CML cells, and the results showed down regulation of *BCR-ABL* in K562 cells after treatment with TQ.[28] In the present research, *BCR-ABL* oncoprotein was targeted by TQ using molecular docking study.

The docked conformation of BCR-ABL protein clearly showed numerous potential interactions with the active conformation of TQ (Figures 2).The chemical interactions between TQ and BCR-ABL pleckstrin homology domain demonstrated a pi donor hydrogen bond to THR82 and three alkyl bonds to MET81, LYS866 and ARG862 with -6.31 Kcal/mol free binding energy (Figure 2A). The chemical interactions between imatiniband BCR-ABL protein demonstrated a hydrogen bond to ARG723, carbon-hydrogen bond with GLU769, MET836 and ASP851, three alkyl bonds with PRO830 and LEU718, and pi sulfur and pi sigma bonds with MET832 with -9.11 Kcal/mol free binding energy (Figure 2B). The interaction of TQ with the active site of BCR-ABL revealedless affinity and higher free binding energy than imatinib.The results agree with previous findings that revealed that two ZINC natural compounds, ZINC08764498 and ZINC12891610, have potential binding affinities toward BCR-ABL oncoprotein.[31]

The docked conformation of PI3K, Akt, and mTOR proteins clearly showed numerous potential interactions with TQ's active conformation (Figures 3, 4, and 5).

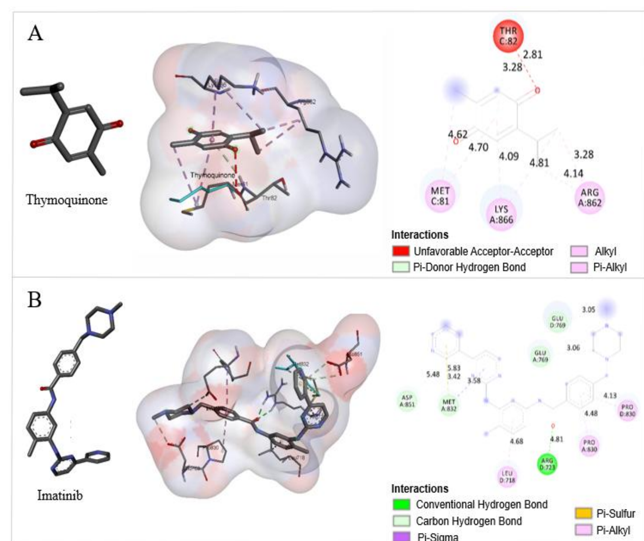

Figure 2: The 3D and 2D configuration of the interactions between BCR-ABL protein and the studied compounds **(A)** TQ's crystallographic structure and the 3D and 2D configuration of TQ and BCR-ABL interactions(**B**) Crystallography structure of imatinib and the 3D and 2D configuration of imatinib and BCR-ABL protein interactions

The chemical interaction between TQ and PI3K showed a pi sigma bond with ILE933, a Pi sulfur bond to CYS883, a pi lone pair to THR886, and five alkyl bonds to VAL930, ARG894, HIS909, ILE899, and PHE938 with a free binding energy of -7.02 Kcal/mol (Figure 3A). Wortmanninand PI3Kchemical interactions revealed three hydrogen bonds toSER623, LEU629, and GLU628, Pi anion bond formed with GLU622, carbon-hydrogen bond to LEU583, and three alkyl bonds to CYS590, CYS627, and MET387 with -10.05 Kcal/ mol free binding energy (Figure 3B). TQ and PI3Kchemical interactions revealed lower affinity and greater free binding energy than wortmannin and PI3Kchemical interactions.

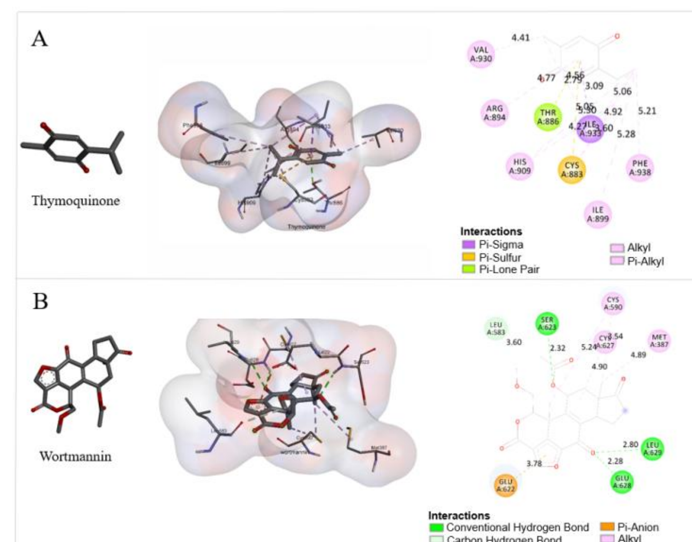

Figure 3: The 2D and 3D configuration of the interaction between PI3K protein and the studied compounds **(A)** TQ's crystallographic structure and the 2D and 3D configuration of TQ and PI3K protein interactions (**B**) Crystallography structure of wortmannin and the 2D and 3D configuration of wortmannin and PI3K protein interactions

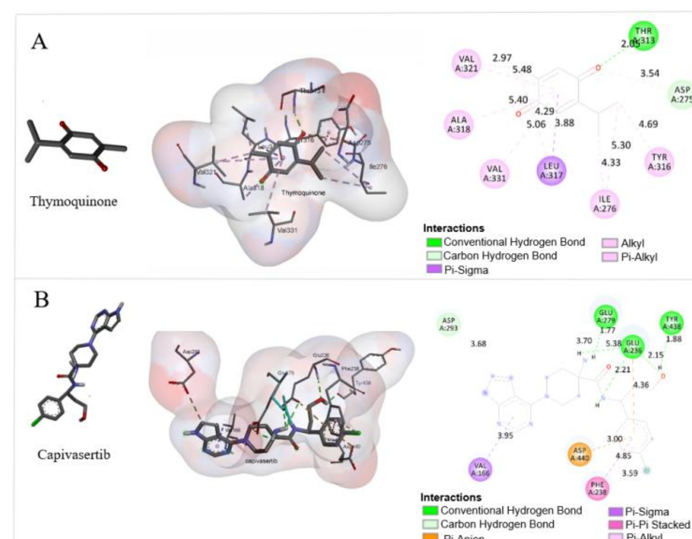

Figure 4: The 2D and 3D configuration of the interactions between Akt protein and the studied compounds **(A)** TQ's crystallographic structure and the 2D and 3D configuration of TQ and Akt protein interactions (**B**) Crystallography structure of capivasertib and the 2D and 3D configuration of capivasertiband Akt protein interactions.

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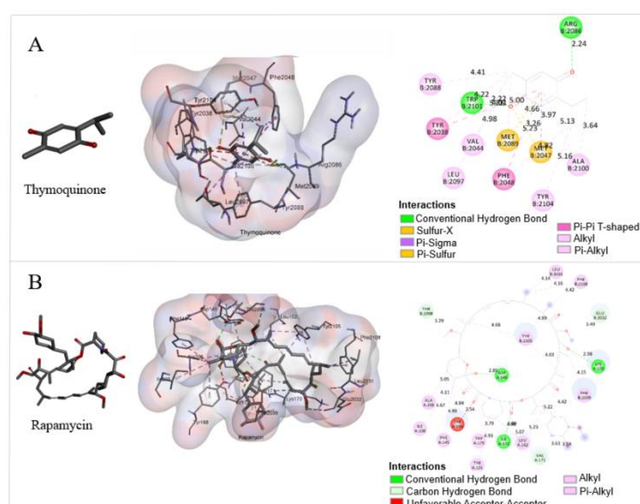

Figure 5: The 2D and 3D configuration of the interactions between mTOR protein and the studied compounds **(A)** TQ's crystallographic structure and the 2D and 3D configuration of TQ and mTOR protein interactions (**B**) Crystallography structure of rapamycin and the 2D and 3D configuration of rapamycin and mTOR protein interactions

TQ and Akt chemical interactions revealed a hydrogen bond to THR313, carbon-hydrogen bond to ASP275, pi sigma bond to LEU317, and five alkyl bonds to VAL321, ALA318, VAL331, ILE276, and TYR316 with -6.4 Kcal/mol free binding energy (Figure 4A). Capivasertiband Aktchemical interactions demonstrated three hydrogen bonds to GLU279, GLU236, and TYR438, a pi sigma bond to VAL166, a carbon-hydrogen bond with ASP293, and a pi anion bond with ASP440 with -9.71 Kcal/mol free binding energy (Figure 4B). The interactions of TQ with the active site of Aktrevealedless affinity and greaterfree-binding energy thancapivasertib.

The chemical interaction between TQ and the mTOR FKBP12Rapamycin binding (FRB) domain revealed two hydrogen bonds to ARG2086 and TRP2101, sulfur bond to MET2089 and MET2047, pi T shaped bond with TYR2038 and PHE2048 and five alkyl bonds formed with TYR2088, VAL2044, LEU2097, TYR2104 and ALA2100 with -6.58 Kcal/mol free binding energy (Figure 5A).Rapamycin, and the FRB domain of mTOR chemical interactions revealed three hydrogen bonds to LYS170, ASP146, and ILE179, carbon-hydrogen bonds to VAL171, THR2098, and GLU2032, and alkyl bonds formed with LEU2031, PHE2108, PHE2039, ALA206, ILE208, PHE145, TRP175, TYR135 and LEU162 with -20.04 Kcal/mol free binding energy (Figure 5B). The interaction of rapamycin with the active site of mTORshowed higher affinity and lower free binding energy thanTQ.

The findings of this research are consistent with previous research that indicated that the peptides contained in the natural products (sea cucumber *Cucumariafrondosa*) showed several interactions with a high affinity toward the active sites of PI3K and Akt to inhibit their enzymatic activities.[23] The results also agree with previous research that showed that several compounds derived from marine natural products bind to the active site of mTOR to inhibit its activity.[32] In addition, the results were consistent with previous research that indicated that the phenolic compounds (pinoresinol, apigenin, luteolin, o. aglycone, and oleuropein) derived from *Olea europaea* showed binding affinities towards PI3K, Akt, and mTOR.[22]

Even though TQ showed a slightly higher free binding energy than the positive controls selected in this study, it showed a multi-targeted tyrosine kinase inhibitory effect by inhibiting the enzymatic activities of several tyrosine kinases with low side effects compared to the currently available TKIs. Interestingly, these results indicate promising potential effects of TQ acting as a multi-targeted TKI for several tyrosine kinases involved in the pathogenesis of leukaemia.

Taken together, TQ could potentially act as a TKI for FLT3-ITD, BCR-ABL, PI3K, Akt, and mTOR tyrosine kinases suggesting that TQ could act as a promising multi-targeted TKI for several tyrosine kinases in myeloid leukemia treatment.

Conclusion

The ability of TQ to act as a TKI forFLT3-ITD, BCR-ABL, PI3K, Akt, and mTORtyrosine kinases for AML and CML treatment was evaluatedby molecular docking study. Based on our current results, the anti-leukaemia effects of TQ are induced by binding to the active sites of FLT3-ITD, BCR-ABL, PI3K, Akt, and mTORtyrosine kinases with high affinity and low free binding energy to inhibit their enzymatic activity, which identifies TQ as a potential multi-targeted TKI for several tyrosine kinases with low side effects compared to the currently available TKIs used for the treatment of leukaemia. The findings of this research indicate TQ as a potential therapeutic agent for AML and CML patients.To further reveal the tyrosine kinase inhibitory properties of TQ, the molecular docking of TQ to other tyrosine kinases as well as assessing the protein and phosphorylation levels of other tyrosine kinases needs to be investigated.

Conflicts of Interest:

The authors declare no conflicts of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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