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 (tupu). 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].
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, 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, kompon, 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 *Psorophora*), 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 *Sarcoppiaga taeniorrhidiais*, *S. iambens*, *Cynomysps 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 calcitrans*, 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-urucul A, prenyl-isotirumalin and prenylutilinol), prenylated flavones (3’-methoxylupinifolin), prenylated flavanones (2S)-6-(γ,γ-dimethylallyl)-5,4′-dihydroxy-3′-methoxy-6″, 6″-dimethylpyran [2″,3″:7,8] flavanone, and prenyutililine, 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.](image-url)
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 Cell      | Inhibition of mitochondrial activity (diminished NADH: ubiquinone oxidoreductase activity) | [41]       |
|                               |               | Inhibition of growth                                                   | [31]       |
|                               | Cell Leishmania| Antileishmaniasis                                                      | [42]       |
|                               | Cell          | Antiproliferative                                                      | [39]       |
|                               | Fish Insect    | Toxic for fish                                                         | [41,43]    |
|                               |               | Insecticide and pesticide                                              | [44]       |
| Rotenolone                    | Rat Cell      | Inhibition of mitochondrial activity (diminished NADH: ubiquinone oxidoreductase activity) (25% less active than rotenone). | [41]       |
|                               |               | Inhibition of growth                                                   | [31]       |
| Deguelin                      | Cell          | Inhibition of mitochondrial activity (diminished NADH: ubiquinone oxidoreductase activity) (50% less active than rotenone). | [41]       |
|                               | Cell Nematode | Nematocide                                                             | [46]       |
|                               | Cell          | Anti-inflammatory in transplants                                        | [46,47]    |
|                               | Cell          | Potent apoptotic and antiangiogenic                                      | [46,49]    |
|                               | Cell          | Inhibition of progression of tumors                                     | [49–53]    |
|                               | Cell          | Inhibition of tumor cell growth and metastasis.                        | [51,52]    |
|                               | Cell          | Chemical adjuvant against leukemia                                      | [54]       |
| Tephrosin                     | Rat Cell      | Inhibition of mitochondrial activity (diminished NADH: ubiquinone oxidoreductase activity) | [41]       |
|                               |               | Inhibition of growth                                                   | [43]       |
| Prenyl-urucuol A              | Cell          | Cytoprotective activity of neurons in rats (Complete fraction)          | [55]       |
| Prenyl-isotirumalin           |               |                                                                         |            |
| Prenylutilinol                |               |                                                                         |            |
| 3′-methoxylupinifolin         |               |                                                                         |            |
| Prenylutiline                 |               |                                                                         |            |
| (2S)-6-(γ,γ-dimethylallyl)-5,  |               |                                                                         |            |
| 4′-dihydroxy-3′-methoxy-6″,    |               |                                                                         |            |
| 6″-dimethylpyran [2 ′′,3′′,7,8]|               |                                                                         |            |
| 4-hydroxylonchocarpin         | Cell          | Inhibition of growth                                                   | [36]       |
| Lonchocarpene                 | Seedling      | Antifungal                                                             | [56]       |
| 4-methoxy/lonchocarpene       | Seedling      | Inhibition of growth/development                                        | [57]       |
| 3,5-dimethoxy-4-hydroxy-3-prenyl-trans-stilbene | Seedling      | Inhibition of growth/development                                        | [57]       |

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′methoxylupinifolin; 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 NADH-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′methoxylupinifolin;
- 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:**

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

![Swiss Target prediction Report Files obtained using Rotenone as query molecule.](image)

| Target                                      | Uniprot ID | Gene code | ChEMBL ID      | Probability | # sim. cmpds (3D / 2D) | Target Class |
|---------------------------------------------|------------|-----------|----------------|-------------|------------------------|--------------|
| Microtubule-associated protein tau          | P10636     | MAPT      | CHEMBL1293224  |             |                        |              |
| NADH-ubiquinone oxidoreductase chain 4      | P03905     | MT-ND4    | CHEMBL4499     |             |                        |              |
| Tyrosyl-DNA phosphodiesterase 1             | Q8NUW5     | TOP1      | CHEMBL1075138  |             |                        |              |
| Cytochrome P450 2C19                        | P33261     | CYP2C19   | CHEMBL3622     |             |                        |              |
| 5-hydroxytryptamine receptor 6              | P50406     | HTR6      | CHEMBL3371     |             |                        |              |
| Cytochrome P450 2E1 (by homology)           | P05161     | CYP2E1    | CHEMBL5281     |             |                        |              |
| Cytochrome P450 2C8 (by homology)           | P10632     | CYP2C8    | CHEMBL3721     |             |                        |              |
| Cytochrome P450 2A6 (by homology)           | P11509     | CYP2A6    | CHEMBL5282     |             |                        |              |
| Cytochrome P450 2C9 (by homology)           | P11712     | CYP2C9    | CHEMBL3397     |             |                        |              |
| Cytochrome P450 2B6 (by homology)           | P20813     | CYP2B6    | CHEMBL4729     |             |                        |              |
| Cytochrome P450 2A7 (by homology)           | P20853     | CYP2A7    | CHEMBL3597     |             |                        |              |
| Cytochrome P450 2F1 (by homology)           | P24902     | CYP2F1    | CHEMBL3597     |             |                        |              |
| Cytochrome P450 2C18 (by homology)          | P33261     | CYP2C18   | CHEMBL2408     |             |                        |              |
| Cytochrome P450 2A13 (by homology)          | Q16694     | CYP2A13   | CHEMBL3597     |             |                        |              |
| Cytochrome P450 19A1                        | P11511     | CYP19A1   | CHEMBL1978     |             |                        |              |

Figure A1. Swiss Target prediction Report Files obtained using Rotenone as query molecule.
### SwissTargetPrediction report:

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

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

| 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             | Q9NUW98    | TCP1      | 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       |
| Cytchrome P450 2C19                         | P32019     | CYP2C19   | CHEMBL3622   |             | 0 / 1                   | Enzyme       |
| Cytchrome P450 2E1 (by homology)            | P05181     | CYP2E1    | CHEMBL5281   |             | 0 / 1                   | Enzyme       |
| Cytchrome P450 2C8 (by homology)            | P10632     | CYP2C8    | CHEMBL3721   |             | 0 / 1                   | Enzyme       |
| Cytchrome P450 2A6 (by homology)            | P15210     | CYP2A6    | CHEMBL5282   |             | 0 / 1                   | Enzyme       |
| Cytchrome P450 2C9 (by homology)            | P11712     | CYP2C9    | CHEMBL3397   |             | 0 / 1                   | Enzyme       |
| Cytchrome P450 2B6 (by homology)            | P20813     | CYP2B6    | CHEMBL4729   |             | 0 / 1                   | Enzyme       |
| Cytchrome P450 2A7 (by homology)            | P20857     | CYP2A7    |             |             | 0 / 1                   | Enzyme       |
| Cytchrome P450 2F1 (by homology)            | P24803     | CYP2F1    |             |             | 0 / 1                   | Enzyme       |
| Cytchrome P450 2C18 (by homology)           | P32260     | CYP2C18   | CHEMBL2408   |             | 0 / 1                   | Enzyme       |
| Cytchrome P450 2A13 (by homology)           | Q16696     | CYP2A13   |             |             | 0 / 1                   | Enzyme       |
**SwissTargetPrediction report:**

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

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

| Target | UniProt ID | Gene code | ChEMBL ID | Probability | # sim. cmpds (3D / 2D) | Target Class |
|--------|------------|-----------|-----------|-------------|------------------------|--------------|
| Tyrosyl-DNA phosphodiesterase 1 | Q2NUW8 | TDP1 | CHEMBL1075138 | | 220 / 20 | Enzyme |
| Omithine decarboxylase | P11926 | ODC1 | CHEMBL1969 | | 1 / 10 | Enzyme |
| Antizyme inhibitor 1 (by homology) | O14977 | A2N1 | CHEMBL1075138 | | 1 / 10 | Enzyme |
| Arginine decarboxylase (by homology) | Q96A70 | ADC | CHEMBL1969 | | 1 / 10 | Enzyme |
| Microtubule-associated protein tau | P10925 | MAPT | CHEMBL123224 | | 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 | P26008 | HTR6 | CHEMBL3371 | | 9 / 1 | Membrane receptor |
| Cytochrome P450 2E1 (by homology) | P55181 | CYP2E1 | CHEMBL5281 | | 2 / 1 | Enzyme |
| Cytochrome P450 2C8 (by homology) | P10632 | CYP2C8 | CHEMBL3721 | | 2 / 1 | Enzyme |
| Cytochrome P450 2A6 (by homology) | P11509 | CYP2A6 | CHEMBL3282 | | 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 | CHEMBL4729 | | 2 / 1 | Enzyme |
| Cytochrome P450 2F1 (by homology) | P24903 | CYP2F1 | CHEMBL4729 | | 2 / 1 | Enzyme |
Figure A4. Swiss Target prediction Report Files obtained using Thephrosin as query molecule.
### SwissTargetPrediction report:

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

####Query Molecule

![Query Molecule](image)

####Frequency of Target Class

| Target                                                | Uniprot ID | Gene code | ChEMBL ID | Probability | # sim. cmpds (3D / 2D) | Target Class               |
|-------------------------------------------------------|------------|-----------|-----------|--------------|------------------------|----------------------------|
| Ornithine decarboxylase                               | P11928     | TDC1      | CHEMBL1869|              | 1 / 10                 | Enzyme                     |
| Antizyme inhibitor 1 (by homology)                    | O14977     | AZN1      | CHEMBL1374|              | 1 / 10                 | Enzyme                     |
| Arginine decarboxylase (by homology)                  | O06A79     | ADC       | CHEMBL1374|              | 1 / 10                 | Enzyme                     |
| Cathepsin L1 light chain (by homology)                | P07711     | CTSL1     | CHEMBL3807|              | 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)                            | O69911     | 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       | P18331     | PTPN1     | CHEMBL335 |              | 20 / 10                | Tyr Phosphatase            |
| Tyrosyl-DNA phosphodiesterase 1                       | Q6W8       | TDP1      | CHEMBL1075138|            | 61 / 18                | Enzyme                     |
| ATP-binding cassette sub-family G member 2            | O9UNQ1     | ABG2      | CHEMBL5393 |              | 17 / 6                 | Unclassified               |
| Endothelin B receptor (by homology)                   | P24530     | EDNRA     | 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     | IKBB     | 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’-methoxylupinifolin as query molecule.
SwissTargetPrediction report:

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

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

| Target                                         | Uniprot ID | Gene code | ChEMBL ID   | Probability | # sim. cmpds (3D/2D) | Target Class      |
|------------------------------------------------|------------|-----------|-------------|-------------|----------------------|-------------------|
| Ornithine decarboxylase                        | P11929     | ODC1      | CHEMBL1869  |             | 7/10                 | Enzyme            |
| Antifreeze inhibitor 1 (by homology)           | Q14977     | AZNI1     |             |             | 7/10                 | Enzyme            |
| Arginine decarboxylase (by homology)           | Q99670     | ADC       |             |             | 7/10                 | Enzyme            |
| Tyrosyl-DNA phosphodiesterase 1                | O2NWW8     | TDP1      | CHEMBL1075138|            | 73/8                 | Enzyme            |
| Nitric oxide synthase, endothelial (by homology)| P29474    | NO53      | CHEMBL4803  |             | 37/8                 | Enzyme            |
| Nitric oxide synthase, brain (by homology)     | P29475     | NO51      | CHEMBL3568  |             | 37/8                 | Enzyme            |
| Nitric oxide synthase, inducible (by homology) | P39228     | NO52      | CHEMBL4481  |             | 37/8                 | Enzyme            |
| MAP kinase-activated protein kinase 2          | P49137     | MAPKAPK2  | CHEMBL2208  |             | 36/1                 | Ser,Thr Kinase    |
| MAP kinase-activated protein kinase 5          | Q8N41      | MAPKAPK5  | CHEMBL3094  |             | 36/1                 | Ser,Thr Kinase    |
| MAP kinase-activated protein kinase 3 (by homology)| Q16644   | MAPKAPK3  | CHEMBL4570  |             | 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  | Q06655     | PRKCD     | CHEMBL2996  |             | 3/1                  | Ser,Thr Kinase    |
| Protein kinase C theta type (by homology)      | Q05759     | PRKCO     | CHEMBL3320  |             | 3/1                  | Ser,Thr Kinase    |

**Figure A6.** Swiss Target prediction Report Files obtained using 4-hydroxylonchocarpin 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

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**Figure A7.** Swiss Target prediction Report Files obtained using Lonchocarpene as query molecule.
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 | Sucumbios |
|                                       |      |             |                                        | Siona            | Sucumbios |
|                                       |      |             |                                        | Unidentified ethnicity | Orellana |
|                                       |      |             |                                        | Tsa’chi           | Napo |
|                                       |      |             |                                        | Cofán             | Zamora |
|                                       |      |             |                                        | Pichincha         | Chinchipe |
|                                       |      |             |                                        | Sucumbios         | Napo |
|                                       |      |             |                                        | Amazon            | Orellana |
|                                       |      |             |                                        | Sucumbios         | Pastaza |
|                                       |      |             |                                        | Napo              | Zamora |
|                                       |      |             |                                        | Chinchipe         | Chinchipe |
|                                       |      |             |                                        | Wao               | Napo |
|                                       |      |             |                                        | Shuar             | Orellana |
|                                       |      |             |                                        |                  | Pastaza |
|                                       |      |             |                                        |                  | Morona Santiago |
| Social, symbolic, and ritual uses      | L    | Leaves, alone or with aji leaves burned | Drives away evil spirits when you sleep in the forest | Unidentified ethnicity | Napo |
| Protection rituals                     |      |             |                                        |                  |                     |
| Other handling                         | R    | Collection and sale (rotenone content) | | | Amazon |
| Commercialization                      |      |             |                                        |                  |                     |
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. Crushed root is placed directly on the skin |
| Hits and body aches     | R    | Crush roots                 |                                                                                               |
| 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.                          |

References

1. World Health Organization (WHO) Neglected Tropical Diseases. Available online: https://web.archive.org/web/20140227152033/http://www.who.int/neglected_diseases/en/ (accessed on 13 December 2019).
2. Katewa, S.S.; Chaudhary, B.L.; Jain, A. Folk herbal medicines from tribal area of Rajasthan, India. *J. Ethnopharmacol.* **2004**, *92*, 41–46. [CrossRef] [PubMed]
3. Carreño-Hidalgo, P.C. La etnobotánica y su importancia como herramienta para la articulación entre conocimientos ancestrales y científicos. In *Trabajo de Grado para Optar a Título de Licenciado*; Universidad Distrital Francisco José de Caldas: Bogotá, Colombia, 2016.
4. Hotez, P.J.; Alvarado, M.; Basáñez, M.-G.; Bolliger, I.; Bourne, R.; Boussinesq, M.; Brooker, S.J.; Brown, A.S.; Buckle, G.; Budke, C.M. The global burden of disease study 2010: Interpretation and implications for the neglected tropical diseases. *PLoS Negl. Trop. Dis.* **2014**, *8*, e2865. [CrossRef] [PubMed]
5. Nemoga Soto, R. Globalización y transformacion de las formas jurídicas: Apropiacion de material genetico. *Pensam. Jurídico* **1**:138-148. ISSN 2557-6170. 2013. Available online: https://revistas.unal.edu.co/index.php/peju/article/view/38893 (accessed on 17 December 2019).
6. Torres Morocho, D.M.; Orea Igarza, U.; Brito Vallina, M.L.; Cordero Machado, E. Estudio de la extracción del follaje de Barbasco (*Lonchocarpus nicou*) como fuente biocida (en condiciones de la Amazonía en Ecuador). *Rev. Cienc. Técnicas Agropec.* **2013**, *22*, 41–49.
7. Luzuriaga-Quichimbo, C.X. Estudio Etnobotánico en Comunidades Kichwas Amazónicas de Pastaza, Ecuador. Ph.D. Thesis, Universidad de Extremadura, Badajoz, España, 2017.
8. Borgtoft, H.; Skov, F.; Fjeldsa, J.; Öllgaard, B. People and Biodiversity. Two case studies from the Andean foothills of Ecuador. Centre for research on cultural and biological diversity of Andean rainforests. *Diva Tech. Rep.* **1998**, *3*, 1–190.
9. Álvarez, C. *Historias desde el Aula*; Abya-Yala: Quito, Ecuador, 2006.
10. GADP-Pastaza. *Estudio del Impacto Ambiental del Proyecto de Construcción del Afirmado Camino Vecinal Latasas-Umupi, Parroquia Canelos, Provincia Pastaza*; Gobierno Autónomo Descentralizado de Pastaza: Puyo, Ecuador, 2013.
11. GADP-Pastaza. *Plan de Desarrollo y Ordenamiento Territorial del Cantón Pastaza, 2015–2020*; Gobierno autónomo Descentralizado de Pastaza: Puyo, Ecuador, 2015.
12. Widdowson, M.-A.; Iuliano, A.D.; Dawood, F.S. Challenges to global pandemic mortality estimation. *Lancet Infect. Dis.* **2014**, *14*, 121–125. [CrossRef]
13. Zuñiga Carrasco, I.R. Miasis: Un problema de salud poco estudiado en México. *Rev. Enferm. Infecc. Pediatr.* **2009**, *22*, 121–125.
14. Tamir, J.; Haik, J.; Orenstein, A.; Schwartz, E. Dermatobia hominis myiasis among travelers returning from South America. *J. Am. Acad. Derm.* **2003**, *48*, 630–632. [CrossRef]
15. Mathieu, M.E.; Wilson, B.B. *Myiasis*, 5th ed.; Co, C.L., Ed.; Churchill Livingstone Co: Philadelphia, PA, USA, 2000.
16. Martinez-Estrada, V.; Aguilera, V.; Jurado, F. *Miasis furunculoide*. *Comun. Caso. Dermatol. Rev. Mex* 2002, 46, 280–284.
17. Mengarelli, R.H.; Cevallos, M.V. Manejo de las miasis en heridas agudas y crónicas: Presentación de casos y revisión de la bibliografía. *Rev. Argent. Dermatol. Ciudad Autónoma Buenos Aires* 2012, 93, 1–8.
18. Ginarte, M.; García Doval, I.; Petero, C.; Toribio, J. *Miasis cutánea* por *Dermatobia hominis*. *Actas Dermosifiliogr.* 1996, 87, 340–342.
19. de Hollanda Ramírez, A.M.; Silva Rodríguez, A.R.; Zaracho, G. Invermectina en el tratamiento de Human Miasis. *La Fac. Cienc. Médicas* 2005, 38, 62–71.
20. Manrique, A.; Manrique, D.; Catacara, J. *Miasis cutánea*: Reporte de un caso y revisión de la literatura. *Folia Derm. Peru* 2009, 20, 23–26.
21. Rubio, C.; de Guevara, C.L.; Martín, M.A.; Campos, L.; Quesada, A.; Casado, M. *Miasis cutáneas* sobre lesiones tumurales: Presentación de tres casos. *Actas Dermosifiliogr.* 2006, 97, 39–42. [CrossRef]
22. Izquierdo, M.J.; Pastor, M.A.; Carrasco, L.; Fariña, M.C.; Martín, L.; Requena, L.; Fernández, R.; Gadea, I. *Miasis furunculoide*: Descripción de dos casos con estudio histológico de las diferentes larvas. *Actas Dermosifiliogr.* 2001, 92, 456–460. [CrossRef]
23. Chan, J.C.M.; Lee, J.S.W.; Dai, D.L.K.; Woo, J. Unusual cases of human *myiasis* due to Old World screwworm fly acquired indoors in Hong Kong. *Trans. R. Soc. Trop. Med. Hyg.* 2005, 99, 914–918. [CrossRef]
24. Moya, J.; Spelta, G.; Gavazza, S.; Barbarulo, A.M.; Fontana, M.I.; Barerra, M.; Jurjo, I.L.; Azcune, R. *Miasis cutánea*: Revisión sobre el tema y presentación de un caso de *miasis furunculoide*. *Arch. Argent. Derm.* 2007, 57, 217–222.
25. Lima, T.C.; Santos, A.D.C.; Costa, D.T.M.; Souza, R.J.; Barison, A.; Steindel, M.; Biavatti, M.W. Chromenes from leaves of *Calea pinnatifida* and evaluation of their leishmanicidal activity. *Rev. Bras. Farm.* 2015, 25, 7–10. [CrossRef]
26. Mishra, T.; Shukla, S.; Meena, S.; Singh, R.; Pal, M.; Upreti, D.K.; Datta, D. Isolation and identification of cytotoxic compounds from a fruticose lichen *Roccella montagnei*, and it’s in silico docking study against CDK-10. *Rev. Bras. Farm.* 2017, 27, 724–728. [CrossRef]
27. dos Santos Passos, C.; Klein-Júnior, L.C.; de Mello Andrade, J.M.; Matté, C.; Henriques, A.T. The catechol-O-methyltransferase inhibitory potential of *Z*-vallesiachotamine by in silico and in vitro approaches. *Rev. Bras. Farm.* 2015, 25, 382–386. [CrossRef]
28. Moraga-Nicolás, F.; Jara, C.; Godoy, R.; Iturriaga-Vásquez, P.; Venturh, H.; Quiroz, A.; Becerra, J.; Mutis, A.; Hormazábal, E. Rhodolirium andicola: A new renewable source of alkaloids with acetylcholinesterase inhibitory activity, a study from nature to molecular docking. *Rev. Bras. Farm.* 2018, 28, 34–43. [CrossRef]
29. Moradi-Afrapoli, F.; Shokrzadeh, M.; Barzegar, F.; Gorji-Bahri, G.; Zadali, R.; Nejad Ebrahimi, S. Cytotoxic activity of abietane diterpenoids from roots of *Salvia hadenica* by HPLC-based activity profiling. *Rev. Bras. Farm.* 2018, 28, 27–33. [CrossRef]
30. Mangul, S.; Martin, L.S.; Langmead, B.; Sanchez-Galan, J.E.; Toma, I.; Hormozdiari, F.; Pevzner, P.; Eskin, E. How bioinformaticists and open data can boost basic science in countries and universities with limited resources. *Nat. Biotechnol.* 2019, 37, 324–326. [CrossRef] [PubMed]
31. Fang, N.B.; Casida, J.E. Cube resin insecticide: Identification and biological activity of 29 rotenoid constituents. *J. Agric. Food Chem.* 1999, 47, 2130–2136. [CrossRef] [PubMed]
32. de Oliveira, D.G.; de Almeida, C.M.C.; Silva, C.; Arruda, M.S.P.; Arruda, A.C.; Lopes, D.C.F.; Yamada, E.S.; da Costa, E.T.; da Silva, M.N. Flavonoids from the Leaves of *Deguelia utilis* (Leguminosae): Structural Elucidation and Neuroprotective Properties. *J. Braz. Chem. Soc.* 2012, 23, 1933–1939. [CrossRef]
33. Lawson, M.A.; Kaouadj, M.; Allais, D.P.; Champavier, Y.; Chulia, A.J. Substituted tubaic acids, new oxidative rotenoid metabolites from Lonchocarpus nicou. *Tetrahedron Lett.* 2006, 47, 451–454. [CrossRef]
34. Lawson, M.A.; Kaouadj, M.; Chulia, A.J. A single chalcone and additional rotenoids from Lonchocarpus nicou. *Tetrahedron Lett.* 2010, 51, 6116–6119. [CrossRef]
35. Lawson, A.M.N.V. O-Benzoquinone and Ester-Linked Hydroxycacetly Acid as Additional compounds from Lonchocarpus nicou. *Open J. Plant Sci.* 2016, 1, 1–4. [CrossRef]
36. Fang, N.B.; Casida, J.E. New bioactive flavonoids and stilbenes in cube resin insecticide. *J. Nat. Prod.* 2000, 63, 293. [CrossRef]
37. Lawson, M.A.; Kaouadji, M.; Chulia, A.J. Nor-dehydrodeguelin and nor-dehydrototene, C(22)
    coumaronochromes from Lonchocarpus nicou. Tetrahedron Lett. 2008, 49, 2407–2409. [CrossRef]
38. Kaouadji, M.; Agban, A.; Mariotte, A.M. Lonchocarpene, a stilbene, and lonchocarpusone, an
    isoflavone—2 new pyronopolyphenols from Lonchocarpus nicou roots. J. Nat. Prod. 1986, 49, 281–285. [CrossRef]
39. Fang, N.B.; Casida, J.E. Anticancer action of cube insecticide. Correlation for rotenoid constituents
    between inhibition of NADH: Ubiquinone oxidoreductase and induced ornithine decarboxylase activities. Proc.
    Natl. Acad. Sci. USA 1998, 95, 3380–3384. [CrossRef] [PubMed]
40. Muhaisen, H.M.H. Introduction and Interpretation of Flavonoids. Adv. Sci. Eng. Med. 2014, 6, 1–16.
    [CrossRef]
41. Caboni, P.; Sherer, T.B.; Zhang, N.J.; Taylor, G.; Na, H.M.; Greenamyre, J.T.; Casida, J.E. Rotenone,
    deguelin, their metabolites, and the rat model of Parkinson’s disease. Chem. Res. Toxicol. 2004, 17, 1540–1548.
    [CrossRef]
42. Fuchino, H.; Yamanaka, A.; Obu, A.; Wada, H.; Mori-Yasumoto, K.; Kawahara, N.; Flores, D.;
    Palacios, O.; Sekita, S.; et al. New Leishmanicidal Stilbenes from a Peruvian Folk Medicine, Lonchocarpus
    nicou. Chem. Pharm. Bull. (Tokyo) 2013, 61, 979–982. [CrossRef] [PubMed]
43. Ibrahim, B.; M’Batchi, B.; Mounzeo, H.; Bourobou, H.P.B.; Posso, P.E. Effect of Tephrosia vogelii and
    Justicia extensa on Tilapia nilotica in vivo. J. Ethnopharmacol. 2000, 69, 99–104. [CrossRef]
44. Sarwar, M. The killer chemicals for control of agriculture insect pests: The botanical insecticides. Int.
    J. Chem. Biomol. Sci. 2015, 1, 123–128. [CrossRef]
45. Fuchino, H.; Sekita, S.; Mori, K.; Kawahara, N.; Satake, M.; Kiuchi, F. A New Leishmanicidal Saponin from
    Brunfelsia grandiflora. Chem. Pharm. Bull. (Tokyo) 2008, 56, 93–96. [CrossRef]
46. Preston, S.; Korhonen, P.K.; Mouchiroud, L.; Cornaglia, M.; McGee, S.L.; Young, N.D.; Davis, R.A.;
    Crawford, S.; Novell, C.; Ansell, B.R.E.; et al. Deguelin exerts potent nematocidal activity via the
    mitochondrial respiratory chain. FASEB J. 2017, 31, 4515–4532. [CrossRef]
47. Kim, W.Y.; Chang, D.J.; Hennessy, B.; Seo, S.Y. A Novel Derivative of the Natural Agent Deguelin for Cancer
    Chemoprevention and Therapy. Cancer Prev. Res. 2009, 2, 186. [CrossRef]
48. Lee, S.-G.; Kim, M.-M. Anti-inflammatory Effect of Scopoletin in RAW264.7 Macrophages. J. Life Sci.
    2015, 28, 1377–1383. [CrossRef]
49. Murillo, G.; Saiti, G.I.; Kosmeder, J.W.; Pezzuto, J.M.; Mehta, R.G. Deguelin inhibits the growth of colon
    cancer cells through the induction of apoptosis and cell cycle arrest. Eur. J. Cancer 2002, 38, 2446–2454.
    [CrossRef]
50. Lee, H.Y.; Oh, S.H.; Woo, J.K.; Kim, W.Y.; Van Pelt, C.S.; Price, R.E.; Cody, D.; Tran, H.; Pezzuto, J.M.;
    Moriarty, R.M.; et al. Chemopreventive effects of deguelin, a novel Akt inhibitor, on tobacco-induced lung
    tumorigenesis. J. Natl. Cancer Inst. 2005, 97, 1695–1699. [CrossRef] [PubMed]
51. Boreddy, S.R.; Srivastava, S.K. Deguelin suppresses pancreatic tumor growth and metastasis by inhibiting
    epithelial-to-mesenchymal transition in an orthotopic model. Oncogene 2013, 32, 3980–3991. [CrossRef]
      [PubMed]
52. Thamilselvan, V.; Menon, M.; Thamilselvan, S. Anticancer efficacy of deguelin in human prostate cancer
    cells targeting glycogen synthase kinase-3 beta/beta-catenin pathway. Int. J. Cancer 2011, 129, 2916–2927.
      [CrossRef]
53. Wang, A.M.; Wang, W.N.; Chen, Y.Q.; Ma, F.Q.; Wei, X.M.; Bi, Y.Y. Deguelin induces PUMA-mediated
      apoptosis and promotes sensitivity of lung cancer cells (LCCs) to doxorubicin (Dox). Mol. Cell. Biochem.
      2018, 442, 177–186. [CrossRef]
54. Bortul, R.; Tazzari, P.L.; Billi, A.M.; Tabellini, G.; Mantovani, I.; Cappellini, A.; Grafone, T.; Martinelli, G.;
    Conte, R.; Martelli, A.M.; et al. PI3K/AKT inhibitor, enhances chemosensitivity of leukaemia cells with an
    active PI3K/AKT pathway. Br. J. Haematol. 2005, 129, 677–686. [CrossRef]
55. Ackerman, J.L.; Bellwood, D.R. Reef fish assemblages: A re-evaluation using enclosed rotenone stations.
    Mar. Ecol. Prog. Ser. 2000, 206, 227–237. [CrossRef]
56. Aladdin, N.-A.; Jamal, J.A.; Talip, N.; Hamsani, N.A.M.; Rahman, M.R.A.; Sabandar, C.W.; Muhammad, K.;
    Hussain, K.; Jalil, J.; Lima, N.M.; et al. Antifungal activity of extracts and phenolic compounds from Deguelia
    duckea. Rev. Bras. Farm. 2018, 28, 697–702. [CrossRef]
57. Lobo, L.T.; da Silva, G.A.; de Freitas, M.C.C.; Souza, A.P.S.; da Silva, M.N.; Arruda, A.C.; Guilhon, G.;
    Santos, L.S.; Santos, A.S.; Arruda, M.S. Stilbenes from Deguelia rufescens var. urucu (Ducke) A. M. G.
Azevedo Leaves: Effects on Seed Germination and Plant Growth. *J. Braz. Chem. Soc.* **2010**, *21*, 1838–1844. [CrossRef]

58. Omura, S. Ivermectin: 25 years and still going strong. *Int. J. Antimicrob. Agents* **2008**, *31*, 91–98. [CrossRef]

59. Ómura, S.; Crump, A. The life and times of ivermectin—a success story. *Nat. Rev. Microbiol.* **2004**, *2*, 984. [CrossRef] [PubMed]

60. Silva, G.; Lagunes, A.; Rodriguez, J.C.; Rodriguez, D. Insecticidas vegetales; una vieja y nueva alternativa en el manejo de insectos. *Rev. Manejo Integr. Plagas Agrocol.* **2002**, *66*, 4–12.

61. Gupta, R.C. *Biomarkers in Toxicology*; Academic Press: Cambridge, MT, USA, 2014; ISBN 9780124046306.

62. McGarry, J.W. Tropical myiasis: Neglected and well travelled. *Lancet Infect. Dis.* **2014**, *14*, 672–674. [CrossRef]

63. World Health Organization (WHO), International Programme on Chemical Safety. *The WHO Recommended Classification of Pesticides by Hazard. Guidelines to Classification*; World Health Organization: Geneve, Switzerland, 2009; ISBN 9789241547963.

64. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int. J. Surg.* **2010**. [CrossRef] [PubMed]

65. Gfeller, D.; Michielin, O.; Zoete, V. Shaping the interaction landscape of bioactive molecules. *Bioinformatics* **2013**, *29*, 3073–3079. [CrossRef]

66. Gfeller, D.; Grosdidier, A.; Wirth, M.; Daina, A.; Michielin, O.; Zoete, V. SwissTargetPrediction: A web server for target prediction of bioactive small molecules. *Nucleic Acids Res.* **2014**, *42*, 32–38. [CrossRef]

67. De la Torre, L.; Navarrete, H.; Muriel, P.; Maciá, J.; Balslev, H. *Enciclopedia de las plantas Útiles en Ecuador*; Escuela de Ciencias Biológicas de la Pontificia Universidad Católica del Ecuador & Herbario AAU del Departamento de Ciencias Biológicas de la Universidad de Aarhus: Quito, Ecuador; Aarhus, Dinamarca, 2008; ISBN 978-9978-77-135-8.

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