GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(RESEARCH ARTICLE)

Check for updates

A compound isolated and identified from *Garcinia mangostana* and used as an anti-colorectal cancer drug *in silico* approach

Inas Osman Khojali [1,*] and Mohammed Yousif Mohammed [2]

[1] *Department of Chemistry and Industrial Chemistry, College of Applied and Industrial Sciences, University of Bahri, Sudan.*
[2] *Department of Biology, College of Applied and Industrial Sciences, University of Bahri, Sudan.*

GSC Advanced Research and Reviews, 2023, 15(02), 038–046

Publication history: Received on 01 April 2023; revised on 10 May 2023; accepted on 13 May 2023

Article DOI: https://doi.org/10.30574/gscarr.2023.15.2.0139

Abstract

From the chloroform extract of the stem bark of *Garcinia mangostana* alpha mangostin was isolated. Characterization of this compound was established by spectral methods (IR, ^{1}HNMR and ^{13}CNMR). In this study through the *in silico* approach, the isolated compound was used for molecular docking as anti-colorectal cancer. The ID of the protein (6MTU) was retrieved from the PDB database. Preparation of alpha mangostin, colorectal cancer protein, and Molecular Docking was carried out using Molecular Operating Environment software (MOE). The docking results of alpha mangostin show potent energy scores for anti-colorectal cancer; further investigations are needed. The pharmacological parameters of alpha mangostin were studied and predicted. It was found that alpha mangostin compound is suitable as an anti-colorectal cancer drug, completing all pharmacokinetic parameters with good figures. Alpha mangostin will be a promising anti-colorectal cancer that targeted specific proteins in the colon cell.

Keywords: *Garcinia mangostana*; Spectral analysis; Colorectal cancer; Molecular docking; Pharmacokinetic properties

1. Introduction

Medicinal plants are the source of substances that produce a definite biological response in the human body. They are an important source of lead compounds for developing new useful drugs (Hassan, S.S.U.,*et al*.) [1] (Naveed, M., *et al*.) [2].

The plants in the genus *Garcinia* are called sap trees, mangosteen (which may also refer specifically to the purple mangosteen, *G.mangostana*), *Garcinias*, or ambiguously, "monkey fruit" (Wong and Klemmer) [3]. The ripe fruits contain many types of xanthones as alpha and beta mangostin , gartanin, 8-disoxyartanin and normangostin. A derivative of mangostin, mangostin-6-di-O-glucoside, is a central nervous system depressant and causes a rise in blood pressure (Kong, *et al*.) [4].

The fruit *mangosteen* is a source of antioxidants called xanthones, these antioxidants are considered to be one of the best health discoveries (Potterate, O.) [5]. The term"xanthone" denotes a chemical compound with the dibenzo—γ-pyrone structure. Some previous studies suggest that *Garcinia* xanthones and their derivatives have significant *in vitro* anticancer activity with promising pharmacology, but the molecular reason behind the activity is not yet explored (Han, Q.-B. and Xu, H.-X) [6]. One of these studies using the combined approach of Quantitative Structure-Activity Relationship (QSAR), docking, Absorption, Distribution, Metabolism & Toxicity (ADMET) and system pharmacology in a pipeline reports the identification of pharmacophore features and activity controlling sites, along with the identification of the mechanism of action based on the structure-activity relationship (Schneider, G. & Fechner, U) [7], (Jorgensen, W. L.) [8], (Kalya anamoorthy, S. & Chen, Y.-P. P.) [9], (Cucurull-Sanchez, L. *et.al*.) [10].

* Corresponding author: Inas Osman Khojali

Xanthones have strong cancer fighting components, according to a study conducted in Japan; it has been found out that a class of xanthones called-alph-mangostin can be used to halt the development of tumors. Another type called garcicone E can prevent cancer in essential body organs such as liver, lung, and colon (Yukihiro, *et. al.,* 2008) [11].

Among a large number of biological activities described for xanthones, the *in vitro* growth inhibitory activity on tumor cell lines appeared to be quite remarkable as they exhibit their activity on a wide range of different cell lines (Pedro, *et. al.*) [12]. It was reported that on the anti-proliferative activities of alpha, beta and gamma mangostins, these xanthones strongly inhibited cell growth of human colon cancer DLD-1 cell line with a correlation between the number of hydroxyl groups in their structures and the anti-proliferative efficiency (Matsumotok, *et. al* .) [13]. Some studies showed that the pericarp of *G. mangostana* contains a variety of xanthones with anti-proliferative activity against human leukemia HL60 cells (Ahmat, *et. al.*) [14]. Among others alpha - mangostin showed complete inhibition at 10 μ M through the induction of apoptosis of tumor cells. There is some other investigations published reporting the anticancer activities of xanthones including cytotoxic properties against breast cancer, epidermoid carcinoma, small cell lung cancer, hepatocellular carcinoma cell lines and others (Chin, *et. al.*) [15] (Huang, *et. al*) [16]. Additionally, a correlation between the structures and cytotoxicity of xanthones was reported. Commercial products of mangosteen added with essential minerals, containing mangosteen, green tea (*Camellia sinensis*), aloe vera, and multivitamins, were used by cancer patients as a dietary supplement (Kondo M.*et.al*) [17]

Recently, *in silico* computational methods have become play important role in the drug discovery area. Molecular docking and modeling approaches is one of the strategies mainly used when the 3D crystal structure of the receptor and the chemical structure of the ligands are known (Kitchen DB.) [18].

Colorectal or colon cancer is one of top five ranking cancer in Sudan with a very high incidence, is a disease in which cells in the colon or rectum grow out of control (Mohammed EA., et.al.) [19]. The cancer cells contain type of protein that called scribble protein that found around that colorectal cancer cells which play a role in the control of cell polarity and impacting many physiological processes. In this research, we targeted this protein with PDB ID (6MTU) and dock with alpha mangostin compound isolated from *Garcinia mangostana* to present its effect as anti-colorectal cancer.

2. Material and methods

2.1. Chemicals

Chloroforn, n-hexane, ethylacetate

2.2. Methods

2.2.1. Extraction and Isolation of alpha mangostin

1.7 Kg of powdered air dried stem bark was percolated at room temperature with distilled hexane for forty-eight hours. The solvent was evaporated *in vacuo*. This procedure was repeated by replacing hexane with chloroform. Yields were found to be 28.08 g (hexane extract), 79.25g (chloroform extract). It was found that alpha and beta mangostin are the major constituents of *Garcinia mangostana* stem bark.

Alpha mangostin was isolated from the chloroform extract as a yellow amorphous powder (57mg), the m.p. 179-181 ℃.

2.2.2. Preparation of the ligand alpha mangostin

The ligand was prepared using MOE software. 3D structure, adding partially charges and setup the energy minimization which leads the atoms of a compound to be a stable as possible so as atoms can be far a part to make easy docking (Elmaaty, A.A., et.al.,2022) [20]. Figure (5) showed the prepared ligand alpha mangostin

2.2.3. Preparation of Protein

The 6MTU protein was used in this study as a receptor for the ligand alpha-mangostin. The crystal structure of (6MTU) was retrieved from Protein data bank and saved in PDB format. Protein structure was prepared using MOE software by adding hydrogen atoms, missed bonds, energy minimization, the active site and natural ligand were identified (Khattab, M. and Al-Karmalawy, A.A., 2021) [21]. Figure (6) showed the prepared protein

2.2.4. Molecular Docking

The docking process was done using MOE software to study the interaction between the prepared protein (6MTU) and the ligand (alpha-mangostin). Different parameters were used for studying the interaction like energy score (S) and Root mean square deviation (RMSD) (Hammoud, M.M.,et.al., 2022) [22]. Figures (7 and 8) showed the docking results.

2.2.5. Pharmacokinetic Properties

Pharmacokinetic profile of alpha mangostin was predicted by using pkCSM:(https://biosig.lab.uq.edu.au/pkcsm/help). It is a machine learning platform to predict small molecules pharmacokinetics properties which rely on distance/pharmacophore patterns encoded as graph-based signatures. The platform is composed of 28 regression and classification models trained and tested on different experimental data set encompassing a diverse and complementary set of ADME.

3. Results and discussion

3.1. Characterization of alpha mangostin

In the IR spectrum alpha mangostin (Figure 1) gave ν_{max} (Cm^{-1}, KBr disc): 720, 808 (C-H, Ar bending), 1050 (C-O), 1377, 1451 (C=C, Ar), 1640 (C=O), 2962, 2916(C-H), 3410(broad OH).

The ^{1}H NMR spectra of compound alpha mangostin (400 MHz, $CDCl_3$) (Figures 2 and 3) revealed four signals at δ 1.83 (s, 3H), δ 1.84(s, 3H), δ 1.77(s, 3H) and δ 1.69(s, 3H) for the four methyl groups. The signals at δ 3.44(d, 2H) and δ 4.09(d, 2H) were assigned to two benzylic methylene groups. The resonance at δ 5.26(t, 2H) corresponds to vinylic protons. The above signals suggest the presence of two isoprenyl moieties. The signal at δ 3.8(s, 3H) is characteristic of a methoxyl resonance. The signals at δ 6.28 and δ 6.8ppm are due to two aromatic protons.

The ^{13}C spectrum (Figure 4) revealed a pattern characteristic of a C24 - skeleton. The δ values are depicted in (Figure 5)

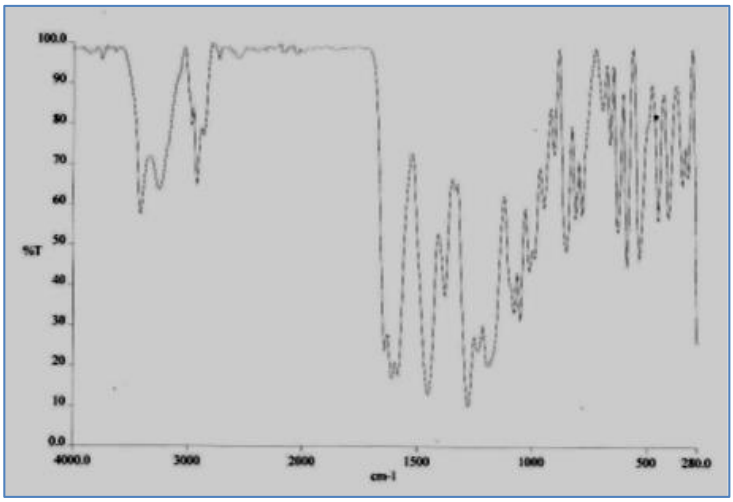

Figure 1 IR Spectrum of alpha mangostin

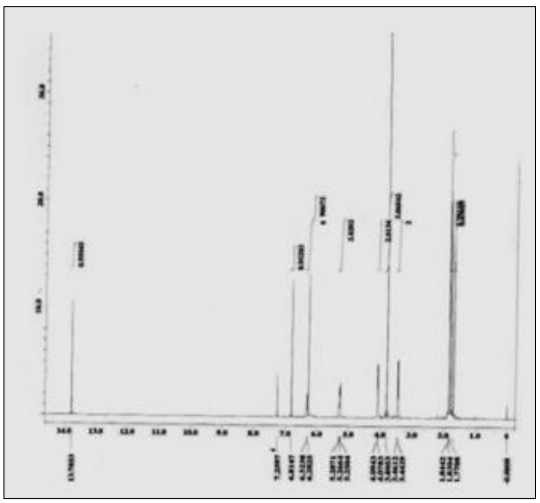

Figure 2 1H NMR spectrum of alpha mangostin

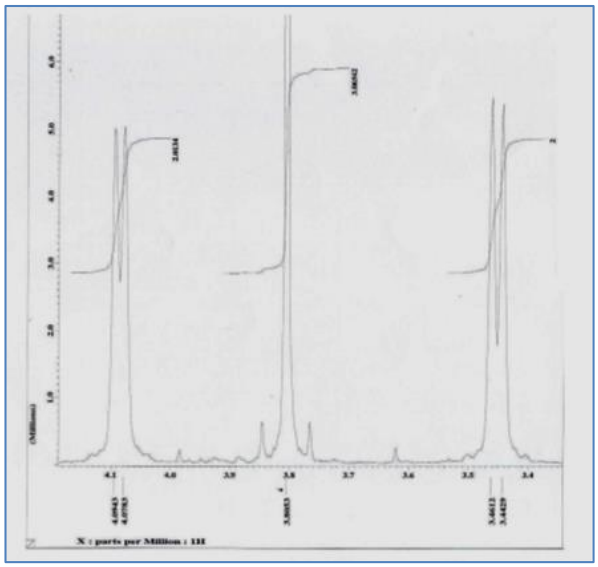

Figure 3 1H NMR spectrum of alpha mangostin

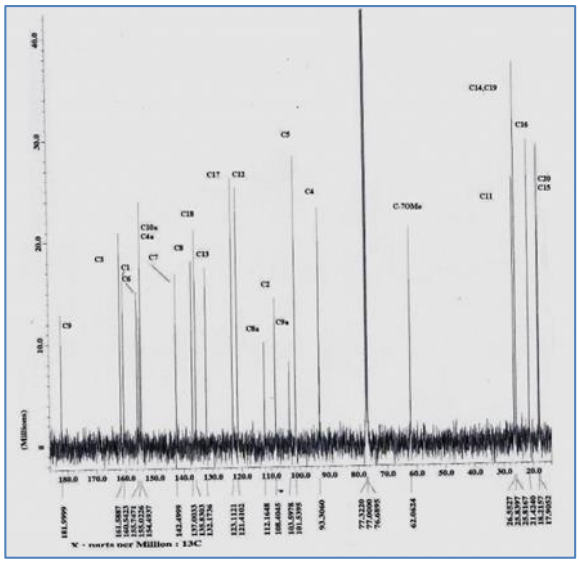

Figure 4 ^{13}C NMR spectrum of alpha mangostin

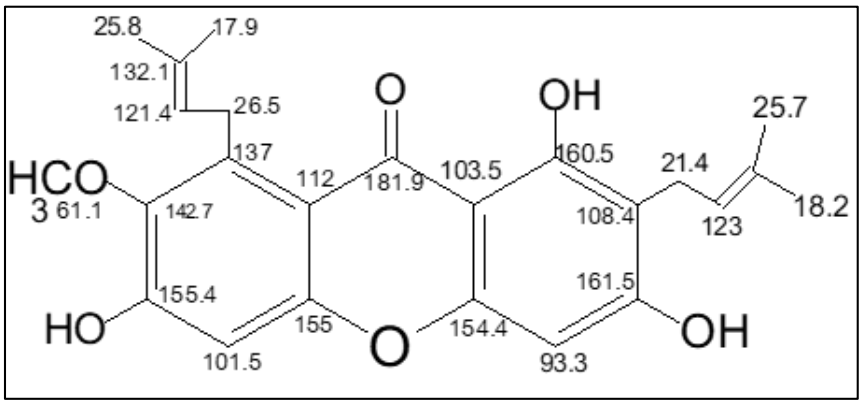

Figure 5 δ- values from ^{13}C spectrum

3.2. Molecular Docking

Both ligand alpha mangostin and the target protein (6MTU) were prepared using MOE software by passing them through many steps to be ready for molecular docking (Figures 6 and 7 respectively).

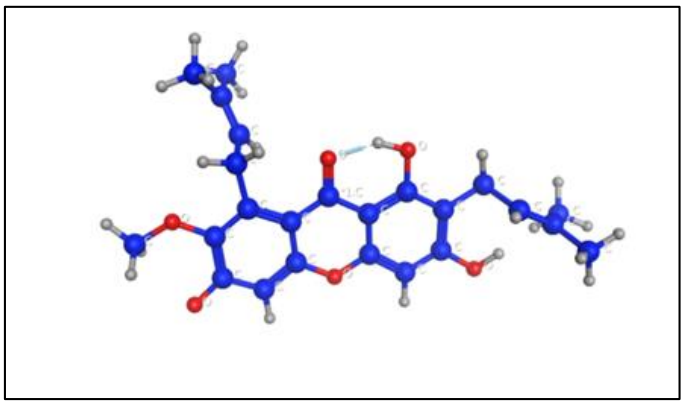

Figure 6 Prepared alpha mangostin

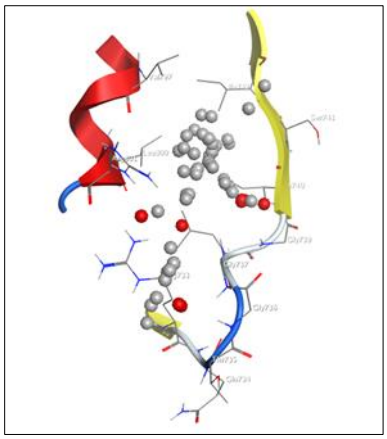

Figure 7 Prepared colorectal cancer protein (largest pocket)

The docking of alpha mangostin with colorectal cancer mutated protein with PDB id (6MTU) is carried out. The result showed the best five poses (Table 1) in which leucine and isolecucine amino acids binding to alpha mangostin with good energy scores indicated good result in binding affinity. The two amino acids bonded to hydrogen atom inside the compound and the rest of the amino acids linked to other peripheral part of the compound and hydrogen present in the water. Figures 8 and 9 showed the docking result.

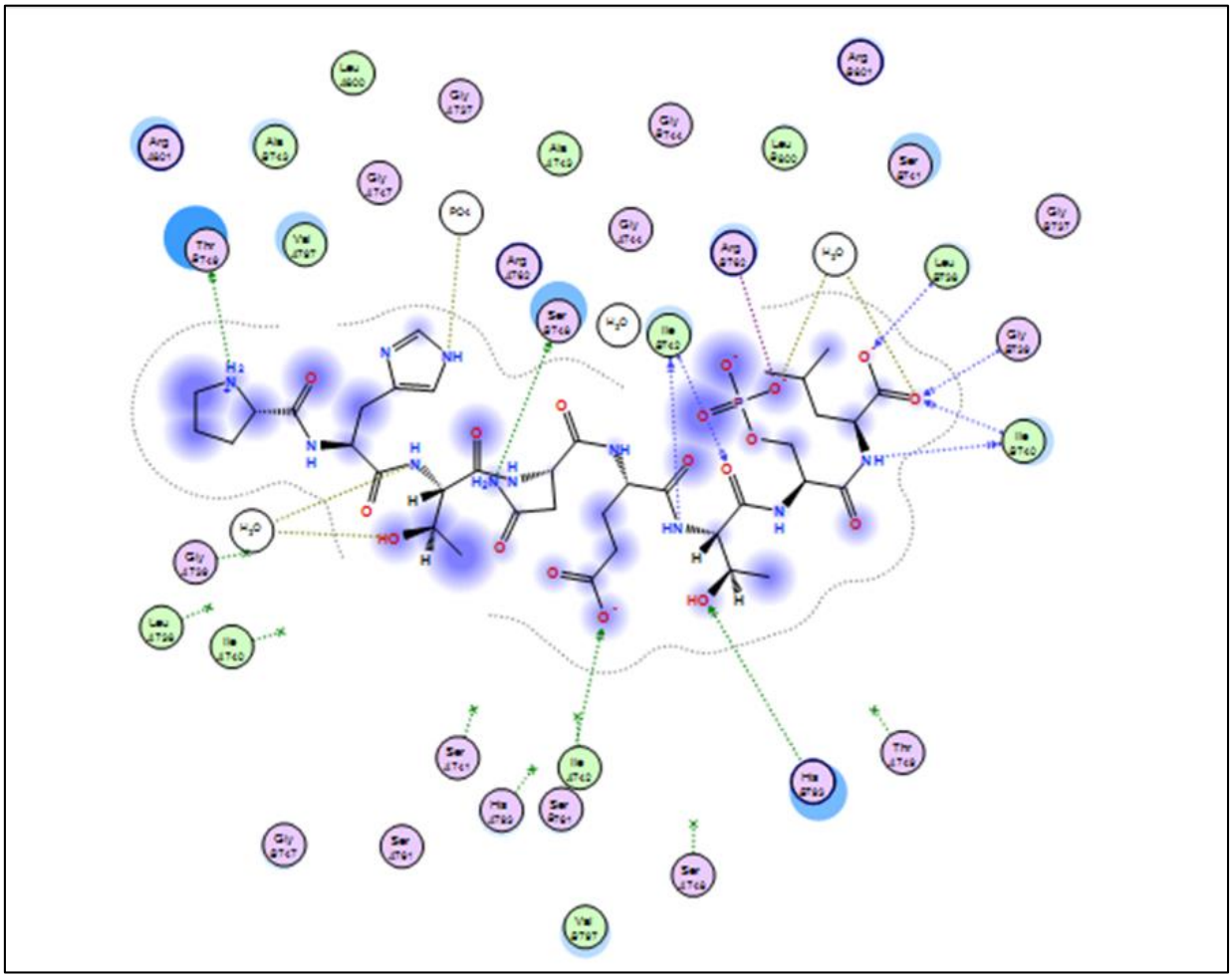

Figure 8 Interactions between alpha mangostin ligand and colorectal cancer protein

Table 1 Docking result of alpha mangostin and colorectal cancer protein

S (ENERGY SCORE)	RMSD (Root mean square deviation) distance between ligand and protein
-10.5183	1.8678 (good)
-10.2333	2.9842 (good)
-9.8658	3.0914 (acceptable)
-9.3431	2.9607 (good)
-9.1994	2.4047 (good)

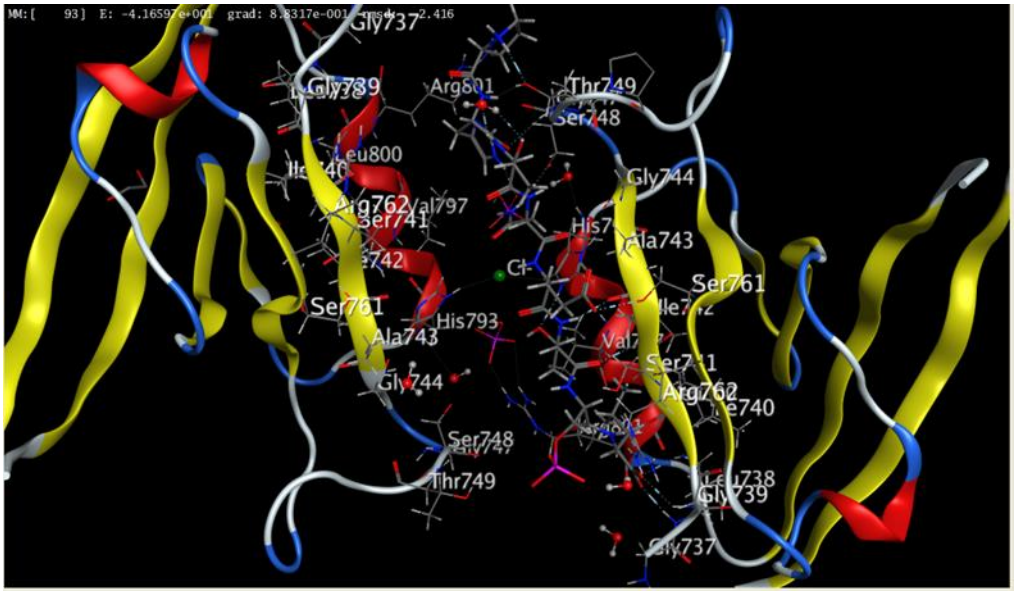

Figure 9 Docking of colorectal cancer protein with alpha mangostin compound

3.3. Pharmacokinetics

3.3.1. Absorption

- Water solubility

The software shows that alpha mangostin is soluble in water with value log -4.067 mol/L which is good when use as anticancer drug.

- Intestine absorption

The percentage of alpha mangostin that will be absorbed through the human intestine is 93.647%, which exceed the 30% of less number. The result showed that alpha mangostin revealed high intestine absorption.

- Skin permeability:

Low skin permeable compound has log kp > - 2.5. In this study alpha mangostin compound gave log kp = - 2.736.

- P-glycoprotein substrate:

The predictor determines alpha mangostin compound as one of p-glycoprotein I/II inhibitor.

3.3.2. Distribution

- VDss in human

The volume of distribution (VDss) is considered to be low if it is below 0.71L/kg. In this study (VDss) in alpha mangostin compound is - 0.282.

- Fraction unbound

Alpha mangostin is zero predicted bound to plasma.

- BBB permeability

Alpha mangostin cannot cross the blood brain barrier with its value of log BB = -1.075. Any given compound is considered to readily cross BBB if log BB > 0.3.

- CNS permeability

Blood brain permeability surface area product (log PS) is a measure of blood brain permeability. Alpha mangostin cannot easy penetrate the central nervous system with log PS = - 1.984.

3.3.3. Metabolism

- CYP2D6 substrate

Alpha magostin cannot be metabolized by CYP2D6 and CYP3A4 which are cytochrome 450s substrates, but can be metabolized by the rest of cytochrome substrate.

3.3.4. Excretion

- Total clearance

The total drug clearance is a combination of both liver and kidney clearance. It is measured by the proportionality constant CLtot. The total clearance of alpha mangostin compound from the liver is log CLtot. = 0.43ml/min/kg

- Renal OCT2 substrate

Organic cation transporter2 (OCT2) is a renal uptake transporter that plays an important role in renal clearance of drugs. The predictor gives that alpha mangostin is unlikely to be an OCT2 substrate.

4. Conclusion

Based on the previous studies *Garcinia mangostana* is a source of a wide range of secondary metabolites. Xanthones have strong cancer fighting components. In this study alpha mangostin compound was extracted and identified from *Garcinia mangostana*. It exhibited significance docking scores as anti-colorectal cancer. The pharmacological parameters show alpha mangostin as a promising drug but further investigations are needed.

Recommendations

- This *in silico* study predicts alpha mangostin compound as an effective ligand for 6MTU receptor but further and comprehensive studies in wet lab before transfer the compound as a ligand drug are recommended.
- More investigations for the efficiency of alpha mangostin are needed.
- The molecular reasons behind the structure and the activity of xanthones must be studied.

Compliance with ethical standards

Acknowledgments

We are thankful to University of Bahri for support and giving the possibilities to complete this work.

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Hassan, S.S.U.; Abbas, S.Q.; Muhammad, I.; Wu, J.-J.; Yan, S.-K.; Ali, F.; Majid, M.; Jin, H.-Z.; Bungau, S.Metals-triggered compound CDPDP exhibits antiarthritic behavior by down regulating the inflammatory cytokines and modulating the oxidative storm in mice models with extensive ADMET, docking and simulation studies. Front. Pharmacol. 2022, 13, 1053744.

[2] Naveed, M.; Batool, H.; Rehman, S.U.; Javed, A.; Makhdoom, S.I.; Aziz, T.; Mohamed, A.A.; Sameeh, M.Y.; Alruways, M.W.; Dablool, A.S. Characterization and Evaluation of the Antioxidant, Antidiabetic, Anti-Inflammatory, and Cytotoxic Activities of Silver Nanoparticles Synthesized Using Brachychiton populneus Leaf Extract. Processes. 2022, 10, 1521.

[3] Wong, L .P. and Klemmer, P. J. Severe lactic acidosis associated with juice of mangosteen fruit, *Garcinia mangostana*, American J of Kidney Disease. 2008, 51 (5), 829- 833.

[4] Kong, L. D., Zhang, Y. and Cheng, C. H. Inhibition of xanthie oxidase by Liquiritigenin and Isoliquiritigenin isolated from Sinofranchetia chinensis, Cell Mol Life Sci. 2000, 57 (3), 500- 505.

[5] Potterate, O. Antioxidants and free radical scavengers of natural origin, Current Org Chem.1997, 1, 415.

[6] Han, Q.-B. & Xu, H.-X. Caged Garcinia Xanthones: Development Since 1937. Current Medicinal Chemistry. 2009, 16, 3775–3796

[7] Schneider, G. & Fechner, U. Computer-based de novo design of drug-like molecules. Nature Reviews Drug Discovery. 2005, 4, 649–663

[8] Jorgensen, W. L. Many Roles of Computation in Drug Discovery. Science. 2004, 303, 1813–1818

[9] Kalya anamoorthy, S. & Chen, Y.-P. P. Structure-based drug design to augment hit discovery. Drug Discovery Today. 2011, 16, 831–839

[10] Cucurull-Sanchez, L., Spink, K. & Moschos, S. Relevance of systems pharmacology in drug discovery. Drug Discovery Today. 2012, 17, 665–670.

[11] Yukihiro, A., Yoshihito, N. and Yoshinori, N. Anticancer effects of xanthones from pericarps of mangosteen. Int. J. Mol. Sci. 2008, 9 (3), 355-370.

[12] Pedro, M., Cerqueira, F. and Pinto, M. Xanthones as inhibitors of growth of human cancer cell lines and their effects on the proliferation of human Lymphocyles in vitro, J. Bioorganic and medicinal chemistry. 2002, 10, 3725- 3730.

[13] Matsumotok, Akao, Y. and Ohguchi, K. Xanthones induce cell cycle arrest and apoptosis in human colon cancer DLD-1 cells, Bioorg. Med. Chem.2005, 13, 6064- 6069.

[14] Ahmat, N. Sidek, N.J. and Abdullah, S. Bioactive xanthones from the pericarp of *Garcinia mangostana* of Middle-East, J. Sci. Research. 2010, 6 ,2, 123- 127.

[15] Chin Y.W., Jung, H. A., Chai, H., Keller, W. J. and Kinghorn, A .D. Xanthones with quinone reductase inducing activity from the fruits of *Garcinia mangostana* (mangosteen), Phytochemistry. 2008, 69, 754- 758.

[16] Huang, Y. L. and Chen, C. C. Garcinone E, a xanthone derivative, has potent cytotoxic effect against hepatocellular Carcinoma cell lines, Planta Med. 2002, 68, 975- 979.

[17] Kondo M, Zhang LL, Ji HP. Bioavailability and antioxidant effects of a xanthone-rich mangosteen (*Garcinia mangostana*) product in humans. J Agr Food Chem. 2009, 57,19,8788–92.

[18] Kitchen DB. Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: Methods and applications. Nat Rev Drug Discov. 2004, 3, 11,935-949.

[19] Mohammed EA, Alagib A. Babiker AI. Incidents of cancer in Sudan: past trends and future forecasts. Afr. J. Math. 2013; 8,136–142.

[20] MOE, (1) Elmaaty, A.A., Darwish, K.M., Khattab, M., Elhady, S.S., Salah, M., Hamed, M.I., Al-Karmalawy, A.A. and Saleh, M.M. In a search for potential drug candidates for combating COVID-19: computational study revealed

salvianolic acid B as a potential therapeutic targeting 3CLpro and spike proteins. Journal of Biomolecular Structure and Dynamics. 2022, 40,19, 8866-8893.

[21] MOE, (2) Khattab, M. and Al-Karmalawy, A.A. Computational repurposing of benzimidazole anthelmintic drugs as potential colchicine binding site inhibitors. Future Medicinal Chemistry. 2021, 13(19), pp.1623-1638.

[22] MOE, (3) Hammoud, M.M., Khattab, M., Abdel-Motaal, M., Van der Eycken, J., Alnajjar, R., Abulkhair, H.S. and Al-Karmalawy, A.A. Synthesis, structural characterization, DFT calculations, molecular docking, and molecular dynamics simulations of a novel ferrocene derivative to unravel its potential antitumor activity. Journal of Biomolecular Structure and Dynamics. 2022, 1-18.