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Promising Potential of *Lonchocarpus utilis* against South American Myasis

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Abstract: Traditional medicine is especially important in the treatment of neglected tropical diseases because it is the way the majority of populations of affected countries manage primary healthcare. We present a case study that can serve as an example that can be replicated by others in the same situation. It is about the validation of a local remedy for myasis in Amazonian Ecuador, which is contrasted by bibliographic chemical reviews and in silico activity tests. We look for scientific arguments to demonstrate the reason for using extracts of *Lonchocarpus utilis* against south American myasis (tupe). We provide a summary of the isoflavonoids, prenylated flavonoids, chalcones, and stilbenes that justify the action. We make modeling predictions on the affinity of eight chemical components and enzyme targets using Swiss Target Prediction software. We conclude that the effects of this extract can be reasonably attributed to an effect of the parasite that causes the disease, similar to the one produced by synthetic drugs used by conventional medicine (e.g., Ivermectine).

Keywords: *Lonchocarpus utilis*; barbasco; rotenoid; in silico; drug discovery; bioinformatic

1. Introduction

The World Health Organization (WHO) has estimated that more than 80% of the world's population routinely uses traditional medicine to meet their primary healthcare needs [1], and many traditional treatments involve the use of plant extracts or their active ingredients [2]. This is especially important in the treatment of neglected tropical diseases (NTD) [1]. The WHO has recognized twenty NTD: buruli ulcer, chagas disease, dengue and chikungunya, dracunculiasis (guinea-worm disease), echinococcosis, foodborne trematodiases, human african trypanosomiasis (sleeping sickness), leishmaniasis, leprosy (Hansen's disease), lymphatic filariasis, mycetoma, chromoblastomycosis and other deep mycoses, onchocerciasis (river blindness), rabies, scabies and other ectoparasites, schistosomiasis, soil-transmitted helminthiases, snakebite envenoming, taeniasis/cysticercosis, trachoma and yaws (endemic treponematoses). These diseases represent an important cause of morbidity, disability, and mortality in the poorest people living in developing countries. They are so named because of the lack of financial investment in the development of new drugs by high-income countries to treat them [3]. In this context, the Amazonian countries have large sectors of the population that use plants from the tropical forests where they live daily as a legacy of their ancestors. This represents knowledge that can be articulated with the Western scientist [4,5]. and

may produce advances in the field of health. We present a case study that can serve as an example for future replicate studies in this direction.

We investigate the plant known in Spanish as barbasco or poison rope, *Lonchocarpus utilis* A.C. Ye. (*Lonchocarpus nicou*, *Lonchocarpus nicou* var. *languidus*, *Lonchocarpus nicou* var. *urucu*, *Deguelia utilis*, Fabaceae). This is a wild bush plant found in the rainforests of Brazil, Colombia, Guyana, Guyana, Peru, Surinam, Venezuela, and Ecuador, which is sometimes cultivated in indigenous communities for its use [6]. It has different common names according to the original language of the population (e.g., shili bun (tsafi'ki), anku hanpi, auka hanpi, hanpi, lumu hanpi, shikitu hanpi, timun hanpi, tullu hanpi, waska hanpi (kichwa), avu signo'mba, macoroje'cho indica'mba, seña'mba (a'ingae), airo eó, eó, eopo eó, jo'ya eó (pai coca), kompago, kompagon, konpago, meneko (wao tededo), timiu (shuar chicham)).

In Ecuador, several indigenous nationalities have used it both in traditional medicine and ancestral fishing procedures (Table A1). During a study carried out by one of the authors [7] in the Bobonaza river province of Pastaza, some uses (Table A2) that had rarely been mentioned in the area were observed [8–11]. These provide good examples of the use of natural resources due to the degree of isolation of the communities.

In this case, the plant was employed to treat a very significant illness locally named the "tupe". This is a myiasis involving the infestation of dipterous larvae favored by the tropical hot and humid climate. More than 170 million people are at risk of contracting this neglected tropical disease [12]. In South America, the largest number of cases are produced by *Dermatobia hominis*, an autochthonous species that acts as a parasite of living tissues [13–15]. When the female is willing to lay eggs, she catches a blood-sucking arthropod, a fly or mosquito (mainly of the genus *Psorophoro*), that acts as an intermediate host and deposits eggs (15 to 30) on her abdomen, which are fixed with a kind of adhesive. The intermediary distributes the eggs when looking for animal or human blood to feed on and these will hatch, releasing young larvae that penetrate the skin over a time period that varies from 5 to 10 min in the location of the bite or through the hair follicles [16]. The preferred places in humans are the trunk, thighs, buttocks, and back [17]. Initially, they are skin lesions of little relevance. Infections are unlikely because the larva itself secretes antibiotics as an adaptive strategy to have food in good condition [18]. Infection is much more likely following scratching, handling without conditions of asepsis, or if the larvae are only partially extracted because remains are left under the skin [19]. In this case, it can turn into erythematous papules that increase in size, becoming pustular. If the larvae penetrate further, they form subcutaneous nodules of 1–2 cm, which can form painful abscesses. There may be regional lymphadenopathy, lymphangitis, and eosinophilia. This can affect the skin, mucous membranes, intestine, genitourinary system, lungs, and brain (migration of larvae by fontanelles) [20]. Others, such as those produced by *Sarcopiiaga tiaemorriioidaiis*, *S. iambens*, *Cynomyopsis cadaverina*, *C. vicina*, *Phaenicia sericata,* and *P. cuprina* are also common if there are predisposing factors such as poor hygiene, advanced age, or poor peripheral vascular circulation [21]. More rare are *Musa domestica, Stomoxys caicitrans,* and *Fannia* spp., which lay eggs on open lesions [22–24]. A great number of cases of myasis are associated with vulnerable people living in rural areas and poverty or underdevelopment [12]. Given the importance of this neglected pathology, the present bibliographical study was designed.

In addition to this, molecular docking studies have been revealed as a useful tool to predict activity [25–29] and to orientate pharmacological research, saving time, and economic resources. Arguments and hypotheses can be reinforced or confirmed using in silico tests. These approaches are becoming more frequent. As was recently written in *Nature* [30], "bioinformatics can boost basic science in countries with limited resources". This can be especially useful for NTD.

Based on the above, our research objective is to find experimental evidence of chemical composition and activity, aimed at a scientific validation of myasis treatment employed by the Kichwa people from Amazonian Ecuador.

2. Results

The phytochemical composition of *L. utilis* has been widely studied [31–38]. The most important compounds found in the leaves, stems, and roots are rotenone (44%), rotenolone (6.7%), deguelin (22%), and thephrosin (4.3%) [39], which are rotenoids—isoflavones with additional pyrane/furane rings. Other significant components are prenylated flavanols (prenyl-urucuol A, prenyl-isotirumalin and prenylutilinol), prenylated flavones (3′-methoxylupinifolin), prenylated flavanones (2*S*)-6-(γ,γ-dimethylallyl)-5,4′-dihydroxy-3′-methoxy-6″, 6″-dimethylpyran [2″,3″:7,8] flavanone, and prenylutiline, chalcones (4-hydroxylonchocarpin), and stilbenes (lonchocarpene, methoxylonchocarpene, 3,5-dimethoxy-4-*O*-prenyl-*cis*-stilbene and 3,5-dimethoxy-4-hydroxy-3-prenyl-trans-stilbene). The structures are organized [40] and summarized in Figure 1.

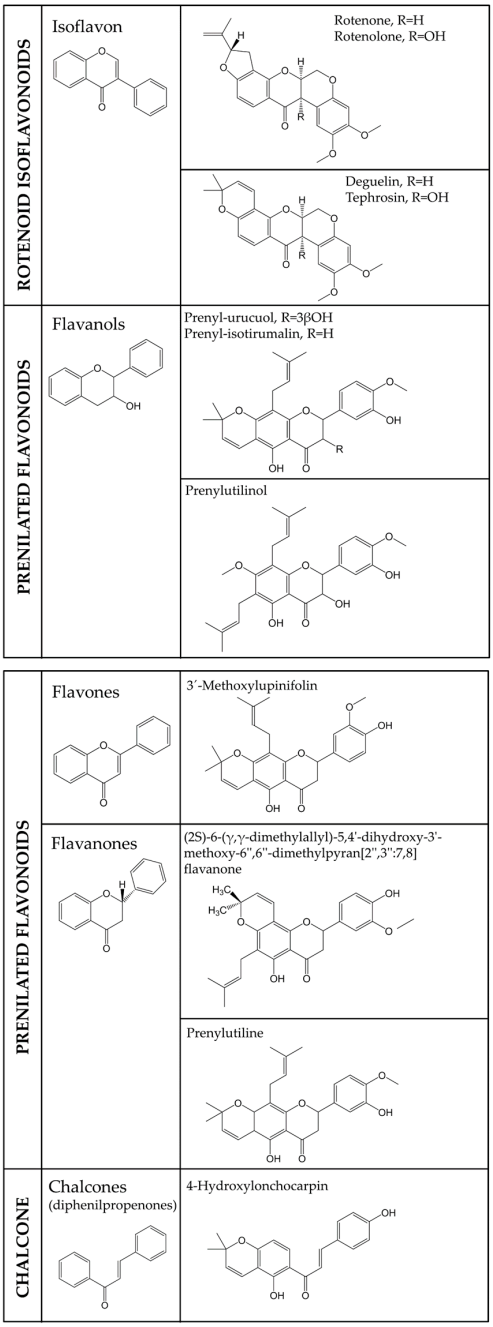

Figure 1. Chemical structures of the main components of *Lonchocarpus utilis.*

The biological activity of these components, experimentally tested by different authors, is summarized in Table 1.

Table 1. Biological activity and applications of some chemical compounds present in *Lonchocarpus utilis*.

Molecule	Tested in	Activity	References
Rotenone	Rat	Inhibition of mitochondrial activity (diminished NADH: ubiquinone oxidoreductase activity)	[41]
	Cell	Inhibition of growth	[31]
	Lehismania	Antilehismaniasic	[42]
	Cell	Antiproliferative	[39]
	Fish	Toxic for fish	[41,43]
	Insect	Insecticide and pesticide	[44]
Rotenolone	Rat	Inhibition of mitochondrial activity (diminished NADH: ubiquinone oxidoreductase activity) (25% less active than rotenone).	[41]
	Cell	Inhibition of growth	[31]
Deguelin		Inhibition of mitochondrial activity (diminished NADH: ubiquinone oxidoreductase activity) (50% less active than rotenone).	[41]
	Cell	Inhibition of growth	[31,45]
	Cell	Antiproliferative	[39]
	Nematode	Nematocide	[46]
		Anti-inflammatory in transplants	[46,47]
	Cell	Potent apoptotic and antiangiogenic	[48,49]
	Cell	Inhibition of progression of tumors such as lung, stomach, prostate, colon, ovary, and pancreas.	[49–53]
	Cell	Inhibition of tumor cell growth and metastasis.	[51,52]
	Cell	Chemical adjuvant against leukemia	[54]
Tephrosin	Rat	Inhibition of mitochondrial activity (diminished NADH: ubiquinone oxidoreductase activity)	[41]
	Cell	Inhibition of growth	[43]
Prenyl-urucuol A Prenyl-isotirumalin Prenylutilinol 3′-methoxylupinifolin Prenylutiline	Cell	Cytoprotective activity of neurons in rats (Complete fraction)	[55]
(2S)-6-(γ,γ-dimethylallyl)-5, 4′-dihydroxy-3′-methoxy-6″, 6″-dimethylpyran [2 ″,3″:7,8] flavanone	Cell	Inhibition of growth	[36]
4-hydroxylonchocarpin		Antifungal	[56]
Lonchocarpene	Seedling	Inhibition of growth/development	[57]
4-methoxylonchocarpene	Seedling		
3,5-dimethoxy-4-hydroxy-3-prenyl-*trans*-stilbene	Seedling		

Figures A1–A7 (Appendix A) belong to the Swiss Target prediction report files obtained using the corresponding cited structures as query molecules: Figure A1—rotenone; Figure A2—rotenolone; Figure A3—deguelin; Figure A4—tephrosin; Figure A5—3′metoxylupinifolin; Figure A6—4-hydroxylonchocarpin; Figure A7—lonchocarpene.

As it can be observed in the probability graphics of these figures, rotenoids have shown the most affinity for ornithine decarboxylase (ODC), tyrosyl-DNA phosphodiesterase 1, arginine decarboxylase, NADH ubiquinone oxidoreductase chai-4, and the microtubule-associated protein tau (the latter especially for rotenone and rotenolone). Rotenone has shown the best relations with the cytochrome P450 group of enzymes.

Chalcones (4-hydroxylonchocarpin) have shown the most affinity with ODC, tyrosyl-DNA phosphodiesterase 1, arginine decarboxylase, and have a probability of more than 50% with different protein kinases.

The prenylated flavone that was tested in our in silico experiments (3′-methoxylupinifolin) showed affinity with ornithine decarboxylase (ODC), tyrosyl-DNA phosphodiesterase 1, and arginine decarboxylase. Lonchocarpene (stilbene) showed affinity with ornithine decarboxylase (ODC), tyrosyl-DNA phosphodiesterase 1, and arginine decarboxylase.

Another stilbene that has been tested (3,5-dimetoxy-4-hydroxy-3 prenyl-trans-stilbene) has not shown any reliable affinity nor activity.

3. Discussion

The hospital treatment of tupe is surgical: the application of local anaesthetics and removal of the larvae through the entrance orifice. For oral medical treatments, the drugs that might be employed are thiabendazole imidazols and macrocyclic lactones. Thiabendazole inhibits fumarate reductase, an enzyme specific for helminths. It is absorbed rapidly in the gastrointestinal tract, is metabolized in the liver, and it is eliminated by the kidney. However, it has many side effects. Ivermectin [58,59] has more selective activity with few systemic effects on mammals. It acts by binding to the anionic glutamate channels of gamma amino butyric acid (GABA) on the nerves and muscle cells of invertebrates, causing pharyngeal paralysis and death of the parasite by asphyxia and starvation. Our results for the Swiss Target prediction reports of isoflavonic rotenoids such as rotenone and rotenolone revealed strong interactions with many cytochrome P450 isozymes, NADH-ubiquinone oxidoreductase, and the microtubule-associated protein tau. Another rotenoid, deguelin, is especially akin to ornithine and arginine decarboxylases, and tephrosin shows affinity to tyrosyl-DNA phosphodiesterase, due to the probability levels shown in the Appendix A predictions. These results obtained by our in silico tests explain the activities of *L. utilis.* We also found a strong relation to the former decarboxylases and other groups of molecules of the extract: stilbenes (as lonchocarpene), chalcones (as 4-hydroxylonchocarpin), and prenylated flavones (such as 3′methoxylupinifolin). Rotenoids have the capacity to act against multiplication or growth, as summarized in the experimental results of Table 1. They cause a lack of energy, respiratory depression, respiratory arrest, and death. They lead to failure in the electron transport chain, which, at the mitochondrial level, translates into a blockade of the passage from ADP to ATP. Their inhibitory effect on NADHU-ubiquinone oxidoreductase has been demonstrated in the laboratory and as a consequence of the (ODC) phorbol ester-induced ornithine decarboxylase [60]. Rotenone is specifically classified as an insecticide type II with low toxicity to humans and warm-blooded animals [61]. The selective toxicity of rotenone in insects and fish versus mammals is related to its poor absorption from the gastrointestinal tract of the latter as well as the overall metabolic differences. Rotenone is converted into highly toxic metabolites in insects and fish. On the contrary, it is converted into non-toxic metabolites in mammals. In the motor system, 5-hydroxytriptamine (5HT) can depress GABA-mediated transmission and structures controlling movement [62]. Rotenone and rotenolone showed a great affinity for the membrane receptors of 5HT in our Swiss Target in silico tests, which is indirect evidence of the capacity of these molecules to behave similarly to Ivermectine when it causes helminth muscle paralysis.

4. Conclusions

In Latin America, myasis, as a disease, remains somewhat misunderstood. It is excluded from basic epidemiological research and hospital treatments are often lacking [63]. In this framework, traditional ethnomedicine is revealed as a powerful ally to improve the state of health, especially considering cases such as this case study. It can serve as an example that can be replicated by others in the same situation. We have looked for scientific arguments to demonstrate the reason for using extracts of *Lonchocarpus utilis* against south American myasis (tupe). We have provided a summary of the isoflavonoids, prenylated flavonoids, chalcones, and stilbenes that justify the action. We have

performed modeling predictions on the affinity of eight chemical components and enzyme targets using Swiss Target prediction software.

We have concluded that the effects of this extract can be reasonably attributed to an effect of the parasite that causes the disease. Once again, the importance of the plant world in the drug discovery processes must be considered, and a call is made for plant conservation to be used as a source of obtaining added value bioproducts.

5. Materials and Methods

5.1. Ethnobotanical Study

All the information regarding the study where the data came from is available in Appendix B. It contains references to the voucher specimens of herbarium material collected, the permits and authorizations obtained, and the procedures applied. Tables A1 and A2 (in Appendix B) summarize the traditional uses given to the species.

5.2. Bibliographic Review

A bibliographic study was performed following the Prisma 2009 flow diagram methodology [64]. The databases accessed were Academic Search Complete, Agricola, Agris, Biosis, CABS, Cochrane, Cybertesis, Dialnet, Directory of Open Access Journals, Embase, Espacenet, Google Patents, Google Academics, Medline, PubMed, Science Direct, Scopus, Theseus, and ISI Web of Science. The aim was to find publications on chemical composition and/or activity. The abovementioned ones and the Latin names of the species and synonyms were used as keywords. The selected citations were summarized. Critical reading of this literature allowed us to elaborate on the discussion of the results and main statements.

5.3. In Silico Activity Test

Swiss Target prediction software [65,66] was eventually used to investigate the activity in silico to reinforce the principal arguments. Prediction reports were made with the following query molecules:

Rotenone;
Rotenolone;
Deguelin;
Tephrosin;
3'metoxylupinifolin;
4 hydroxylonchocarpin;
Lonchocarpene.

Author Contributions: Methodology, T.R.-T., C.E.C.-M. and C.X.L.-Q.; Validation J.B.-S.; Formal Analysis, J.C.A.-G.; Investigation, C.X.L.-Q.; Data Curation, C.E.C.-M. and C.X.L.-Q.; Writing—Original Draft Preparation, T.R.-T.; Writing—Review & Editing, J.B.-S. and J.C.A.-G.; Visualization, J.C.A.-G.; Supervision, C.X.L.-Q.; Project Administration, T.R.-T.; Funding Acquisition, C.X.L.-Q. and T.R.-T. All authors have read and agreed to the published version of the manuscript.

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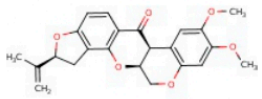
Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

SwissTargetPrediction report: Rotenone

Reference:
Gfeller D., Michielin O. & Zoete V. Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule



Frequency of Target Class

Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		553 / 27	Unclassified
NADH-ubiquinone oxidoreductase chain 4	P03905	MT-ND4	CHEMBL4499		5 / 5	Enzyme
Tyrosyl-DNA phosphodiesterase 1	Q9NUW8	TDP1	CHEMBL1075138		60 / 20	Enzyme
Cytochrome P450 2C19	P33261	CYP2C19	CHEMBL3622		1 / 1	Enzyme
5-hydroxytryptamine receptor 6	P50406	HTR6	CHEMBL3371		5 / 1	Membrane receptor
Cytochrome P450 2E1 *(by homology)*	P05181	CYP2E1	CHEMBL5281		1 / 1	Enzyme
Cytochrome P450 2C8 *(by homology)*	P10632	CYP2C8	CHEMBL3721		1 / 1	Enzyme
Cytochrome P450 2A6 *(by homology)*	P11509	CYP2A6	CHEMBL5282		1 / 1	Enzyme
Cytochrome P450 2C9 *(by homology)*	P11712	CYP2C9	CHEMBL3397		1 / 1	Enzyme
Cytochrome P450 2B6 *(by homology)*	P20813	CYP2B6	CHEMBL4729		1 / 1	Enzyme
Cytochrome P450 2A7 *(by homology)*	P20853	CYP2A7			1 / 1	Enzyme
Cytochrome P450 2F1 *(by homology)*	P24903	CYP2F1			1 / 1	Enzyme
Cytochrome P450 2C18 *(by homology)*	P33260	CYP2C18	CHEMBL2408		1 / 1	Enzyme
Cytochrome P450 2A13 *(by homology)*	Q16696	CYP2A13			1 / 1	Enzyme
Cytochrome P450 19A1	P11511	CYP19A1	CHEMBL1978		9 / 34	Enzyme

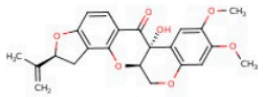
Figure A1. Swiss Target prediction Report Files obtained using Rotenone as query molecule.

SwissTargetPrediction report:

Rotenolone

Reference:
Gfeller D., Michielin O. & Zoete V. Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule



Frequency of Target Class

Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		181 / 28	Unclassified
Tyrosyl-DNA phosphodiesterase 1	Q9NUW8	TDP1	CHEMBL1075138		38 / 20	Enzyme
5-hydroxytryptamine receptor 6	P50406	HTR6	CHEMBL3371		1 / 1	Membrane receptor
Quinone oxidoreductase *(by homology)*	Q08257	CRYZ	CHEMBL6118		1 / 4	Enzyme
NADH-ubiquinone oxidoreductase chain 4	P03905	MT-ND4	CHEMBL4499		0 / 5	Enzyme
Cytochrome P450 2C19	P33261	CYP2C19	CHEMBL3622		0 / 1	Enzyme
Cytochrome P450 2E1 *(by homology)*	P05181	CYP2E1	CHEMBL5281		0 / 1	Enzyme
Cytochrome P450 2C8 *(by homology)*	P10632	CYP2C8	CHEMBL3721		0 / 1	Enzyme
Cytochrome P450 2A6 *(by homology)*	P11509	CYP2A6	CHEMBL5282		0 / 1	Enzyme
Cytochrome P450 2C9 *(by homology)*	P11712	CYP2C9	CHEMBL3397		0 / 1	Enzyme
Cytochrome P450 2B6 *(by homology)*	P20813	CYP2B6	CHEMBL4729		0 / 1	Enzyme
Cytochrome P450 2A7 *(by homology)*	P20853	CYP2A7			0 / 1	Enzyme
Cytochrome P450 2F1 *(by homology)*	P24903	CYP2F1			0 / 1	Enzyme
Cytochrome P450 2C18 *(by homology)*	P33260	CYP2C18	CHEMBL2408		0 / 1	Enzyme
Cytochrome P450 2A13 *(by homology)*	Q16696	CYP2A13			0 / 1	Enzyme

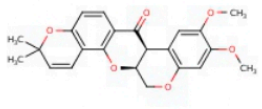
Figure A2. Swiss Target prediction Report Files obtained using Rotenolone as query molecule.

SwissTargetPrediction report:

Deguelin

Reference:
Gfeller D., Michielin O. & Zoete V. Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule



Frequency of Target Class

Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Tyrosyl-DNA phosphodiesterase 1	Q9NUW8	TDP1	CHEMBL1075138		220 / 20	Enzyme
Ornithine decarboxylase	P11926	ODC1	CHEMBL1869		1 / 10	Enzyme
Antizyme inhibitor 1 *(by homology)*	O14977	AZIN1			1 / 10	Enzyme
Arginine decarboxylase *(by homology)*	Q96A70	ADC			1 / 10	Enzyme
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		1904 / 25	Unclassified
NADH-ubiquinone oxidoreductase chain 4	P03905	MT-ND4	CHEMBL4499		5 / 5	Enzyme
Cytochrome P450 2C19	P33261	CYP2C19	CHEMBL3622		2 / 1	Enzyme
5-hydroxytryptamine receptor 6	P50406	HTR6	CHEMBL3371		9 / 1	Membrane receptor
Cytochrome P450 2E1 *(by homology)*	P05181	CYP2E1	CHEMBL5281		2 / 1	Enzyme
Cytochrome P450 2C8 *(by homology)*	P10632	CYP2C8	CHEMBL3721		2 / 1	Enzyme
Cytochrome P450 2A6 *(by homology)*	P11509	CYP2A6	CHEMBL5282		2 / 1	Enzyme
Cytochrome P450 2C9 *(by homology)*	P11712	CYP2C9	CHEMBL3397		2 / 1	Enzyme
Cytochrome P450 2B6 *(by homology)*	P20813	CYP2B6	CHEMBL4729		2 / 1	Enzyme
Cytochrome P450 2A7 *(by homology)*	P20853	CYP2A7			2 / 1	Enzyme
Cytochrome P450 2F1 *(by homology)*	P24903	CYP2F1			2 / 1	Enzyme

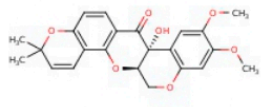
Figure A3. Swiss Target prediction Report Files obtained using Deguelin as query molecule.

SwissTargetPrediction report:

Tephrosin

Reference:
Gfeller D., Michielin O. & Zoete V. Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule



Frequency of Target Class

Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Tyrosyl-DNA phosphodiesterase 1	Q9NUW8	TDP1	CHEMBL1075138		36 / 19	Enzyme
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		113 / 22	Unclassified
Cathepsin L1 light chain *(by homology)*	P07711	CTSL1	CHEMBL3837		19 / 1	Cysteine Protease
Cathepsin S	P25774	CTSS	CHEMBL2954		19 / 1	Cysteine Protease
Cathepsin K	P43235	CTSK	CHEMBL268		19 / 1	Cysteine Protease
Cathepsin L2 *(by homology)*	O60911	CTSL2	CHEMBL3272		19 / 1	Cysteine Protease
Tyrosine-protein phosphatase non-receptor type 1	P18031	PTPN1	CHEMBL335		3 / 9	Tyr Phosphatase
Tyrosine-protein phosphatase non-receptor type 2 *(by homology)*	P17706	PTPN2	CHEMBL3807		3 / 9	Tyr Phosphatase
Ornithine decarboxylase	P11926	ODC1	CHEMBL1869		0 / 10	Enzyme
Antizyme inhibitor 1 *(by homology)*	O14977	AZIN1			0 / 10	Enzyme
Arginine decarboxylase *(by homology)*	Q96A70	ADC			0 / 10	Enzyme
5-hydroxytryptamine receptor 6	P50406	HTR6	CHEMBL3371		2 / 1	Membrane receptor
Cytochrome P450 2C9	P11712	CYP2C9	CHEMBL3397		1 / 1	Enzyme
Cytochrome P450 2C19	P33261	CYP2C19	CHEMBL3622		1 / 1	Enzyme
Cytochrome P450 2E1 *(by homology)*	P05181	CYP2E1	CHEMBL5281		1 / 1	Enzyme

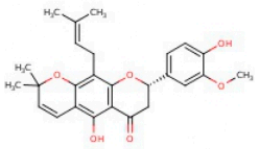
Figure A4. Swiss Target prediction Report Files obtained using Thephrosin as query molecule.

3'-methoxylupinifolin

SwissTargetPrediction report:

Reference:
Gfeller D., Michielin O. & Zoete V. Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule



Frequency of Target Class

Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Ornithine decarboxylase	P11926	ODC1	CHEMBL1869		1 / 10	Enzyme
Antizyme inhibitor 1 *(by homology)*	O14977	AZIN1			1 / 10	Enzyme
Arginine decarboxylase *(by homology)*	Q96A70	ADC			1 / 10	Enzyme
Cathepsin L1 light chain *(by homology)*	P07711	CTSL1	CHEMBL3837		24 / 1	Cysteine Protease
Cathepsin S *(by homology)*	P25774	CTSS	CHEMBL2954		24 / 1	Cysteine Protease
Cathepsin K	P43235	CTSK	CHEMBL268		24 / 1	Cysteine Protease
Cathepsin L2 *(by homology)*	O60911	CTSL2	CHEMBL3272		24 / 1	Cysteine Protease
Tyrosine-protein phosphatase non-receptor type 2 *(by homology)*	P17706	PTPN2	CHEMBL3807		20 / 10	Tyr Phosphatase
Tyrosine-protein phosphatase non-receptor type 1	P18031	PTPN1	CHEMBL335		20 / 10	Tyr Phosphatase
Tyrosyl-DNA phosphodiesterase 1	Q9NUW8	TDP1	CHEMBL1075138		61 / 18	Enzyme
ATP-binding cassette sub-family G member 2	Q9UNQ0	ABCG2	CHEMBL5393		17 / 6	Unclassified
Endothelin B receptor *(by homology)*	P24530	EDNRB	CHEMBL1785		42 / 101	Membrane receptor
Endothelin-1 receptor *(by homology)*	P25101	EDNRA	CHEMBL252		42 / 101	Membrane receptor
Inhibitor of nuclear factor kappa-B kinase subunit beta	O14920	IKBKB	CHEMBL1991		33 / 4	Ser_Thr Kinase
Inhibitor of nuclear factor kappa-B kinase subunit alpha *(by homology)*	O15111	CHUK	CHEMBL3476		33 / 4	Ser_Thr Kinase

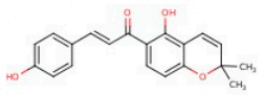
Figure A5. Swiss Target prediction Report Files obtained using 3′ metoxylupinifolin as query molecule.

4-hydroxylonchocarpin

SwissTargetPrediction report:

Reference:
Gfeller D., Michielin O. & Zoete V. Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule



Frequency of Target Class

Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Ornithine decarboxylase	P11926	ODC1	CHEMBL1869		7 / 10	Enzyme
Antizyme inhibitor 1 *(by homology)*	O14977	AZIN1			7 / 10	Enzyme
Arginine decarboxylase *(by homology)*	Q96A70	ADC			7 / 10	Enzyme
Tyrosyl-DNA phosphodiesterase 1	Q9NUW8	TDP1	CHEMBL1075138		73 / 8	Enzyme
Nitric oxide synthase, endothelial *(by homology)*	P29474	NOS3	CHEMBL4803		37 / 8	Enzyme
Nitric oxide synthase, brain *(by homology)*	P29475	NOS1	CHEMBL3568		37 / 8	Enzyme
Nitric oxide synthase, inducible *(by homology)*	P35228	NOS2	CHEMBL4481		37 / 8	Enzyme
MAP kinase-activated protein kinase 2	P49137	MAPKAPK2	CHEMBL2208		36 / 1	Ser_Thr Kinase
MAP kinase-activated protein kinase 5	Q8IW41	MAPKAPK5	CHEMBL3094		36 / 1	Ser_Thr Kinase
MAP kinase-activated protein kinase 3 *(by homology)*	Q16644	MAPKAPK3	CHEMBL4670		36 / 1	Ser_Thr Kinase
Protein kinase C gamma type	P05129	PRKCG	CHEMBL2938		5 / 1	Ser_Thr Kinase
Protein kinase C beta type	P05771	PRKCB	CHEMBL3045		5 / 1	Ser_Thr Kinase
Protein kinase C alpha type *(by homology)*	P17252	PRKCA	CHEMBL299		5 / 1	Ser_Thr Kinase
Protein kinase C delta type regulatory subunit	Q05655	PRKCD	CHEMBL2996		3 / 1	Ser_Thr Kinase
Protein kinase C theta type *(by homology)*	Q04759	PRKCQ	CHEMBL3920		3 / 1	Ser_Thr Kinase

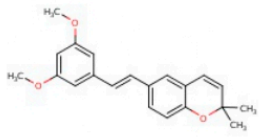
Figure A6. Swiss Target prediction Report Files obtained using 4-hydroxylonchocarpin as query molecule.

SwissTargetPrediction report:

Lonchocarpene

Reference:
Gfeller D., Michielin O. & Zoete V. Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule



Frequency of Target Class

Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Ornithine decarboxylase	P11926	ODC1	CHEMBL1869		1 / 10	Enzyme
Antizyme inhibitor 1 *(by homology)*	O14977	AZIN1			1 / 10	Enzyme
Arginine decarboxylase *(by homology)*	Q96A70	ADC			1 / 10	Enzyme
Arachidonate 5-lipoxygenase	P09917	ALOX5	CHEMBL215		7 / 38	Enzyme
Arachidonate 15-lipoxygenase *(by homology)*	P16050	ALOX15	CHEMBL2903		7 / 38	Enzyme
Arachidonate 12-lipoxygenase, 12S-type *(by homology)*	P18054	ALOX12	CHEMBL3687		7 / 38	Enzyme
Arachidonate 15-lipoxygenase B *(by homology)*	O15296	ALOX15B	CHEMBL2457		7 / 38	Enzyme
Arachidonate 12-lipoxygenase, 12R-type *(by homology)*	O75342	ALOX12B			7 / 38	Enzyme
Epidermis-type lipoxygenase 3 *(by homology)*	Q9BYJ1	ALOXE3			7 / 38	Enzyme
Vascular endothelial growth factor receptor 1 *(by homology)*	P17948	FLT1	CHEMBL1868		175 / 1	Tyr Kinase
Vascular endothelial growth factor receptor 3 *(by homology)*	P35916	FLT4	CHEMBL1955		175 / 1	Tyr Kinase
Vascular endothelial growth factor receptor 2	P35968	KDR	CHEMBL279		175 / 1	Tyr Kinase
Prostaglandin G/H synthase 1	P23219	PTGS1	CHEMBL221		11 / 90	Enzyme
Prostaglandin G/H synthase 2	P35354	PTGS2	CHEMBL230		11 / 90	Enzyme
Nitric oxide synthase, brain *(by homology)*	P29475	NOS1	CHEMBL3568		12 / 3	Enzyme

Figure A7. Swiss Target prediction Report Files obtained using Lonchocarpene as query molecule.

Appendix B

The Kichwa community of Pakayaku lies in a fairly isolated Amazonic region of the Bobonaza River in Pastaza, Ecuador. One of us (C.X.L.-Q.) was based at the Biological Station Pindo Mirador in the northern river basin (S1°27′09″–W 78°04′51″), and plant collection permissions were granted by the Ministry of the Environment: Reference MAE-DPAP-2016-2243. Plant vouchers were deposited at the QAP Herbarium José Alfredo Paredes, Universidad Central de Ecuador, Quito with the following code numbers: QAP 92494, QAP 92519, QAP 92523, QAP 92623, QAP 92838, QAP 92920, QAP 93783, QAP 93785; QAP 93789, QAP 93794.

To perform the ethnobotanical survey under the Nagoya Protocol rules, collective written research consent was granted by the community president of the Assembly, Mrs. Luzmila Gayas. Prior individual consents had been obtained from the persons taking part in our survey. The survey

consisted of a series of planned residential visits accompanied by Kichwa interpreters. Semi-structured interviews were recorded. Four knowledgeable elders of the Pakayaku community acted as informants and agreed to reveal their knowledge on the barbasku tree. The informants answered freely on several topics, including the common name of Kichwa, the part of the plant used, a description of its usage, the harvest season, storage (if any), preparation of concoctions, and the target of the treatment. After the fieldwork, the data were included in an spreadsheet Excel 2016 (Microsoft, Redmon, WA, USA). The existing ethnobotanical literature from Ecuador included in Table A1 was compared with the recorded uses that are summarized in Table A2.

Table A1. Synthesis of the ethnobotanical knowledge of *Lonchocarpus utilis* A.C.Sm. from the indigenous communities of Ecuador based on [67] and the bibliographic revision of [7]. R, root; L, leaves; S, stem.

Use Category	Part	Preparation	Traditional Knowledge	Native Community	Province of Ecuador
Medicinal					
Digestive system	R	Plaster	Stomach pain and diarrhea	Kichwa of Eastern	Napo
				Unidentified ethnicity	Pastaza
Skin and subcutaneous cellular tissue	R	Plaster	*Chupos* treatment: abscesses with pus	Kichwa of Eastern	Napo
				Unidentified ethnicity	Pastaza
Other infectious and parasitic diseases	R	Crushed	Mycosis treatment	Kichwa of Eastern	Orellana
Symptoms of undefined origin	L	Milled	Chronic pain caused by witchcraft	Kichwa of Eastern	Pastaza
Toxic uses					
Poison, Insecticide Pesticide	R, L, S	Crushed and spread in the river	Catch fish	Secoya	Sucumbíos
				Siona	Sucumbíos
				Unidentified ethnicity	Orellana
					Napo
					Zamora Chinchipe
				Tsa'chi	Pichincha
				Cofán	Sucumbíos
					Amazon
				Kichwa of Eastern	Sucumbíos
					Napo
					Orellana
					Pastaza
					Zamora Chinchipe
				Wao	Napo
					Orellana
				Shuar	Orellana
					Pastaza
					Morona Santiago
Social, symbolic, and ritual uses Protection rituals	L	Leaves, alone or with ají leaves burned	Drives away evil spirits when you sleep in the forest	Unidentified ethnicity	Napo
Other handling Commercialization	R		Collection and sale (rotenone content)	Cofán	Amazon

Table A2. Specific ethnobotanical uses of *Lonchocarpus utilis* reported in the fieldwork (Pakayaku, Pastaza, Ecuador). Local names: *intillama shilu*, *barbasku*. Vouchers: QAP Herbarium.

Use Categories	Part	Preparation	Method of Usage/Purpose of Use
Human Medicine			
Used against myiasis: "to kill the tupe" (human bot fly)	R	Extraction of "milk" by pressure	The "milk" is deposited on a piece of paper and placed where tupe has stung
Hits and body aches	R	Crush roots	Crushed root is placed directly on the skin
Veterinary			
External antiparasitic	R	Extraction of "milk" by pressure	The "milk" is deposited on a piece of paper and placed where tupe has stung
Toxic			
Catch fish	R	Crushed roots to be used as soon as possible (in 1–2 days)	The "milk" obtained is spread in the water of rivers and ravines

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