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Damnacanthal from Morinda citrifolia L.: Experimental Characterization, Biological Evaluation, *In Silico* ADMET Assessment, and Future Perspectives in AI-Assisted Anticancer Drug Discovery

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Abstract

Natural products are a prominent source of structurally diverse bioactive molecules for anticancer drug discovery. Among these, anthraquinones are a class of compounds with antioxidant, anti-inflammatory, antimicrobial, and anticancer activities. Damnacanthal is a naturally occurring anthraquinone from *Morinda citrifolia L.*, which has been reported to possess diverse biological activities; however, its detailed experimental characterisation and *in silico* analysis are lacking. The current study aimed to isolate Damnacanthal from *M. citrifolia* and evaluate its antioxidant activity. In addition, the cytotoxic potential of the compound was assessed against Dalton's lymphoma ascites (DLA) cells. The drug-likeness and pharmacokinetic properties of the compound were predicted *in silico*. The compound isolated from *M. citrifolia* was identified as Damnacanthal through UV-Vis, FTIR, ^{1}H, and ^{13}C NMR, and LC-HRMS spectroscopy. Damnacanthal showed significant antioxidant activity through the FRAP assay. The compound exhibited cytotoxic potential against Dalton's lymphoma ascites cells in a concentration-dependent manner. Furthermore, the compound showed excellent physicochemical properties, oral drug likeness, and promising pharmacokinetic properties. The present study demonstrated that Damnacanthal is a potential natural anticancer candidate for further drug discovery and development. This study also highlighted the recent trends in AI-driven drug discovery for anticancer drug development, including QSAR, ADMET prediction, molecular docking, molecular dynamics simulation, XAI, and generative AI for de novo design. Although AI-driven approaches were not used in the present study, the results provide an AI-ready dataset to explore the anticancer potential of Damnacanthal and other anthraquinone derivatives for anticancer drug discovery and development.

Keywords: *Morinda citrifolia*; Damnacanthal; Anticancer activity; *In silico*; AI-assisted drug discovery

1. Introduction

Natural products have historically featured prominently as lead compounds for the discovery of drug molecules with useful biological activity. Nearly half of all small-molecule drugs are natural products, natural product derivatives or are inspired by natural products. Their significance lies in both their structural diversity and range of targets, offering a rich source of inspiration for the design of modern therapeutics. Natural products have proven particularly valuable in cancer therapy, where their diversified structures can be tailored to affect multiple targets at once.

Despite great progress in the field, cancer chemotherapy is hampered by issues such as drug resistance, toxicity, lack of target specificity and high costs [1]. Therefore, an urgent need remains for the development of more effective and tolerable anti-cancer drugs. Many successful chemotherapeutic agents currently in use were either natural products or derived from natural product precursors [2].

Anthraquinones represent an important class of naturally occurring aromatic polyketides. This class of secondary metabolites is characterized by a broad range of structural modifications and biological activities, which are reflected in their extensive use in medicinal chemistry [3]. Naturally occurring anthraquinones possess antioxidant, antimicrobial, anti-inflammatory, antiviral, antidiabetic, and anticancer activities and are widely distributed in the Kingdom Plantae, including the Morinda, Rubia, Cassia, Aloe and Rheum genera [4].

Damnacanthal (3-hydroxy-1-methoxy-2-formylanthraquinone) is one of the two major bioactive anthraquinones found in the leaves and fruit of *Morinda citrifolia L.* (noni). This molecule has received considerable attention due to its reported antioxidant, antiproliferative and anti-inflammatory activities. A variety of molecular mechanisms have been implicated in this natural product's anticancer activity, including inhibition of tyrosine kinases, regulation of apoptosis and cell-cycle pathways, induction of anti-angiogenic effects, and reduction of oxidative stress [3], [4]. Its multitarget nature and overall biological activity profile make damnacanthal a promising lead candidate for the development of novel anticancer therapeutics. However, before clinical applications, it is crucial to characterize this molecule's structure, biology and pharmacokinetics in greater detail.

Modern computational approaches allow researchers to characterize natural product leads in silico and estimate their therapeutic potential with greater accuracy. For example, in silico ADMET prediction can guide the selection of promising natural product candidates and help eliminate toxic compounds before laboratory trials [5].

1.1. Artificial Intelligence in Modern Medicinal Chemistry

Modern drug discovery makes extensive use of artificial intelligence (AI) for virtual screening, lead optimization and molecular design. AI-driven approaches are being used to analyze big chemical databases and identify structure–activity relationships using machine learning (ML), deep learning (DL), graph neural networks, and transformer-based language models. Similarly, generative models, including diffusion models, can be used to design novel organic molecules or optimize existing ones. These approaches have proven extremely useful in accelerating the drug discovery process since they significantly reduce the time spent on traditional hit-to-lead campaigns [6].

The application of AI in natural product research and development is similarly promising, primarily because many NP-derived compounds feature diverse and complex chemical structures amenable to ML-driven optimization. Some ML methods, such as Quantitative Structure-Activity Relationship (QSAR) models, have been extensively used in medicinal chemistry for decades. With the advent of modern ML methods, QSAR entered a new stage of development, utilizing approaches such as Random Forest, Support Vector Machine, Artificial Neural Networks, and Gradient Boosting to study large chemical data sets and identify structure-activity trends [7]. While QSAR analysis was not employed in this study, the wealth of structural, biochemical and pharmacokinetic data collected for damnacanthal can be leveraged to build QSAR models for other anthraquinone derivatives and identify trends that could inform the selection of future natural product candidates. More importantly, with the advent of powerful AI-driven drug design technologies, such as graph neural networks and diffusion models, the medicinal chemistry insights gained from this study could be used to create novel anthraquinone derivatives with improved pharmacological properties.

The last few years have witnessed the appearance of numerous AI-driven pharmacokinetic evaluation tools capable of predicting key ADMET parameters with high accuracy. In this study, conventional computational chemistry approaches were used to estimate the pharmacokinetic properties and assess the drug-likeness of damnacanthal. However, many modern *in silico* ADMET prediction tools, including SwissADME and PreADMET, employ sophisticated ML algorithms to characterize the absorption, distribution, metabolism, excretion, and toxicity profiles of the compound.

Similarly, molecular docking and molecular dynamics (MD) simulation offer valuable insights into molecular interactions at the atomic level, allowing researchers to estimate binding affinities and study protein-ligand interactions in detail. At the same time, AI-driven approaches such as structure-based scoring functions can facilitate the analysis of molecular interactions and improve hit and lead identification in structure-based drug design [8]. Furthermore, XAI methods such as SHAP and LIME can help elucidate the molecular basis of AI model predictions, thus guiding the process of molecular optimization and fragment-based drug design [9]. While none of these approaches was used in this study, they represent a powerful direction for future research. The application of AI-driven approaches to natural product pharmacology is also an emerging field, and the results of this study could serve as a valuable foundation for future studies in this area.

1.2. Generative AI, research gap and study objectives

Generative AI is a developing field that is being explored to design novel molecules with pre-set desirable properties through its ability to generate chemically valid molecules. With the application of AI-driven QSAR, ADMET, molecular docking and MD simulation, generative models allow for rapid optimization of natural product scaffolds before experimental investigations [10]. Studies on Damnacanthal have been limited in their scope to either structural elucidation, antioxidant activity, cytotoxicity or pharmacokinetics and have not attempted to combine biological evaluation with *in silico* ADMET profiling or contemporary AI-driven analysis.

It was therefore hypothesized that it would be informative to isolate and characterize Damnacanthal from *Morinda citrifolia* and assess its antioxidant and cytotoxic properties while also evaluating its drug-likeness using conventional *in-silico* approaches. While the application of AI-driven approaches was beyond the scope of this study, it is discussed how such an analysis can be utilized in future research and it is argued that the data generated can serve as the foundation for future AI-driven optimization of Damnacanthal analogues as anti-cancer agents.

2. Materials and Methods

2.1. Plant Material and Chemicals

Morinda citrifolia L. (noni) was the source of damnacanthal. The collection of the plant material and processing was done according to the protocol described in the thesis. Moreover, all analytical grade solvents and other reagents used for extraction, chromatographic purification, spectroscopic analysis, antioxidant and cytotoxicity assays were purchased from commercial vendors. Distilled or deionized water was used for all experiments.

2.2. Preparation of Plant Extract

The collected plant material was washed thoroughly with running water to remove adhering dirt and shade-dried to obtain a fine powder. The extract was obtained by using ethanolic extraction followed by evaporation

of the solvent. The obtained crude extract was purified by passing it through a chromatography column to obtain a dark yellow to orange-brown extract after Soxhlet.

2.3. Isolation and Purification of Damnacanthal

The crude extract was purified by using column chromatography with suitable solvents. The elution of the column was done in such a way that the compounds of interest appeared as distinct bands. Observation showed that the lower fraction of the column was of light yellow colour, whereas the upper fraction was orange-brown in colour. Thin layer chromatography and Paper chromatography were done for the fractions to separate different extracts.

2.4. Spectroscopic Characterization

The compound was characterized by using various spectroscopic and analytical techniques.

2.4.1. UV-Visible spectroscopy

The electronic absorption spectrum of the compound was recorded. The spectrum was compared with the electronic absorption spectrum of damnacanthal reported in the literature to infer the structure of the compound. The absorption spectrum was recorded for the compound to identify the absorption maxima of the compound in the ultraviolet-visible range.

2.4.2. Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy was used to identify the functional groups of the compound. The characteristic frequencies of the compound were compared with the characteristic frequencies of the hydroxyl group, quinone group, methoxy, and aromatic groups that are present in damnacanthal to identify different functional groups of the compound.

2.4.3. Nuclear Magnetic Resonance Spectroscopy

The structure of damnacanthal was further established by using ^{1}H NMR and ^{13}C NMR. ^{1}H NMR was used to determine the protons in the compound, such as aromatic protons, aldehyde protons, hydroxyl protons, and methoxy protons. The ^{13}C NMR was used to determine quinone carbons, aromatic carbons, methoxy carbons, and aldehyde carbons. Comparison of the obtained spectra with literature values helped identify the features of the compound.

2.4.4. Liquid Chromatography-High-Resolution Mass Spectrometry (LC-HRMS)

The accurate mass of the compound was determined to confirm its identity. The fragmentation pattern of the compound was also analyzed to determine its identity.

2.5. In Silico Drug-Likeness and ADMET Analysis

The chemical structure of damnacanthal was drawn using ChemDraw and was submitted to SwissADME and PreADMET servers for drug-likeness and ADMET analysis as described in the thesis.

SwissADME was used to predict the physicochemical properties, lipophilicity, water solubility, gastrointestinal absorption, brain/plasma partition coefficient, P-glycoprotein substrates, cytochrome P450 interactions, oral bioavailability, lead-likeness, and synthetic accessibility of the compound [11]. Lipinski's "Rule of Five" was used to evaluate the drug-likeness of the compound. Other rules that were used to evaluate the drug-likeness of damnacanthal included Veber's rule, Ghose's rule, Egan's rule, and Muegge's rule [12].

PreADMET was used to predict human intestinal absorption, Caco-2 permeability, MDCK permeability, plasma protein binding, cytochrome P450 interactions, mutagenicity, carcinogenicity, hERG inhibition potential, and aquatic toxicity of damnacanthal [13]. The results of ADMET analysis will be helpful in predicting the therapeutic potential of damnacanthal as a pharmaceutical entity.

2.6. Ferric Reducing Antioxidant Power (FRAP) Assay

The ferric reducing antioxidant power of damnacanthal was determined by using the FRAP assay [14]. The serial dilution of the sample and standard solution consisting of ascorbic acid was set up and incubated in a water bath for 5 minutes. After the incubation period, 0.35% w/v TCA and 1% w/v ferric chloride were added to each test tube. The reaction mixture was then centrifuged at 3000 rpm for 1 minute. The optical density of the resulting solution was then measured spectrophotometrically at 490 nm against a blank solution. The % inhibition of the ferric ion was determined from the graph that was plotted using the mean values of % inhibition against the serial dilutions of the standard solution and sample solution. The IC_{50} value of the sample was finally reported as the concentration of the sample solution required to reduce the ferric ion by 50%. In the experiment described in the thesis, 1 mL of the sample solution was transferred into a test tube and was diluted with 15 mL of distilled water. The diluted solution was then incubated at 50℃ in a water bath for 30 minutes. TCA and ferric chloride were then added to the contents of the test tube, vortexed, and centrifuged at 3000 rpm for 1 minute. The supernatant was then decanted into a clean test tube, which was further diluted with 4 mL of distilled water and was measured spectrophotometrically at 490 nm.

2.7. In Vitro Cytotoxicity Assay

The in vitro cytotoxic effect of damnacanthal was determined by using Dalton's lymphoma ascites cancer cells [15]. The Dalton's lymphoma ascites (DLA) cells were obtained from the peritoneal cavity of tumour-bearing mice by centrifugation of the ascites fluid collected from the mice at a speed of 1000 rpm. The cells were then resuspended in phosphate-buffered saline (PBS) and were counted using a haemocytometer. Cell suspensions of appropriate cell densities were dispensed into different microplates. To each of the microplates, 4 different concentrations of sample solution were added and incubated at 37 ℃ for 3 h, followed by a trypan blue exclusion assay to determine cell viability. In the trypan blue exclusion assay, a cell suspension of appropriate cell densities was dispensed into counting chambers of a haemocytometer. Cells with intact cell membranes will exclude trypan blue solution, whereas cells with damaged cell membranes will take up the trypan blue solution. Therefore, the cell count was done and the percentage of viable cells was estimated as cells without blue spots divided by the total number of cells counted multiplied by 100 %.

3. Results and Discussion

3.1. Isolation and Purification of Damnacanthal

Ethanolic Soxhlet extraction of *Morinda citrifolia* yielded a dark yellow to orange-brown crude extract, which was purified by column chromatography. Distinct light-yellow and orange-brown bands were observed during elution, indicating efficient separation of phytochemical constituents. TLC analysis produced an experimental Rf value of 0.55, which closely matched the reported value (0.50) for Damnacanthal, while paper chromatography gave an Rf value of 0.53, confirming successful isolation of the target anthraquinone.

3.2. Structural Characterization

The isolated compound was identified as Damnacanthal by using various spectroscopic techniques [16],[17].

The UV–Visible spectrum showed absorption maxima at 221.5–239.3 nm, which corresponded to π→π transitions and 305.9, 340.2 and 364.4 nm, which corresponded to n→π transitions of the isolated compound.

FTIR spectral analysis revealed the presence of a phenolic –OH group at 3298.8 cm^{-1}, quinone C=O stretching vibrations at 1680-1587.8 cm^{-1}, aromatic C–H bending vibrations at 1397.8 cm^{-1} and C–O stretching vibrations at 1235.9 cm^{-1}.

The ^{1}H NMR spectrum showed phenolic –OH protons at δ 12.5–13.5 ppm, aldehyde –CHO protons at δ 10.37 ppm, aromatic protons at δ 6.8–8.3 ppm and methoxy $-OCH_3$ protons at δ 3.53 ppm.

The ^{13}C NMR spectrum showed quinone –C=O carbons at δ 181–192 ppm, aldehyde –CHO carbon at δ 190–195 ppm, $-OCH_3$ oxygenated aromatic carbons at δ 57–165 ppm and aromatic carbons of the anthraquinone ring.

In addition, the molecular ion peak (M+) of the isolated compound was recorded at m/z 284 by LC–HRMS analysis, which corresponds to the molecular formula, $C_{16}H_{12}O_{5,}$ of Damnacanthal.

Table 1. Spectroscopic characterization of Damnacanthal

Technique	Experimental result	Structural significance
UV–Vis	λmax 221.5–239.3, 305.9, 340.2, 364.4 nm	Anthraquinone chromophore
FTIR	3298.8, 1680–1587.8, 1397.8, 1235.9 cm^{-1}	O–H, C=O, aromatic C–H, C–O
^{1}H NMR	δ 12.5–13.5, 10.37, 6.8–8.3, 3.53 ppm	OH, CHO, aromatic H, OCH_3
^{13}C NMR	δ 181–192, 190–195, 57–165 ppm	Quinone carbonyls, aldehyde, oxygenated carbons
LC–HRMS	m/z 284	Molecular ion of Damnacanthal

3.3. Drug-Likeness and ADMET Prediction

SwissADME predicted that Damnacanthal has good drug-like properties. It was found that the compound follows Lipinski's, Lead-like, and CMC-like rules without any violations and passes the Veber, Ghose, Egan, and Muegge filters. It was predicted that the compound will have high human gastrointestinal absorption and low blood-brain barrier penetration. Overall, it was concluded that the substance has an appropriate set of physicochemical properties for oral absorption of the drug.

PreADMET predicted that Damnacanthal has a high human intestinal absorption (HIA%) of 95.47%. Thus, it can be concluded that the compound is considered to be highly absorbed. The MDCK permeability of the substance was 16.81 nm/s, which suggests low permeability. The prediction also showed that 82.55% of protein binding will occur in the plasma, which means that it is not highly bound to proteins. The compound was predicted to inhibit CYP2C19 and CYP2C9 enzymes, but not CYP2D6 and CYP3A4, while it was neither a substrate for CYP2D6 nor CYP3A4. It was also found that the substance has a positive Ames mutagenicity test, medium inhibition of hERG channels, and high aquatic toxicity; therefore, toxicity optimization is required for the future lead compound.

Table 2. Summary of SwissADME and PreADMET predictions

Parameter	Prediction
Human intestinal absorption	95.47%
BBB penetration	Low
MDCK permeability	16.81 nm/s
Plasma protein binding	82.55%
Lipinski Rule	Passed
Lead-likeness	Passed

CYP2C19	Inhibitor
CYP2C9	Inhibitor
CYP2D6	Non-inhibitor
CYP3A4	Non-inhibitor
Ames test	Positive
hERG inhibition	Medium risk

The computational analyses suggested that Damnacanthal possesses favourable drug-like characteristics while highlighting the need for comprehensive safety evaluation during future preclinical development [18].

3.4. Antioxidant Activity

The antioxidant activity of Damnacanthal was evaluated using the FRAP assay and compared with ascorbic acid.

Table 3. Percentage of inhibition shown by Damnacanthal

Concentration (µg/mL)	Mean absorbance	% Inhibition
25	0.062	20.00
50	0.0875	49.71
100	0.192	77.08

The corresponding inhibition values for ascorbic acid were 22.35%, 48.24% and 74.49%, respectively. The calculated IC_{50} of Damnacanthal was approximately 50 µg/mL, which was comparable to that of ascorbic acid (~52 µg/mL), demonstrating strong antioxidant activity.

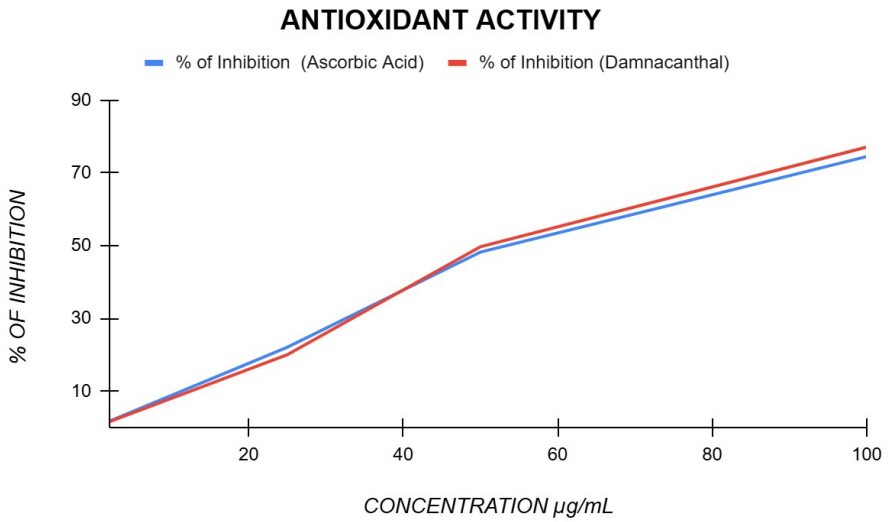

Fig. 1. Percentage of inhibition shown by ascorbic acid and Damnacanthal

3.5. Cytotoxic Activity Against DLA Cells

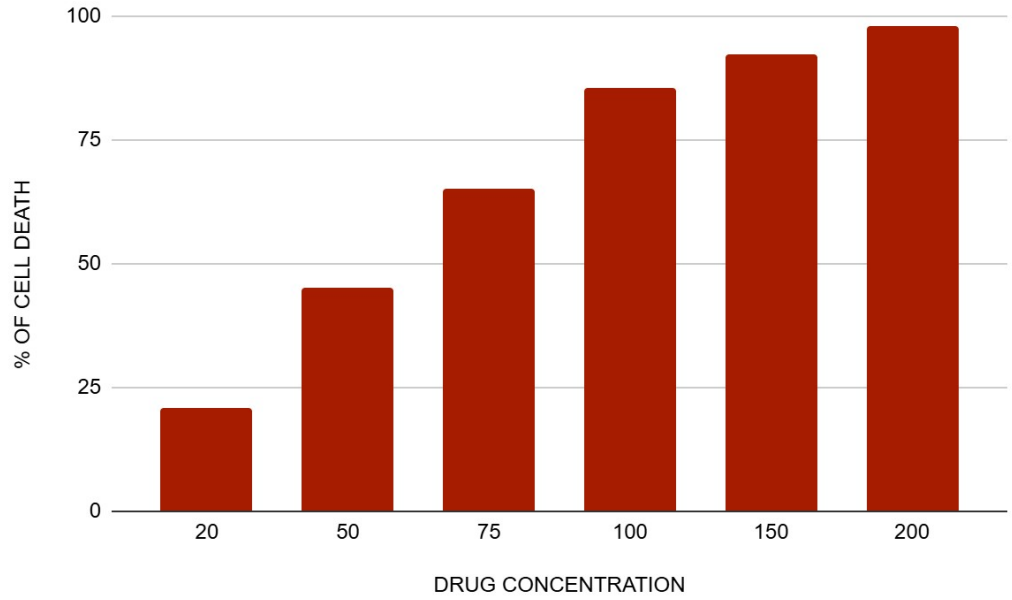

Fig. 2. Damnacanthal exhibited concentration-dependent cytotoxicity against DLA cells.

The observed dose–response relationship indicates that Damnacanthal exerts significant cytotoxic activity against DLA cells and supports its potential as a promising natural lead compound for further anticancer investigation.

3.6. Integration of the Present Findings with AI-Assisted Drug Discovery and Clinical Implications

Artificial intelligence (AI) is disrupting modern drug discovery by enabling faster lead identification, optimization and decision-making via data-driven approaches. Although AI methods were not employed in the current study, the experimental data reported herein can be leveraged *in silico* to design future studies that employ AI-driven drug discovery approaches. Machine learning-based Quantitative Structure-Activity Relationship (QSAR) modelling, AI-based ADMET prediction, molecular docking, molecular dynamics (MD) simulation, Explainable AI (XAI) and generative AI can be utilized to predict biological activity, optimize pharmacokinetic/pharmacodynamic (PK/PD) properties, identify molecular targets and design novel anthraquinone derivatives with enhanced potency and reduced toxicity. Moreover, the physicochemical properties and drug-likeness of Damnacanthal predicted using SwissADME and PreADMET software can also be utilized to guide future in silico optimization of this anthraquinone.

3.7. Summary of Findings

The current study isolated Damnacanthal from *M. citrifolia* and established its physicochemical properties, drug-likeness and preliminary pharmacokinetic properties using *in silico* approaches. Besides, the antioxidant and cytotoxic potentials of the anthraquinone were evaluated and empirically validated. The findings of the current study demonstrate that Damnacanthal is a promising anthraquinone with desirable physicochemical properties, decent drug-likeness, preliminary pharmacokinetic properties and biological activities.

The information reported in this study can be utilized in future studies to perform mechanistic experiments, medicinal chemistry optimization and employ AI-assisted QSAR modelling, advanced ADMET prediction, molecular docking, molecular dynamic simulation and generative AI.

4. Future Perspectives

The findings of the current study demonstrate that Damnacanthal is a promising lead compound with significant antioxidant activity, dose-dependent cytotoxic potential and desirable physicochemical properties. Although this study focused on the physicochemical analysis, pharmacokinetic properties, antioxidant activity and cytotoxic potential of Damnacanthal, the information reported herein can be used to guide future medicinal chemistry optimization studies as well as AI-assisted drug design approaches.

For instance, QSAR modelling can be performed to elucidate the structure-activity relationship of this anthraquinone using the data reported in this study. Future studies can also employ molecular docking and molecular dynamics simulation to identify potential molecular targets as well as investigate the molecular mechanism of action of this natural product drug lead. Moreover, future studies can apply advanced ADMET prediction tools to optimize the absorption, distribution, metabolism and excretion profile of this anthraquinone to minimize potential toxicity and enhance its therapeutic efficacy. Similarly, XAI can be employed to identify the most relevant molecular descriptors that can be used to guide future medicinal chemistry optimization studies [19].

Generative AI can also be used to generate novel analogues of this anthraquinone with enhanced potency, reduced toxicity, improved drug-likeness and optimized metabolic stability before any target-based in vitro and in vivo trials [20]. Thus, it is envisaged that the findings of this study will contribute to future AI-assisted drug discovery studies aimed at optimizing the potency and safety profile of natural product drug leads to promote their clinical translation.

5. Conclusion

The current study isolated and characterized the bioactive constituent of *Morinda citrifolia L* and evaluated its antioxidant activity, cytotoxic potential and pharmacokinetic properties using conventional *in silico* approaches. The chemical structure of the isolated anthraquinone was elucidated using various chromatographic, spectroscopic and high-resolution mass spectrometric techniques. The antioxidant potential of the anthraquinone was evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, whereas its cytotoxic potential was evaluated using the MTT cell viability assay. The findings of this study demonstrate that the isolated anthraquinone is a promising lead candidate with appreciable cytotoxic potential against Dalton's lymphoma ascites (DLA) cells and significant antioxidant activity.

The physicochemical properties and drug-likeness of the anthraquinone were predicted using SwissADME and PreADMET software. The results of this study indicate that the isolated anthraquinone has desirable physicochemical properties, appreciable drug-likeness and preliminary pharmacokinetic properties. This natural product drug lead can, therefore, be further investigated using advanced pharmacokinetic and pharmacodynamic studies to further validate its safety and efficacy profile. Overall, this study demonstrates the enormous medicinal potential of traditional herbal medicine and the ability of conventional *in silico* biochemical approaches to explicate the biological activity of natural products. In addition, future studies can integrate artificial intelligence into natural product drug discovery pipelines to elucidate the structure-activity relationship, molecular mechanism of action, ADMET profiles and optimize the potency and safety profile of potential natural product drug candidates.

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