*(Eco)*toxicokinetic Evaluation of the Natural Larvicide Cardanol Diene Against *Aedes aegypti*

Avaliação *(eco)*Toxicocinética do Larvicida Natural Cardanol Dieno Contra *Aedes aegypti*

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Abstract

Dengue is an arbovirus that has become a public health problem in Brazil, and its control generally consists of the use of insecticides belonging to the organophosphate and pyrethroid groups, which can cause deleterious effects on human health and the environment. Therefore, the identification of molecules presents in plants that are potentially active against the dengue virus is an initial step in the development of systems for the dengue treatment. In this context, the natural compound cardanol diene extracted from the medicinal plant *Myracrodruon urundeuva* Fr. All. has a high larvicidal potential against dengue, but there is a lack of data on its toxicological safety in non-target organisms. Therefore, this work aims to investigate the human toxicokinetic and ecotoxicological properties in computational models that provide general insight into biomonitoring and toxicokinetic effects in various organisms, since there is an absence of studies in this modality. The exposure of cardanol diene in aquatic organisms did not show immediate toxicity (acute and chronic), however, it has a high potential for bioaccumulation, bioconcentration and persistence, causing the transfer of the compound along the trophic chain, providing its insertion into human body fluids causing deleterious effects: hepatoxicity, cardiotoxicity, neuropathological response and carcinogenesis. This research shows the toxic effect of chemical compounds along the trophic chain using predictive models.
Keywords: Cardanol Diene. ADMET Properties. Ecotoxicology. Environmental Biomonitoring.

Resumo

A dengue é uma arbovirose que se tornou um problema de saúde pública no Brasil, e seu controle geralmente consiste no uso de inseticidas pertencentes aos grupos dos organofosforados e dos piretróides, que podem causar efeitos deletérios à saúde humana e ao meio ambiente. Portanto, a identificação de moléculas presentes em plantas que são potencialmente ativas contra o vírus da dengue é um passo inicial no desenvolvimento de sistemas para o tratamento da dengue. Nesse contexto, o composto natural cardanol dieno extraído da planta medicinal Myracrodruon urundeuva Fr. All. tem um alto potencial larvicida contra a dengue, mas faltam dados sobre sua segurança toxicológica em organismos não-alvo. Este estudo teve como objetivo investigar as propriedades toxicocinéticas e ecotoxicológicas humanas em modelos computacionais que fornecem uma visão geral sobre biomonitoramento e efeitos toxicocinéticos em vários organismos, uma vez que há uma ausência de estudos nessa modalidade. A exposição do cardanol dieno em organismos aquáticos não apresentou toxicidade imediata (aguda e crônica), porém, possui alto potencial de bioacumulação, bioconcentração e persistência, ocasionando a transferência do composto ao longo da cadeia trófica, proporcionando sua inserção nos fluidos corporais humanos causando efeitos deletérios: hepatoxicidade, cardiotoxicidade, resposta neuropatológica e carcinogênese. Esta pesquisa mostra o efeito tóxico de compostos químicos ao longo da cadeia trófica usando modelos preditivos.
Palavras-chave: *Cardanol Dieno. Propriedades ADME. Ecotoxicologia. Biomonitoramento Ambiental.*

1 Introduction

Dengue is an arbovirus of viral and classic etiology; in its severe form, it presents itself as hemorrhagic, becoming a serious public health problem in Brazil and other tropical regions of the world (Wong et al., 2020). It is essentially an urban transmission system, where all the fundamental factors for its occurrence are present: people, virus, media, and especially political, economic, and cultural conditions that constitute the structures that allow the establishment of chains of transmission, development, and proliferation of the Aedes aegypti mosquito (Santos et al., 2023; Wilder-Smith et al., 2019).

Dengue viruses belong to the *Flaviviridae* family and integrate into four closely related but antigenically distinct serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) (Harapan *et al*., 2020). The dengue virus (DENV) genome consists of positive-sense RNA expressing structural and nonstructural proteins, most notably NS1, which plays a role in viral genome replication and cell signaling pathways modulated by HepG2 cells constitutively expressing NS1, which alters the activation profile of proteins in the NF-kB pathway (Carneiro *et al*., 2015; Muller; Depelsenaire; Young, 2015).

The control of Aedes aegypti occurs through the development and innovation of new biological agents such as fish (*Betta splendens*) and chemicals using neurotoxic

insecticides belonging to the organophosphate and pyrethroid groups, repellents, and insecticide and larvicides resistance management, however, the indiscriminate use of pesticides has led to increased resistance in mosquito populations and public health problems (Lima *et al*., 2011; Zara *et al*., 2016).

The caatinga biome of Brazil has some of the most demanding and unique environmental and ecological conditions, which means that much of its biological heritage cannot be found anywhere else on earth (Sá-Filho *et al*., 2020). The therapeutic properties of many plants secondary metabolites have led to the search for active ingredients from various species. The exploration of these resources can help identify natural products that may lead to the development of new therapeutic substances to aid in the control of dengue outbreaks, especially because of the improved biodegradability of these products (Dantas *et al*., 2019; Ribeiro *et al*., 2014; Vieira *et al*., 2023).

Thus, the cardanol diene molecule isolated from an ethanolic extract of the plant *Myracrodruon urundeuva* Fr, and known as "aroeira-do-sertão", a medicinal tree species belonging to the *Anacardiaceae* family, commonly found in the caatinga of semi-arid northeastern Brazil, may be an alternative to a new natural larvicide (Souza *et al*., 2012).

Using the ADMETlab 2.0, an advanced online platform for predicting ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of chemical compounds, the objective of this work is to investigate toxicokinetic and ecotoxicological properties, presenting a risk analysis for human biological systems and aquatic organisms, since there is an absence of studies in this modality.

2 Material and Methods

2.1 Ecotoxicological assessment: ECOSAR® and JANUS®

Ecological Structure Activity Relationships - ECOSAR® is a software that enables a quantitative assessment of toxic effects on aquatic organisms based on available data on substances of the same chemical class (De Haas; Eikelboom; Bouwman, 2011). The program predicts acute (high:<1 mg/L; moderate: between 1 and 100 mg/L and low:>100 mg/L) and chronic toxicity (high:<0.1 mg/L; moderate: between 0.1 and 10 mg/L and low:>10 mg/L) of chemicals to aquatic organisms such as fish, invertebrates, and algae, as well as to terrestrial organisms such as earthworms in some cases (Sanderson *et al*., 2003).

$$y = mx + b \quad (1)$$

$$ChV = log\left(\frac{LOEC\ x\ NOEC}{2}\right) \quad (2)$$

(y): toxic effect concentration (LC50 in mmol/L or mg/L); **(x):** log kow employed for compounds that were not tested.

The prediction model in aquatic organisms uses measured data to predict toxicity in chemicals that lack data based on structure-activity relationships (QSARs) that estimate acute and chronic toxicity given through the geometric mean of the unobserved effect concentration (NOEC) and the lowest observed effect concentration (LOEC) (Reuschenbach *et al*., 2008) (Eq. 1 and Eq. 2). In short, ECOSAR® has a library of chemical class-based QSARs allowing common aquatic toxicity prediction with the expert decision tree to select the appropriate chemical class (Asmiyenti *et al*., 2019).

Nevertheless, JANUS® is a software tool that makes it possible to identify chemical compounds that are of interest to the environment and human health (Pizzo *et al*., 2016). Above all, it allows a conceptual evaluation using different QSAR/QSPR models which focuses on identification such as PBT (persistent, bioaccumulative, and toxic), CMR (carcinogenic, mutagenic, and reprotoxic), and ED (endocrine disruptor) (Benfenati *et al*., 2019).

The output page (results) of the target compound (cardanol diene) incorporates enables a global prediction for each of these properties, providing an estimate and reliability given in a range of colors that equate in a qualitative model to how much the input compound causes concern to the environment, however, the results of this step will be addressed in adaptation to the core model (Manganelli *et al*., 2022). In line with this, the final scores (vPvB: very Persistent and very Bioaccumulative, SVHC: Substances of very high concern, and PBT: Persistent, Bioaccumulative, and Toxic) determined in a quantitative model with a threshold measure between 0-1, generally used to investigate the correlation with the qualitative model, are also included (Lombardo *et al*., 2022; Manganaro *et al*., 2020).

2.2 Bioactivity by the virtual screening

The SwissTargetPrediction online tool algorithm[1] uses reverse screening to predict, through structural similarities between molecules, possible biological target receptors. A similarity test was performed between the rendered and optimized molecular structure of cardanol diene (*i*) and each compound in the ChEMBL dataset (*j*), embedded in the server, from the smallest Manhattan distance between the 18-dimensional vectors between the calculated distances (20 x 20) across all possible conformations of each molecule (Eq. 3).

$$1 / \left((1 + 1/18\, d\_ij)\right) \quad (3)$$

$$d = \sum_{s=1}^{18} |xs - ys| \quad (4)$$

Then, the Manhattan distance (d) is applied to compare the vectors (**x** and **y**) between two molecules (Eq. 4), resulting in the 3D/2D similarity order with known active compounds (Gfeller *et al*., 2014). The results were supported by bioactivity

1 (http://www.swisstargetprediction.ch/)

scoring from the Molinspiration Cheminformatics online tool[2].

2.3 Physicochemical space and pharmacokinetics

The two-dimensional structure of cardanol diene was reported from the ChemSpider molecular database (http://www.chemspider.com/) to the acid ionization constant (pKa) calculation engine of ChemAxon's bioinformatics calculation service available online, Playground[3]. Then, the structure was subjected to the medicinal chemistry filters of Lipinski's "rule of five" (Lipinskil, 2004), GSK's rule (Ritchie *et al*., 2009), and Pfizer's rule (Hughes *et al*., 2008), embedded in the ADMETlab 2.0 online server[4] for evaluation of the physicochemical space occupied by the substance. And then, the molecule was subjected to estimation of pharmacokinetic descriptors from ADMETlab 2.0, PreADMET (https://preadmet.qsarhub.com/adme/), and ADMET - LMC (http://qsar.chem.msu. ru/admet/), which include passive permeability in canine renal Madin-Darby cells (Papp MDCK), P-glycoprotein (P-gp) substrate, human intestinal absorption (HIA), the volume of distribution (Vd), hepatic clearance rate (CLint,u), and permeability at the blood-brain barrier (BBB).

2.4 Site of metabolism and liver injury

The linear notation in SMILES (Simplified molecular-input line-entry system) of cardanol diene was loaded into the online Xenosite server[5] for estimation of the structural contributions susceptible to biotransformation by cytochrome P450 (CYP450) isoforms in the human liver microsome (HLM). Then, the results were supported by the prediction of action as substrate or inhibitor of the majority CYP450 isoforms (2C19, 2C9, 2D6, and 3A4) from the ADMETlab 2.0 and PreADMET servers, as well as structure-based toxic effects from the eMolTox server[6].

2.5 Estimate of hERG blocker effects

The cardiotoxicity endpoint was estimated using the similarity test with inhibitory substructures of the hERG (the human Ether-a-go-go-Related Gene) ion channel from the Pred-hERG 4.2 online server (http://predherg.labmol.com.br/), where a 2D probability map with the positive and negative structural contributions of cardanol diene was generated, and the predictive tool Playground - ChemAxon, where the activity potential (pAct) of the substance against hERG channels was estimated.

3 Results and Discussion

3.1 Ecotoxicological assessment

From the results provided by the ECOSAR® software corresponding to the acute and chronic toxicity of the compound cardanol diene, the following parameters were established: duration, lethality, dose, and non-target organisms, some prepositions were proposed (Asmiyenti *et al*., 2019).

Table 1 - Neutral organic toxicity (cardanol diene) predicted by ECOSAR®

Neutral organic SAR (Baseline toxicity)			
Organism	**Duration**	**End pt**	**Mg/L (ppm)**
Fish	96hr	LC50	0.000355
D. magna	48hr	LC50	0.000367
Green Algae	96hr	EC50	0.003*
Fish		ChV	7.04e-005
D. magna		ChV	0.000191
Green Algae		ChV	0.003*

Source: research data.

From Table 1, it was inferred that during the acute and chronic toxicity tests, the target compound does not present any initial risk of toxicity to non-target organisms (fish, microcrustaceans, and green algae), due to its high possibility of adsorption in soil/sediment compartment, because it binds in a highly stable way with particulate material present in the aquatic environment and is unavailable for these organisms, thus the effect level exceeded the water solubility by 10x, no effects are normally reported at saturation (NES) (Bu *et al*., 2021), however, through this, it may cause a massive biomagnification process in aquatic organisms (G. Algae).

In its environmental toxicokinetic profile, the compound cardanol diene presents a high value of log know, a measure that corresponds to the ratio between the chemical concentration in the octanol phase and in water of a two-phase/water system in thermodynamic equilibrium (Lambert *et al*., 2022) in which it provides a high persistence and bioconcentration both in the aquatic compartment with greater notoriety, and the possibility of transferring the contaminant (cardanol diene) along the trophic chain.

Table 2 - Kinetic profile and endpoints of the compound cardanol diene

	Persistence (Days)			
Log Kow	**Water**	**Soil**	**Sediment**	**Toxicity**
8.5	1072	23	13	No
BCF*	Carcino	Mutag	R. Toxicity (µg/L)*	E. Disruptor*
2.61	Yes	No	Yes (29.24)	No

Notes (*): BCF (bioconcentration factor), Carcino (Carcinogenicity), Mutag (Mautagenicity), Reproductive toxicity (Zebrafish embryo AC50 prediction) and endocrine disruptor.
Source: research data.

2 (https://www.molinspiration.com/)
3 (https://disco.chemaxon.com/calculators/demo/playground/)
4 (https://admetmesh.scbdd.com/)
5 (https://swami.wustl.edu/xenosite)
6 (https://xundrug.cn/moltox)

However, considering the transfer of the compound in a trophic chain and chronic exposure can cause deleterious effects: developmental/reproductive toxicity to zebrafish embryos and carcinogenic profile, in addition, it presents biosafety regarding mutagenicity and endocrine disrupting processes (Table 2).

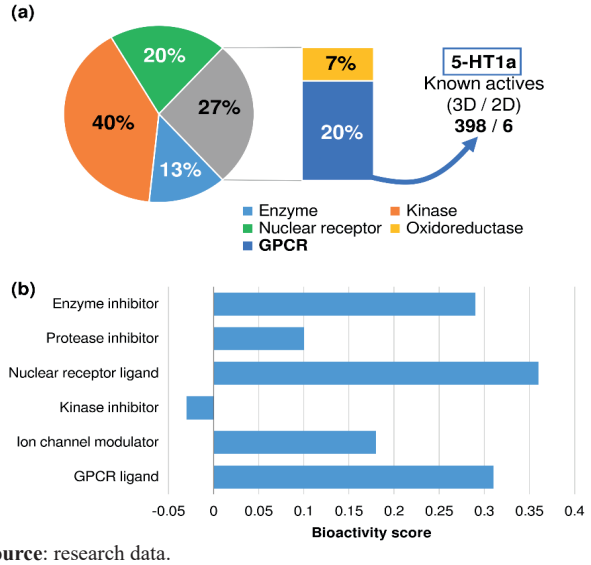
Regarding the toxicokinetics data and toxicity endpoints, the compound cardanol diene as a prototype larvicide and possible diffusion in the social environment, consists of a substance may present a high potential for concern (score: 0.852), i.e. it may provide serious impacts to human and environmental health.

Aimed at authorization and restriction guidelines for chemicals, cardanol diene is prone to high concern at its high potential bioaccumulative, bio concentrative (score: 0.519), and persistence (0.617) diffused through physicochemical properties (log kow and BCF) directly interfering with substance kinetics in environmental compartments and toxicity in non-target organisms) and toxicity endpoints (carcinogenicity and developmental toxicity) data exemplified in article 57 of the REACH Regulation.

3.2 Bioactivity by the virtual screening

The results of the structure-based virtual screening can be visually inspected in Figure 2. From the analysis, cardanol diene has in the majority 40% of its biological interactions with kinase targets (Figure 2a) within the Homo sapiens organism, although it is a weak inhibitor of this class of targets (bioactivity score -0.03) (Figure 2b).

Figure 2 - Structure-based virtual screening pie chart (a) and bioactivity score against main targets of Homo sapiens organism (b)



Source: research data.

It is observed that the substance showed a structural similarity with 398 compounds, within the class of G-protein-coupled receptors (GPCRs) from the ChEMBL database, capable of interacting with serotonin 1A (5-HT1a) receptors (Figure 2a) and may act as a modulator of the activity of most known GPCRs (bioactivity score>0.30) (Figure 2b). In addition, cardanol diene can act as a ligand for nuclear receptors (bioactivity score>0.35) and can modulate gene expression activity and cellular stress response.

Physicochemical space and pharmacokinetics

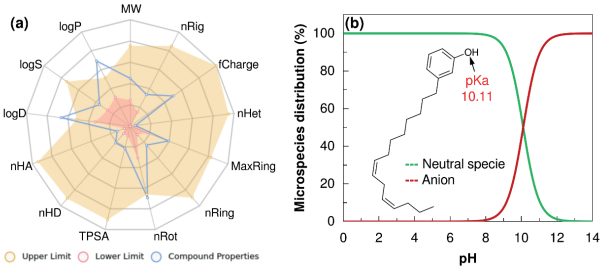
From the physicochemical space radar in Figure 3a, despite the high lipophilicity (logP>5), cardanol diene is within the spectrum of molecular weight and H-bond acceptors/donors of Lipinski's "rule of five" (MW≤500 g/mol, nHA≤10 and nHD≤5) (Lipinskil, 2004), suggesting that the substance can be absorbed by the human body. Furthermore, the calculated TPSA of 20.23 Å² (R-OH) indicates that the polar surface area is within the physicochemical space where there is a higher incidence of toxicity (logP>3 and TPSA≤75Å²) due to higher mobility to physiological compartments, including the risk of penetration into the BBB and modulation in CNS activity, as warned in the Pfizer filter (Table 3) (Hughes *et al*., 2008).

Table 3 - Calculated physicochemical properties and evaluation of drug likeness of the Cardanol diene

Property	Value	Physicochemical Space
Molecular Weight (MW)	300.25 g/mol	100~600 g/mol
logS	-4.29	-4~0.5
logP	5.6	0~3
$logD_{7.4}$	4.7	1~3
nHA	1	0~12
nHD	1	0~7
TPSA	20.23 Å²	0~140 Å²
nRot	12	0~11
nRing	1	0~3
MaxRing	6	0~18
nHet	1	1~15
fChar	0	-4~4
nRig	8	0~30
Lipinski rule		**Accepted**
GSK rule		**Alert**
Pfizer rule		**Alert**

Notes: nHA (number of H-bond Acceptors); nHD (number of H-bond Donors); TPSA (Topological Polar Surface Area); nRot (number of Rotatable Bonds); nRing (number of Rings); MaxRing (number of atoms in the biggest ring); nHet (number of Heteroatoms); fChar (formal charge); nRig (number of Rigid bonds).
Source: research data.

Figure 3 - Physicochemical space occupied by the cardanol diene (a) and microspecies distribution as a function of the pH variations (b)



Source: research data.

In the chart of Figure 3b, it is possible to note the distribution of the microspecies of the cardanol diene molecular system as a function of pH. From the estimated pKa of 10.11 for the phenolic hydroxyl, the side chain of the molecule offers a little contribution to the formation of the conjugate base at physiological pH (pH of approximately 7.4), with a relative concentration of only 0.2%. At more basic pH levels, it is possible to observe that the chemical equilibrium shifts towards the formation of the ionized species (O-) starting at pH 10.11, a behavior that affects the buffer lipophilicity (logD7.4=4.7) relative to the intrinsic lipophilicity (logP =5.6), following an order of ratio logP > logD at pH 7.4 (Table 3).

3.4 Estimate of bioavailability and CNS activity

The results of the prediction of pharmacokinetic descriptors can be seen in Table 3 and visually inspected by the regressions in Figure 4a and Figure 4b. The estimated Papp value on the order of $3.0x10^{-5}$ cm/s leads to a high passive cellular permeability of the substance, with low susceptibility to being a substrate of P-gp, which, when combined with the predicted low CLint,u rate of 5.80 mL/min/kg, may lead to the high bioavailability of cardanol diene in the bloodstream, with a volume of distribution that allows access to biological tissues (Vd = 3.92 L/kg) (Waterbeemd; Gifford, 2003). These predictions corroborate with the estimated high intestinal absorption of 95.57% (Figure 4a), where the polar surface of the R-OH group (20.23 Å²) favors penetration into the BBB, given the logBB permeability coefficient on the order of -0.16 that allows the passage of at least 10% of the molecular fraction of cardanol diene in the CNS (Figure 6b) (Dyabina *et al*., 2016), agreeing with brain/blood distribution coefficient (Cbrain/Cblood) in the order of 19.42 (Table 4).

Table 4 - Predicted pharmacokinetic descriptors by the consensual test between ADMETlab 2.0 and PreADMET web

Property	Value	Source
P_{app} MDCK	$3.0x10^{-5}$ cm/s	ADMETlab 2.0
P-gp substrate	No	ADMETlab2.0
HIA	High	Consensual
Vd	3.92 L/kg	ADMETlab 2.0
$CL_{int,u}$	5.80 mL/min/kg	ADMETlab 2.0
BBB penetration	Yes (P: 0.54)	ADMETlab 2.0
BBB (C_{brain}/C_{blood})	19.42	PreADMET
HLM	CYP2D6 (P: 0.97) CYP2C9 (P: 0.92)	ADMETlab 2.0
CYP2C19 inhibitor	Yes (P: 0.80)	Consensual
CYP2C9 inhibitor	Yes (P: 0.46)	Consensual
CYP2D6 inhibitor	No (P: 0.93)	Consensual
CYP3A4 inhibitor	Yes (P: 0.75)	Consensual

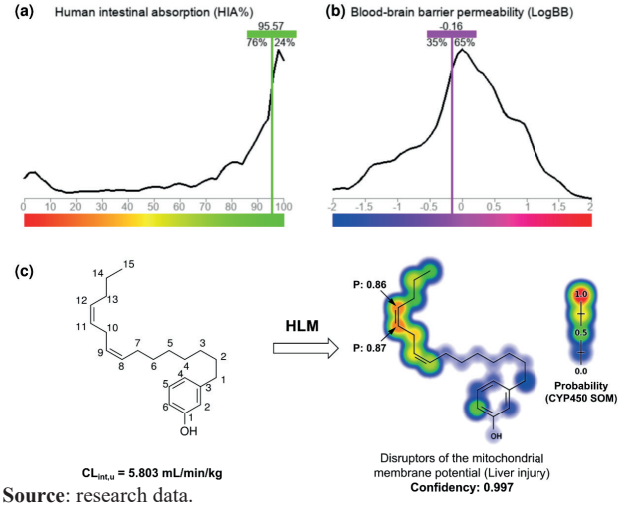
Notes: Papp MDCK (Passive permeability predicted by the Madin-Darby Canine Kidney cells model); P-gp (P-glycoprotein); HIA (Human intestinal absorption); Vd (Volume of distribution); CLint,u (Clearance); BBB (Blood-brain barrier); HLM (Human liver microsome); and CYP (Cytochrome P450 isoenzymes).
Source: research data.

3.5 Site of metabolism and liver injury

The structural contributions of cardanol diene in its metabolic processes can be visualized in the heatmap of Figure 4c. The analysis suggests that the most unprotected isolated phenol group alkene (atoms 11 and 12) constitutes a region susceptible to aliphatic hydroxylation biotransformation's by the CYP450 isoforms of the 2D6 and 2C9 subfamily, in the human liver microsome (HLM).

In addition, the substance showed an order of similarity of 0.997 with a compound capable of inducing disruption in the mitochondrial membrane in the HLM system, within the eMolTox web-server database (Ji *et al*., 2018), leading to a pharmacokinetic model susceptible to inducing lesions in the human liver.

Figure 4 - Structure-based statistical regressions for prediction of HIA (a) and BBB penetration (b) and estimation of site of metabolism and liver injury (c)



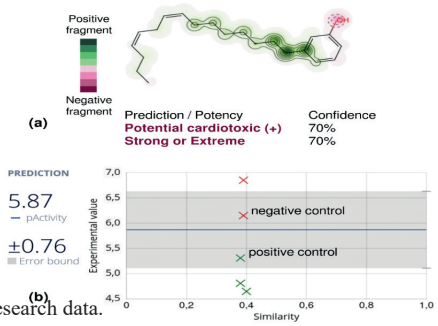
Source: research data.

Also, it is worth noting that the prediction showed, with a higher degree of confidence, that the compound tends to act as an inhibitor of CYP450 isoforms 2C19 and 3A4 and may alter the plasma concentration and pharmacological effect of co-administered substrates of these isoforms (Table 4).

Estimate of hERG blocker effect

The results of the model prediction of cardiotoxicity by hERG channel inhibition can be seen in Figure 5.

Figure 5 - Structural contributions of cardanol diene to the hERG block effect (a) and similarity test with cardiotoxic compounds in the ChemAxon database (b)



Source: research data.

The analysis suggests that despite the structural contributions of the alkyl chain (green color), evidenced in the 2D probability map of Figure 5a, the ph-OH fragment constitutes a fragment capable of inhibiting hERG channels (magenta color), resulting in a strong cardiotoxic risk estimated with 70% test reliability. This can be easily observed by the similarity test shown in Figure 5b, where the measured potential activity (pAct) in the order of 5.87±0.76 falls within the cardiotoxicity incidence spectrum (pAct ~0.6), showing similarity with at least 1 potentially cardiotoxic structure from the ChemAxon database.

The ecotoxicological evaluation was based on the combination of several models that were obtained algorithmically from experimental assumptions corresponding to the selected endpoints. Thus, it is observed that the relative toxicity classification (acute and chronic) depends on the chain behavior, degree of hydroxylation reactions, or ionic exchanges proposed by the compound, thus, analyzing the kinetic profile, the cardanol diene compound expresses log P(kow)>7, that is, presenting high bioconcentration potential and persistence given through the bioconcentration factor (BCF>2000, log BCF>3.301) (BCF KNN model) (Lombardo *et al*., 2022; Manganaro *et al*., 2020; Pizzo *et al*., 2016) but constitutes "rapid" biodegradability, a fact due, to sorption of the compound to soil colloids.

The exposure of the cardanol diene compound to the non-target organisms studied can occur by direct route, i.e. the dispersion of the substance in the environment (water, soil, and sediment) in which neutral organic chemical compounds constitutes its toxicological predictability related to log kow, thus, it can be established that as kow increases the toxicity decreases (absence of toxicity in fish, however, with the increase of log kow there is an increase in bioaccumulative, bioconcentrative and biomagnificative tendencies (high rate of clearance of the compound in any environmental compartment) causing transfer of the contaminant along the trophic chain.From the high adsorption of the contaminant (cardanol diene) in a given compartment and trophic transfer made possible through the octanol/water partition coefficient (log kow), bioconcentration factor and persistence, a process of biochemical and molecular responses begins: reproductive toxicity and carcinogenesis as toxicity endpoints in this case.

Thus, virtual screening was based on chemical structure as an initial prediction to drive the bioactivity of cardanol diene in human organisms. The technique is aided by machine learning functions to drive the biological activity of a foreign substance against the human biological system, mediated by similarity tests with ligands deposited in databases with characterized biological activity (Li *et al*., 2021). The results explored here show a theoretical model whose larvicide administration can lead to modulations in the activities of neural receptors and receptors responsible for cellular gene expression.

In molecular studies recently published by the pharmaceutical company Pfizer, Inc., the effort to devise new algorithms that move the physicochemical space of ingested substances into a space of unlikely toxic risk is notable. In their dataset, compounds active in the CNS present a fundamental toxicity assessment pathway, physicochemical space formed by substances with high logP and low TPSA (Hughes *et al*., 2008; Wager *et al*., 2016). In this study, it was possible to combine several software and resources available online to estimate the possible toxic response arising from the activity of cardanol diene in the CNS, occupying the physicochemical space prone to adverse effects.

Predicting the biotransformation of xenobiotics is a key point for toxicological evaluation from the chemicals formed in first-pass metabolism in the liver. The estimation allows us to avoid substances that form liver-damaging secondary metabolites from the oxidative mechanisms of CYP450 (Yu *et al*., 2014; Wu *et al*., 2019). In this study, it was possible to note that cardanol diene tends to form more water-soluble hydroxylated products for excretion, but which are susceptible to causing endocrine disruption in human liver cells (Zheng *et al*., 2009).

Another structure-based predictive toxicity model is associated with the cardiotoxicity model through the inhibition of hERG channels, which are responsible for ion transport in the cardiovascular system (Radchenko *et al*., 2017). The database used in this study was capable of driving a theoretical model where the structural contributions of cardanol diene may result in a cardiotoxic response by ingestion, constituting a human health risk chemical (Braga *et al*., 2015).

4 Conclusion

Given the potential of the larvicide cardanol diene, it does not show significant toxicity in aquatic organisms. However, it has a high bioconcentration potential associated with metabolic reactions, due to the small polar surface area generated by the phenolic hydroxyl, which can distribute the substance to various body compartments and inhibit the activities of receptors and transporters, showing various toxicological responses including cerebral, cardiac, modulation of gene expression in liver cells (carcinogenesis) or reproductive dysfunction.

It is noteworthy that the study corresponds to the initial stage of methods and computational models that can enable actions of environmental biomonitoring in the investigation of environmental and physiological pathways, i.e., from the primary organism there is the incorporation of chemicals to human pathways correlating cause-effect throughout the food chain.

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