Elkhawas *et al.*
Future Journal of Pharmaceutical Sciences (2023) 9:87
https://doi.org/10.1186/s43094-023-00538-5

Future Journal of Pharmaceutical Sciences

RESEARCH Open Access

Antiproliferative and apoptotic activities of tomato bioactive metabolite on MDA-MB-435 cell line: in silico molecular modeling and molecular dynamics investigation

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Abstract

Background As an external organ, the skin protects the whole body against hazardous external influences. Ultraviolet (UV) radiation is one of these influences which in high amount can cause DNA damage, and even skin cancer. Hence, it is important to promote skin protection with commercially available remedies, and with a healthy diet. Certain vegetables when applied topically or consumed orally may help minimize the effect of UV radiation. The study's goal is to isolate lycopene from tomatoes and evaluate its influence on cell cycle and viability in melanoma cell lines. The cell cycle was examined using flow cytometry, and apoptotic cells were identified using annexin/propidium iodide (PI) markers. Moreover, a molecular modeling and molecular dynamics (MD) simulation were performed to evaluate the stability and dynamics behavior of the compound.

Results The obtained results revealed that lycopene caused apoptosis and stopped the cell cycle in human skin carcinoma MDA-MB-435 cells with an IC_{50} value of 12.14 ± 3.37 uM. It demonstrated a noteworthy ability to inhibit cell growth and improve apoptosis. The effect was dose dependent leading to suppression of cell cycle progression in the G2/M phase. In silico molecular docking investigation confirmed these findings, where the tested compound showed hydrophobic binding with key amino acids. ADME/TOPKAT study along with the Swiss ADME online tool revealed that lycopene exhibits good drug-like properties.

Conclusion According to our results, lycopene may be effective in treating human skin carcinoma.

Keywords Cell cycle, MDA-MB-435, Melanoma, Molecular docking, Molecular dynamic, ADME, Tomato

Background

Ayurvedic medicine has traditionally recognized the advantageous benefits of diet and plants on human health. For eras, the formation of health conditions and elimination of illness conditions constituted the main focuses of the holistic Ayurvedic medical approach [1]. This observation recalls the explanation of a nutraceutical as a food component or food which delivers health or medical advantages, involving the avoidance and/or healing of an illness [2]. Several natural sources were employed throughout human history because of their curative and healing benefits, including garlic, ginger,

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cinnamon, honey, and many others [3, 4]. The number of publications and debates on the possible consumption of food supplements and nutraceuticals was significantly expanded in recent decades [5]. The interest of the scientific world as well as the public in functional foods and nutraceuticals was dramatically elevated recently [6]. Because of the widespread use of inactive prescriptions and the increased usage of chemical substances in food, there is a demand to explore molecules found genuinely in unrefined foods which serve as functional and health boosters [7]. Phytochemical supplementation was recognized to provide both dietary and health benefits comprising polyphenols, carotenoids, and organo-sulfur compounds [8]. The growing patient demand for healthy lives, reflected by more nutritional eating and acceptance of complementary therapeutic techniques was in favor of scientific research, especially in the field of nutraceuticals [9].

Skin carcinoma is a very prevalent type of cancer [10] that is frequently initiated by UV ray exposure, which is a major contributor to the development of melanoma [11]. Several in vitro studies have revealed that pre-exposure to lycopene in human keratinocytes increases the expression of the apoptosis regulator gene BAX in UV-B-irradiated skin cells. This creates a cell cycle delay during the S-phase transition, reducing the cells number in the G0/G1 phase. Lycopene exerts a defensive effect on irradiated cells, which may show indications for skin cancer treatment [12].

Lycopene "carotenoid" gives the crimson color to tomatoes, papaya, watermelon, and guava [13]. Tomatoes act as the market most significant source of lycopene delivering a huge amount of it [14]. Many studies reported the health benefits of lycopene, such as antioxidant properties [15], its ability to treat degenerative diseases [16], cardiovascular conditions, as well as its effectiveness against prostate cancer [17, 18], breast cancer [19], and its involvement in skin anti-aging mechanism [20]. Lycopene consumption has not only been linked to positive health effects, also it is also well tolerated in the human body [21].

Cyclin-dependent kinases (CDKs) are serine/threonine enzymes that require a regulatory subunit called cyclin for their activation. CDKs have vital functions in regulating cell division and influencing transcription in response to various external and internal signals. The expansion of the CDK family in mammals has led to their classification into three subfamilies related to the cell cycle (Cdk1, Cdk4, and Cdk5) and five subfamilies related to transcription (Cdk7, Cdk8, Cdk9, Cdk11, and Cdk20). This CDK family plays a central role in numerous signaling pathways that control both transcription and cell cycle progression. Recent research has revealed that Cyclin-dependent kinase 1 (CDK1) can stimulate replicative DNA synthesis and potentially contribute to resistance to chemotherapy. These findings provide new insights into how cell cycle regulation and DNA replication are coordinated to maintain genomic stability. Cdc2/cdk1 is a specific cyclin-dependent protein kinase that governs the transition of cells from the G2 phase to the M phase of the cell cycle [22].

In the current study, it was suggested that lycopene with its antioxidant/anti-inflammatory effects isolated from carotenoids exhibited an apoptotic effect highlighting its possible use in melanoma prevention and treatment. To prove this theory, in vitro screening of the antitumor activity toward melanoma cell lines (MDA-MB-435) was performed for lycopene isolated from tomatoes grown in Egypt. Toxicity was also studied on normal cells in vitro. To further explore the mechanism of antineoplastic behavior presented by lycopene for CDK1, in vitro assays were performed along with in silico molecular modeling studies using Discovery Studio 4.1. Furthermore, to evaluate the pharmacokinetic features from the standpoint of absorption, distribution, metabolism, and excretion, ADMET tests were projected using the SwissADME [23] online tool alongside in silico toxicity studies to determine the safety of the lycopene extracted, and finally the results of the findings were then compared to ADMET results generated by Discovery studio client.

Results

Compound identification

Lycopene Fig. 1 was separated as a red powder (1.5 mg) where its methanol solution gave one spot on 1D and 2D silica-coated TLC. The identification of lycopene was achieved via the addition of concentrated sulfuric acid to lycopene solution in methanol where it gave an indigo-blue color to the solution. Additionally, NMR data agreed with those reported data for lycopene [24]. NMR spectral data are illustrated in Additional file 1: Fig. S1.

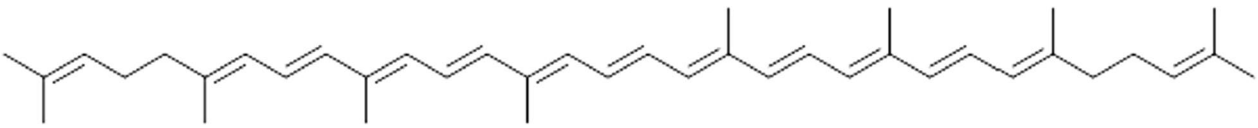

Fig. 1 The chemical structure of Lycopene

In vitro assessment of cytotoxic activity of lycopene using MTT assay

Antitumor drugs typically cause cytotoxicity by activating several signal pathways that end up in causing apoptosis. Several studies revealed that apoptosis is induced, and G2/M arrest is the mechanism by which clinical anticancer agents work in human cancers [25]. The cytotoxic activity of lycopene was tested against the mutant MDA-MB-435 skin cancer cell line [26]. Lycopene showed good cytotoxicity (IC_{50} 12.14 ± 3.37 uM) (Fig. 2). Lycopene resulted in the induction of programmed cell death and cell cycle arrest in MDA-MB-435 skin carcinoma cell lines Fig. 3.

DNA analysis using flow cytometry for cell cycle and apoptosis

Results obtained from the flow cytometry experiment for cell cycle investigation revealed that when treated with lycopene, cells where increased in the G0–G1 phase along with enhancing the G2/M phase, however, the percentage of cells in S decreased compared to the control group. The control cells displayed a normal pattern of DNA content indicating the pre G1, S, G2/M, and G0/G1 phases of the cell cycle. Lycopene-treated cells exhibited cell cycle arrest at the G2/M phase (Fig. 4, Table 1).

In silico studies: molecular docking

Molecular docking study using CDOCKER protocol in Discovery Studio 4.1 Software was carried out. The isolated compound was docked into the CDK1 active site. The X-ray crystallographic structure of CDK1 protein (PDB ID: 4YC6) was downloaded from PDB [49] Protein was cleaned, unneeded chains were removed, and hydrogens were added. Simulation using CHARMm forcefield and partial charge MMFF94 was applied, and

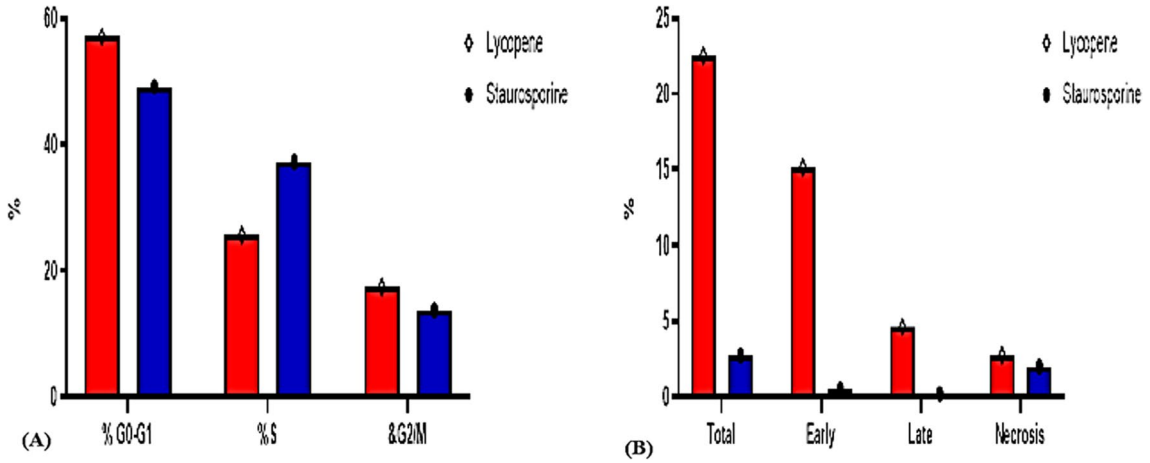

Fig. 2 Effect of lycopene (**A**) and staurosporine (**B**) on MDA-MB-435 cells showing IC_{50} (µM) using MTT assay

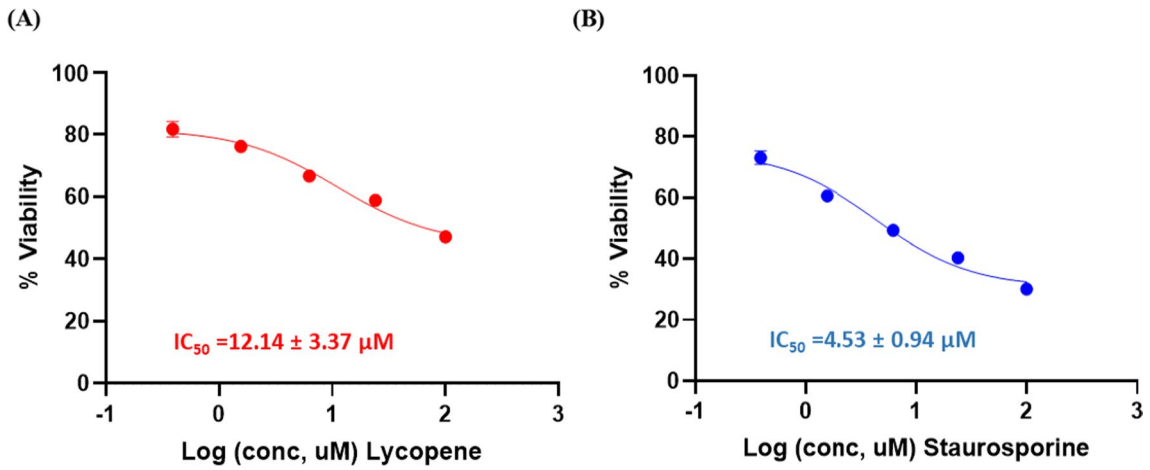

Fig. 3 Bar charts showing the effect of lycopene and staurosporine on cell cycle arrest and apoptosis (**A**); flow cytometry analysis (**B**)

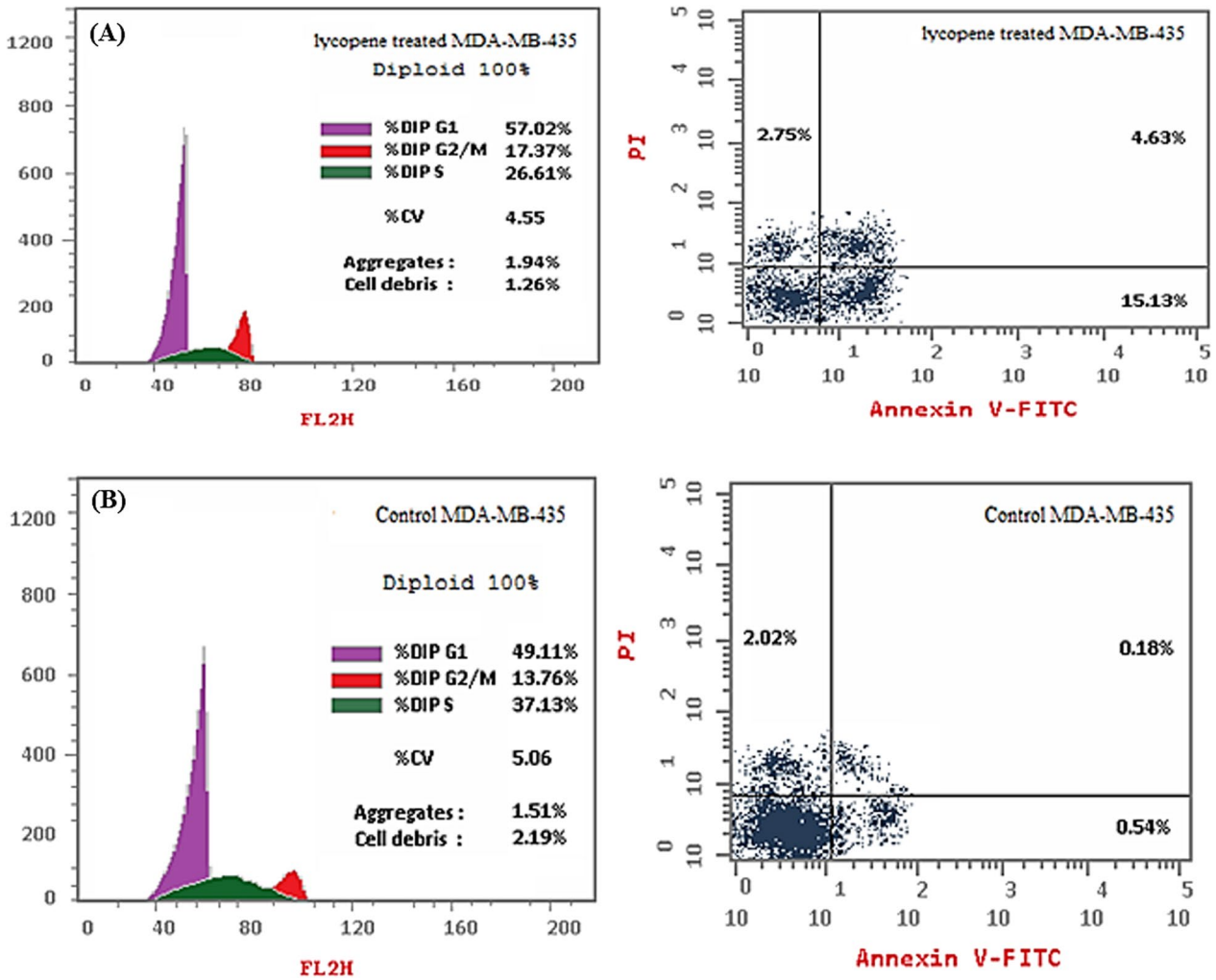

Fig. 4 Bar charts showing the effect of lycopene and staurosporine on cell cycle arrest and apoptosis (**A**); flow cytometry analysis (**B**)

Table 1 Flow cytometric analysis for cell cycle distribution of Lycopene on MDA-MB-435 cells

	Results DNA content			
	%G0–G1	%S	%G2/M	Comment
Control/MDA-MB-435	49.11	37.13	13.76	–
Lycopene/MDA-MB-435	57.02	26.61	17.37	Cell growth arrest@ G2/M Phase

a heavy atom was created. Constraints were turned to be fixed and minimization of proteins took place. Receptor and binding site were identified from the complex ligand interaction site. The validity of the docking protocol was substantiated by subjecting virtual screening datasets containing established ligands targeting CDK1 active sites to rigorous computational assessments. This entailed a comprehensive docking and redocking analysis of the ligand sets, accompanied by a meticulous examination of their resultant binding modes. The root-mean-square deviation (RMSD) calculations arising from these investigations yielded values within the range of 0.2–0.9 Å. The binding mode of the lycopene extract was studied to explain its biological results and to gain further insight into binding orientations and interactions.

Upon docking, the most active conformer of lycopene displayed – (energy of C-docker interaction) = – 80.35 kcal/mol. Six essential HB (hydrophobic bonds) with PHE 82, ILE 10, LEU 135, VAL 18 and LYS 89 were shown along with extra hydrophobic bindings which might explain its activity as a CDK1 inhibitor with an antineoplastic effect, as shown in Fig. 5.

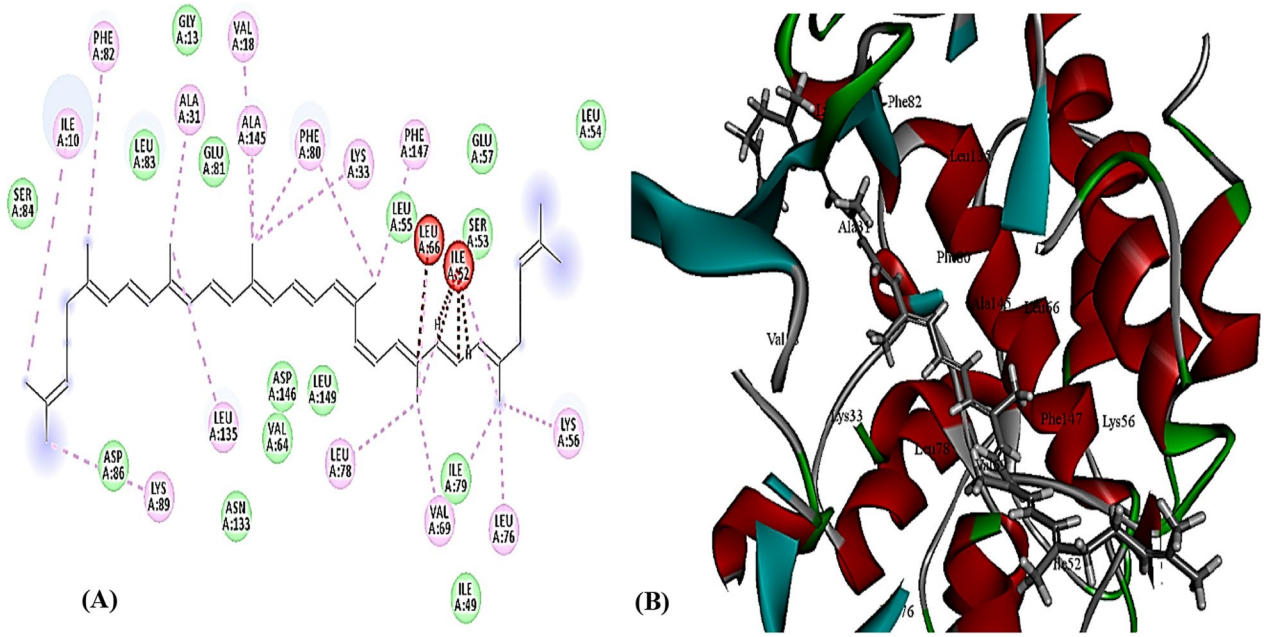

Fig. 5 2D and 3D binding modes of lycopene in hCDK1 binding pocket in both 2D (**A**) and 3D (**B**) modes; for the 2D picture: green means hydrogen bond, purple means hydrophobic interactions, while red means positive-positive interactions, however for the 3D picture: Blue color ribbons represent beta sheets, red color ribbons represent helix, gray color ribbons represent turns and green color ribbons represent residues less than 10 Å

Dynamic simulations

Dynamic simulation and trajectory analysis were performed to prove the stability of the interaction between lycopene and CDK1. The primary goal of the dynamic simulation is to determine whether the interaction between Lycopene and CDK1 was stable or not. Figure 6 shows the total energy versus time range 16–24 ps of lycopene upon interaction. The energy levels fluctuate between − 9270 and − 9285 which presents stable and preferred mode of interaction. The docked complex's root mean square deviation (RMSD) measures how much the positions of atoms in the Lycopene-CDK1 complex change over time compared to their initial positions. Here the RMSD values range between 0 and 4.25, suggesting that the complex remains relatively stable with only minor deviations. This is a sign of a well-preserved interaction. Furthermore, the root mean square fluctuations (RMSF) were used to assess flexibility during this simulation. In this case, low RMSF values indicate stringent binding, which means that the interaction between lycopene and CDK1 is tight and inhibitory. It implies that Lycopene effectively interact with CDK1 in a way that restricts its movements and activity. In summary, the study used dynamic simulation and various analyses to demonstrate that lycopene forms a stable and preferred interaction with CDK1, which inhibits its activity and suggests potential therapeutic implications.

Ramachandran plot

Predicted torsion angles verification within the targeted receptor could be done throughout performing Ramachandran plot. Discovery Studio 4.0 was used before and after docking to authorize the interaction of our compound in correct binding sites and reveal the topological changes applied to CDK1 protein. The conventional terms used to represent the torsion angles on either side of alpha carbons in peptides could be represented by low energy conformations for ϕ (phi) and ψ (psi). The graphical representation of Fig. 8 displayed the same number in favorable green areas during interaction with Lycopene when compared to the free protein, thus, ease of multiple conformations within the binding sites of the protein (Fig. 7).

ADME and TOPKAT toxicity studies

ADME and TOPKAT toxicity studies were carried out using Discovery Studio 4.1 to delve deeper into the pharmacokinetic features of the proposed drug. The compound's intestinal absorption, solubility, hepatotoxicity, ability to cross the blood brain barrier (BBB), and ability to attach to plasma protein (PPB) were all evaluated. Results showed that BBB takes the level of 3 and therefore, it is not capable of passing the blood brain barrier and can be consumed safely without causing any CNS effects. Absorption level is 0 which indicates good human

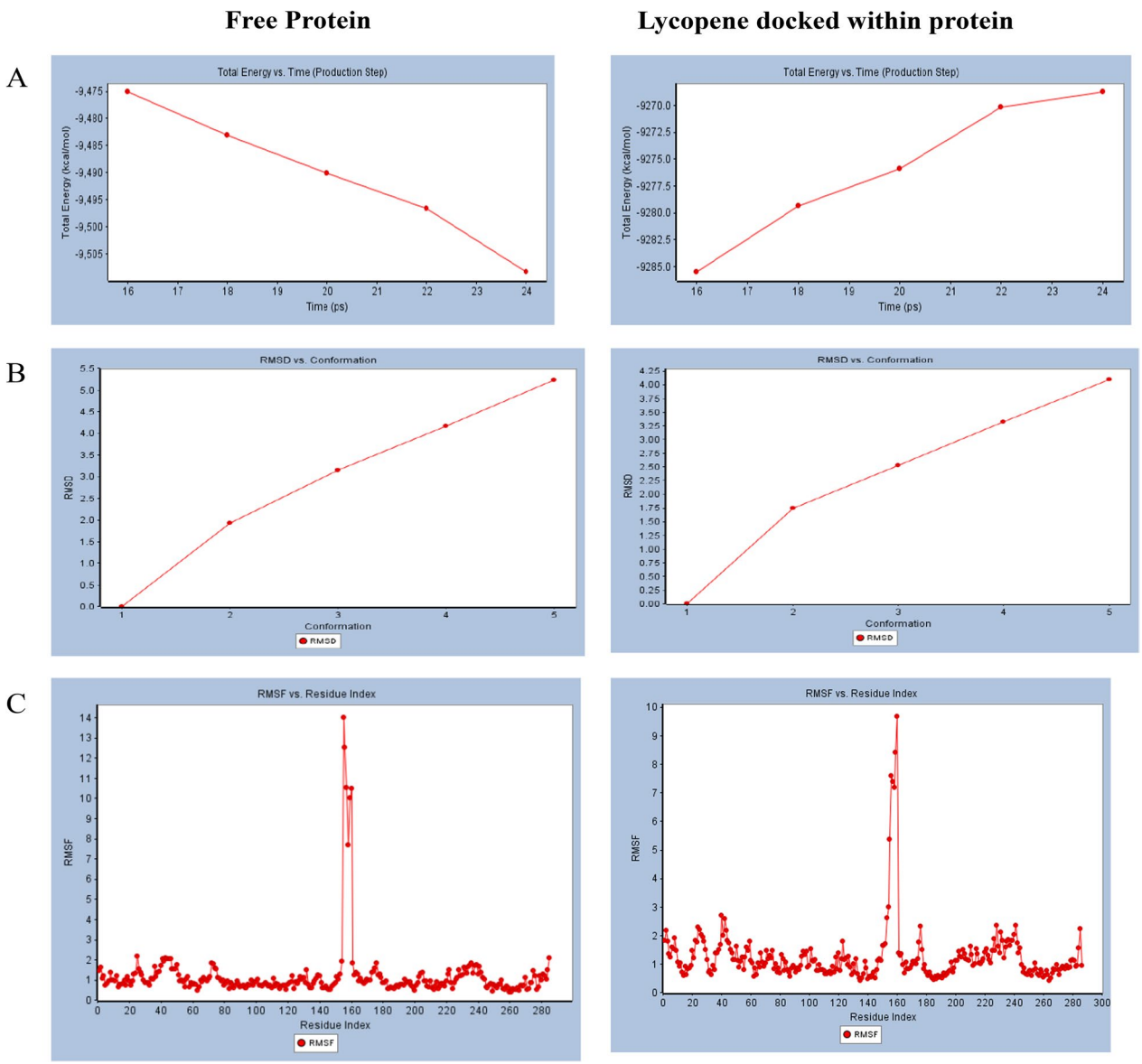

Fig. 6 **A** Total energy versus Time in production step, **B** RMSD versus Conformations, **C** RMSF versus Residue Index, for free protein and lycopene docked within the protein pocket

intestinal absorption. Regarding the aqueous solubility lycopene, stated its level to be 3 indicating a good aqueous solubility level. The key property (PSA) was connected to drug bioavailability. It showed plasma protein binding level of 0 indicating less than 90% binding potential. Hence, passively absorbed molecules with PSA > 140 are assumed to have lesser bioavailability. The addressed compound is expected to have good passive oral effect and it also displayed good bioavailability results with PSA of 106.179. Besides, LogP98 descriptor of lipophilicity showed a value of 1.005. Lycopene showed certain hepatotoxicity. Also, it is considered a non-inhibitor to Cytochrome P450 2D6 (CYP2D6). Accordingly, the tested compound's pharmacokinetic characteristics were anticipated using the SwissADME online tool, and the obtained findings came along with the results obtained from Discovery studio ADMET study. The tested compound showed high GIT absorption. Regarding BBB penetration, lycopene was found to locate away from the blood brain barrier yellow region Fig. 8, this means its inability to penetrate the BBB. Furthermore, the bioavailability radar chart presented lycopene to be in the desired pink region of 5 parameters out of 6 used for the estimation of oral absorption: FLEX (Flexibility),

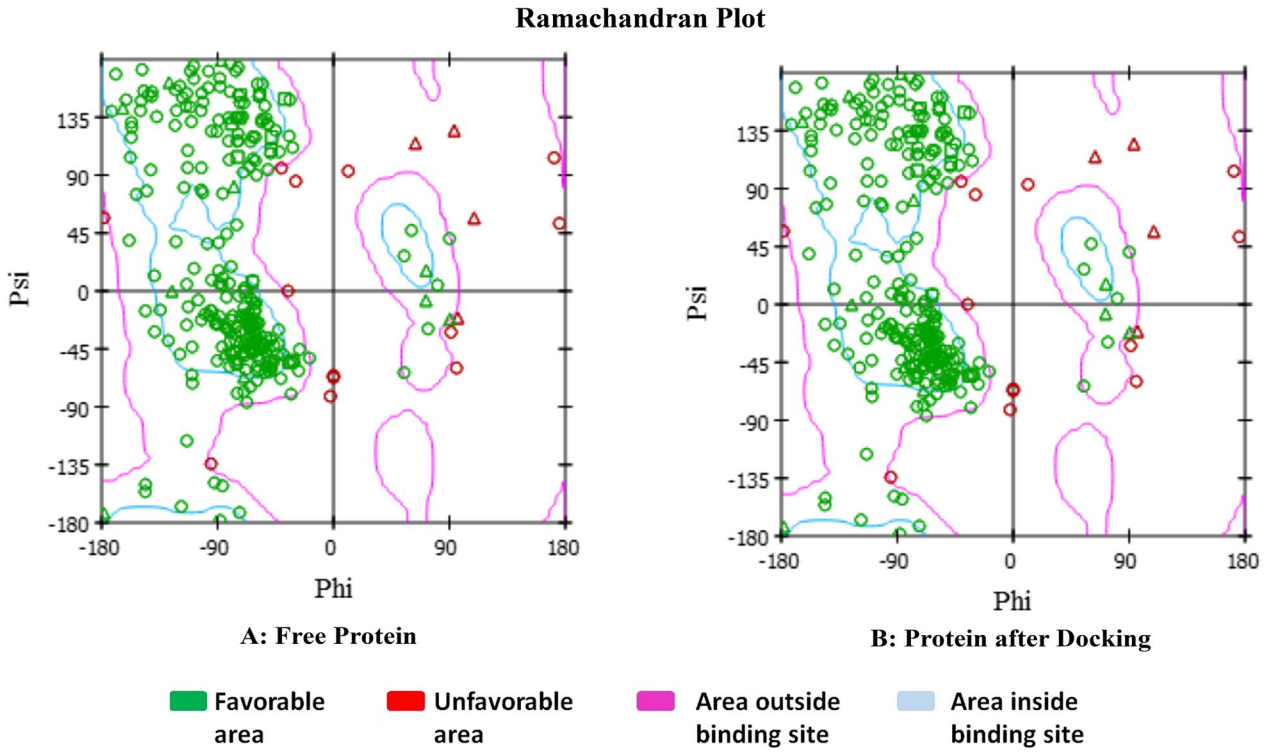

Fig. 7 Ramachandran plot presenting torsional energy conformations for interaction between lycopene and CDK1

SIZE and POLAR (Polarity), INSOLU (Solubility), LIPO (Lipophilicity). The Ames toxicity protocol was used in the TOPKAT investigation to test potential toxicity to the extracted lycopene. All TOPKAT Ames probability (0.49×10^{-8}), application and score (-50.6) showed that lycopene is neither mutagenic, carcinogenic nor irritant, weak skin sensitization and was all in the expected ranges. Additionally, TOPKAT rat oral LD_{50} is 10.653 g/kg b. wt.; TOPKAT rat max tolerated dose feed is 0.046 g/kg b. wt.; TOPKAT carcinogenic potency TD_{50} mouse is 16.60 g/Kg b. wt./day and TOPKAT carcinogenic potency TD_{50} rat is 253.252 g/Kg b. wt./day.

Discussion

In this study, in vitro screening of the antitumor activity toward melanoma cell lines (MDA-MB-435) was performed for lycopene isolated from tomatoes grown in Egypt. Lycopene gives apricot, tomato, papaya, watermelon, rosehip, guava, passion fruits, and other fruits and vegetables their red color. Tomatoes and tomato market products are a valuable source of lycopene in diets; thus, the majority of lycopene research centers on tomatoes and tomato products [27]. Several techniques for extracting lycopene were used, however supercritical fluid extraction with CO_2 yields superior findings than other approaches [28].

Despite the increased urbanization and lifestyle changes, skin carcinoma remains the most frequent human cancer, especially in the white population. Every year, millions of new incidences are detected around the world. Even though excellent therapeutic techniques such as photodynamic therapy, immunotherapy, and chemotherapy have been discovered, the problem of skin cancer remains chronic [29]. In recent decades, the consumption of functional foods of natural source has attracted the concern of scientists in the potential use of functional foods for treating skin cancer. Lycopene, the primary phytochemical present in tomatoes and a popular component in skin-care products has revealed numerous linked biological activities for skin tissue, including anti-inflammatory, antibacterial, and anti-aging benefits [30].

According to recent research, lycopene not only scavenges free radicals well, but it also assists to preserve the equilibrium of the endogenous defense system. It has been mentioned as an antitumor drug, as demonstrated by several in vivo, in vitro, and epidemiological investigations [31]. Different studies reported the cell cycle arrest and proapoptotic outcome of lycopene on varies human cancer cell lines like such as cervical (Hela), liver (HepG2), prostate (DU-145), laryngeal (Hep-2), colon (HT-29, T84), lung (A-549), and breast (MCF-7) tumors [32–34]. The effect was dose

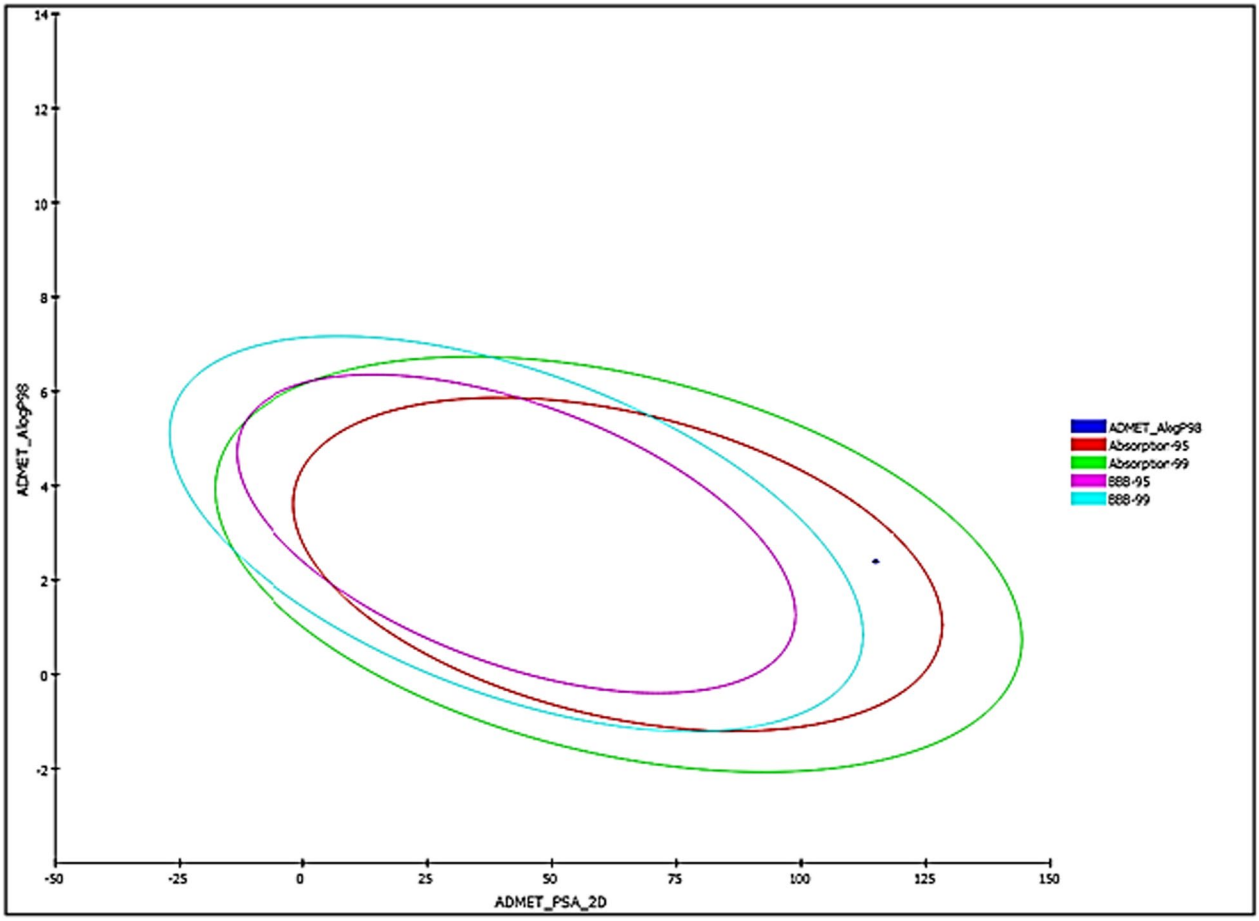

Fig. 8 Plot demonstrating Lycopene's Effects: Intestinal Absorption, Aqueous Solubility, Hepatotoxicity, BBB Permeability, and Cytochrome P450 Interaction"

dependent leading to suppression of cell cycle progression in the G2/M phase, and strong apoptotic action by elevating caspase-3 levels. Additionally, lycopene was examined in vivo against different cancer types. It showed synergistic anticancer effect in mice with prostate cancer when used with enzalutamide and lung cancer in combination with sorafenib. These combinations decreased the tumor volume, metastasis, reduced MMP-2, MMP-9, NF-κb, nuclear translocation, and DNA binding [35–37]. Furthermore, it was mentioned by Correa et al. [38] that lycopene is known to work by altering redox sensitive cell targets such as protein kinases, protein tyrosine phosphatases, Mitogen Activated Protein Kinases, and transcription factors, in addition to ROS scavenging. It also has antiproliferative activity on breast cancer cell lines by lowering the expression of cell cycle regulatory proteins and cyclin-dependent kinases, in addition to inhibiting insulin-like growth factor activity [39]. These findings are corroborated by epidemiological researches in which the consumption of tomatoes were linked to a lower risk of numerous forms of cancer, including prostate, lung, and colon tumors [40].

In several cancer cell lines research, anticancer experiments revealed that lycopene is relatively efficient at > 5 mM. The variable percent cytotoxicity of lycopene in various tumor cell lines could be attributed to variation in the mode of cell growth, condition of cell metabolism, and composition of the membrane [41].

Methods

Plant material

Fresh tomato fruits (*Solanum lycopersicum* var. saladette L. Family Solanaceae) were collected from Mepaco-medifood pharmaceutical company's medicinal farm in El Sharqiya, Egypt. Dr. Labib, T. Taxonomist of the Botanical Orman Garden, Egypt, generously authenticated them.

Lycopene extraction

Fresh tomatoes were cleaned with tap water, then mixed with a home blender and the homogenate of seeds and skins was strained. Sixty-five mL of methanol was added to fifty grams of tomato paste. To avoid hard lumps formation, the mixture was immediately agitated. The thick solution was filtered after 2 h, and the red residue was agitated for an extra 15 min with 70 mL of methanol and carbon tetrachloride mixture of equal parts before being separated by filtration. The carbon tetrachloride layer was moved to a separating funnel, followed by the addition of one volume of water and vigorous shaking, and then the carbon tetrachloride phase was separated and evaporated. Consequently, the residue was diluted with 2 mL of benzene then 1 mL of boiled methanol, and immediately, lycopene crystals were formed. Further purification on active acidic alumina column chromatography using toluene as mobile phase was done. The dark red zone was gathered, evaporated, and stored in a dark vial to avoid oxidation [24].

Lycopene identification by nuclear magnetic resonance (NMR) spectrometer

The identification of lycopene was done by nuclear magnetic resonance (NMR) spectrometer using Bruker Ascend 400/R (Bruker®, AVANCE III HD, 400 MHz, Switzerland)-Ain Shams University- Cairo, Egypt, Faculty of Pharmacy, Drug Discovery, Research and Development center [42–45].

Assessment of cytotoxic activity of lycopene using MTT assay

American Type Culture Collection (ATCC) provided the cell line MDA-MB-435. DMEM (Invitrogen/Life Technologies) supplemented with 10% FBS (Hyclone), 10 ug/mL of insulin (Sigma), and 1% penicillin–streptomycin was used to cultivate the cells. The remaining chemicals, components, and reagents were all purchased from Sigma Chemical Co. At 37 °C and 5% CO_2, MDA-MB-435 cells were sub-cultured into a 96-well plate with 1 × 104 cells per well in medium before being exposed with or without several dilutions of test agents, each in triplicate for 24 h. PBS was used at the end of the incubation period to wash the harvested cells. To each well a concentration of 20 µL of MTT was poured and incubated for 2 h before adding the 200 µL of DMSO. At a wavelength of 570 nm, the absorbance was measured using an ELISA reader (Multiskan EX, Lab Systems) [46, 47].

DNA analysis using flow cytometry for cell cycle and apoptosis.

Before the cells were harvested, MDA-MB-435 cells (2 × 105 cells/well) in 12-well plates were exposed to various concentrations of the lycopene-testing compound for various amounts of time. The cells were suspended in PBS containing 40 g/mL protease inhibitor, 0.1 mg/mL RNase A (Sigma, USA), and 0.1% triton x-100 after being gently fixed in 70% ethanol (in PBS) on ice for an overnight period. The cells were examined by flow cytometry (Becton–Dickinson, San Jose, CA, USA) using an argon laser at 488 nm after 30 min at 37 °C in the dark. After that, the cell cycle and apoptosis were identified and analyzed [26, 48, 49].

In silico studies: molecular modeling studies

Utilizing the CDOCKER protocol and the Discovery Studio 4.1 Software, a molecular docking study was conducted. The isolated component underwent docking against the CDK1 active site. CDK1 X-ray crystallographic protein structure was obtained from PDB (ID: 4YC6) [50]. Hydrogens were added, unnecessary chains were cut out, the protein was cleaned, and heavy atoms were created. CHARMm forcefield along with MMFF94 as a partial charge were used for simulation. Fixed constraints and protein minimization were carried out. Complex ligand interaction site was used for the identification of the receptor binding site. Lycopene binding mode was examined to justify its biological effectiveness in addition to gain further perception into binding interactions and orientations, where the best pose out of ten was chosen.

Standard dynamic simulations

The dynamic simulation investigation were carried out with Discovery Studio 4.1 and applied to free protein and Lycopene docked against CDK1. Standard Dynamic Cascades was applied where the first minimization algorithm was set to steepest descent with maximum steps 2000 and RMS gradient 1.0. The second minimization algorithm was set to conjugate gradient with maximum steps 1000. The initial temperature was set to 50, and the target temp. 300 with a maximum velocity of 2000. On the other hand, the equilibration phase was set with a simulation time of 10 Ps and an interval of 2 Ps. The Implicit Solvent Model was set to Generalized Born with Simple Switching (GBSW).

Ramachandran plot

Ramachandran Plot was generated using Discovery Studio 4.1 for both free protein and lycopene to verify predicted torsion angles in protein during interaction with it.

ADMET/TOPKAT prediction

Discovery studio 4.1software was used to conduct the in-silico ADMET studies. Results were then compared

to that obtained by the drug-likeness studies applying Swiss-ADME Boiled egg chart (https://www.swissadme.ch/index.php) [51]. These investigations were utilized to speculate on the pharmacokinetic features of the drug under consideration. The results also afforded the structure requirements for estimation of the probable antitumor activity. ADMET protocol was applied to prepare ligands of the extracted lycopene. Graph plots and numerical schedules were created and displayed. Similarly, the TOPKAT Toxicity protocol was applied to the same prepared lycopene after the criteria to be measured were determined, which are Ames Applicability, Prediction, Score, Probability, Skin Irritancy, Rat Oral LD_{50}, and Rat Max. Tolerated Dose Feed Carcinogenic Potency TD_{50} for both Mice and Rats [52, 53].

Conclusion

In conclusion, our study demonstrates that lycopene exhibits significant cytotoxic activity against the mutant MDA-MB-435 skin cancer cell line. With an IC_{50} value of 12.14 ± 3.37 uM, lycopene shows promising potential as a therapeutic agent for combating this particular cancer. Furthermore, our findings reveal that lycopene's cytotoxic effects are attributed to its ability to induce programmed cell death and arrest the cell cycle in MDA-MB-435 skin carcinoma cells. These results underscore the importance of further exploring lycopene as a potential candidate for the development of novel anticancer treatments targeting skin carcinoma. This was augmented by the in silico molecular modeling studies which proved the ability of lycopene to bind with the essential amino acids and act as a CDK1 inhibitor explaining its antitumor effect. Lycopene also revealed promising physicochemical properties. Further studies may be carried out to incorporate lycopene into formulations which protect the skin such as sunscreens.

Abbreviations

ATCC	American Type Culture Collection
ADMET	Absorption, distribution, metabolism, excretion, and toxicity
BBB	Blood brain barrier
ELISA	Enzyme-linked immunosorbent assay
MD	Molecular dynamics
MDA-MB-435	Human skin carcinoma
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
NMR	Nuclear magnetic resonance
PI	Annexin/propidium iodide
PPB	Plasma protein
RMSF	Root mean square fluctuations.
TOPKAT	Toxicity Prediction using Komputer Assisted Technology
UV	Ultraviolet

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43094-023-00538-5.

Additional file 1: Figure S1. H^1NMR of lycopene in $CDCl_3$.

Acknowledgements

Not applicable.

Author contributions

Data curation, YAE, MAE, HAE, MHG and NK; Conceptualization, YAE, MAE, HAE, MHG and NK; Formal analysis, YAE, MAE, HAE, and NK; Investigation, YAE, MAE, HAE, and NK; Methodology, YAE, MAE, HAE, MHG and NK; Project administration, YAE and NK; Resource, YAE and NK; Supervision, YAE, MAE, HAE, MHG and NK; Validation, YAE, MAE, HAE, and NK; Visualization, YAE, MAE, HAE, MHG, NK; Writing—original draft preparation and editing, YAE, MAE, HAE, and NK; Reviewing, YAE, MAE, HAE, MHG and NK; Software, MAE, and HAE. All authors have read and agreed to the published version of the manuscript.

Funding

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The authors declare no conflict of interest.

Competing interests

The authors declare that they have no competing interests.

Received: 9 September 2023 Accepted: 4 October 2023
Published online: 13 October 2023

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