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Antimalarial Drug Mefloquine Strongly Inhibits PI3K (Phosphoinositide 3-kinase) and Exerts Anticancer Activity: A Literature based In Silico Study

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Abstract: Mefloquine (MFQ) is an effective medication for the prevention and treatment of malaria. However, it has anticancer effects found in the literature. The main focus of this study is to review the anticancer activity of MFQ and also find the macromolecules or receptors that are mainly responsible for anticancer activity. For this reason, data was gathered (as of June 30, 2024) by utilizing a variety of reliable and well-known search engines. The molecular docking of MFQ with the selected macromolecules was performed. Our study findings showed that MFQ strongly showed anticancer activity by inhibiting proliferation, tumor growth, mitochondrial respiration, PI3K, MMP, IKK activation, Bcl-2, MCl-1, XIAP, and induced cell death, apoptosis, ROS, and PARP. In addition, an *in silico* study demonstrated that MFQ showed the highest binding affinity (–8.7 kcal/mol) against PI3K, whereas co-crystal ligand exhibited –8.6 kcal/mol binding affinity. The study also predicted that MFQ has better pharmacokinetics and toxicity parameters. However, we recommend additional evaluation and clinical research to further explore MFQ as a reliable PI3K inhibitor and an anticancer agent.

Keywords: Cancer; Mefloquine; Molecular docking; PI3K inhibitor; Pharmacokinetics

1. Introduction

Cancer, regarded as a complicated and therapeutically challenging disease, refers to a group of conditions where the cells of an individual multiply in an inappropriate and uncontrolled manner, with the ability to spread and invade adjacent tissues and organs, which cause a huge number of deaths each year around the world (Norton et al., 2023). Cancer has emerged as the primary cause of death in prosperous countries. However, annually, more than 12 million new cases of cancer are reported worldwide. The number of new cases is found to be increasing day by day, and it is predicted that by 2030, almost 8.3 billion people will be diagnosed with cancer and 8.9 billion by 2050 (Thun et al., 2010). At the molecular level, the formation of cancer is thought to be a complicated cascade of events that involves mutation and selection for cells with improved capacities for invasion, proliferation, metastasis, and survival, as well as several individual mechanisms (Bhuia et al., 2023a; Aktar et al., 2024).

The causes of cancer are multifaceted and can be broadly categorized into genetic factors (e.g., BRCA1 and BRCA2 genes, etc.) (Welcsh & King, 2001), lifestyle factors (e.g., smoking, diet, alcohol, obesity, etc.) (Katzke et al., 2015), environmental exposures (e.g., UV, hazards, pollution, etc.) (Baudouin et al., 2002), infections (e.g., human papilloma, hepatitis B and C, and human immunodeficiency virus, helicobacter pylori bacteria, etc.) (Williams & Williams, 2019; Zur Hausen, 2007), and hormonal factors (Salehi et al., 2008). However, cancer is a multifaceted disease that interacts with various physiological systems and other diseases, leading to significant impacts on a person's overall health (Stein et al., 2008). For example, cancer influences cardiovascular disease, diabetes, depression, and anxiety (Shang et al., 2019).

The treatment of cancer has been an extremely complicated procedure. Traditional treatment methods like surgery, chemotherapy, and radioactive therapy have been widely used, but they also have several limitations, including high cost, side effects, and low efficacy. However, recent advancements have included novel methods such as targeted therapy, stem cell therapy, nanoparticles, natural antioxidants, synthetic drugs, and ferroptosis -based therapy (Debela et al., 2021). Existing anticancer medications have several drawbacks, such as the development of

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resistance, toxicity, limited effectiveness, and high expenses. This is the reason why it is necessary to create new, safe, and efficient medications for treating cancer.

Synthetic drugs are produced chemically and designed to imitate or increase the therapeutic properties of natural substances (Mathur & Hoskins, 2017). Conversely, derivatives are chemically altered forms of a parent molecule that are frequently used to improve their therapeutic effectiveness, reduce adverse effects, or overcome resistance mechanisms (Wanka et al., 2013). Today, in cancer treatment, several types of derivatives and synthetics are frequently used, for example, methotrexate (Shariatifar et al., 2022), carboplatin (Jakimov et al., 2023), paclitaxel (Sati et al., 2024), etc. However, mefloquine (MFQ) ($C_{17}H_{16}F_6N_2O$), a synthetic drug commonly known as Lariam, is an FDA-approved drug (white or slightly yellow crystalline powder) with a molecular weight of 378.31 g/mol that is available in the form of hydrochloride salt or in combination with sulfadoxine and pyrimethamine and has a strong antimalarial property (Karbwang et al., 1990; Yan et al., 2013a). Different studies have found that it has strong anticancer activity in various types of cancer cells (Li et al., 2018; Sharma et al., 2012; Xu et al., 2018). **Fig. 1** depicts the 2D structure of MFQ.

Molecular docking is an essential technique used in the fields of structural molecular biology and computer-assisted drug development (Fan et al., 2019). Ligand-receptor docking aims to determine the primary binding modes between a ligand and a receptor with a known 3D structure. Efficient docking techniques effectively investigate high-dimensional spaces and apply a scoring function that accurately provides potential dockings, which is used for various purposes, including the visualization of large groups of compounds and optimizing potential drug candidates (Morris & Lim-Wilby, 2008; Meng et al., 2011). The purpose of this study is to evaluate the molecular mechanism behind MFQ's anticancer action using *in silico* studies and current literature. This study additionally investigates the toxicological and pharmacokinetic features that make it more effective to prove that this is a safe and reliable anticancer agent.

2. Methodology

2.1. Literature review

2.1.1. Search strategy

A search was carried out using the commonly used term "mefloquine" in a number of databases, including Wiley Online, Science-Direct, Springer Link, PubMed, Web of Science, and Google Scholar, as of June 30, 2024. The search terms were consequently combined with words including "cancer," "tumor," "anticancer activity," "anti-proliferation activity," "cytotoxic activity," "antitumor activity," "human cancer," "biological activities," "pharmacological effects," "pharmacological activities," "chemical features," "*in vivo* studies," and "*in vitro* studies." The search criteria did not include any restrictions on language or time. The comprehensive evaluation of the investigations covered the sources, dosage/concentration, test system, recommended action mechanism, overall conclusion, and suggestions.

2.1.2. Inclusion and exclusion criteria

2.1.2.1. Inclusion criteria

1. Research done *in vitro*, *ex vivo*, or *in vivo*, with or without the use of tissues or cells produced from laboratory animals, such as mice, rats, rabbits, and humans.
2. Research on mefloquine's anticancer properties and botanical sources.
3. Research that suggests potential mechanisms of action or not.

2.1.2.2. Exclusion criteria

1. Research showed instances of duplicate data and titles and/or abstracts that did not adhere to the inclusion requirements.
2. Mefloquine does not address the present problem in other investigations.
3. Documents composed in languages apart from English.
4. Research with no full text accessible.
5. Letters, editorials, commentary, and case reports.

2.2. In silico study

2.2.1. Ligand preparation

From the PubChem (https://pubchem.ncbi.nlm.nih.gov/, accessed on June 30, 2024) online database, we have collected the SDF file format of 3D structures of mefloquine (Compound CID: 40692) and within each co-crystal ligand of their particular macromolecules. The chosen ligand's energy was minimized by using the Discovery Studio software packages (Akbor et al., 2023).

2.2.2. Macromolecule's preparation

From the literature study, we have selected and focused on nine proteins that are connected to the creation of cancer cells and their growth. The crystal 3D structures of the proteins NF-κB (1SVC), Bcl-2 (3ZLN), AKT (6HHF), PI3K (5DXT), ERK (6SLG), MCL 1 (5FDR), JNK (3V6R), PARP (7KK6), and XIAP (5OQW) were obtained from the RCSB protein data bank database (https://www.rcsb.org/, accessed on June 30, 2024). Using the GROMOS96 force field (Chowdhury et al., 2024), the Swiss-PDB Viewer software tool (version 4.1.0) was utilized to minimize the energy of the chosen protein structure. PyMOl (version 1.7.4.5) was subsequently employed to remove all heteroatoms and water molecules from proteins before docking (Bhuia et al., 2023c; Hasan et al., 2024).

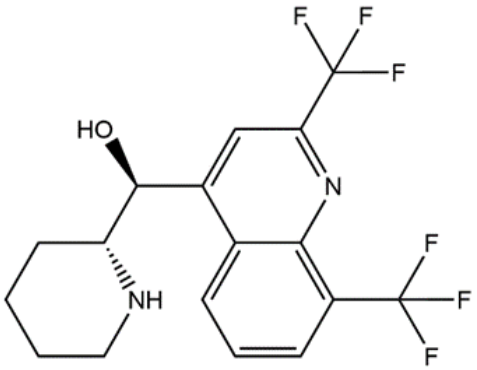


Fig. 1. The 2D structure of mefloquine

2.2.3. Molecular docking and visualization

Molecular docking is the computational study through which it is possible to predict interactions between ligands and proteins, as well as new drug discovery (Li et al., 2019; Islam et al., 2025). We evaluated MFQ's molecular docking with nine proteins involved in the development and proliferation of cancer cells. We performed molecular re-docking of co-crystal ligands within corresponding proteins to validate our docking study. In order to predict binding affinities, drug candidates were docked with proteins using the PyRx-virtual screening tool (Version 0.8) (Islam et al., 2024). The grid box dimensions were maximized for the x, y, and z axes during the docking process and the docking was performed blindly. There were 2000 steps involved in the calculation (Afroz et al., 2024). Using Drug Discovery Studio (version 16.1.0.15350), the active binding sites on the target protein were analyzed. The assessment of different interactions, such as hydrogen bonding, van der Waals forces, and hydrophobic interactions was the main objective of this investigation. We used an amalgamated file that we downloaded from the PyMOL visualizer application in order to carry out the visualization (Chowdhury et al., 2023).

2.2.4. Pharmacokinetics prediction

In drug discovery, toxicity, ADME (absorption, distribution, metabolism, and excretion) evaluation, and pharmacokinetics, one of the newest and fastest-growing methods is the computational approach (Ferdous et al., 2024). Using the SwissADME server protocol (http://www.swissadme.ch/), the ADME prediction for MFQ was ascertained. The MFQ's physiochemical characteristics were disclosed by the prediction. It also verifies if there are any violations of the Lipinski rules of five.

2.2.5. Toxicity prediction

For the purpose of eliminating compounds with a high likelihood of failing in clinical trials, computational toxicity prediction is very helpful in the early phases of drug research (Cavasotto & Scardino, 2022). The toxicity prediction of MFQ was determined by using the ProTox 3.0 web server tool (https://tox.charite.de/protox3/). The ProTox 3.0 server targets a variety of parameters, including cytotoxicity, hepatotoxicity, mutagenicity, carcinogenicity, and immunotoxicity. The LD_{50} value and toxicity class were also determined via toxicity prediction.

3. Results and discussion

3.1. Anticancer activity of mefloquine with underlying mechanism; literature review

3.1.1. Induction of oxidative stress

Oxidative stress refers to the condition when an abundant amount of reactive oxygen species (ROS) accumulates in the cell compared to antioxidants, which is associated with neurodegenerative diseases, heart disease, diabetes mellitus, and carcinogenic disorders (Hayes et al., 2020). The induction of oxidative stress can be a potential therapeutic mechanism to prevent cancer (Jelic et al., 2021).

Different studies investigated the effect of MFQ on the induction of oxidative stress in different cancer cells. Yan and his team members conducted two different studies that revealed the anticancer activity of MFQ by inducing oxidative stress in prostate cancer cells (Hs68, DU145, and PC3) by moderating the levels of ROS at concentrations of 5-40 μM (Yan et al., 2013a; Yan et al., 2013b). Another *in vitro* and *in vivo* study carried out by Li et al. (2017) reported that MFQ could induce oxidative stress in cervical cancer cells (Hela, SiHa, and C-33A) by upregulating the cellular concentrations of ROS at a dose of 40 μM (Li et al., 2017). MFQ also induced oxidative stress in gastric cancer cell lines (AGS, Hs746T, MNK45, MNK74, NCI-N87, SNU1, SNU16, YCC1, YCC10, and YCC11) via stimulating ROS levels at 0.5-5 μM (Liu et al., 2016).

3.1.2. Cytotoxicity

Cytotoxicity is the primary method by which therapeutic medicines induce cell damage. These medications have been designed to particularly target and destroy malignant cells that have a rapid rate of cell division, with the aim of inhibiting the growth and progression of tumors (Bhuia et al., 2023a; Al Hasan et al., 2025). So, the presence of toxicity in an element greatly enhances its possibility for being used as a treatment for cancer (Childs et al., 2015).

According to a research report, it is suggested that MFQ could induce cytotoxicity in colorectal cancer cells via stimulating PARP and IκBα kinase and suppressing NF-κB, p65 phosphorylation, as well as IKK activation (Xu et al., 2018). An additional study carried out by Yan and his team revealed that MFQ could stimulate cytotoxicity in prostate cancer cells (Hs68, DU145, and PC3 cells) via increasing ROS, ERK, JNK, and AMPK and diminishing the level of MMP, colony formation, and Akt Ser473 phosphorylation (Yan et al., 2013a).

3.1.3. Cell cycle arrest

Cell cycle arrest refers to the process of blocking the progression of cell growth and division (Xie et al., 2019). The capacity of cancer cells to undergo cell cycle progression and division is crucial for their proliferation. Disruption of the cell cycle hinders the growth of tumor cells and triggers the activation of cell apoptosis (Wang et al., 2010). Cell growth arrest leads to the activation of nutrient-sensing pathways such as mTOR, even in the absence of cell division, and the growth resulting from this stimulation induces cellular senescence. The process of cell cycle arrest is facilitated by the activation of either the p53/p21CIP1 or p16INK4A/pRb tumor suppressor pathways (Princilly et al., 2023). Through the restoration of the regulatory approach and pathways, the division of cancer cells can be stopped. This significant mechanism is utilized by leading anticancer medications in cancer therapy (Torgovnick & Schumacher, 2015).

MFQ has a remarkable ability to induce cell cycle arrest, which has been reported in different studies. Li et al. (2018) found that MFQ could significantly suppress cyclin D1, followed by the block of cell cycle progression (Li et al., 2018). Another investigation carried out by Yan and his colleagues investigated whether MFQ could induce cell cycle arrest at the S phase and G2/M phases (Yan et al., 2013b).

3.1.4. Apoptotic cell death

Apoptosis, also called programmed cell death, is crucial for several biological processes that take place during fetal development and in adult tissues. Defects in the regulation of apoptotic cell death have a role in various diseases, such as those that involve uncontrolled cell growth (cancer, restenosis) (Reed et al., 2000). The inhibition of apoptosis is a significant factor in the development of tumors. Different proteins and pathways are associated with apoptotic processes, including Bax, Bcl-2, caspases 3, 7, and 9, AKT pathways, NF-κB pathways, and JAK/STAT pathways (Vaskivuo et al., 2000; Ola et al., 2011; Wang et al., 2012; Deng et al., 2019; Al Hasan et al., 2024).

Researchers find the strong apoptosis-inducing activity of MFQ in various types of cancer cells, like breast, colorectal, cervical, gastric, and prostate cancer cells. An investigation conducted by Sharma et al. (2012) reported that MFQ could remarkably induce apoptosis in breast cancer cells (MDA-MB-231, MDA-MB-468, and T47D) at 15-20 μM concentrations (Sharma et al., 2012). Besides the apoptosis-inducing effect of MFQ investigated in an *in vitro* and *in vivo* study

conducted by Xu and his co-workers in colorectal cancer cells (HT-29, HCT116, RKO, SW620, and Lovo), It increased apoptosis by stimulating the expressions of caspase 3 and PARP while downregulating the levels of NF-κB, Bcl-2, and MCl-1 (Xu et al., 2018). Another study found that MFQ could significantly induce apoptosis by increasing PARP levels along with diminishing mitochondrial respiration, MMP, ATP level, and Ki67 in cervical cancer cells (Hela, SiHa, and C-33A cells) (Li et al., 2017). In gastric cancer cells, MFQ induces apoptosis greatly by inducing ROS and suppressing PI3K, AKT, and mTOR (Liu et al., 2016). These findings demonstrated that MFQ has a great inducing capability of apoptosis in different cancer cells.

3.1.5. Inhibition of cancer cell proliferation

Cellular proliferation is a key phenomenon in the biological processes of growth, development, and repair of damages (Kumari & Gupta, 2021). Proliferation is an essential factor in the start and progression of cancer. Cell growth is additionally promoted by the persistent activation of various signaling pathways (Feitelson et al., 2015; Jahan Oni et al., 2024). The PI3K/AKT/mTOR pathways are the most frequently activated signaling mechanisms in human tumors. It is associated with the development of cells, their survival, and proliferation. Abnormal mTOR activation is frequently observed in cancer and is an important step in the progression of the cancer (Peng et al., 2022; Bithi et al., 2025). In addition, STAT3 plays an essential role in regulating many biological functions associated with the initiation of malignant transformation, specifically the accelerated proliferation of cancer cells (Jin, 2020). Suppressing these pathways could be a promising target for the development of drugs for the treatment of cancer.

Different investigations have found the anti-proliferative effect of MFQ in various cancer cells. An investigation conducted by Li et al. (2018) found that MFQ suppressed the proliferation of liver cancer cells (CD133 and HepG2) by lowering the expression of the β-catenin pathway, cyclin D1, LCSCs, tumor growth, and CD133 at a dose of 10 mg/kg in nude mice and 10 μM in an *in vitro* experiment (Li et al., 2018). Sharma et al. (2012) reported the significant anti-proliferative activity of MFQ in breast cancer cell lines by triggering ER stress, chemosensitivity, and apoptosis at 3-12 μM concentrations (Sharma et al., 2012). MFQ also suppressed the proliferation of cervical cancer cells via inducing PARP and decreasing mitochondrial respiration, MMP, ATP level, and Ki67, as reported by *in vitro* and *in vivo* investigations (Li et al., 2017). Another study revealed that MFQ could remarkably alleviate cell proliferation in gastric cancer cells by evoking apoptosis and suppressing PI3K, AKT, mTOR, and rS6 (Liu et al., 2016). In prostate cancer cells (PC3), MFQ elevated the level of ROS and consequently diminished cell proliferation by increasing cell cycle arrest (Yan et al., 2013a). These results showed that MFQ has a strong inhibitory capability for cell proliferation. However, the anticancer activity of MFQ in several mechanisms is shown in **Table 1** and **Fig. 2** demonstrated a proposed mechanism based on literature.

Table 1. Anticancer activity of mefloquine based on existing literature

Cancer type	Experimental model/ cell lines	Dose/ concentration (R/A)	IC_{50}	Results/ mechanisms	References
Breast cancer	MDA-MB-231, MDA-MB-468 and T47D, *in vitro*	15-20 μM	3-12 μM	↓Autophagy, proliferation, colony formation ↑Cell death, apoptosis, ER stress, chemosensitivity	Sharma et al., 2012
Cervical cancer	Hela, SiHa, and C-33A cells, *in vitro*	40 μM	-	↓Proliferation, mitochondrial respiration, MMP, ATP level, tumor cells, Ki67 ↑Apoptosis, ROS, PARP	Li et al., 2017
	SCID mice, *in vivo* (n=10)	100 mg/kg (i.p)			
Colorectal cancer	HT-29, HCT116, RKO, SW620 and Lovo cells, *in vitro*	30 μmol/L	-	↓NF-κB, p65 phosphorylation, IKK activation, Bcl-2, MCl-1, XIAP, tumor growth ↑Growth arrest, apoptosis, caspase-3, PARP, cell death, cytotoxicity	Xu et al., 2018
	Female nude mice, *in vivo*	30 mg/kg (s.c.)			
Gastric cancer	10 unique gastric cancer cell lines (YCC1, YCC10, YCC11, MNK45, MNK74, SNU1, SNU16, Hs746T, AGS and NCI-N87), *in vitro*	0.5-5μM	-	↓Proliferation, tumor growth, PI3K, AKT, mTOR, rS6 ↑Apoptosis, ROS	Liu et al., 2016
Liver cancer	CD133+HepG2 cells, *in vitro*	1-10 μM	-	↓Proliferation, self-renewal, β-catenin pathway, cyclin D1, LCSCs, tumor growth, CD133+ sphere forming cells	Li et al., 2018
	Male BALB/c-nu/nu nude mice, *in vivo*	10 mg/kg			
Prostate cancer	Hs68, DU145 and PC3 cells, *in vitro*	5-40 μM	~10 μM	↓MMP, colony formation, AKT Ser473 phosphorylation ↑ROS, cytotoxicity, ERK, JNK, AMPK	Yan et al., 2013a
Prostate cancer	Male C57BL/6J mice, *in vivo* (n=4)	200 μg (i.p)	10 μM	↓Proliferation, S phase, G2/M phases ↑ROS, cell death, G1 cell-cycle arrest	Yan et al., 2013b
	PC3 cell lines, *in vitro*	10-40 μM			

↑:Increase/up-regulation/stimulation; ↓:Decrease/down-regulation/inhibition; AKT: AK strain transforming; AMPK: AMP-activated Protein Kinase; ATP: Adenosine Triphosphate; Bcl-2: B-cell Lymphoma 2; ER: Endoplasmic reticulum; ERK: Extracellular signal-regulated kinase; IKK: IκB Kinase; JNK: c-Jun N-terminal Kinase; MCl-1: Myeloid Cell Leukemia 1; MMP: Matrix Metalloproteinases; mTOR: Mechanistic target of rapamycin; NF-κB: Nuclear factor kappa B; PARP: Poly (ADP-ribose) polymerases; PI3K: Phosphoinositide 3-kinase; ROS: Reactive oxygen species; rS6: Ribosomal Protein S6; Ser473: Serine 473; XIAP: X-linked Inhibitor of Apoptosis Protein;

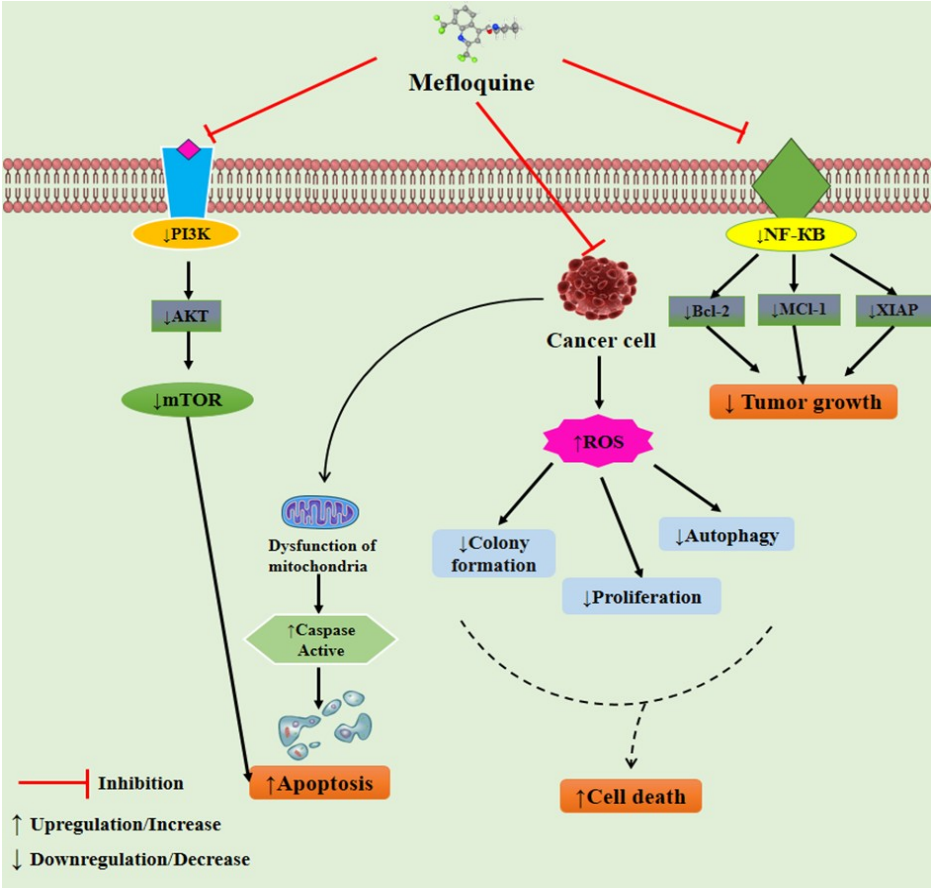


Fig. 2. Proposed mechanism of mefloquine as PI3K inhibitor and exerts anticancer activity based on the literature. [AKT: AK strain transforming; mTOR: Mechanistic target of rapamycin; PI3K: Phosphoinositide 3-kinase; ROS: Reactive oxygen species]

3.2. In silico study

3.2.1. Molecular docking and visualization

Molecular docking is a crucial method in the fields of drug design, discovery, and development (Ferreira et al., 2015). In biological cells, hydrogen bonds are an essential part of molecular interactions and have a big impact on drug discovery and design (Lu et al., 2012). However, in our *in silico* investigation, we found MFQ and the co-crystal ligand exhibited markedly greater binding affinities towards the AKT protein, with values of –10.4 and –13.5 kcal/mol, respectively. In relation to the AKT protein, MFQ established two hydrogen bonds with VAL A: 271 (2.68 Å) and GLN A: 79 (3.60 Å) amino acids. In addition, MFQ formed hydrophobic interactions with certain amino acids in the protein structure, including THR A: 291 (Halogen), LEU A: 264 (Pi Sigma, Pi-Alkyl), TRP A: 80 (Pi-Pi Stacked, Pi-Alkyl), LEU A: 210 (Alkyl), LYS A: 268 (Pi-Alkyl), VAL A: 270 (Pi-Alkyl), and TYR A: 272 (Pi-Alkyl). The interaction between co-crystal and AKT protein occurs via the establishment of three hydrogen bonds with particular amino acid residues, namely ARG A: 273 (2.91 Å), GLU A: 17 (2.88 Å), and ASP A: 274 (3.45 Å). Furthermore, the co-crystal established hydrophobic interactions with specific amino acids in the protein structure. These amino acids include ARG A: 273 (Pi-Cation), ASP A:292 (Pi-Anion), ILE A:84 (Pi-Sigma), TRP A:80 (Pi-Pi Stacked), ARG A:273 (Alkyl), LEU A:210 (Pi-Alkyl), LEU A:264 (Pi-Alkyl), LYS A:268 (Pi-Alkyl), VAL A:270 (Pi-Alkyl), ILE A:84 (Pi-Alkyl). MFQ exhibited a greater binding affinity for PI3K than its co-crystal ligand. MFQ showed a binding affinity value of –8.7 kcal/mol with the PI3K protein. In relation to the PI3K protein, MFQ formed two hydrogen bonds with GLN A: 630 (2.42 Å) and ARG A: 818 (2.55, 3.50, 3.41 Å). In addition, MFQ established hydrophobic contacts with GLN A: 630 (Halogen), HIS A: 670 (Halogen, Pi-alkyl), and PHE A: 666 (Pi-Pi T-shaped, Pi-alkyl) amino acids inside the protein's binding pocket. The PI3K protein and its co-crystal ligand formed two hydrogen bonds with ASN A: 170 (2.62 Å) and VAL A: 166 (2.69 Å). Additionally, hydrophobic interactions occurred with specific amino acids, including PHE A: 666 (Pi-Sigma), PRO A: 168 (Alkyl), ARG A: 662 (Alkyl, Pi-Alkyl), PRO A: 757 (Pi-Alkyl), and ALA A: 758 (Pi-Alkyl). The binding affinity of this interaction was measured at –8.6 kcal/mol. These findings demonstrated that MFQ strongly inhibited PI3K with a binding affinity of –8.7 kcal/mol and formed six hydrogen bonds.

The binding affinities and interactions between other proteins with MFQ and their corresponding co-crystal ligands are shown in the provided **Table 2**. **Fig. 3** illustrates the 2D and 3D arrangements of the non-bonded interactions between MFQ and a co-crystal ligand with the AKT protein, as well as MFQ with the PI3K protein.

3.2.2. Drug likeness and pharmacokinetics

Pharmacokinetics (PK) is the study of a drug and/or its metabolite kinetics in the body (Ruiz-Garcia et al., 2008). Pharmacokinetic evaluation has become an essential component of the drug discovery process due to the demand on pharmaceutical corporations to increase the success rate of new medications. When it comes to drug discovery, pharmacokinetics is most useful when it provides kinetic data for lead optimization and justification for the selection of novel drug candidates for additional research (Lin et al., 2002; Khatun et al., 2025). The PK study of MFQ was done by SwissADME. MFQ is a quinoline-methanol compound

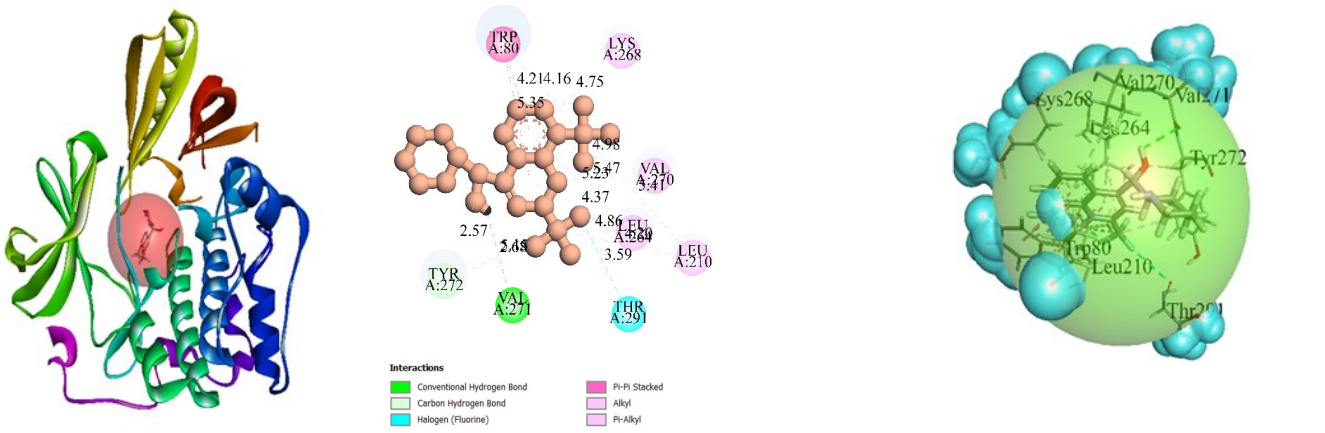
Table 2. The binding affinity, number of hydrogen bonds, type of bonds of mefloquine and co-crystals with the proteins

MM	BA (kcal / mol) of MFQ	No. of HB	AA Residues		BA of co-crys-tal	No. of HB	Co-crystal AA residues	
			HB (Bond length Å)	Others			HB (Bond length Å)	Others
NF-κB	–6.7	3	SER P:113 (2.83), LYS P:149 (2.29), ARG P:157 (2.67,)	THR P:153 (Pi-Sigma), LYS P:149 (Alkyl), VAL P:61 (Pi-Alkyl), LEU P:143 (Pi-Alkyl), VAL P:145 (Pi-Alkyl), LYS P:149 (Pi-Alkyl)	-	-	-	-
Bcl-2	–9.1	1	GLY A:138 (1.79)	ARG A:102 (Halogen), SER A:106 (Halogen), GLU A:129 (Halogen), ARG A:132 (Halogen), LEU A:130 (Pi-Sigma), PHE A:105 (Pi-Pi Stacked), LEU A:130 (Alkyl, Pi-Alkyl), ALA A:142 (Alkyl, Pi-Alkyl), ARG A:139 (Pi-Alkyl), ALA A:142 (Pi-Alkyl), PHE A:97 (Pi-Alkyl), TYR A:101 (Pi-Alkyl), PHE A:105 (Pi-Alkyl)	–11.7	9	ARG A:91 (3.15) GLU A:44 (3.15, 2.43, 2.92, 2.83, 2.80, 1.90) THR A:41 (3.08, 2.78, 2.92, 2.67), SER A:43 (3.08, 2.78, 2.83, 2.51, 2.07), ALA A:85 (2.67), VAL A:86 (2.25), GLU A:42 (2.25), LYS A:87 (2.07), GLN A:88 (1.90)	ALA A:85 (Electrostatic), GLU A:44 LYS A:8 (Electrostatic), ARG A:91 (Electrostatic),
AKT	–10.4	2	VAL A:271 (2.68) GLN A:79 (3.60)	THR A:291 (Halogen), LEU A:264 (Pi-Sigma, Pi-Alkyl), TRP A:80 (Pi-Pi Stacked, Pi-Alkyl), LEU A:210 (Alkyl), LYS A:268 (Pi-Alkyl), VAL A:270 (Pi-Alkyl), TYR A:272 (Pi-Alkyl)	–13.5	3	ARG A:273 (2.91), GLU A:17 (2.88), ASP A:274 (3.45),	ARG A:273 (Pi-Cation), ASP A:292 (Pi-Anion), ILE A:84 (Pi-Sigma), TRP A:80 (Pi-Pi Stacked), ARG A:273 (Alkyl), LEU A:210 (Pi-Alkyl), LEU A:264 (Pi-Alkyl), LYS A:268 (Pi-Alkyl), VAL A:270 (Pi-Alkyl), ILE A:84 (Pi-Alkyl)
PI3K	–8.7	2	GLN A:630 (2.42), ARG A:818 (2.55, 3.50, 3.41)	GLN A:630 (Halogen), HIS A:670 (Halogen, Pi-Alkyl), PHE A:666 (Pi-Pi T-shaped, Pi-Alkyl),	–8.6	2	ASN A:170 (2.62), VAL A:166 (2.69)	PHE A:666 (Pi-Sigma), PRO A:168 (Alkyl), ARG A:662 (Alkyl, Pi-Alkyl), PRO A:757 (Pi-Alkyl), ALA A:758 (Pi-Alkyl)
ERK	–8.6	2	SER A:153 (2.40), LYS A:54 (2.09)	GLN A:105 (Halogen), ASP A:106 (Halogen), VAL A:39 (Pi-Sigma, Pi-Alkyl), LEU A:156 (Pi-Sigma, Pi-Alkyl), ALA A:52 (Alkyl, Pi-Alkyl), ILE A:84 (Alkyl), LYS A:54 (Alkyl), CYS A:166 (Alkyl, Pi-Alkyl)	–9.0	4	LEU B:3 (1.87), ASP A:124 (1.87), PHE B:5 (2.79), LEU B:3 (2.79)	ALA B:1 (Electrostatic), ASP A:124 (Electrostatic), CYS A:161 (Pi-Sulfur), PHE B:5 (Pi-Sulfur, Pi-Alkyl), TYR A:128 (Pi-Pi Stacked), HIS A:125 (Pi-Pi Stacked), LEU B:3 (Pi-Alkyl)

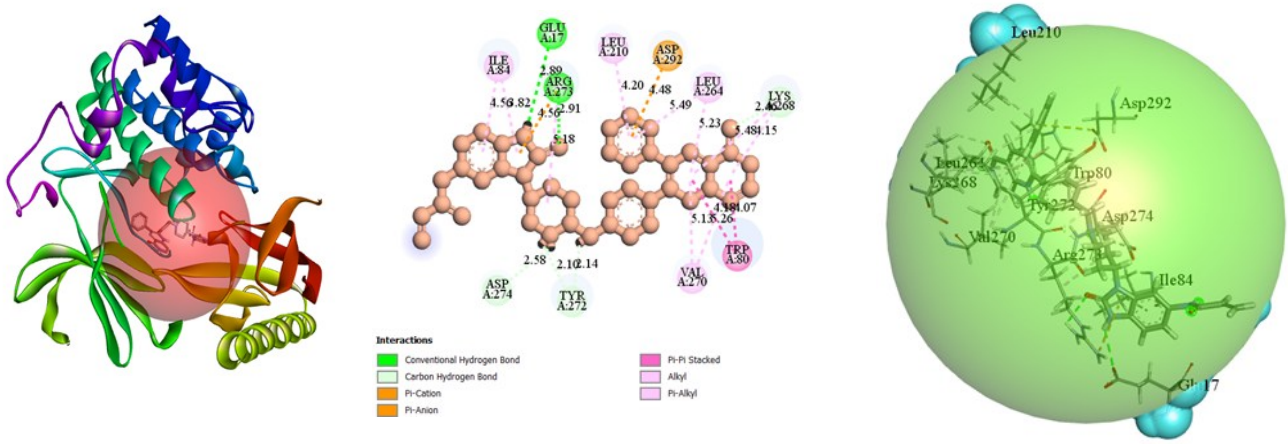
Table 2. *Continued*

MM	BA (kcal/mol)	No. of HB	AA Residues		BA	No. of HB	Co-crystal AA residues	
			HB (Bond length Å)	Others			HB (Bond length Å)	Others
MCL 1	–9.2	0	-	LEU C:246 (Halogen, Alkyl), VAL C:249 (Halogen, Alkyl), MET C:250 (Pi-Sigma, Pi-Sulfur, Alkyl, Pi-Alkyl), PHE C:270 (Pi-Pi T-shaped, Pi-Alkyl), VAL C:253 (Alkyl), LEU C:235 (Alkyl)	–10.4	3	ASN A:223 (2.20, 2.46), THR B:266 (2.77), ASN A:223 (2.45)	ARG B:263 (Pi-Cation), ALA B:227 (Pi-Sigma, Alkyl, Pi-Alkyl), VAL B:253 (Pi-Sigma), MET B:231 (Pi-Sulfur, Alkyl), HIS B:224 (Pi-Pi Stacked, Pi-Alkyl), MET B:250 (Alkyl), VAL B:253 (Alkyl), VAL A:220 (Alkyl), LEU B:267 (Alkyl), PHE B:270 (Pi-Alkyl), ARG A:222 (Pi-Alkyl), ARG B:263 (Pi-Alkyl)
JNK	–9.0	2	MET B:149 (2.19), LEU B:148 (3.55)	GLU B:147 (Halogen), MET B:146 (Pi-Sulfur, Alkyl), LYS B:93 (Alkyl), LEU B:206 (Alkyl, Pi-Alkyl), ILE B:70 (Alkyl, Pi-Alkyl), VAL B:196 (Alkyl, Pi-Alkyl), ALA B:91 (Alkyl), ILE B:124 (Alkyl), MET B:149 (Alkyl), VAL B:78 (Alkyl, Pi-Alkyl), ALA B:91 (Pi-Alkyl)	–9.9	6	ARG A:110 (2.28), THR A:213 (2.46), ASN A:194 (2.89), ASP A:207 (3.49), GLU B:164 (3.67), VAL B:361 (3.49),	ASP A:207 (Pi-Anion), LEU A:210 (Pi-Sigma), ARG A:107 (Alkyl)
PARP	–7.6	2	GLN B:759 (2.54), MET B:890 (2.08)	ASP B:766 (Pi-Anion), TYR B:889 (Pi-Pi T-shaped), TYR B:896 (Pi-Alkyl)	–9.1	4	GLY B:863 (2.09, 2.36), TYR B:896 (2.45), TRP B:861 (2.47), GLU B:763 (3.58)	HIS B:862 (Pi-Pi Stacked, Pi-Alkyl), TYR B:896 (Pi-Pi Stacked), TYR B:907 (Pi-Pi Stacked, Pi-Alkyl), HIS B:909 (Pi-Alkyl)
XIAP	–8.1	2	LEU A:256 (2.57), THR A:254 (2.44)	PRO A:257 (Halogen), ARG A:258 (Halogen, Pi-Donor Hydrogen Bond, Pi-Sigma, Pi-Alkyl), CYS B:351 (Pi-Sigma, Pi-Sulfur), GLU B:350 (Amide-Pi Stacked), LEU A:256 (Alkyl), LEU B:344 (Alkyl), LEU B:348 (Alkyl), CYS B:351 (Alkyl), PRO A:260 (Alkyl)	–8.6	4	GLY A:326 (2.67), GLY A:304 (1.82), PRO A:325 (3.12), ASN A:249 (3.34)	TRP A:323 (Pi-Alkyl), TYR A:324 (Pi-Alkyl), PRO A:251 (Pi-Alkyl), PRO A:325 (Pi-Alkyl),

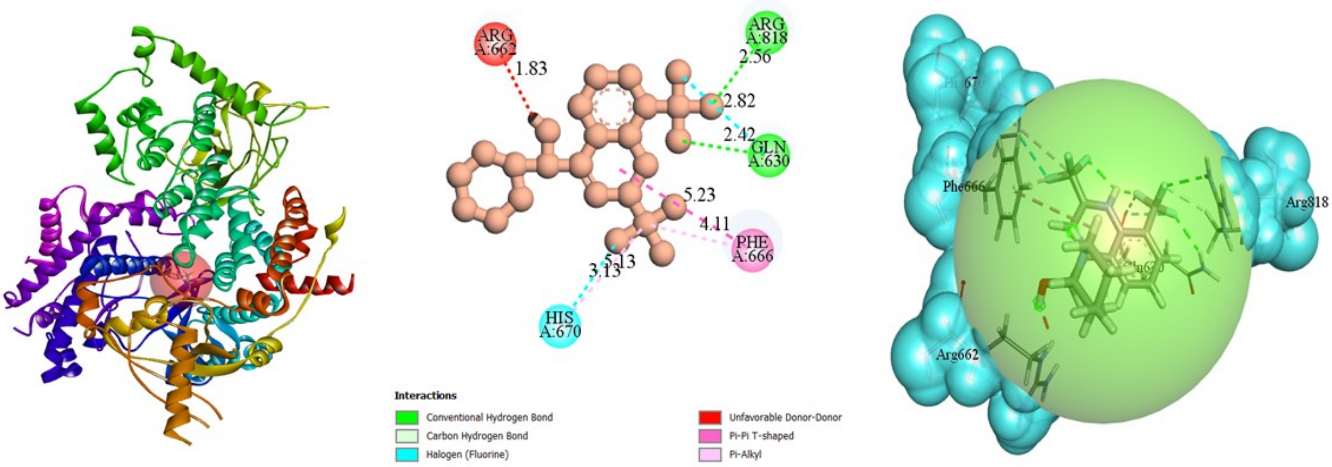
AA: Amino acid; BA: Binding affinity; HB: Hydrogen bond; MM: Macromolecules; MFQ: Mefloquine



MFQ Vs AKT



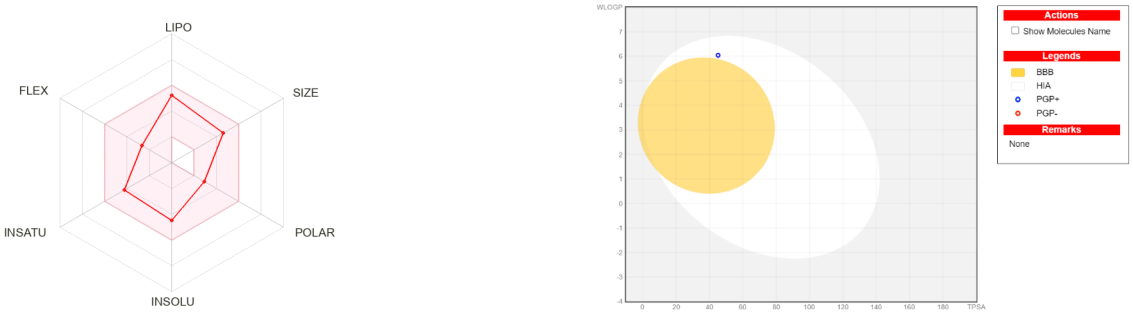
Co-crystal Vs AKT



MFQ Vs PI3K

Fig. 3. The 2-dimentional and 3-dimentional figure of the non-bonded interactions between mefloquine and a co-crystal ligand with the AKT protein, as well as mefloquine with the PI3K protein. [MFQ: Mefloquine, PI3K: Phosphoinositide 3-kinase; AKT: Ak strain transforming]

structurally related to quinine (White, 1994). The physiochemical parameters revealed that the molecular mass of MFQ is 378.31 g/mol, which is under 500 and has a number of heavy atoms, rotatable bonds, H-bond acceptors, and donors of 26, 4, 9, and 2, respectively. Since most binding targets have more hydrophobic elements than hydrophilic ones, lipophilic substances often have a higher affinity for binding proteins (Chagas et al., 2018). The lipophilicity of MFQ is 3.43. The compound is moderately solubilized. The brain is protected from hazardous blood-borne, endogenous, and exogenous chemicals by the dynamic blood-brain barrier (BBB), which also keeps the homeostatic microenvironment in place (Zhao et al., 2002). MFQ has a high GI absorption but cannot cross BBB. MFQ abides by the Lipinski rules of five without violation, which assesses the pharmacological activity with a better bioavailability score of 0.55. However, **Table 3** and **Fig. 4** demonstrated the pharmacokinetics, drug-likeness, and Lipinski rule parameters of MFQ.



Mefloquine

Fig. 4. An overview of mefloquine's pharmacokinetic, physiochemical, and toxicological characteristics. [The appropriate physicochemical space for oral bioavailability is the colored zone; SIZE: 150 g/mol < MV < 500 g/mol; LIPO (lipophilicity): −7 < XLOGP3 < + 5.0; INSOLU (in-solubility): −6 < log S (ESOL) < 0; POLAR (polarity): 20 Å^2 < TPSA < 130 Å^2; INSATU (in-sat-uration): 0.25 < Fraction Csp3 < 1; FLEX (flexibility): 0 < num. rotatable bonds < 9].

Table 3. Mefloquine's pharmacokinetics, drug-likeness, and Lipinski rule parameters

Parameters	Values/ status
Physicochemical properties	
Molecular mass	378.31g/mol
Number of heavy atoms	26
Number of aromatic heavy atoms	10
Number of rotatable bonds	4
Number H-bond acceptors	9
Number H-bond donors	2
Molar refractivity	86.51
TPSA	45.15 Å^2
Lipophilicity	
Log Po/w(MLOGP)	3.43
Log S (ESOL)	−4.49
Water solubility	
Solubility class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
Drug-likeness	
Lipinski	Yes, 0 violation
Ghose	No; 1 violation: WLOGP > 5.6
Veber	Yes
Egan	No; 1 violation: WLOGP > 5.88
Muegge	Yes
Bioavailability score	0.55

BBB: Blood-Brain Barrier; GI: Gastrointestinal: TPSA: Topological Polar Surface Area;

3.2.3. In silico toxicity prediction

Toxicity testing is one of the most significant processes in determining whether chemical chemicals may cause undesirable consequences. For instance, chronic chemical exposure is frequently linked to the development of human genotoxicity, carcinogenicity, immunotoxicity, and reproductive and developmental toxicity (Guengerich, 2011). Given the substantial expenses associated with medication failure resulting from toxicity discovered later in the research phase, toxicity needs to be ascertained as early as feasible to direct production (Dearden, 2003). MFQ toxicity was predicted through the use of the ProTox 3.0 server protocol. MFQ has an LD_{50} value of 880 mg/kg and a toxicity class of 4, according to the data. It doesn't show any cytotoxic, carcinogenic, or hepatotoxic properties. It exhibits neither mutagenicity nor immunotoxicity. This prediction indicates that MFQ may be authorized for use as a potential drug. **Table 4** and **Fig. 5** demonstrated the toxicological data of MFQ.

4. Concluding remarks

MFQ, originally developed as an antimalarial drug, has demonstrated significant anticancer activities through multiple mechanisms, as supported by extensive literature and *in silico* studies. These findings reveal that MFQ can inhibit cancer cell proliferation, induce oxidative stress, and stimulate apoptosis in various types of cancer cells, including breast, colorectal, cervical, gastric, and prostate cancers. The molecular docking studies highlighted its strong binding affinity to key cancer-related proteins, particularly PI3K, indicating its potential as a PI3K inhibitor. Moreover, MFQ exhibits promising pharmacokinetic and toxicity profiles, suggesting its viability as a therapeutic agent. However, despite these encouraging results, further research is essential to fully elucidate MFQ's anticancer potential as PI3K inhibitor. Clinical trials and additional evaluations are necessary to confirm its efficacy and safety in humans. The continued exploration of MFQ could contribute significantly to the development of new, effective cancer therapies.

Conflict of interest

The authors declared no conflict.

Data availability

Data is contained within the article.

Table 4. Toxicity prediction data of mefloquine

Parameters		Report/ predicted value
		Mefloquine
Type of toxicity	Toxicity class	4
	LD_{50} (mg/kg)	880
	Carcinogenicity	Inactive
	Cytotoxicity	Inactive
	Immunotoxicity	Inactive
	Hepatotoxicity	Inactive
	Mutagenicity	Inactive

LD_{50}: Lethal dose 50

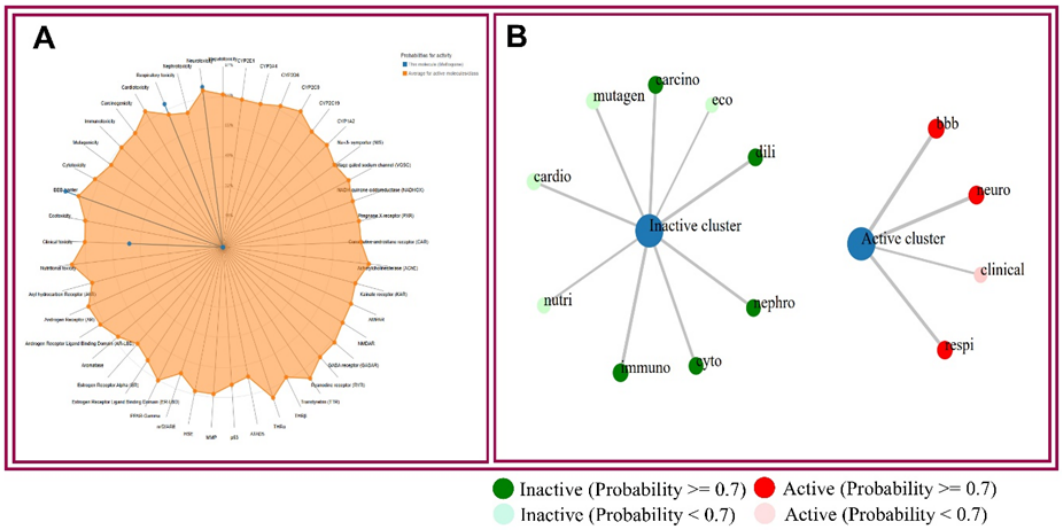


Fig. 5. *In silico* toxicity prediction data of mefloquine. A) The toxicity radar chart of mefloquine is intended to quickly illustrate the confidence of positive toxicity results compared to the average of its class; B) The network chart is intended to quickly illustrate the connection between the selected compound and predicted activities. [nutri: nutritional toxicity; cardio: cardiotoxicity; mutagen: mutagenicity; nephro; nephrotoxicity; dili: drug induced liver injury ; carcino: carcinogenicity; immuno: immunotoxicity; neuro: neurotoxicity; bbb: blood brain barrier; eco: ecotoxicity; clinical: clinical toxicity; cyto: cytotoxicity; respi: respiratory toxicity]

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Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas that is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and confirming to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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