August 30, 2019

PharmacologyOnLine

Archives • 2019 • vol.2 • 259-268

# IN SILICO STUDIES OF FOUR ANTHRAQUINONES OF *SENNA ALATA L.* AS POTENTIAL ANTIFUNGAL COMPOUNDS

Sium Ahmed; Abdullah Mohammad Shohael*

Department of Biotechnology and Genetic Engineering, Jahangirnagar University, Savar, Dhaka-1342, Bangladesh.

Email address: amshohael@juniv.edu

## Abstract

*Senna alata* L. is a traditionally used medicinal plant for dermatophyte infections. The use of *Senna alata* leaves as an antifungal agent has been implicated in a considerable number of published ethno pharmacological studies. Some of these studies have mentioned the possible role of anthraquinone or its derivatives as the active agents. The present study was aimed to discover the role of four anthraquinones named aloe-emodin, chrysophanol, emodin, and rhein as the antifungal compounds through in silico molecular docking studies. For this purpose, Lanosterol 14-$\alpha$-demethylase (CYP51) has been utilized as the protein target which is one of the key enzymes of sterol biosynthesis and essential for the metabolism of fungi. According to Glide docking score of Schrödinger Maestro program, aloe-emodin (-7.81), chrysophanol (-7.493) and rhein (-8.518) showed higher score than the native drug fluconazole (-6.856) while the other compound emodin (-6.717) showed a little less docking score. Furthermore, the selected compounds were subjected to drug likeliness prediction and absorption, distribution, metabolism, excretion, toxicity (ADME/T) analysis to predict their possible potential to be utilized as a naturally derived antifungal agent. The compounds were evaluated based on Lipinski's rule of five and found to be satisfactory as they fulfilled all the criteria. Finally, ADME/T analysis gave a clear indication of their pharmacokinetic parameters.

**Keywords**: *Anthraquinones, Antifungal, In Silico, Senna alata*

## Introduction

*Senna alata* (*L.*) is a shrub of the Fabaceae family which is native to Central America. It has also been introduced into many other countries of the tropical climate. It is commonly known as candle bush and ringworm tree or DadMordon in Bengali because of its traditional use against fungal infection (1). *S. alata* possesses great ethnomedicinal importance and has been utilized for centuries in herbal medicine. There are various reports of its effectiveness in different types of medical conditions including- constipation (2), dermatologic diseases (3), infection caused by bacteria (4) and fungi (5), hyperglycemia (6) and wound healing (7).

Fungal infections have become a major health concern and the incidence of systemic fungal infection led to complications in immunocompromised patients which often resulted in increased morbidity and mortality (8). *S. alata* has been extensively utilized for its antifungal property and leaves are mainly utilized for this purpose in several studies (9–11). The antifungal activity is attributed to the presence of anthraquinones (12). Anthraquinones, also called anthracenediones or dioxoanthracenes, are important members of the quinone family, and constitute a large structural variety of compounds among the polyketide group (13). Various plants contain anthraquinones. Among them, aloe-emodin, rhein, emodin, and chrysophanol have been shown to be the active antifungal agents in some studies (14,15).

50% of the drugs currently being used for various diseases are either developed or inspired from naturally derived compounds. That's why medicinal plants have considerable importance in modern drug discovery and the investigation of their active component's molecular mode of action against various diseases is getting more attention (16). To overcome problems associated with synthetic antifungal agents, natural products and their derivatives are interesting alternatives. The antifungal agents can be purified, identified and may be used as a new and renewable, natural compound against infectious and pathogenic fungi and may replace synthetic antifungal drugs.

The mechanism of action of some antifungal drug is based on targeting the ergosterol biosynthesis pathway or its end product (17). Lanosterol 14-$\alpha$-demethylase (CYP51) is one of the key enzymes of sterol biosynthesis which is essential for fungi to maintain various metabolic function (18).

In silico studies provide insights into the drug-protein interaction and by the application of molecular docking method various compounds can be checked extensively for its desired activity. This reduces labor and cost associated with laboratory work, give exact direction to the target, provide leads for prior optimization or modification before going into further investigations (19). It is not clear in the studies how antifungal agents are working especially the molecular mechanism of interaction is yet to be understood. That's why in silico studies are employed to uncover the underlying mechanisms.

Although *S. alata* has been validated scientifically to possess antifungal property, there is no information on the possible mechanism by which this plant elicits its antifungal effect. Therefore, the aim of this study was to determine the inhibitory effect of anthraquinone derivatives of *S. alata* on fungal protein lanosterol 14-$\alpha$-demethylase (CYP51) as well as its mode of inhibition and binding energy of these compounds. The study also aimed to assess drug likeliness, and selected pharmacokinetic properties in terms of absorption, distribution, metabolism, excretion and toxicity (ADME/T).

## Methods

*Selection of compounds*

The selection of compounds as ligands such as aloe-emodin (PubChem CID: 10207), chrysophanol (PubChem CID: 10208), emodin (PubChem CID: 3220) and rhein (PubChem CID: 10168) was based on previous literatures which mentioned the presence of these compounds in *S. alata* and also utilized them as potential candidate for antifungal activity in vitro (20–22). The structures of the compounds were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). The protein Lanosterol 14-$\alpha$-demethylase (CYP51) was utilized as a protein receptor which is a target for commercial antifungal drugs such as ketoconazole, fluconazole etc. The selection of receptor is also based on previous literatures (23,24). *Mycobacterium tuberculosis*lanosterol 14-$\alpha$-demethylase has high homology to that of lanosterol 14-$\alpha$-demethylase

from Candida species (23,25). Therefore, docking studies were carried out using X-ray crystal structure of lanosterol 14- α-demethylase from *Mycobacterium tuberculosis* in complex with fluconazole (PDB ID: 1EA1)(26). The three-dimensional structure of the lanosterol 14- α-demethylase in complex with fluconazole (PDB ID: 1EA1) was derived from the Protein Data Bank (https://www.rcsb.org). The two-dimensional structure of the anthraquinones and three-dimensional structure of the protein were given in Figure 1.

*Preparation of ligands*

Ligands were structurally plotted in three-dimensions and "Ligprep" wizard of Maestro v10.1 was used for ligand preparation (27). Ligands ionization states were generated at pH 7.0±2.0 using Epik 3.1 in Schrödinger suite. The ligands were prepared by choosing "retain specified chiralities" to maintain the chiral information and Optimized Potentials for Liquid Simulations (OPLS) 2005 force field was used to minimize the structures(28).

*Preparation of Protein*

The X-ray crystal structure of the target protein lanosterol 14-α-demethylase (PDB ID: 1EA1) was prepared by the "protein preparation wizard" of Schrödinger-Maestro v10.1 (29). The preparation involves the addition of hydrogen atoms, correcting bond orders, adding missing residues/side chains using the prime module, conversion of selenomethionine to methionine and removal of waters. Finally, the OPLS 2005 force field was utilized to minimize the protein at neutral pH where heavy atoms were converged to Root Mean Square Deviation (RMSD) value of 0.30 A°.

*Generation of Receptor grid*

Prior to docking, the receptor grid was generated to define the active site of the protein. The grid box was generated using the default parameters and by selecting the native ligand present in the crystal structure. A cubic box generated around the centroid of the active site residues to essentially accommodate the ligands. The bounding box having dimensions of 10 A° x 10 A° x 10 A°.

*Molecular Docking*

Molecular docking of selected anthraquinones with the target protein was carried out using the Glide extra precision (XP) method of Maestro v10.1 (30). Flexible ligand docking was employed where all other parameters were set to default. Ligand poses were generated for each input molecule and Glide docking score represents the binding affinity of these molecules to the target protein. After molecular docking, the Discovery Studio Visualizer v19.1 was used to visualize the interaction in three dimensions (31).

*Prediction of drug likeliness and pharmacokinetic parameters*

For the prediction of drug likeliness two online servers Swiss ADME (http://www.swissadme.ch) (32) and MolinspirationChemoinformatics tools (https://www.molinspiration.com/cgi-bin/properties) were used. Another online program AdmetSAR (http://lmmd.ecust.edu.cn/admetsar1/predict) was utilized to evaluate the pharmacokinetic parameters in terms of drug absorption, distribution, metabolism, excretion, and toxicity (ADME/T).

## Results

*Molecular docking*

In silico molecular docking studies were performed in order to achieve detailed insight into the binding mode of the anthraquinone compounds to lanosterol 14-α-demethylase. In the present study, we have utilized the drug compound fluconazole as control which was present in the crystal structure of lanosterol 14-α-demethylase (PDB ID: 1EA1) as a native ligand. So, fluconazole was docked against the protein structure to achieve the docking score and binding patterns to make it easy for comparison to the selected anthraquinones. All four anthraquinones (aloe-emodin, chrysophanol, emodin and rhein) were docked to the target protein structure. The visualizations of docking results are shown in Figure 2. The results showed that all four compounds successfully bound to the active site of the protein. The Glide docking scores and Glide energies (Kcal/mol) of the anthraquinones and the control drug fluconazole are given in Table 1. The result showed that aloe-emodin, chrysophanol and rhein showed higher docking score than fluconazole. rhein has the highest docking score followed by aloe-emodin and chrysophanol. emodin

showed a docking score little less than fluconazole. However, in terms of glide energy fluconazole showed the highest energy followed by rhein, aloe-emodin, emodin and chrysophanol.

There were total 9 non-bond interactions found for aloe-emodin (Figure 2a). Among them 4 hydrogen bond interaction with amino acid residues Tyr76, His259, Ile323, and Arg96. The bond distance ranged from 1.73 A° to 3.0 A°. Other interactions were electrostatic and hydrophobic interactions. There were 1 Pi-Sigma, 2 Pi-Pi and 1 Pi-Alkyl interaction of hydrophobic types. The amino acid residues involved in hydrophobic interactions were Tyr76 and Leu321 with bond distance ranging from 2.91 A° to 4.97 A° (Figure 2a).

Chrysophanol formed 2 hydrogen bonds, 1 Pi-Cation, Pi-Sigma, 2 Pi-Pi, 2 Alkyl and 3 Pi-Alkyl bonds with the target protein. The amino acid residues involved were Tyr76, His259, Arg96, Leu321, Met433, Phe78. The bond distance ranged 1.93 A° to 2.70 A° for hydrogen bonds and 2.96 A° to 4.96 A° for hydrophobic interactions (Figure 2b)

In the case of emodin, among 9 favorable non bonded interactions, 2 hydrogen bonds were found with amino acid residues Tyr76, Arg96. Other than that, 7 hydrophobic interactions such as 1 Pi-Sigma, 2 Pi-Pi, 1 Alkyl, and 3 Pi-Alkyl interactions were found with bond distances ranging from2.89 A° to 5.23 A°. Tyr76, Phe78 and Leu321 were the amino acid residues involved in the hydrophobic interactions (Figure 2c).

Rhein was very efficient in terms of binding affinity as it had the highest docking score. 3 hydrogen bonds formed by amino acid residues Tyr76, His259 and Met433 to the ligand with bond distance ranging from 1.94 A° to 2.80 A°. 1 Electrostatic Pi- cation bonds formed with the amino acid residue Arg96. Among 5 hydrophobic interactions, 1 Pi-Sigma, 3 Pi-Pi, and 1 Pi-Alkyl interaction were found where bond distances were ranged from 2.78 A° to 5.25 A° (Figure 2d).

Fluconazole was utilized as a control to evaluate its binding affinity and comparison with other drugs. That's why it was redocked to the active site of the target protein. 4 hydrogen bonds formed with fluconazole to the amino acid residues Tyr76, Arg96, and Ala256. As fluconazole has halogen atom fluorine present in its structure there were 3 halogen bonds formed which involved amino acid residues His259, Ile323 and Met433. 2 Pi-Pi and 3 Pi-Alkyl bonds were found as hydrophobic interactions between the ligand and the amino acid residues Phe78, Met79, Phe255, Ala256 and Leu321 with bond distance ranging from 3.23 A° to 5.43 A° (Figure e).

*Prediction of drug likeliness and pharmacokinetic parameters*

The drug likeliness of the selected anthraquinones was evaluated based on the Lipinski's rule of five which helps in distinguishing between drug like and non-drug like molecules. The results were shown in Table 2. Where it can be easily understood that all four anthraquinones were favorable and acceptable in terms of all five properties. The selected pharmacokinetic properties are shown in Table 3. Evaluation of absorption, distribution, metabolism, excretion, and toxicity (ADME/T) showed us the selected anthraquinones are non-carcinogens with a positive score for blood-brain barrier and intestinal absorption (Table 3). They were found to be a weak inhibitor of Human Ether-a-go-go-Related Gene Inhibition (hERG) (Table 3). We found class II acute oral toxicity for aloe-emodin, chrysophanol and rhein and class III acute oral toxicity for emodin while the control drug showed Class III acute oral toxicity (Table 3). The aqueous solubility ranged from -3.2460 to -2.5294 for anthraquinone compounds while it was -1.8626for the control drug fluconazole. The rat aqueous toxicity showed that all anthraquinones had higher LD50 (mol/Kg) value than fluconazole (Table 3).

## Discussion

In silico molecular docking studies provide more detail insight into the interactions that occurred between the selected anthraquinones and the lanosterol 14-$\alpha$-demethylase (Cyp51). The native ligand fluconazole provides some idea whether the selected compounds can be utilized as a promising drug or not. It is clear after the study that all four compounds are promising in terms of their binding affinity and their pharmacokinetic properties.

In Glide, GlideScore supplemented by Epik state penalties is defended as the docking score. GlideScore includes a steric-clash term, adds other rewards and penalties such as buried polar terms,

amide twist penalties, hydrophobic enclosure terms, and excluded volume penalties. Docking score is intended to be more suitable for comparing the binding affinities of different ligands than is the "raw" Coulomb-van der Waals interaction energy which is expressed as the glide energy (30). That's why in our study, we showed both docking score and glide energy which represents the actual scenario of binding affinity. According to the docking score, all 4 compounds are suitable in binding affinity when compared to the control drug. Rhein has the highest docking score followed by aloe-emodin. The formation of hydrogen bonds and higher number of hydrophobic interactions are responsible for their higher score. According to the docking score, rhein is most effective as an antifungal compound. In the study conducted by Wuthi-udomlert et al. (2010) reported that In vitro evaluation of the antifungal activity of Anthraquinone derivatives showed better result where TLC analysis demonstrated the presence of rhein and aloe-emodin(12). the active site of Lanosterol 14-$\alpha$-demethylase (CYP51) is divided into four subsites: a coordination bond with the iron of the heme group, the hydrophobic region, the hydrophilic H-bonding region, and the narrow hydrophobic cleft formed (23). All four compounds fitted exactly in the same fashion as the fluconazole to the active site of Lanosterol 14-$\alpha$-demethylase (CYP51). The two-dimensional interaction map showed that a coordination bond with the iron of the heme group occurred with all 4 compounds as like the control drug fluconazole. In this sense, The Hem460 is a very important residue in terms of binding to the active site. Nafiz et al. (2017) studied the in silico antifungal effect of new Benzimidazole-Triazoles derivatives. The active site components and interacting residues are very similar to our investigations (23). This result demonstrated that the selected anthraquinones can be a good candidate as an antifungal agent.

In-silico ADME/T analysis utilizes computer simulations and modeling to predict how a compound will behave in the body. It can be applied as an alternative strategy before implementing in vivo testing and can be used in the early stages of drug discovery and development. For being a drug compound, the candidate must fulfill some criteria which were addressed in our study to assess whether our selected compounds can be used as a potential antifungal agent or not. Although *S. alata* has been traditionally used against dermatophytes, the active antifungal compounds can be utilized against other fungi too. Our study showed positive human intestinal absorption which means higher bioavailability, distribution and drug metabolism(33). As the selected compounds were weak inhibitors of Human Ether-a-go-go-Related Gene (hERG), it will not cause adverse drug-drug interactions and cardiac side effects (34). While evaluating the toxicity, the selected anthraquinone compounds showed class II (50mg/kg - 500mg/kg) or Class III (500mg/kg - 5000mg/kg)acute oral toxicity which is the indication of their lower toxic effects(35). In terms of rat acute toxicity, the selected compounds the prediction showed higher IC50 value than the control drug. That means the selected anthraquinone compounds may be selected as a potential candidate for antifungal activity as they have shown better-predicted results in terms of absorption, distribution, metabolism, excretion, and toxicity (ADME/T).

In the current work, 4 selected anthraquinone compounds were subjected to in silico molecular docking studies to find their antifungal activities. Results of the study indicated that all 4 compounds have a significant antifungal as determined from computational calculation. Since the selectivity of the compounds is a very important parameter to become a good drug candidate, the in silico ADME/T prediction provides fundamental insights into such compounds. As a result, it can be concluded that the anthraquinones are promising candidates as a naturally derived antifungal agent in the future. However, more intense research should be employed to assess in further studies to develop these antifungal agents for their higher potency and improved safety profile.

## Acknowledgments

This research was partially supported by the research grant provided by GARE (Grant for Advanced Research in Education No. 37.20.0000.004.033.020.2016.7725) funded by Ministry of Education, Bangladesh and Special Allocation in Science and Technology provded by the Ministry of Science and Technology (No.

39.00.0000.009.14.004.19/BS-139/150), Bangladesh. We are thankful to our lab members for their kind assistance.

## References

1. Hennebelle T, Weniger B, Joseph H, Sahpaz S, Bailleul F. Senna alata. Fitoterapia. 2009;80(7):385–93.

2. Thamlikitkul V, Bunyapraphatsara N, Dechatiwongse T, Theerapong S, Chantrakul C, Thanaveerasuwan T, et al. Randomized controlled trial of Cassia alata Linn. for constipation. J Med Assoc Thailand= Chotmaihet thangphaet. 1990;73(4):217–22.

3. Benjamin T V, Lamikanra A. Investigation of Cassia alata, a plant used in Nigeria in the treatment of skin diseases. Q J Crude Drug Res. 1981;19(2–3):93–6.

4. Alalor CA, Igwilo CI, Jeroh E. Evaluation of the antibacterial properties of aqueous and methanol extracts of Cassia alata. J Pharm Allied Heal Sci. 2012;2(2):40–6.

5. Sule WF, Okonko IO, Joseph TA, Ojezele MO, Nwanze JC, Alli JA, et al. In vitro antifungal activity of Senna alata Linn. crude leaf extract. Res J Biol Sci. 2010;5(3):275–84.

6. Kazeem MI, Azeez GA, Ashafa AOT. Effect of senna alata (L) roxb (fabaceae) leaf extracts on alpha-amylase, alpha-glucosidase and postprandial hyperglycemia in rats. Trop J Pharm Res. 2015;14(10):1843–8.

7. Palanichamy S, Amala Bhaskar E, Bakthavathsalam R, Nagarajan S. Wound healing activity of Cassia alata. Fitoterapia. 1991;62(1):153–6.

8. Richardson MD. Changing patterns and trends in systemic fungal infections. J Antimicrob Chemother. 2005;56(suppl_1):i5–11.

9. Palanichamy S, Nagarajan S. Antifungal activity of Cassia alata leaf extract. J Ethnopharmacol. 1990;29(3):337–40.

10. Somchit MN, Reezal I, Nur IE, Mutalib AR. In vitro antimicrobial activity of ethanol and water extracts of Cassia alata. J Ethnopharmacol. 2003;84(1):1–4.

11. Ibrahim D, Osman H. Antimicrobial activity of Cassia alata from Malaysia. J Ethnopharmacol. 1995;45(3):151–6.

12. Wuthi-udomlert M, Kupittayanant P, Gritsanapan W. In vitro evaluation of antifungal activity of anthraquinone derivatives of Senna alata. J Heal Res. 2010;24(3):117–22.

13. Fouillaud M, Caro Y, Venkatachalam M, Grondin I, Dufossé L. Anthraquinones. CRC Press; 2018.

14. Zhou X, Song B, Jin L, Hu D, Diao C, Xu G, et al. Isolation and inhibitory activity against ERK phosphorylation of hydroxyanthraquinones from rhubarb. Bioorg Med Chem Lett. 2006;16(3):563–8.

15. Agarwal SK, Singh SS, Verma S, Kumar S. Antifungal activity of anthraquinone derivatives from Rheum emodi. J Ethnopharmacol. 2000;72(1–2):43–6.

16. Arya H, Syed SB, Singh SS, Ampasala DR, Coumar MS. In Silico Investigations of Chemical Constituents of Clerodendrum colebrookianum in the Anti-Hypertensive Drug Targets: ROCK, ACE, and PDE5. Interdiscip Sci Comput Life Sci. 2018;10(4):792–804.

17. Ahmad A, Khan A, Manzoor N, Khan LA. Evolution of ergosterol biosynthesis inhibitors as fungicidal against Candida. Microb Pathog. 2010;48(1):35–41.

18. Jacob SK, Ganguly S, Kumar P, Poddar R, Kumar A. Homology model, molecular dynamics simulation and novel pyrazole analogs design of Candida albicans CYP450 lanosterol 14 α-demethylase, a target enzyme for antifungal therapy. J Biomol Struct Dyn. 2017;35(7):1446–63.

19. Xia X. Bioinformatics and drug discovery. Curr Top Med Chem. 2017;17(15):1709–26.

20. Panichayupakaranant P, Sakunpak A, Sakunphueak A. Quantitative HPLC Determination and Extraction of Anthraquinones in Senna alata Leaves. J Chromatogr Sci [Internet]. 2009 Mar 1 [cited 2019 Apr 8];47(3):197–200. Available from: https://academic.oup.com/chromsci/article-lookup/doi/10.1093/chromsci/47.3.197

21. Chatsiriwej N, Wungsintaweekul J, Panichayupakaranant P. Anthraquinone Production in Senna alata. Root Cultures. Pharm Biol. 2006;44(6):416–20.

22. Dave H, Ledwani L. A review on anthraquinones isolated from Cassia species and their applications. 2012;

23. Can NÖ, Acar Çevik U, Sağlık BN, Levent S, Korkut B, Özkay Y, Kaplancıklı ZA, Koparal AS. Synthesis, Molecular Docking Studies, and Antifungal Activity Evaluation of New Benzimidazole-Triazoles as Potential Lanosterol 14α-Demethylase Inhibitors. Journal of Chemistry. 2017;2017.

24. Nascimento JET do, Rodrigues ALM, Lisboa DS de, Liberato HR, Falcão MJC, da Silva CR, et al. De novo design of non-coordinating indolones as potential inhibitors for lanosterol 14-α-demethylase (CYP51). Evidence-Based Complement Altern Med. 2018;62(1):16–24.

25. González-Chávez R, Martínez R, Torre-Bouscoulet ME, Gallo M, González-Chávez MM. De novo design of non-coordinating indolones as potential inhibitors for lanosterol 14-α-demethylase (CYP51). Chem Pharm Bull. 2014;62(1):16–24.

26. Podust LM, Poulos TL, Waterman MR. Crystal structure of cytochrome P450 14α-sterol demethylase (CYP51) from Mycobacterium tuberculosis in complex with azole inhibitors. Proc Natl Acad Sci. 2001;98(6):3068–73.

27. LigPrep Schrödinger, LLC, New York, NY, USA, 2015.

28. Kaminski GA, Friesner RA, Tirado-Rives J, Jorgensen WL. Evaluation and reparametrization of the OPLS-AA force field for proteins via comparison with accurate quantum chemical calculations on peptides. J Phys Chem B. 2001;105(28):6474–87.

29. Maestro, version 10.1, Schrödinger, LLC, New York, NY, USA, 2015.

30. Friesner RA, Murphy RB, Repasky MP, Frye LL, Greenwood JR, Halgren TA, et al. Extra precision glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. J Med Chem. 2006;

31. Dassault Systèmes BIOVIA, Discovery studio Visualizer, 19.1, San Diego: Dassault Systèmes, 2019

32. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7:42717.

33. Shen J, Cheng F, Xu Y, Li W, Tang Y. Estimation of ADME properties with substructure pattern recognition. J Chem Inf Model. 2010;50(6):1034–41.

34. Jing Y, Easter A, Peters D, Kim N, Enyedy IJ. In silico prediction of hERG inhibition. Future Med Chem. 2015;7(5):571–86.

35. Walum E. Acute oral toxicity. Environ Health Perspect. 1998;106(suppl 2):497–503.

**Table 1.** The docking score and glide energy (Kcal/mol) of the native ligand and selected anthraquinones.

| Compound | Docking Score | Glide energy (kcal/mol) |
|---|---|---|
| **Fluconazole** | -6.856 | -36.505 |
| **Aloe-emodin** | -7.81 | -31.729 |
| **Chrysophanol** | -7.493 | -22.515 |
| **Emodin** | -6.717 | -23.367 |
| **Rhein** | -8.518 | -35.526 |

**Table 2.** Drug likeliness prediction of the selected anthraquinones according to Lipinski's rule of five.

| Compound | Molecular weight(Dalton) | Number of H-bond acceptors | Number of H-bond donors | LogP value | Molar Refractivity |
|---|---|---|---|---|---|
| **Aloe-emodin** | 270.24 | 5 | 3 | 2.42 | 69.92 |
| **Chrysophanol** | 254.24 | 4 | 2 | 3.54 | 68.76 |
| **Emodin** | 270.24 | 5 | 3 | 3.01 | 70.78 |
| **Rhein** | 284.22 | 6 | 3 | 3.00 | 70.75 |

**Acceptable ranges:**

Molecular weight: < 500 Dalton

Hydrogen bond acceptor: ≤ 10

Hydrogen bond donor: ≤5

High Lipophilicity (expressed as LogP): <5

Molar refractivity: 40-130


ISSN: 1827-8620

**Table 3.** Selected pharmacokinetic parameters after ADME/T prediction.

| Parameters | Fluconazole | Aloe-emodin | Chrysophanol | Emodin | Rhein |
|---|---|---|---|---|---|
| **Blood-Brain Barrier** | +(0.9382) | +(0.7385) | +(0.6546) | +(0.5663) | +(0.7615) |
| **Human Intestinal Absorption** | +(0.9894) | +(0.9815) | +(0.9942) | +(0.9878) | +(0.9689) |
| **Human Ether-a-go-go-Related Gene Inhibition** | Weak inhibitor | Weak inhibitor | Weak inhibitor | Weak inhibitor | Weak inhibitor |
| **Carcinogenicity** | Non-carcinogens | Non-carcinogens | Non-carcinogens | Non-carcinogens | Non-carcinogens |
| **Aqueous solubility, LogS** | -1.8626 | -2.5294 | -3.1234 | -3.0170 | -3.2460 |
| **Acute Oral Toxicity** | III(0.7944) | II(0.4555) | II(0.4970) | III(0.6654) | II(0.4905) |
| **Rat Acute Toxicity LD50, mol/kg** | 2.4136 | 2.9280 | 2.9132 | 2.5826 | 2.7118 |

**Figure 1.** Structure of the compounds utilized in the present study. (a) The common structure of anthraquinones. (b) The crystal structure of lanosterol 14-*α*-demethylase in complex with fluconazole (PDB ID: 1EA1).

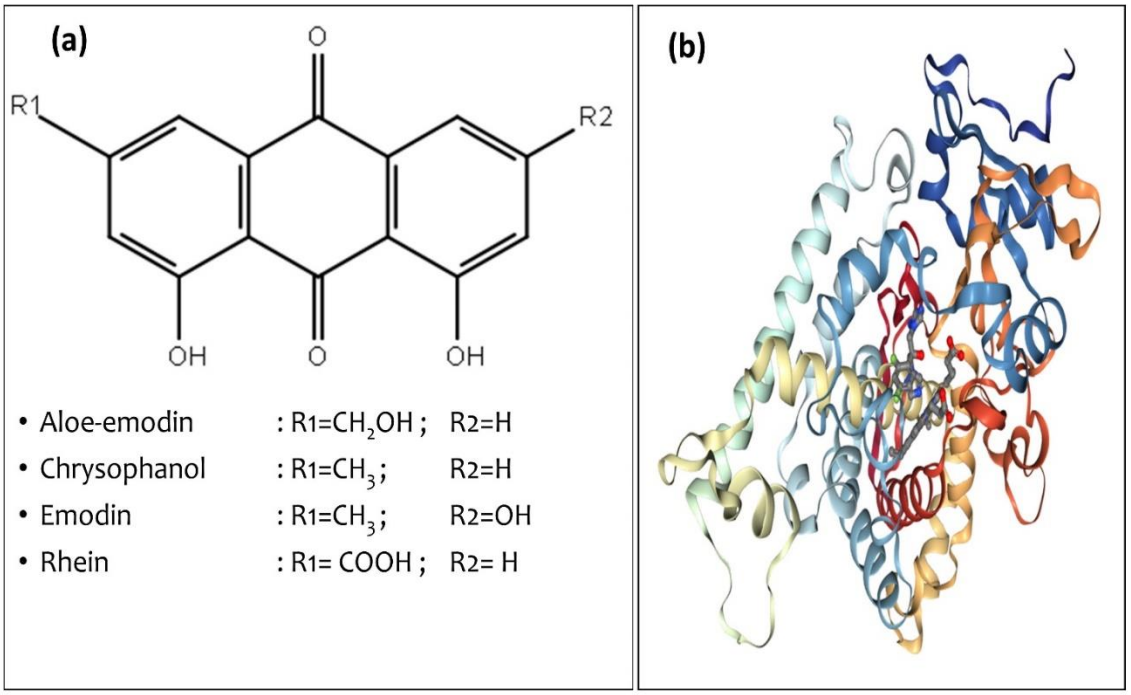

**Figure 2.**Amino acid residues of Lanosterol 14-$\alpha$-demethylase (CYP51) involved in the interactions with the ligands shown in three- dimensions (left) and two-dimensions (right). (a) Aloe-emodin, (b) Chrysophanol, (c) Emodin (d) Rhein (e) Fluconazole, (f) Aloe-emodin, (g) Chrysophanol, (h Emodin (i) Rhein (j) Fluconazole, (k) Legends for two dimensional interaction map. For three-dimensional visualization, Hem460 group is not shown.