

In the two models of liver disease;

- Chemical Hepatitis (Con A Model)
- Hepatic fibrosis (bile duct ligation model)
  - Liver function and morphology
  - Fatigue-behaviour Assessment Paradigms

A4+ improved liver enzymes in a widely used model of immune-mediated hepatitis.

A4+ improved sickness behaviour in bile duct ligated mice.

In anti-viral studies effects A4+L reduced the amount of Hepatitis C (HCV) RNA copies found in both supernatant and within the cell by over 80% at the highest tested concentration. Confirmed using Western blot using NS3 and protein detection.

The anti-oxidant activity of A4+ and its constituents were evaluated using an in vitro assay in which a stable free radical (1, 1-diphenyl-2-picrylhydrazyl, DPPH) was allowed to interact with the test substance. This showed that A4+ is a potent anti-oxidant, attributed to the Cordia and Annona components.

In additional studies a widely used test for assessing the anti-inflammatory actions of drugs is the “air pouch” model. Zymosan was used as the inflammatory agent and Indomethacin was used as a positive control. A4+ was shown to have significant anti-inflammatory effects on leucocyte infiltration and prostaglandin (PGE<sub>2</sub>) release. This effect was due mostly to the Corda Lutea with smaller contributing effects from the Annona in A4+.

The major limitation to the use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of disorders such as arthritis is ulceration in the gastrointestinal tract. At this time there is

a substantial clinical need for agents that can reduce the ulcerogenic effects of NSAIDs.

A4+ was tested on Male Wister rats given indomethacin orally. It was found that A4+ reduced the indomethacin-induced gastric damage when given four hours prior to Zymosan.

Overall A4+:

- Is safe and passed all toxicity tests
- Contains a variety of known beneficial chemicals as well as many uncharacterized ones
- Exhibits anti-viral, anti-oxidant and anti-inflammatory properties
- Protects against stomach ulceration
- Protects the liver from Hepatitis
- Shows beneficial effects on behaviour in animals sick with liver disease

For further information or to order please go to our website:

[www.sabell.ca](http://www.sabell.ca)



**A4+** is a nutraceutical approved by Health Canada “to alleviate symptoms of liver disease, promote liver healing and maintain liver health.”

In testing A4+ has been shown to have anti-viral, anti-oxidant properties, and to be an anti-inflammatory. In additional testing it has also been shown to protect the liver from Hepatitis and the stomach from ulcers.

Harvested at the Isula Biological Preserve and Research station in Peru under ethnobotanical research practices from the Amazon rain forest.

A4+ is produced by the Isula Biological Preserve and Research Station located in Peru that is a conservation, retreat, and conference centre. Isula conducts ethnobotanical research, the testing and marketing of herbal medicines such as A4+, a liver tonic and treatment for chronic hepatitis and is developing products for malaria, asthma, and more.

A4+ was developed by Dr. José Cabanillas (Executive Vice President, Research & Development). Born in Lima, Peru, is a medical doctor with strong familial roots in healing. His philosophy is one of the integration of natural medicine with modern scientific medicine that takes the patient's whole being into account.

Dr. Cabanillas learned traditional healing methods from his parents and then continued his formal medical education. He completed his undergraduate studies at the Colegio Union Incaica in Lima along with his medical internship, obtaining his M.D. degree at the University of Xochicalco Baja California in Mexico.

Since graduating Dr. Cabanillas has continued his medical practice with patients in Peru as well as internationally. Along with his practice he continues his ethnobotanical research in Peru, acts as the medical advisor and consultant to Sabell Corporation and is an internationally recognized speaker on topics such as rain forest conservation, health and nutrition, and rain forest pharmaceuticals.

*"For every gift we receive, thanks must be made. When you have been given the opportunity to learn from nature, some payment is expected. For me that payment is medicine."*

*Dr. José Cabanillas*

A4+ is composed of all natural ingredients found in the Amazon basin and coastal region of Peru.

Each contains:

*Cordia lutea* (flower-80%)

- Curcumin
- Tumerone
- Furanodiene
- Curzerene



*Annona muricata* (leaf-10%)

- Flavanol glycosides
- Quercetin
- Rutin



*Curcuma longa* (rhizome-10%)

- Rutin
- Kaemferol
- Acetogenins
- Other complex components



Acetogenins have the following properties:

- Anti-cancer
- Insecticidal
- Anti-bacterial
- Immunosuppressive
- Mitochondrial complex inhibition
- At high concentrations; cytotoxic and neurotoxic

In order to meet Health Canada requirements testing included:

- Studies for toxicity and chemistry
- 7 and 28 day repeated dose tests
- Mutagenicity (Ames test)
- Genotoxicity (Micronucleus test)
- Analytical chemistry (high performance liquid chromatography, HPLC and electrospray mass spectrometry)

To be approved by Health Canada as a nutraceutical requirements for approval included:

- Critical review of the plants, including their therapeutic uses and toxicity
- Botanical verification of the plants, processing, and storage.
- Review for interactions with other drugs/neutraceuticals
- Chemical analysis and purity from batch to batch
- Testing of the nutraceutical and its constituents for toxicity
- Testing of the nutraceutical and its constituents for efficacy (animals and human data)
- Testing for stability
- Packaging
- Reporting of adverse effects

Testing concluded that for toxicity that a no adverse effect does level (NOAEL) of 2000 mg/kg was assigned for toxicity, including; genotoxicity, bone marrow toxicity, neurotoxicity and cardiac toxicity.

On conclusion of testing a product license application (PLA) was submitted to Natural Health Products Directorate - Health Canada which included:

- A non-traditional use claim
- Safety and efficacy information to satisfy the evidentiary requirements for such a claim
- The application was approved July 3, 2012, NPN # 80033347.

A4+ has been approved by Health Canada to be marketed as a nutraceutical "to alleviate the symptoms of liver disease, promote liver healing, and maintain liver health."