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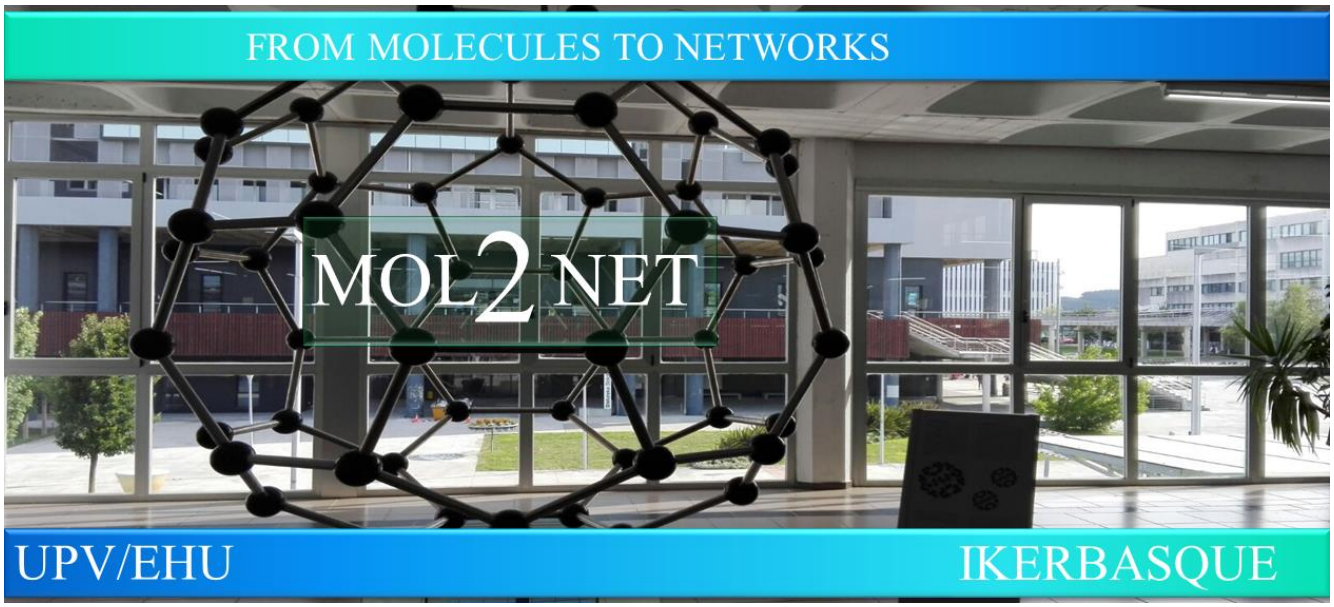

In silico study and molecular docking of flavonoid derivatives with potential biological activity against *Leishmania braziliensis*

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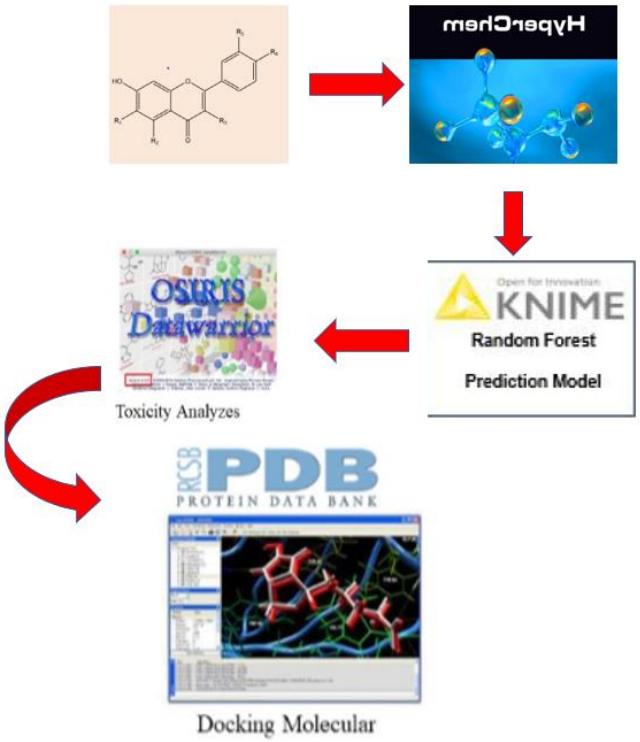
Graphical Abstract



Abstract.

Leishmaniasis belongs to the neglected disease group, has a high prevalence and is responsible for approximately 70.000 deaths per year worldwide. Recent studies have shown resistance of the parasite to drugs used in the treatment of the disease. From this perspective, the objective of this work is to conduct an *in silico* study aiming to identify flavonoid derivatives with potential activity against *Leishmania braziliensis*.

Introduction

Leishmaniasis belongs to the group of neglected tropical parasitic diseases, it is estimated that the worldwide prevalence is around 12 million cases, and that causes more than 70,000 deaths per year, moreover, studies show an annual incidence of 1.3 million cases and that this number tends to increase [1]. This disease has as etiological agent different species of protozoa of the genus Leishmania, among the main ones is Leishmania braziliensis. Transmission occurs by the bite of infected female sandbrats [2].

In relation to clinical manifestations, leishmaniasis is characterized in four main forms: cutaneous, mucosal, cutaneomucosa and visceral [3]. Leishmania braziliensis causes a typical tegumentary leishmaniasis, which can evolve to a mucous form [4].

Leishmania braziliensis is a clinically and epidemiologically important species, due to the wide distribution of the parasite in Latin America and also because of the high resistance to drugs used in the first-line treatment [5].

Thus, the present work aims to conduct an *in silico* study of ten flavonoid derivatives, aiming to identify compounds with possible activity against *Leishmania braziliensis*.

Materials and Methods

Initially, ten flavonoid derivatives were selected in the literature, which served as the basis for the design of the studied molecules. After design, the compounds were optimized in the HyperChem 7.5 TM software (RMS 0.1 kcal. Å-1.mol-1 in 800 cycles) [6]. Soon after, they were improved by the molecular mechanics MM+ and the semiempirical method AM1, to then be submitted to the biological activity model developed from the free software KNIME Analytics Platform 3.7 [7,8] and RandombForest was used as a classifier and Weka 3.7 as a predictor. At the end of this process the compounds are classified as active or inactive.

Osiris DataWarrior 5.0 [9] software analyzed toxicological parameters: mutagenicity, tissue irritability, carcinogenicity and effects on the reproductive system. According to this study model, substances that have any of the effects mentioned will be considered toxic. In addition, the oral absorption rate was also analyzed.

The next step was molecular docking, for this purpose molegro Virtual Docker 6.0 (MVD) software [10] was used, in this step two *Leishmania braziliensis*-related proteins published in the PDB with ID 5l42 and 4KCE respectively were used.

Results and Discussion

After minimizing the energy of the molecules with the HyperChem software, they were imported into a model of prediction of biological activity against *Leishmania braziliensis*. According to the proposed methodology only the molecule represented by figure 1 presented activity.

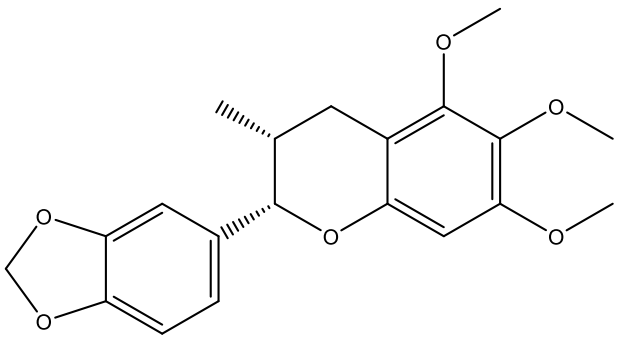


Figure 1: Structure of the composed with promising activity.

Table 1. Statistical result for *Leishmania braziliensis* model

row ID	Teste	Cross
VP	17	28
FP	4	16

VN	14	24
FN	4	10
Accuracy	0.809524	0.636364
Sensitivity	0.809524	0.736842
Specificity	0.777778	0.6
MCC	0.587302	0.339533
Accuracy	0.794872	0.666667
ROC Curve	88.35979	77.56579

In the ROC graph (Figure 1) it is possible to observe that the model used presented a good predictive performance and with this a good reliability of the results presented in this study.

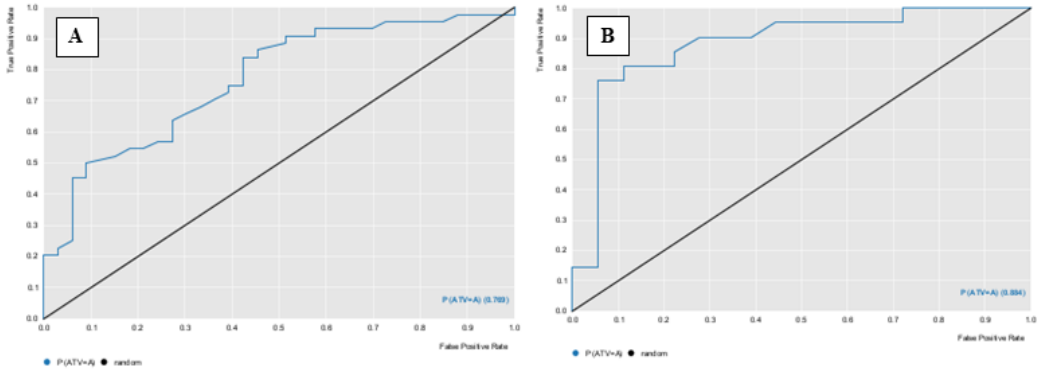


Figure 2. Characteristic graph curve (ROC), A- Cross Validation, B- Test. Source: author.

In relation to the activity domains, the sustance was reliable, in addition to the activity presented 52.5% of activity against *Leishmania braziliensis*. Since this compound did not present any of the toxic effects reported in the methodology, it was submitted to molecular docking, in order to verify what are the types of interactions with the chosen proteins.

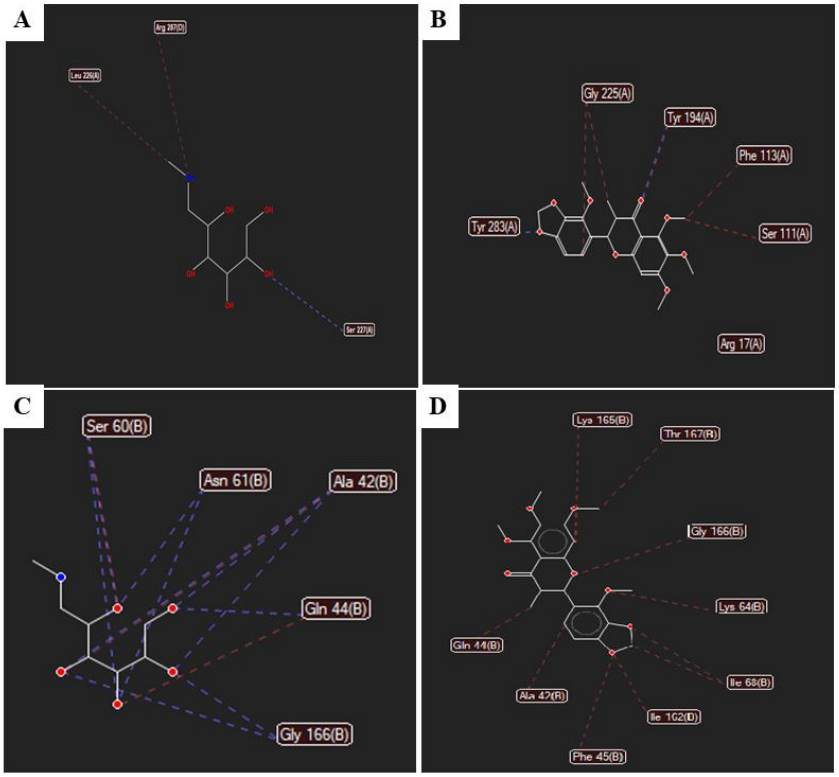


Figure 2. Interaction of structures with amino acids of protein **A:** Interactions of control with protein 5l42; **B:** interactions of the active molecule with 5l42 proteins; **C:** Interaction of control with 4KCE protein and **D**: interaction of the active molecule with the 4KCE protein.

Table 2. Interactions of control and active molecule with amino acid residues of proteins.

Protein	Molecules	Waste	Hydrogen Interaction	Steric Interaction
5L42	N-methylglucamine antimoniate	Leu 226	0	1
		Arg 287	0	1
		Ser 227	1	0
	Active molecule	Tyr 283	1	0
		Gly 225	0	2
		Tyr 194	1	0

		Phe 113	0	1
		Ser 111	0	1
		Arg 17	0	0
4KCE	N-methylglucamine	Ala 42	3	1
	antimoniate	Gln 44	1	1
		Ser 60	1	1
		Asn 61	2	0
		Gly 66	2	0
	Active molecule	Ala 42	0	1
		Gln 44	0	1
		Phe 45	0	1
		Lys 64	0	1
		lle 68	0	1
		Lle 162	0	1
		Lys 165	0	1
		gly 166	0	1
		Thr 167	0	1

Conclusions

Leishmania braziliensis is a parasite of great medical importance, because of the prevalence in several countries and the difficulty of treating the disease produced by the species. Thus, studies are needed to seek new therapeutic alternatives to combat the pathology.

The present work analyzed the *in silico* activity of ten flavonoid derivatives against *Leishmania braziliensis*, among the compounds analyzed only one presented absence of toxic effects and good activity against the parasite. Therefore, it can be concluded that the compound presented itself as a promising candidate for the development of further studies on its application in the fight of the parasite.

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