

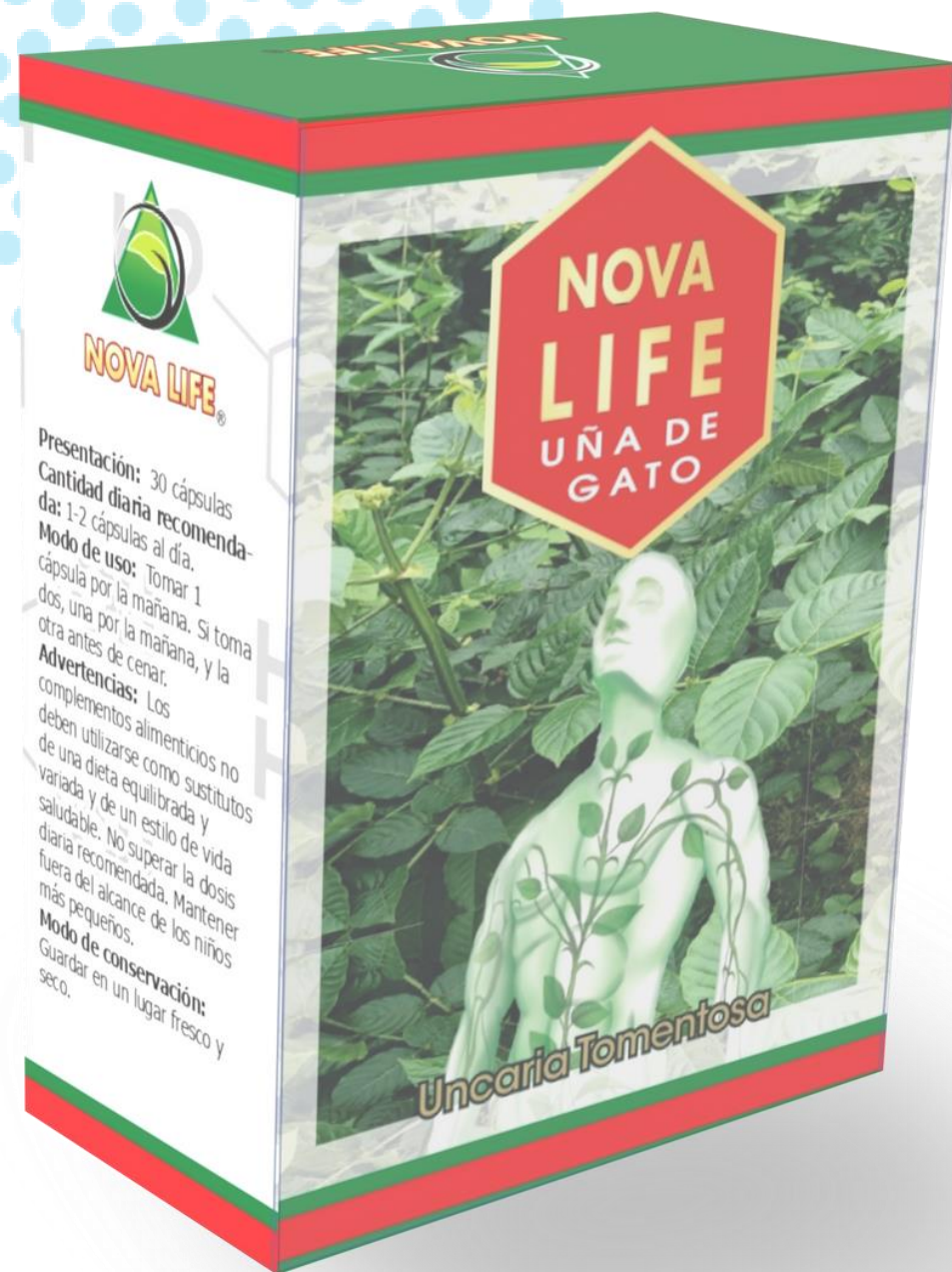


NOVA LIFE

Technical dossier for professionals
August, 2021

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Nova Life is a food supplement created from the extract of *Uncaria Tomentosa* (cat's claw) leaves of the highest quality from Costa Rica.

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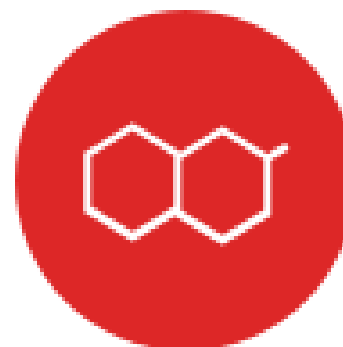
healththerapies4us.com

European manufacturing quality

Product distributed exclusively by Health therapies LLC.



NOVA LIFE



The capsules of extracts from cat's claw leaves (*Uncaria tomentosa*) are a food supplement of the highest quality and pharmacological importance. They have a high content of bioactive compounds for the treatment and prevention of diseases, the main source being the **proanthocyanidins** of natural origin from cat's claw.



Potential for prevention and treatment of degenerative, cancerous, infectious and other pathogenic diseases



Patent of obtaining an extract enriched in proanthocyanidins developed by the Food Research Center (CIAL) of the Spanish National Research Council (CSIC) and the Bioactivity for Sustainable Development Group (BIODESS) of the University of Costa Rica (UCR).



Research product with in-vitro tests on respiratory pathogens, antioxidant potential and anticarcinogenic effect, being safe and beneficial to health as demonstrated by user testimonials (<https://naturalnovalife.com>).

Scientific Evidence



More than 8000 scientific studies have been developed on cat's claw (*U. tomentosa*), which have demonstrated:

- Beneficial evidence at the cellular, cytological, biochemical, pharmacological, pre-clinical and clinical levels.
- Pro-apoptosis, demonstrating its potential as an anti-cancer agent in the prevention and treatment of onco-cellular diseases.

Numerous studies demonstrate therapeutic properties of **proanthocyanidins** which benefits in the immune system, cancer, neurodegenerative and infectious diseases, among others.



**NOVA LIFE
HEALT
BENEFITS**

rheumatism
cardiovascular

cancer bleedings
inmunomodulation

metabolic
diseases

antiprotozoals

diabetes

obesity

gastric ulcers

asthma arthritis

infectious
diseases



The Best Vegetal Material

Commercially available products are usually made from bark. By thoroughly analyzing all parts of the plant, different studies were able to demonstrate that the plant material of the leaves of the Atlantic region possesses a significant amount of bioactive flavan-3-ol type compounds such as **procyanidins** and **propelargonidines** as well as **alkaloids**.

Plant material grown under controlled conditions in Pococí de Limón in Costa Rica. The domestication of medicinal plants is an active conservation strategy that allows control over the reproduction rate for commercial purposes and also preserves the genetic material.

Comparing the results of the studies has confirmed the superior feasibility of the leaves as a starting material for obtaining extracts rich in bioactive compounds.



Uncaria tomentosa: Healthful compounds predominant in the leaves

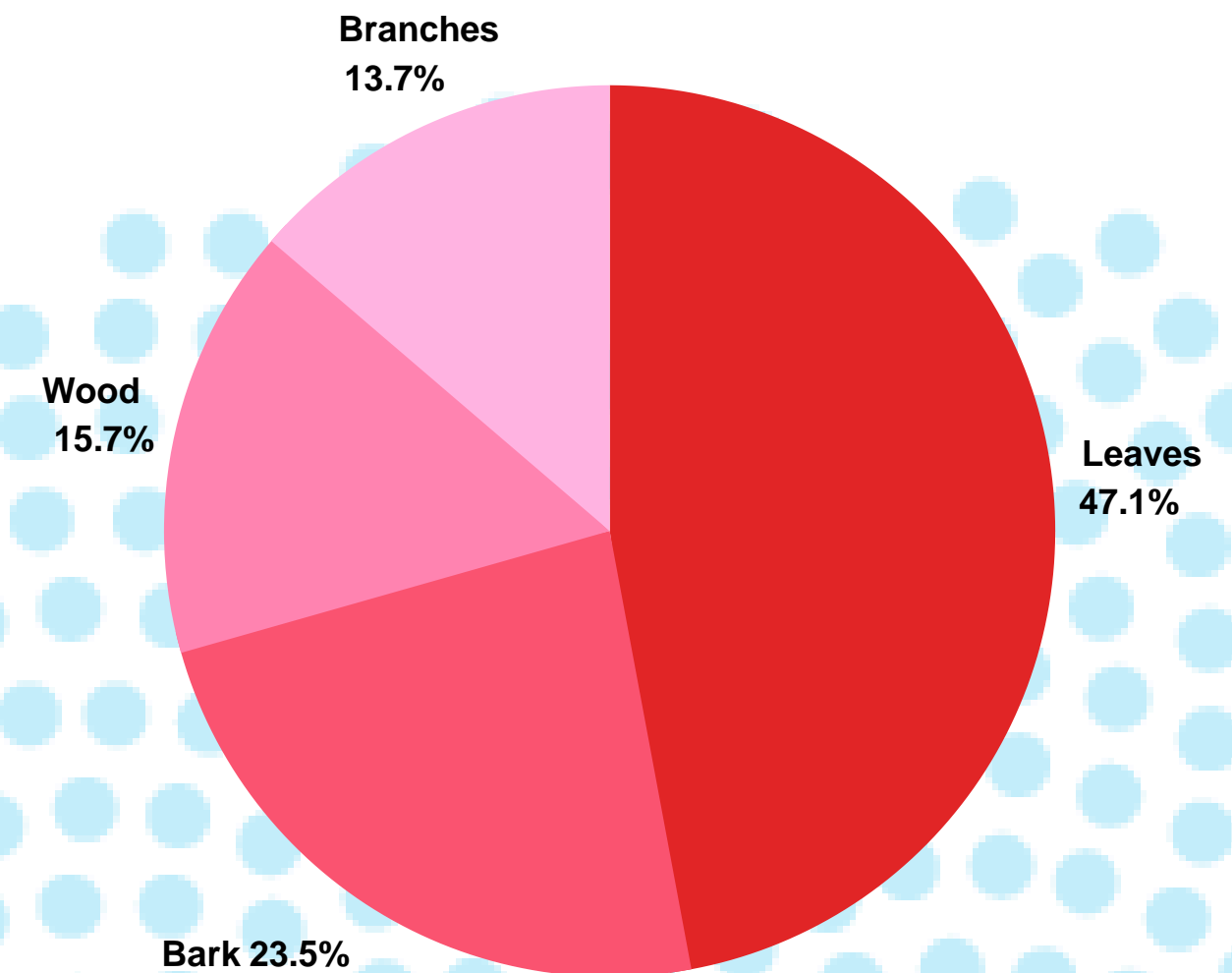
Prospecting the composition of bioactive compounds in plants is the mainstay of pharmacological discovery.

In *U. tomentosa* the most studied and therefore most characterized resource has traditionally been the bark.

- Comparative prospecting. It is obtained by quantitatively describing the samples to be studied and comparing leaves, bark, stems and internal wood, proving that the leaves have the highest level of biological activity..

Identification of 32 compounds: procyanidins, propelargonidins and flavalignans as well as other non-flavanoid phenols and alkaloids. These were found in higher amounts in Costa Rican cat's claw compared to studies on plants of other origin.

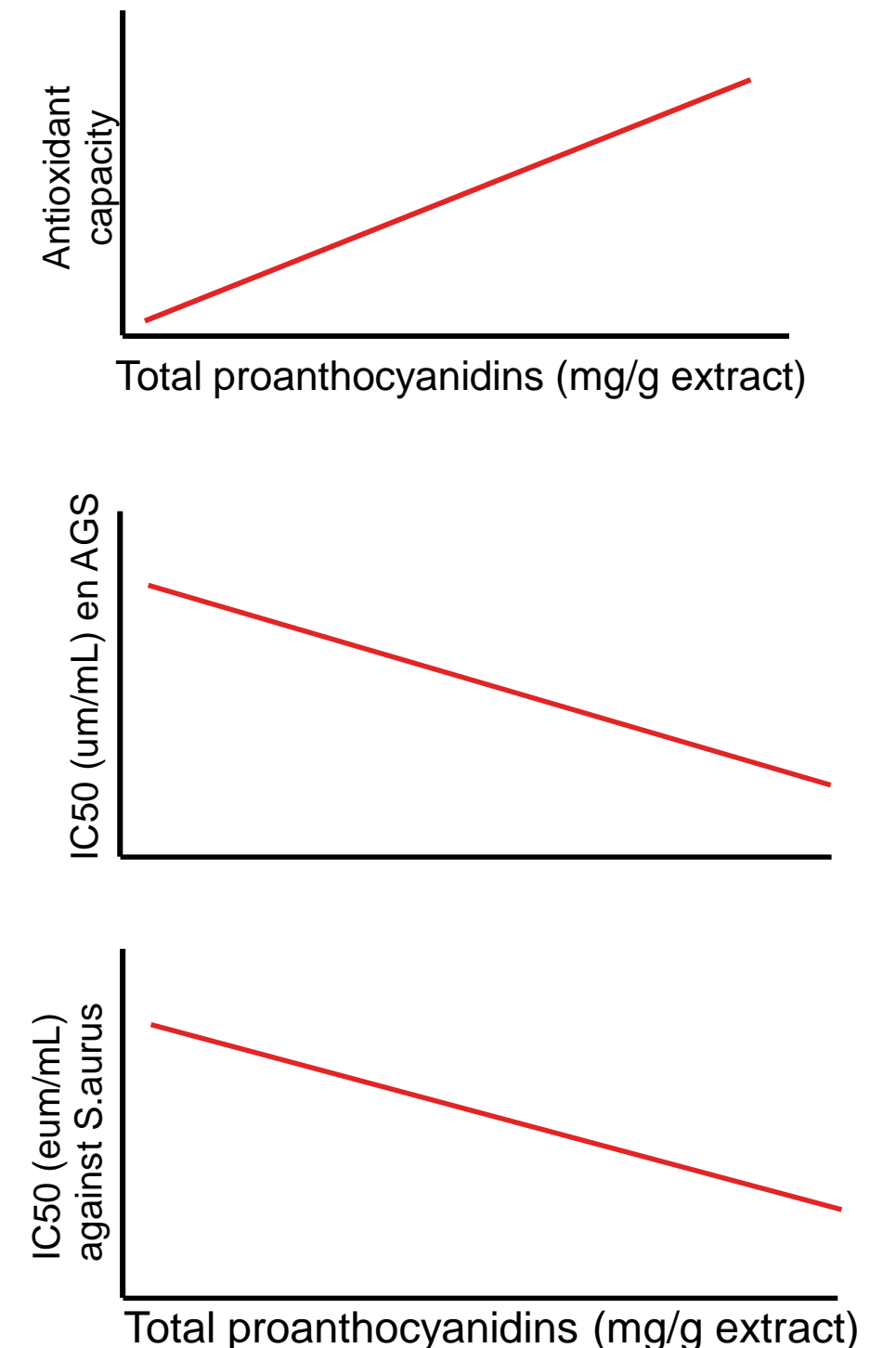
- In addition, there was clear evidence that the best quantification and bioactivity yields are obtained in the leaves.



The most promising material for the development of a food supplement are the leaves of *U. tomentosa*

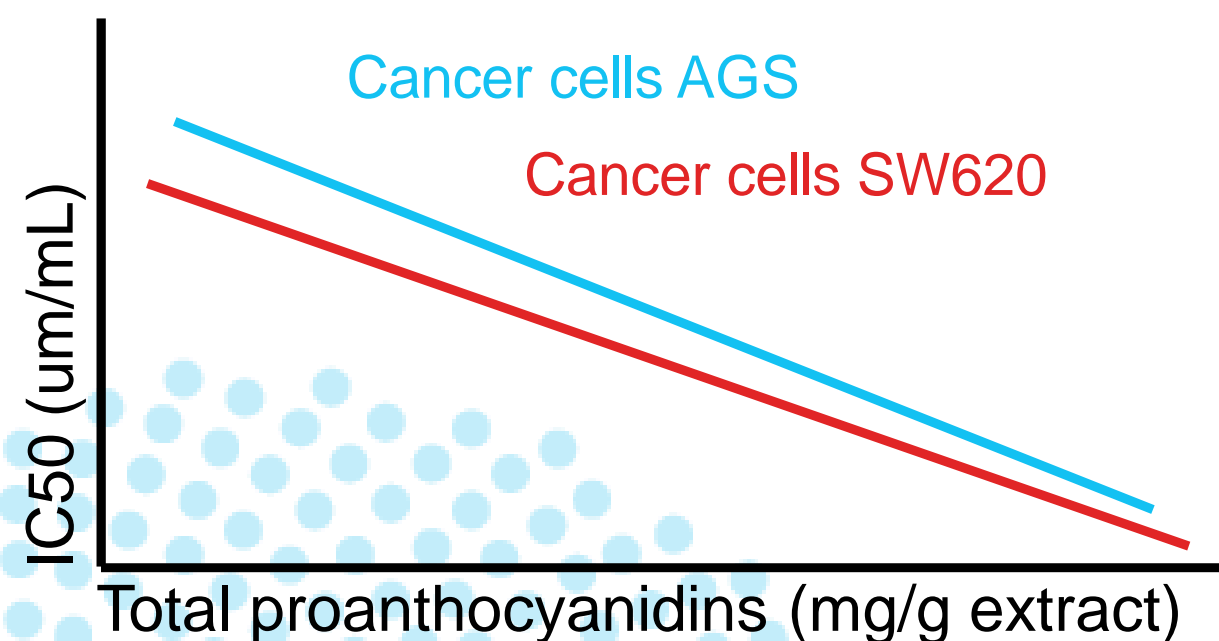
Antimicrobial activity against respiratory pathogens and effects on cancer cells

- Cat's claw extracts from the Atlantic slope of Costa Rica were analyzed and characterized for all parts of the plant.
- The presence of oligomeric procyanidins, especially in the leaves, is a very important novel finding since different bioactivities have been reported.
- Cat's claw leaves stand out in their antioxidant capacity and their anti-microbial activity against respiratory pathogens
- Analysis of their activity on colon cancer cells SW620 and gastric cancer cells AGS showed that this activity is closely linked to the high amount of proanthocyanidins in cat's claw leaves.
- These results make **Nova Life** a health-promoting food supplement.



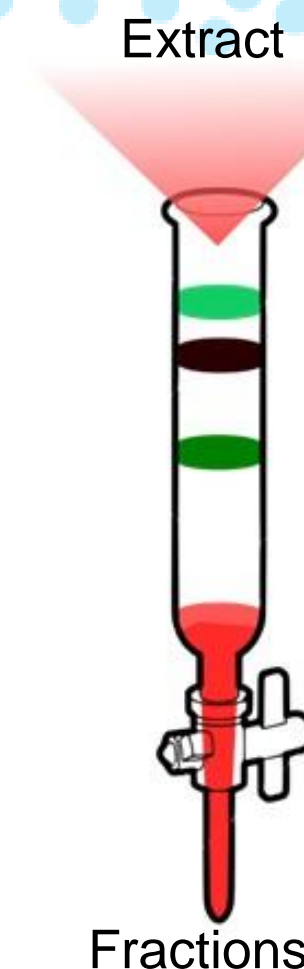
Superior antioxidant activity and anticarcinogenic activity

To further corroborate the bioactivity exerted by the leaf extracts, the components were separated into different enriched fractions by chromatography, and the antioxidant and anti-carcinogenic activity was evaluated.



- The correlation found with proanthocyanidins reaffirms the initial observation made on the original extracts.
- Those extracts with the highest amount of propelargonidins and procyanidins showed the highest bioactivity of all, both antioxidant as assessed by ORAC, as well as cytotoxicity against colon adenocarcinoma cells SW620 and gastric AGS.

- Proanthocyanidin-rich extracts were found to possess selective cytotoxicity against the aforementioned cells compared to healthy cells. This is an essential characteristic of a quality nutraceutical, which is selective against pathology but does not affect normal cells.
- By proving that the majority families of compounds in the samples are responsible for the bioactivity recorded for cat's claw, the benefits of Nova Life are also proven.



Nova Life health benefits



In the industry, the processing of the material to obtain a derivative as an extract, requires grade solvents for the preservation of all compounds, and therefore the functional characteristics of the plant.



By analyzing aqueous and ethanolic extractions of all parts of the Costa Rican cat's claw plant, it was found that indeed, these industry standard conditions retain all 32 compounds identified above. Proanthocyanidins from the Nova Life extract are the type of compounds with the most prominent activity.



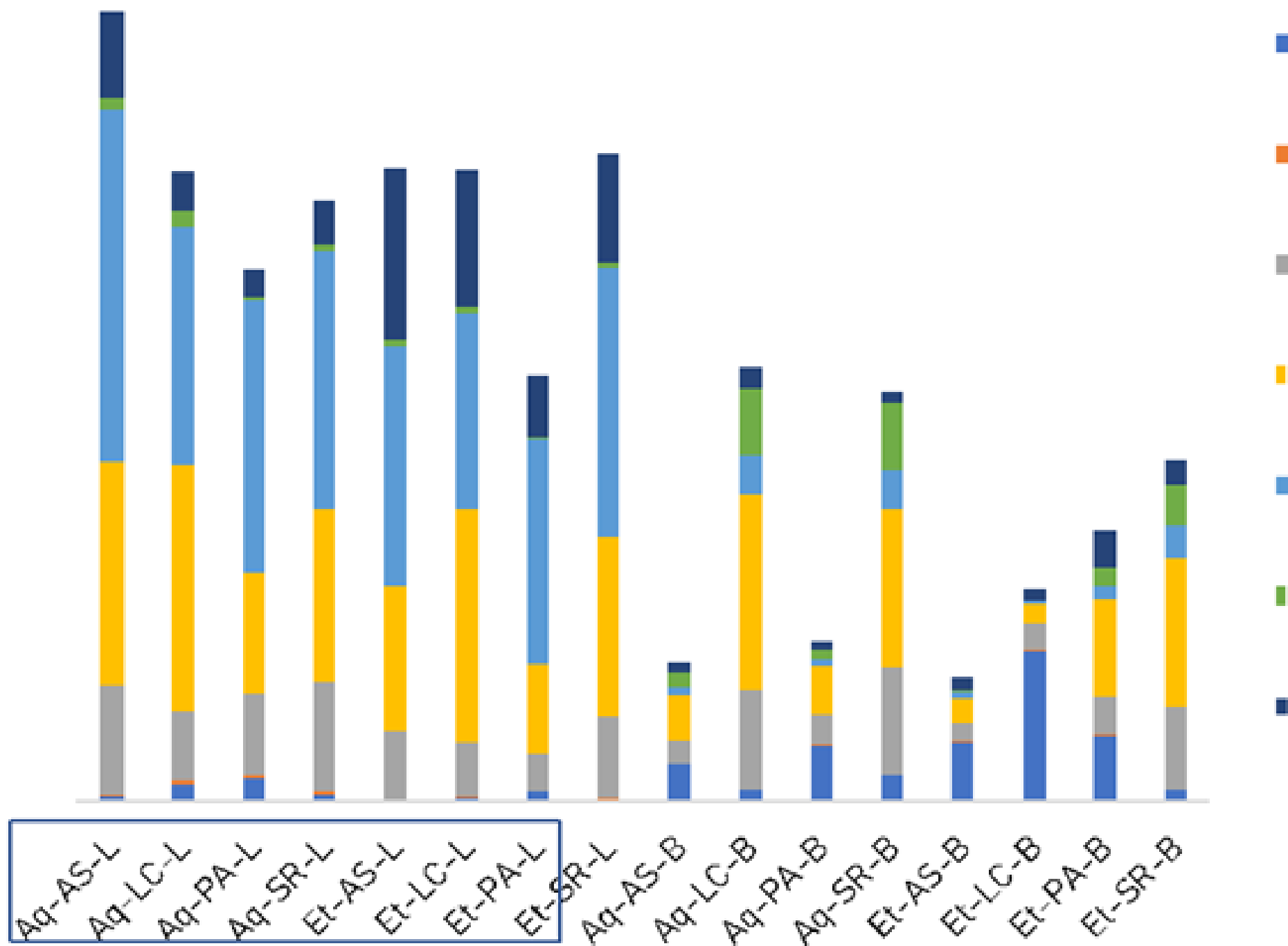
Leaves are indeed the richest and most concentrated starting material in these bioactive compounds. If we analyze the individual composition of the compounds depending on the geographical origin of the sample, we see that all leaf samples are similar to each other, which is an advantage in terms of product quality.



It ensures that the Costa Rican plant species can be cultivated without altering the quality of the final product, providing advantages also to the final consumer, who is assured that his product is constant and harmless.

Health benefits of **Nova Life** under conditions of the food supplement industry

The leaf samples are far superior compared to the bark samples..



Quality far superior to the products currently traded in the market



Most of the commercial samples studied correspond to ground cat's claw bark and showed low levels of proanthocyanidins, compared to our samples of Costa Rican *Uncaria tomentosa* leaves with our processing.


The antioxidant capacity correlates positively with proanthocyanidins and this activity was higher in the only product that corresponded to a mixture with extract, but in a much lower percentage than the one with proanthocyanidins. **Nova Life.**

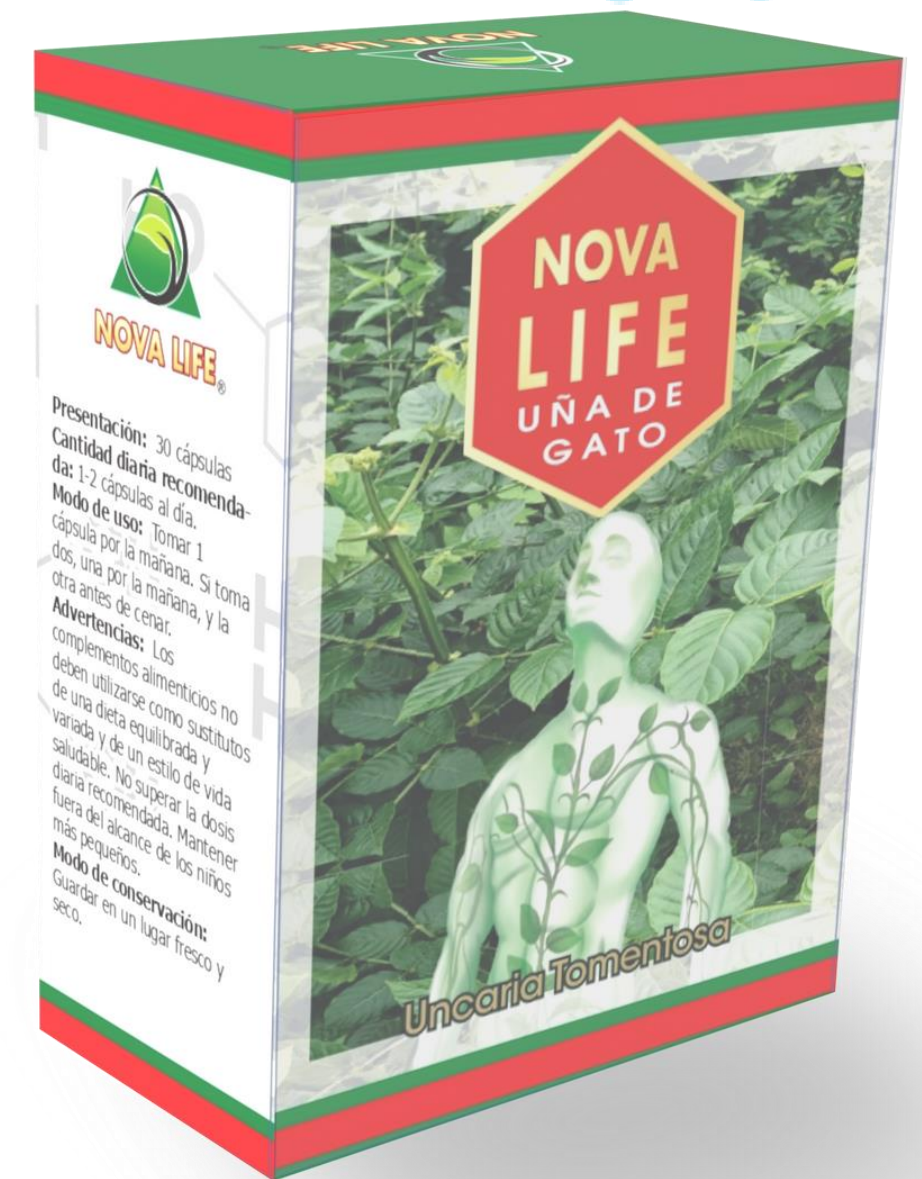


This confirms that **Nova Life** is a superior quality product compared to the eighteen brands of cat's claw plant material capsules marketed in Europe and America.

Our product have a higher quality due to the use of the proanthocyanidin-enriched extract of *Uncaria tomentosa* leaves.

Technical sheet

| Ingredients | Amount per capsule per (mg) | Provides |
|--|-----------------------------|---|
| Mixture with dry extract of cat's claw (<i>Uncaria tomentosa</i>) (35% polyphenols) * | 400 | 140 mg polyphenols |
| Microcrystalline cellulose (freight agent) E-460 | 95 |  NOVA LIFE |
| Silicon dioxide, thixosil (anticaking agent) E-551 | 5 | |
| Pistachio green hard gelatin capsules (Gelatin, brilliant blue E-133, iron oxide yellow E-172) | 100 | |
| Capsules weight (product+wrapper): 600mg+5% | | |



Precautions for use

Food supplements should not be used as a substitute for a balanced and varied diet and a healthy lifestyle. Keep out of reach of children.

In conditions of pregnancy, lactation, children under six years of age, any special health condition or disease, you should consult with your doctor before consumption.

Side effects: may cause allergic reactions in cases of hypersensitivity to any ingredient of the product. No precaution/intoxications have beenprecaution/intoxications in the usual doses.

The administration of any product (even herbal) should be consulted with a medical specialist, for possible interactions or contraindications with medications you are using.



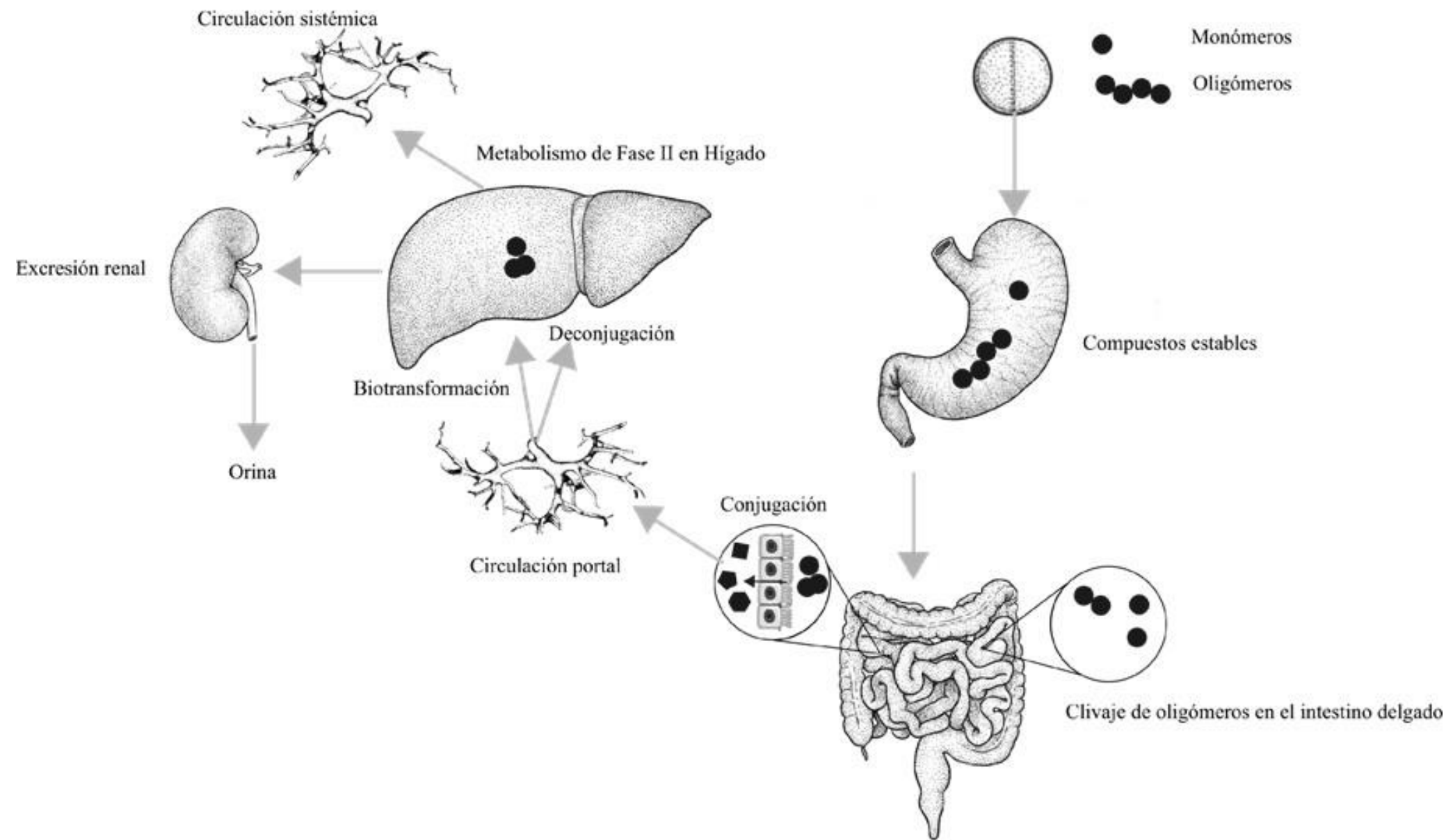
<https://www.webmd.com/vitamins/ai/ingredientmono-395/cats-claw> Technical sheet of Nova Life, ALPULI EUROPA S.L.

Toxicity

European Medicines Agency (EMA)
Assessment Report: *Uncaria tomentosa*

- 100% Tolerability.
- There is no evidence of DNA damage (genotoxicity).
- No symptoms of acute toxicity were found, when administered daily as a supplement. Also evidenced by user testimonials.

Metabolism



Proanthocyanpidins: are a transformation of high molecular weight oligomeric chains into smaller molecules. These in turn are transformed into conjugates that are also bioactive.

Inmuno Biochemistry

Proanthocyanidins act at multiple sites and mechanisms.

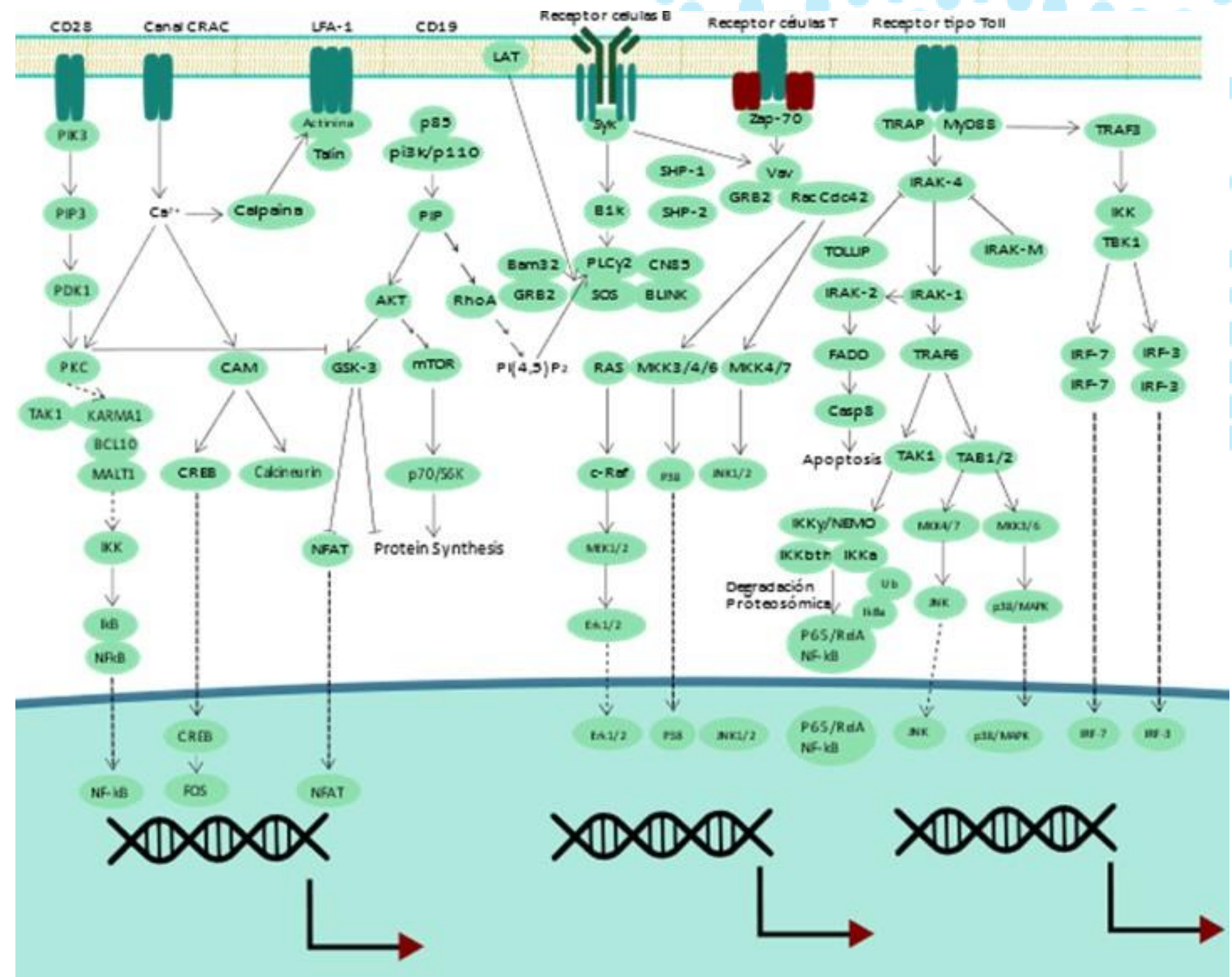
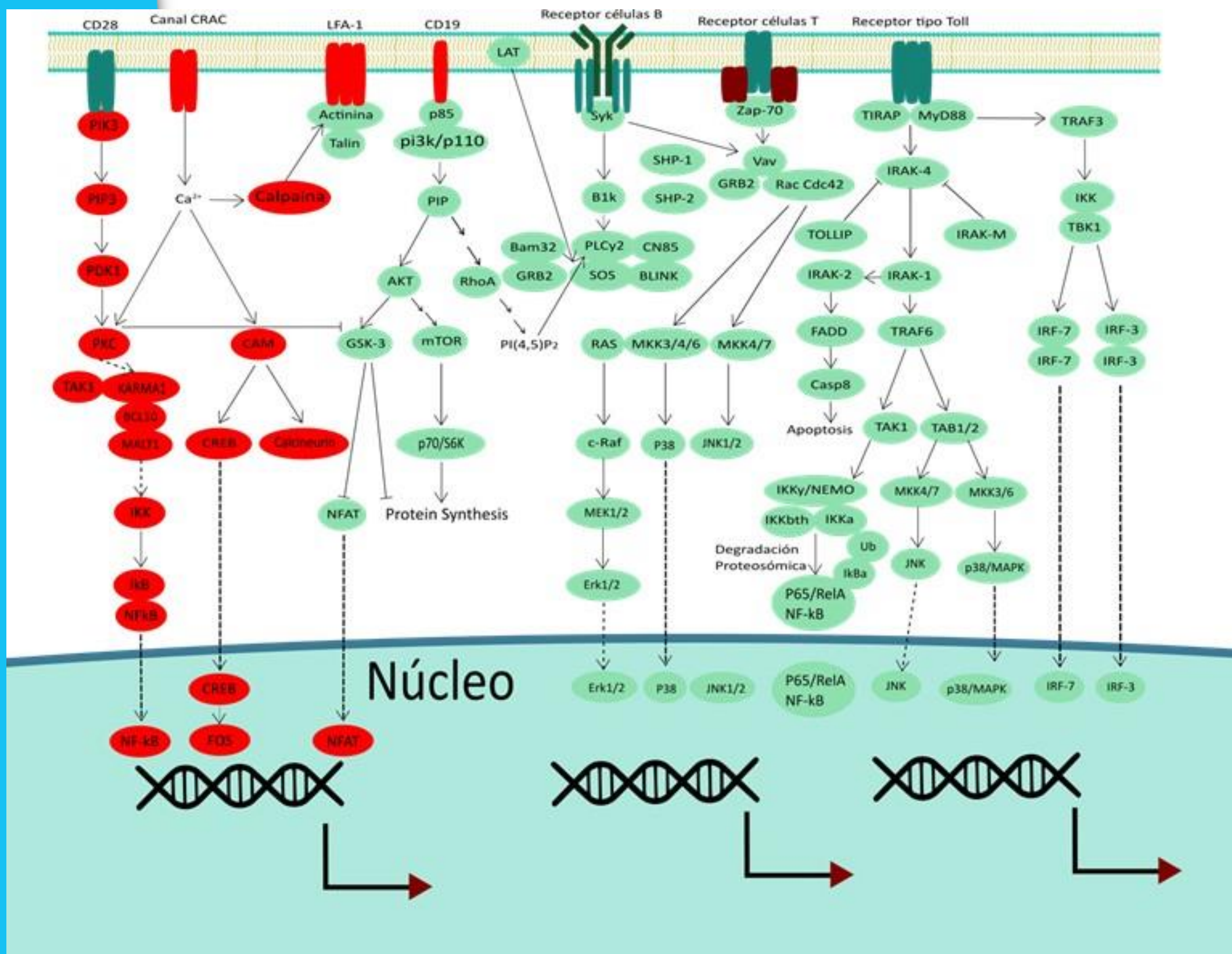


Figura de <https://www.apexbt.com/signaling-pathways/immunology-inflammation.html>



With the biochemical interaction of proanthocyanidins and the receptors or enzymes that initiate the immune response, the action of many proteins can be modified at the same time, as illustrated by the proanthocyanidins modulated by proanthocyanidins.

Figura modificada de <https://www.apexbt.com/signaling-pathways/immunology-inflammation.html>

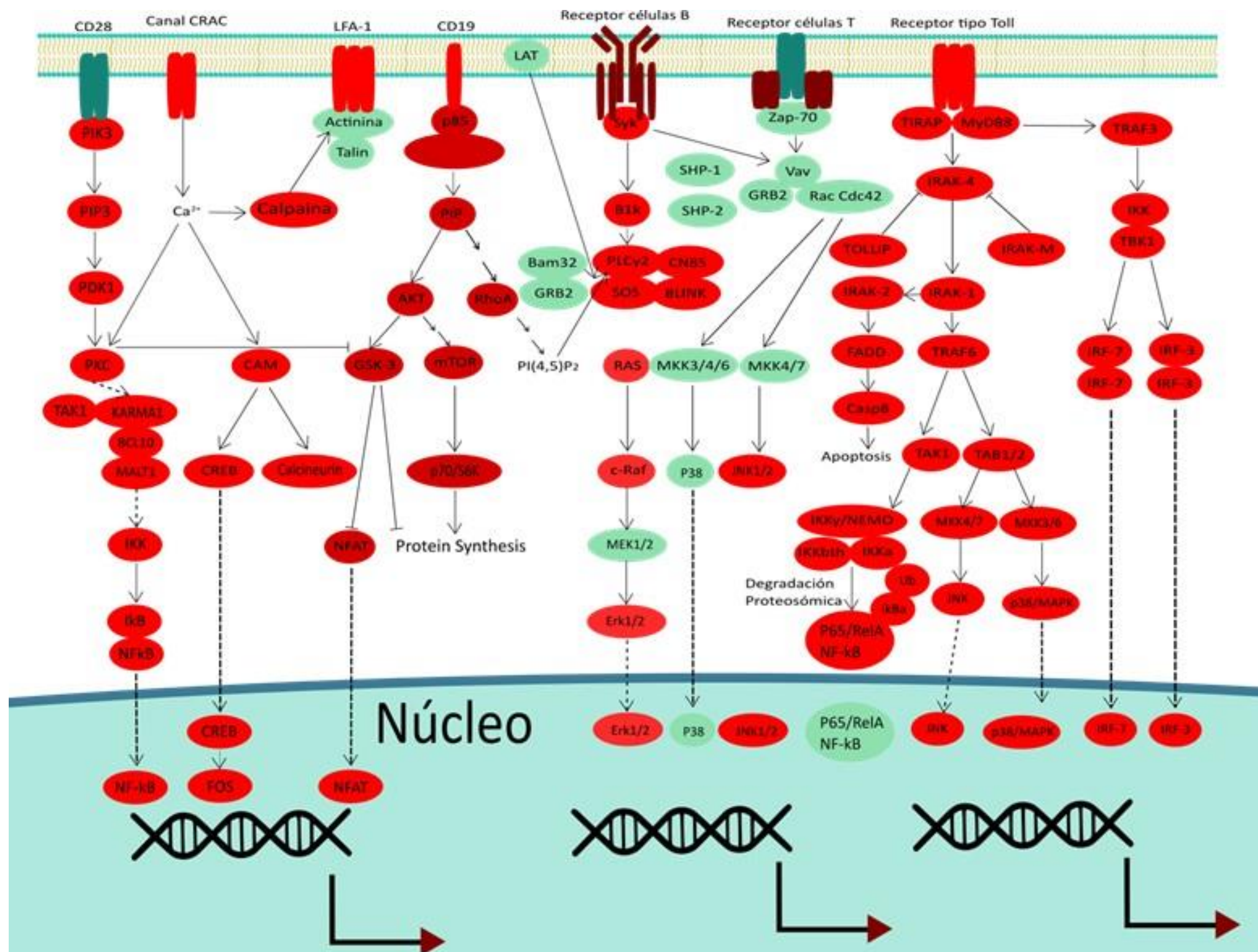


Figura modificada de <https://www.apexbt.com/signaling-pathways/immunology-inflammation.html>

The proanthocyanidins of **Nova Life**, have been identified as direct or indirect modulators of these immunosignaling pathways.

<https://dx.doi.org/10.3390%2Fmolecules201019014>

<https://doi.org/10.3109/13880200490893500>

<https://dx.doi.org/10.1111%2Fjcm.15074>

<https://doi.org/10.1080/01635581.2014.868914>

<http://dx.doi.org/10.1016/j.ejphar.2017.04.015>

<https://dx.doi.org/10.3390%2Fmolecules201019014>

<http://dx.doi.org/10.1016/j.fitote.2008.10.003>

<http://dx.doi.org/10.3945/ajcn.2009.27716>

<http://dx.doi.org/10.1002/mc.22461>

Effects of **PROANTHOCYANIDINS** on the **IMMUNE SYSTEM** impact on multiple disease associated processes

cardiovascular

metabolic

diseases

rheumatism

diabetes

gastric ulcers

asthma

arthritis

infectious

diseases

cancer bleedings

inmunomodulación

antiprotozoals

obesity

Cancer and proanthocyanidins biochemistry

Incidence shared with immunobiochemistry.

Growth factors



Protein

Reference

| | |
|-------------|---|
| (VEGF)/VEGF | https://doi.org/10.1016/j.nutres.2012.05.012 |
| CTGF | https://doi.org/10.1016/j.jnutbio.2008.02.005 |
| GM-CSF | https://doi.org/10.1159/000191103 |
| FGF | https://dx.doi.org/10.1016%2Fj.cyto.2015.05.030 |
| TGF-beta | https://doi.org/10.1002/biof.1019 |
| VEGF | https://doi.org/10.1177%2F153537020422900306 |

Kinases



| | |
|-----------------|---|
| Angiopoietine I | https://doi.org/10.1016/j.nutres.2012.05.012 |
| MAPK/ERK | https://doi.org/10.1371/journal.pone.0071071 |
| ErbB2 | https://doi.org/10.1177%2F153537020422900306 |

Inflammatory
cytokinins



| | |
|-------|---|
| IFN-γ | https://doi.org/10.1155/2014/365258 |
| IL-2 | https://doi.org/10.1155/2014/365258 |
| IL-4 | https://doi.org/10.1016/j.foodchem.2016.07.141 |
| IL-5 | https://doi.org/10.1016/j.foodchem.2016.07.141 |
| IL-6 | https://doi.org/10.1016/j.freeradbiomed.2013.02.007 |
| IL-8 | https://doi.org/10.3969/j.issn.1674-8115.2019.02.003 |
| TNF | https://doi.org/10.1016/j.jnutbio.2008.02.005 |

Additionally, proacianidins affect other biochemical pathways involving many families of enzymes and receptors.

Cancer and proanthocyanidins biochemistry

Incidence shared with immunobiochemistry.

Transcription factors



Protein

NF- κ B
AP-1
STAT

Reference
<https://doi.org/10.1016/j.foodres.2014.01.046>
<https://doi.org/10.1016/j.foodres.2014.01.046>
<https://doi.org/10.1016/j.foodres.2014.01.046>

Membrane receptors



AR
EGFR
ER alpha
HER-2

Reference
<https://doi.org/10.1177%2F1934578X1200700321>
<https://doi.org/10.1177%2F1934578X1200700321>
<https://doi.org/10.1080/10408398.2016.1231168>
<https://doi.org/10.2174/18715206113139990135>

Apoptotic



Caspase-8
Bcl-2

Reference
<https://doi.org/10.1093/carcin/bgm198>
<https://doi.org/10.3892/mmr.2021.11906>

Most of the evidence in cancer biochemistry is directly related to the regulation of the immune response.

Multidirected effects in pharmacology mechanisms.



Diseases at the molecular level are usually multifactorial, as in immunological and metabolic disorders.

The trend for the treatment of these diseases is the design of multi-targeted drugs and is being applied in neurodegenerative diseases as well as in cardiovascular problems.

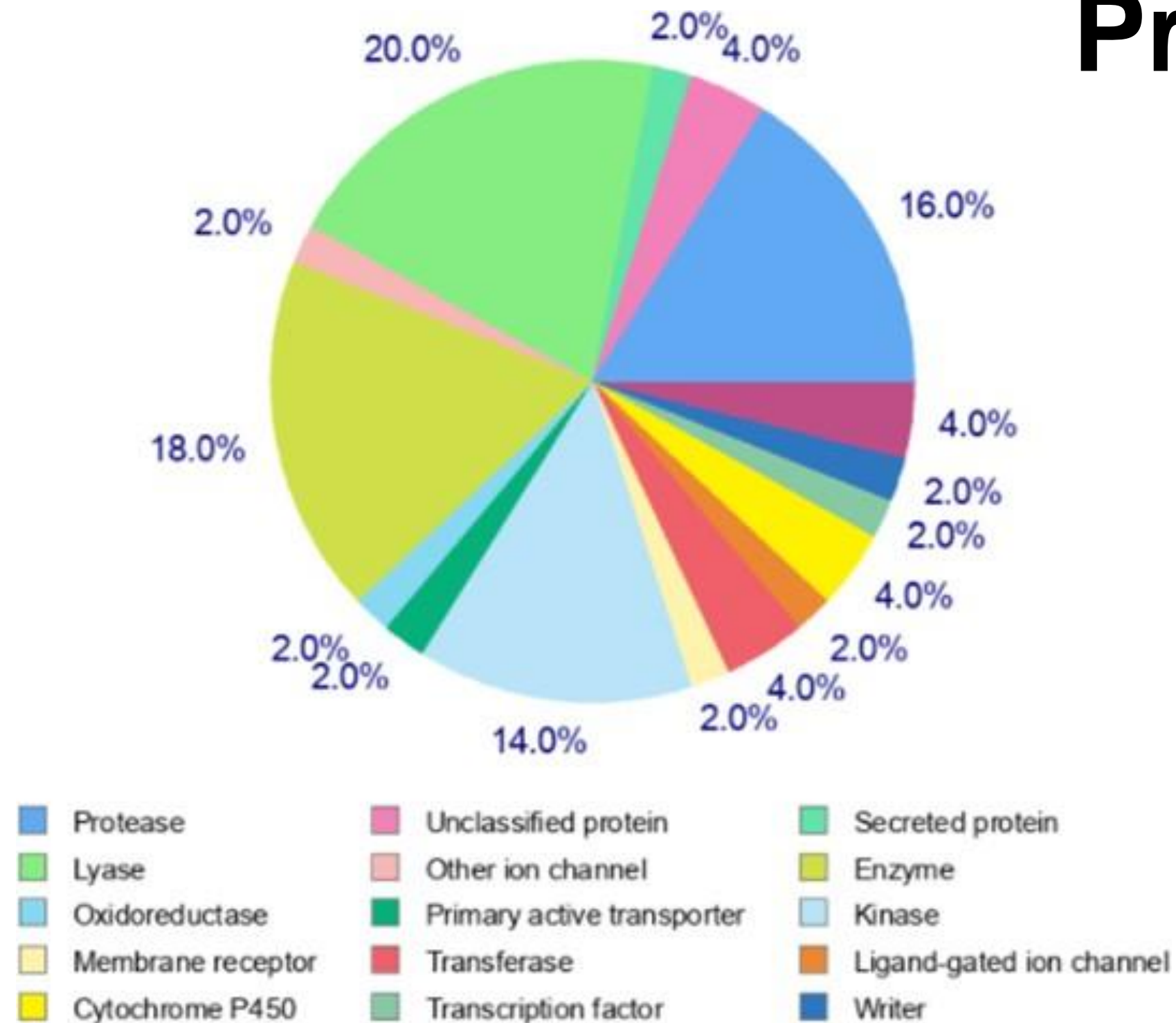
Proanthocyanidins interact with many elements of metabolic and immune signaling cascades.



Prediction of therapeutic targets

Proanthocyanidins interact with all protein families.

Proteases, enzymes, lyases, kinases and kinases predominate as therapeutic targets.



Carbonic anhydrase and diseases

| Target | Common name | Uniprot ID | ChEMBL ID | Target Class | Probability* | Known actives (3D/2D) |
|--------------------------------------|-------------|------------|---------------|----------------------|-----------------|-----------------------|
| Matrix metalloproteinase 2 | MMP2 | P08253 | CHEMBL333 | Protease | 0.595750693854 | 20 / 4 |
| Placenta growth factor | PGF | P49763 | CHEMBL1697671 | Unclassified protein | 0.33437200269 | 3 / 3 |
| Vascular endothelial growth factor A | VEGFA | P15692 | CHEMBL1783 | Secreted protein | 0.33437200269 | 3 / 3 |
| Matrix metalloproteinase 9 | MMP9 | P14780 | CHEMBL321 | Protease | 0.181167389532 | 22 / 2 |
| Carbonic anhydrase II | CA2 | P00918 | CHEMBL205 | Lyase | 0.0912088498733 | 26 / 3 |
| Carbonic anhydrase I | CA1 | P00915 | CHEMBL261 | Lyase | 0.0912088498733 | 17 / 2 |
| Carbonic anhydrase VII | CA7 | P43166 | CHEMBL2326 | Lyase | 0.0912088498733 | 5 / 7 |
| Carbonic anhydrase III | CA3 | P07451 | CHEMBL2885 | Lyase | 0.0912088498733 | 1 / 2 |
| Carbonic anhydrase VI | CA6 | P23280 | CHEMBL3025 | Lyase | 0.0912088498733 | 1 / 2 |
| Carbonic anhydrase XII | CA12 | O43570 | CHEMBL3242 | Lyase | 0.0912088498733 | 8 / 7 |
| Carbonic anhydrase IV | CA4 | P22748 | CHEMBL3729 | Lyase | 0.0912088498733 | 5 / 7 |
| Carbonic anhydrase VB | CA5B | Q9Y2D0 | CHEMBL3969 | Lyase | 0.0912088498733 | 1 / 2 |
| Carbonic anhydrase VA | CA5A | P35218 | CHEMBL4789 | Lyase | 0.0912088498733 | 3 / 2 |
| Beta-secretase 1 | BACE1 | P56817 | CHEMBL4822 | Protease | 0.0912088498733 | 24 / 12 |

Carbonic anhydrases are targets of recent research for their relationship with various diseases such as Alzheimer's disease, glaucoma, neuropathic pain, epilepsy, edema, hypoxic tumors and obesity.

Nova life proanthocyanidins as carbonic anhydrase inhibitors

- Carbonic anhydrase isoforms are involved in important physiological functions.
- Its inhibitors are used for the treatment of diseases such as **Alzheimer's disease, neuropathic pain, epilepsy, glaucoma, edema, hypoxic tumors, and obesity.**
- The phenolic substructure is inhibitory against many isoforms, hence the versatility of **polyphenols** provides multidirected therapy.



doi: 10.4155/fmc-2017-0223
doi: 10.3390/molecules21121649.
doi: 10.1517/14740338.2014.897328
doi: 10.1080/13543776.2018.1523897

More evidence of health benefits of proanthocyanidins in clinical trials

Cardiovascular effects

<https://clinicaltrials.gov/ct2/show/NCT00742287>

Reduction of triglycerides

<https://clinicaltrials.gov/ct2/show/NCT01688154>

Alopecia

<https://pubmed.ncbi.nlm.nih.gov/11406858/>

Adjuvant in prostate cancer

<https://www.cancer.gov/clinicaltrials/NCI-2016-02058>

Blood pressure

<https://doi.org/10.1016/j.phrs.2020.105329>

U. tomentosa in human and *in vivo* models



- Reduction of bronchial hyper-responsiveness and inflammation in murine models of asthma

<https://doi.org/10.1016/j.jep.2018.02.013>

- Inhibitory effects against pulmonary thromboembolism of *U. tomentosa* in murine models

<https://dx.doi.org/10.5530/pj.2020.12.29>



- Inhibition of metastasis in melanomas in murine models

<https://hdl.handle.net/20.500.12866/766>

- Inhibition of chronic inflammation in human skin

U. tomentosa: effects in metabolic diseases

Molecular, animal and clinical evidence for the treatment of complications from **obesity and diabetes**.



High blood pressure



High cholesterol



High sugar
Insulin resistance



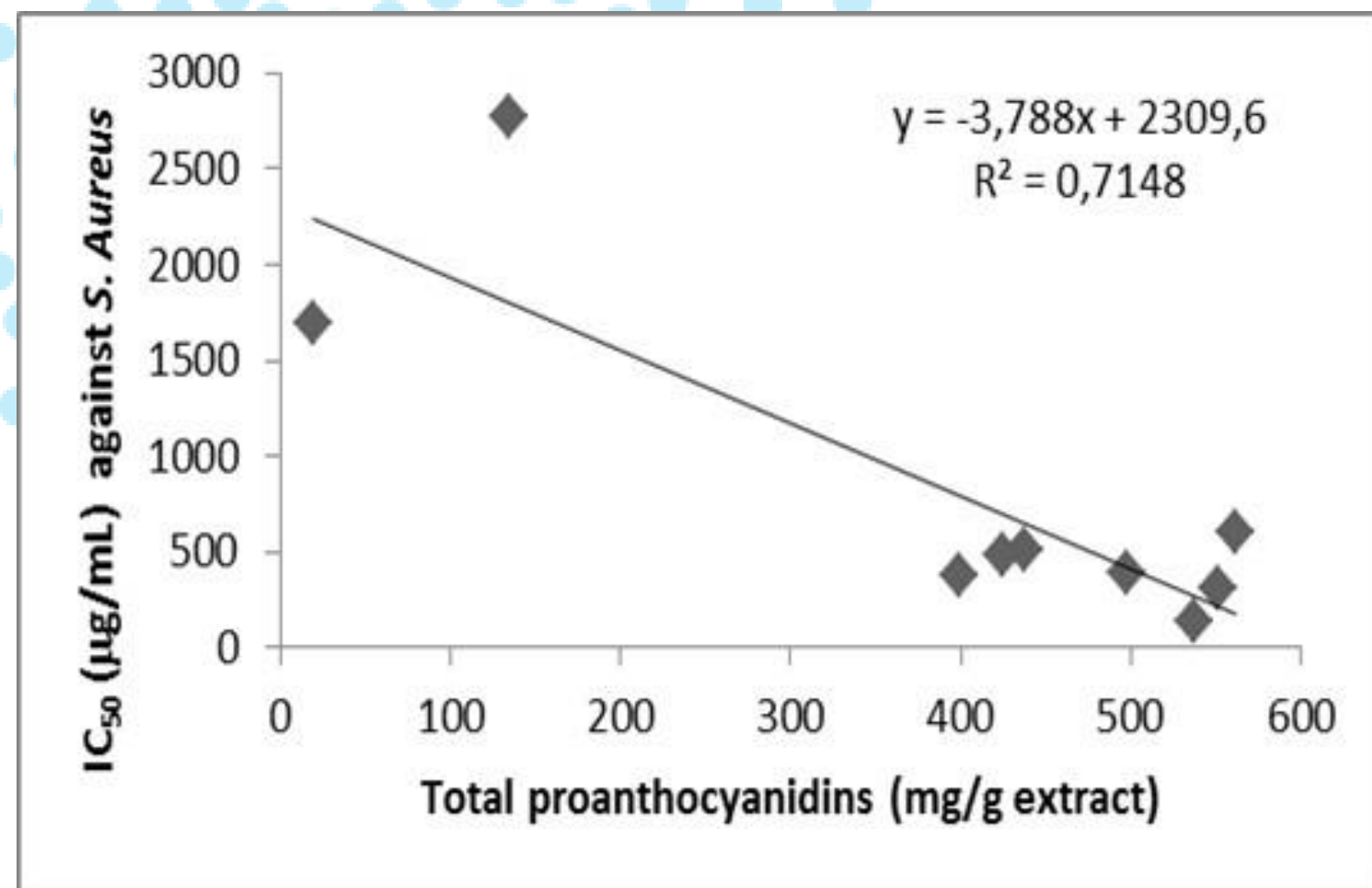
Intolerance glucose



Inflammation

10.5772/intechopen.84665

Respiratory infectious diseases



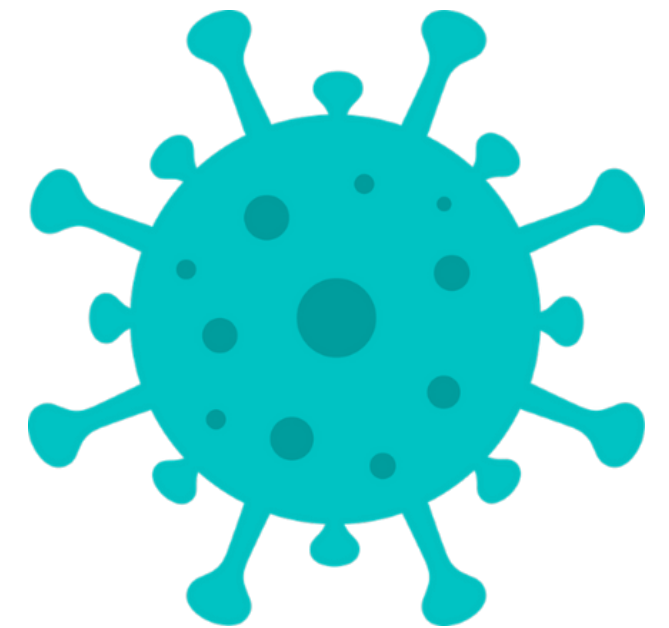
Uncaria tomentosa proanthocyanidins are also noted for their antimicrobial activity against respiratory pathogens, correlating, for example, with activity against *Staphylococcus aureus*.

Advances against COVID-19

- There is evidence that **hydroalcoholic extracts of Uncaria tomentosa** have an inhibitory effect on SARS-Cov2 infection.
- The study contemplates the biochemical effects of the extract on the function of cellular processes involved in infection and propagation within the organism.
- A double effect of *U. tomentosa* extract is proposed:

On the one hand it interacts with the important sites of viral proteins that bind to cellular receptors as shown by docking.

On the other hand, it predicts an important effect of proanthocyanidins in the inhibition of kinases specific to humans and involved in the virus life cycle as shown in the following page.



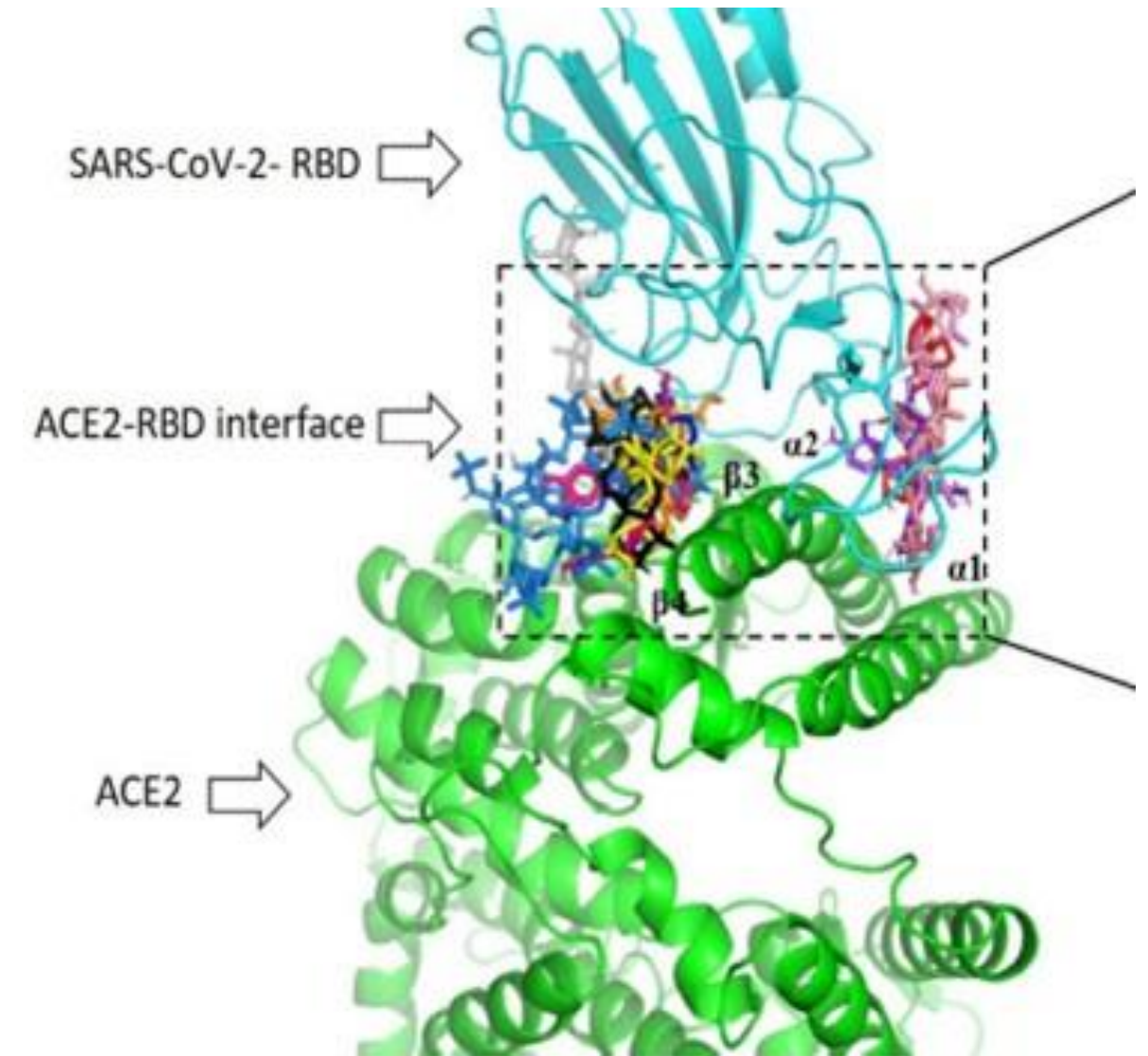
Nova Life components and potential effects against SARS-CoV-2 virus

Proanthocyanidins from *U. tomentosa* present in **Nova Life** show predicted binding affinity for the ACE2-RBD complex.

Likewise, procyanidins C1, B4, B2 have the highest binding rates to the SARS-Cov-2 crown glycoprotein in its open state.

Docking simulations demonstrate both the feasibility of the free binding energy predicted by the docking protocols and the stability of the protein ligand complex coupling.

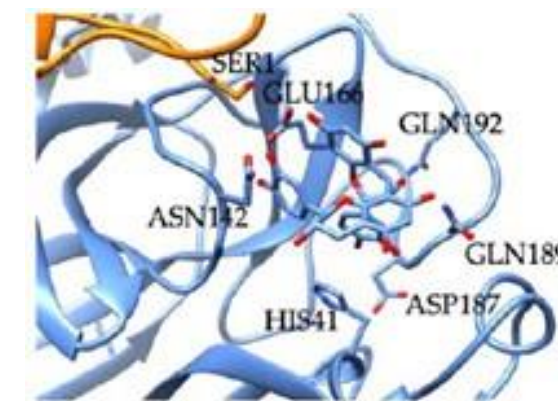
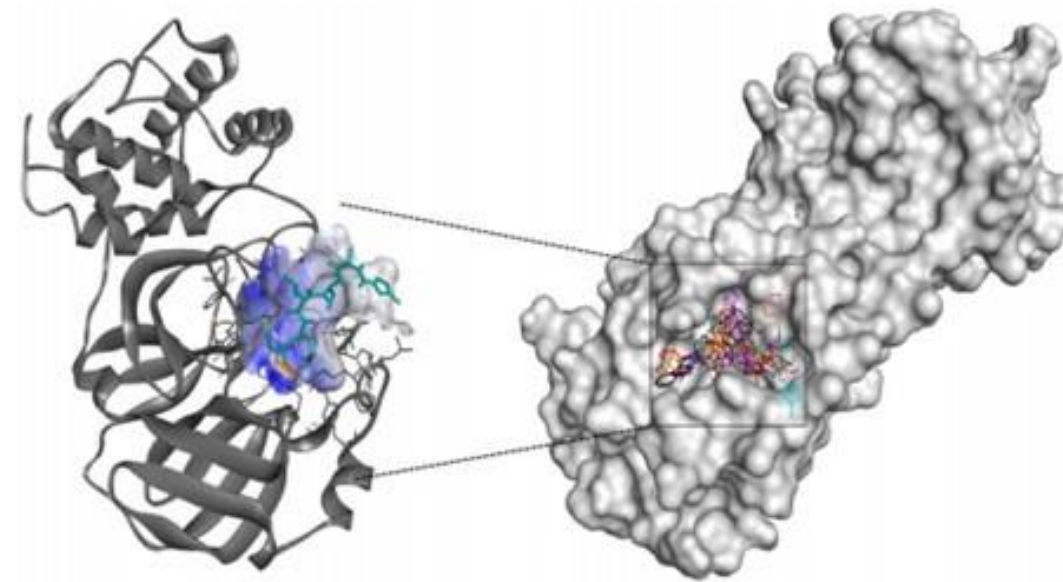
In other words, potential beneficial effects of **Nova Life's** proanthocyanidins against the SARS-COV-2 virus causing COVID-19 have been demonstrated.



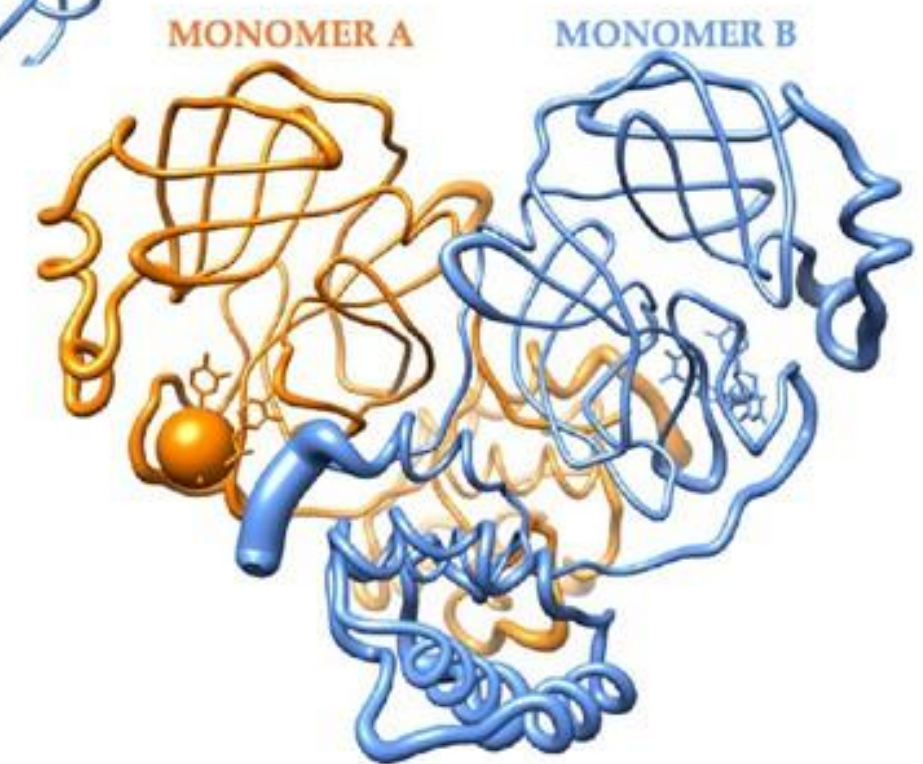
Superimposition of the best conformation of the active compounds against the ACE-2-RBD binding interface..

More **Nova Life** components and potential effects against SARS-CoV-2 virus

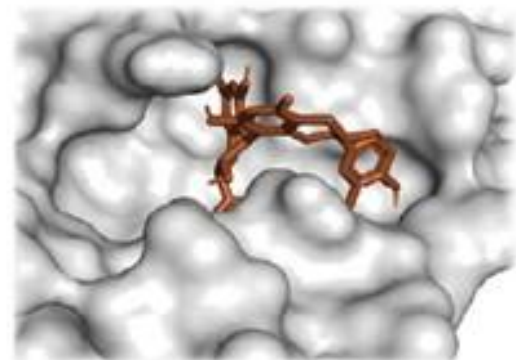
Superposition of the best conformation of the active compounds of *U. tomentosa*, including procyanidins and propelargonidins in the e3CL PRO.



SARS-CoV-2 3CL PRO anchor site with the most important interactions with Procyanidin B2.



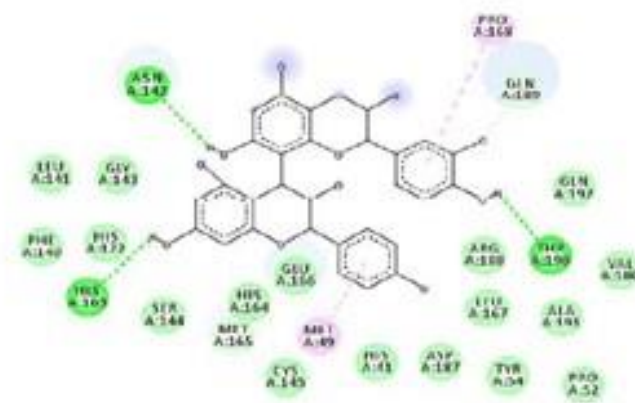
2D interactions of propelargonidines..



- | | |
|-------------------------|-------------------------------|
| van der Waals | Pi-Sulfur |
| Carbon Hydrogen Bond | Alkyl |
| Pi-Sigma | Pi-Alkyl |
| Unfavorable Donor-Donor | Conventional Hydrogen Bond |
| Pi-Pi T-shaped | Unfavorable Acceptor-Acceptor |

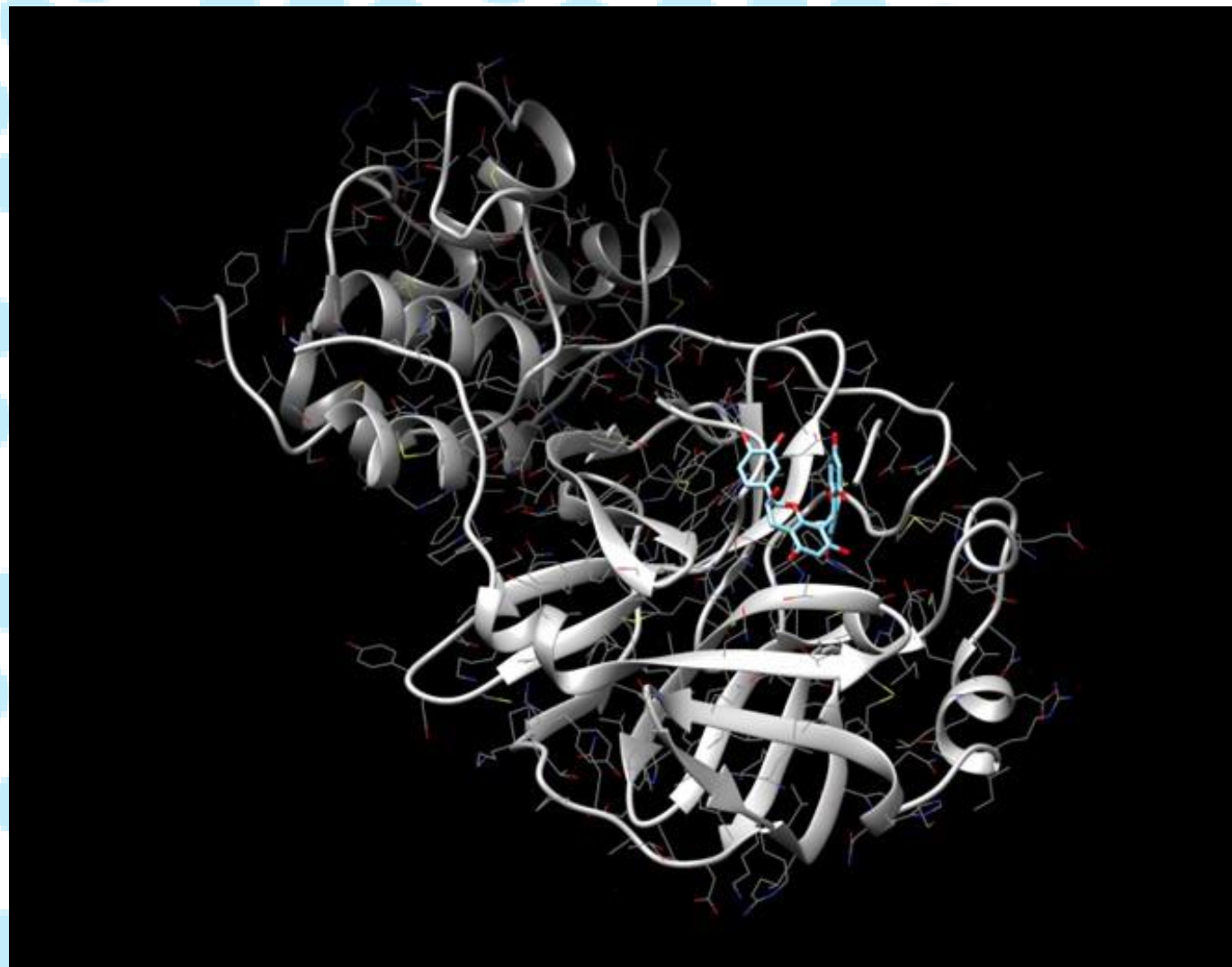
Epiafzelechin-4β-8-Epicatechin

→
ΔG -- - 8.9 Kcal.mol⁻¹





Nova Life components and potential effects against SARS-CoV-2 virus



Predicted coupling between **procyanidin B2** and viral protease **3CLPRO** suggests inhibitory effect (UCSF Chimera Software).

2021. Alvarado D., BIODISS.
Binding modes are scored using their FullFitness and clustered. Grosdidier
et. al., Proteins. 2007 Jun 1;67(4):1010-25.



Nova Life components and potential effects against SARS-CoV-2 virus



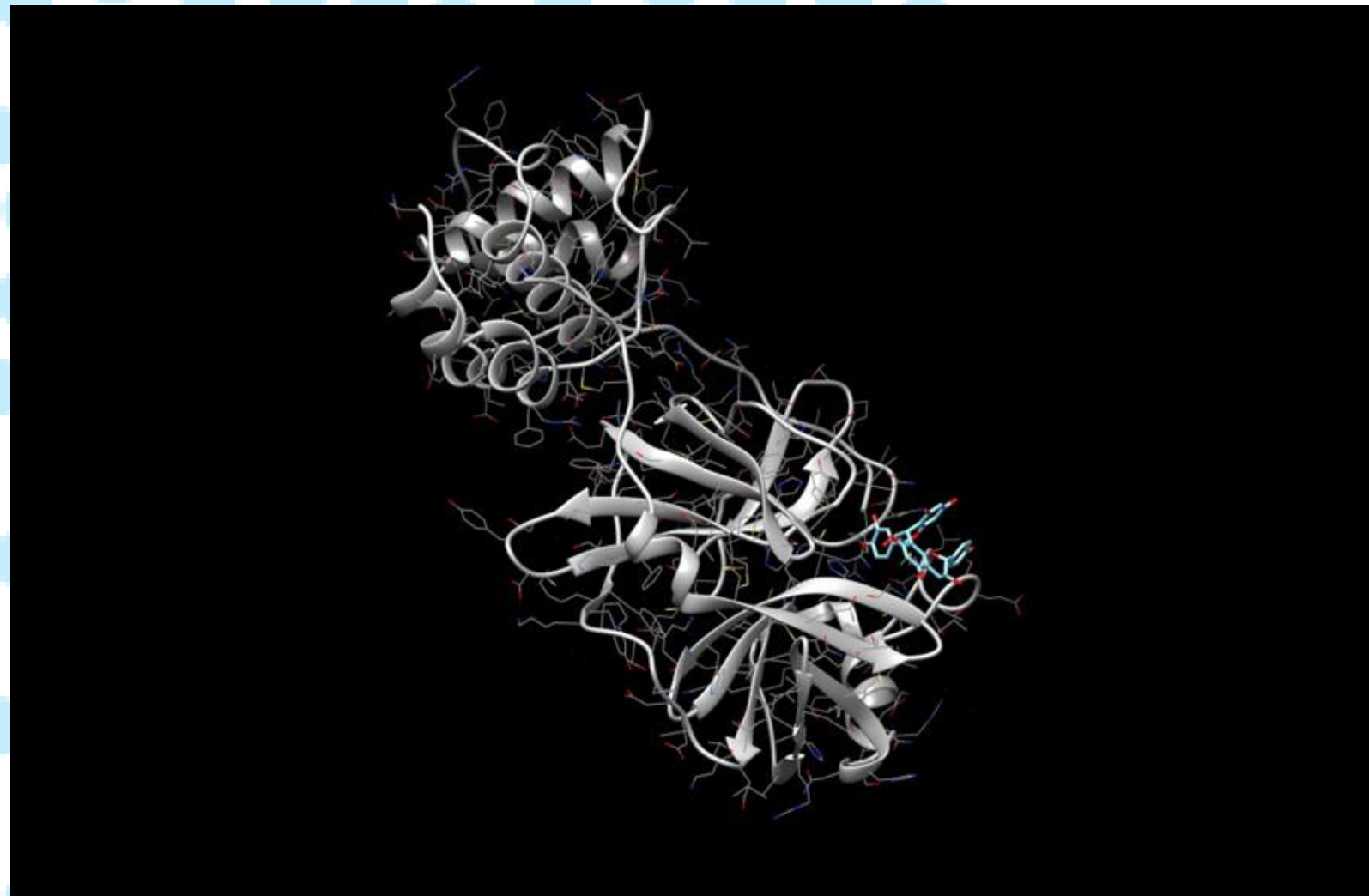
Predicted coupling between **procyanidin B4** and viral protease **3CLPRO** suggests inhibitory effect (UCSF Chimera Software).

2021. Alvarado, D.,
BIODESS

Binding modes are scored using their FullFitness and clustered. Grosdidier et. al., Proteins. 2007 Jun 1;67(4):1010-25.



Nova Life components and potential effects against SARS-CoV-2 virus



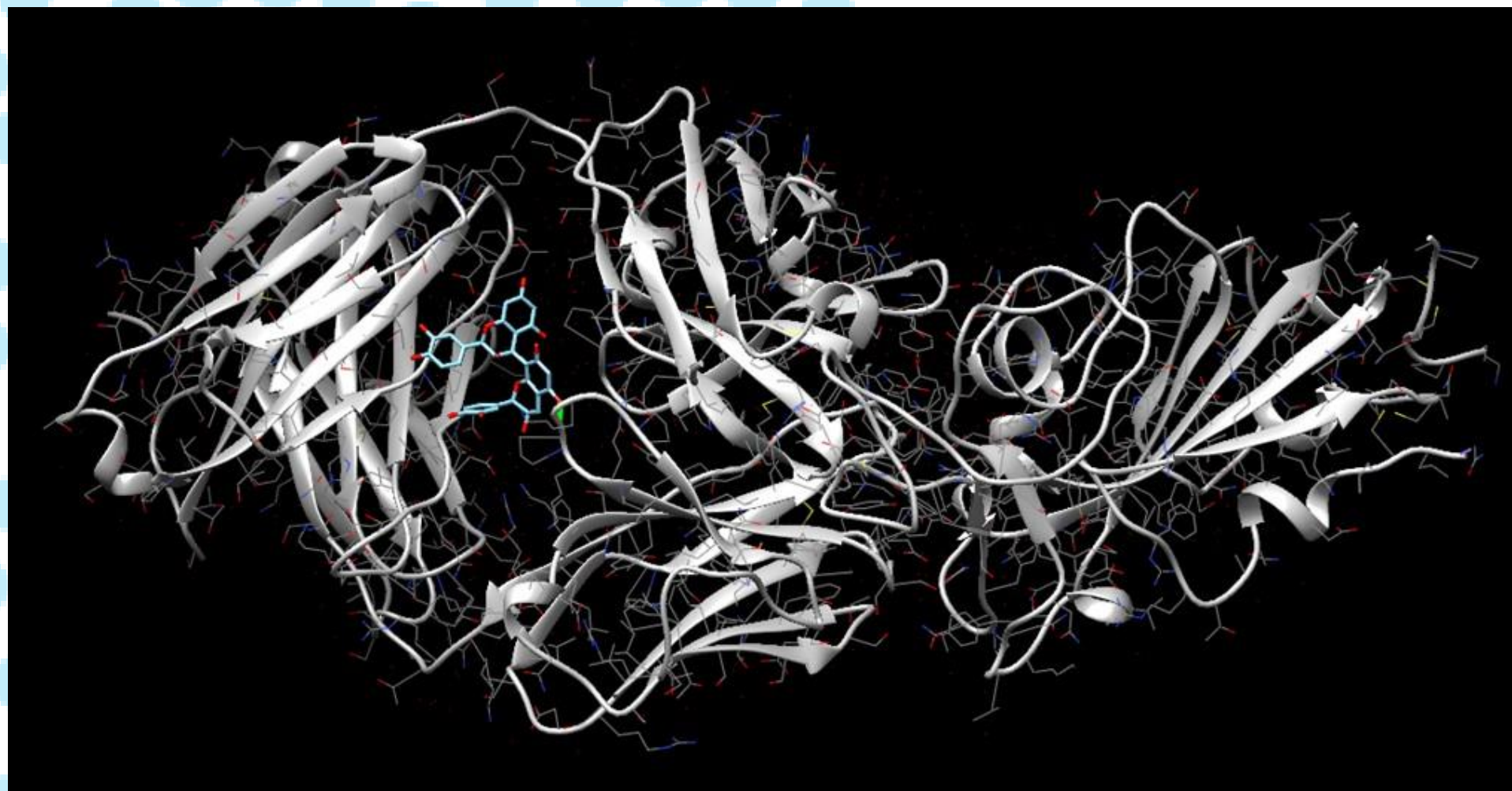
Prediction of coupling between **propelargonidine** and the viral protease **3CLPRO** suggests inhibitory effect (UCSF Chimera Software).).

2021. Alvarado, D.,
BIODESS.

Binding modes are scored using their FullFitness and clustered.
Grosdidier et. al., Proteins. 2007 Jun 1;67(4):1010-25.



Nova Life components and potential effects against SARS-CoV-2 virus



Molecular docking prediction for **procyanidin B2** and **SARS-Cov2-Spike Protein** (PBD).

2021. Alvarado, D.,
BIODESS.

Binding modes are scored using their FullFitness and clustered. Grosdidier et. al., Proteins. 2007 Jun 1;67(4):1010-25.

Nova Life components and potential action sites against SARS-CoV-2 virus



- | | |
|---|---|
| ● Inhibidores de MAP/ERK | ● Inhibidores ErbB |
| ● Inhibidores de CDK | ● Inhibidores de ABI |
| ● Inhibidores de NAK | ● Inhibidores de Src |
| | ● Inhibidores de PI3K/kt/mTOR |

Signaling of
proantiocyanidin sites of
action from **Nova Life**.

<https://doi.org/10.1371/journal.pone.0071071>
<https://doi.org/10.1371/journal.pone.0071071>
<https://doi.org/10.1177%2F153537020422900306>
<https://doi.org/10.1186/s12906-021-03225-1>
<https://doi.org/10.18632/oncotarget.24528>
<https://doi.org/10.1016/j.foodchem.2013.06.038>
 2021. Alvarado, D. BIODISS.
 Renderizado con Inkscape.

Aftermath of SARS-CoV-2 virus

Invasive aspergillosis in respiratory tract.

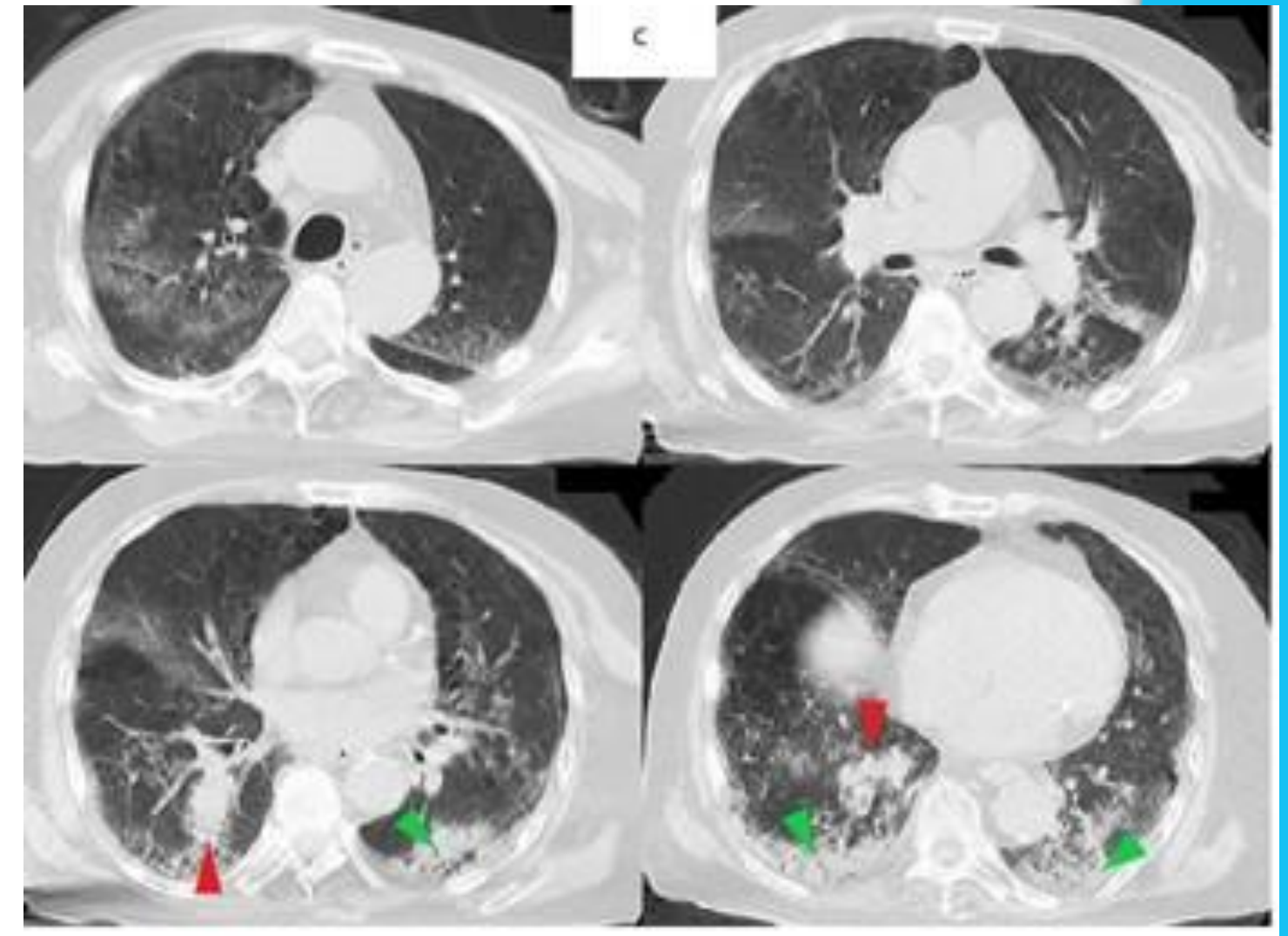
<https://dx.doi.org/10.1007%2Fs11046-020-00462-9>

Mucomycosis in patients after infection. Cases documented in 2020 including in Latin America.

<https://doi.org/10.36393/spmi.v33i4.568>

Use and abuse of glucocorticoids suppresses the immune system.

On the other hand, the proanthocyanidins in **Nova Life** are well known for their beneficial effect on the immune system. In addition, an inhibitory effect on respiratory pathogens has been demonstrated *in vitro*.



Progress towards the generation of **Nova Life**



Identification of bioactive molecules

In-vitro evidence

Intellectual property

Production

Availability

More than 100 international scientific citations of BIODISS and CSIC publications in relation to **Nova Life**

Protocols for identification, quantification and quality control.

Bioactivity tests confirm beneficial health results beyond the observations of traditional uses.

European patent for obtaining an extract enriched in proanthocyanidins.

Controlled cultivation of cat's claw, scaling up to obtain the extract and manufacturing under European quality standards.

Product ready for marketing and consumption.



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