Toxicology, Pharmacology and Clinical Reports of a Peruvian Herbal Formulation (A4+) for Treating Liver Disease

José Cabanillas[1], Francis H.Y. Green[2], Hugh A. Semple[3], B. Duff Sloley, Grishma Shrestha[2], Steven K.H. Aung[4]

[1]Sabell Corporation; [2] Snyder Institute for Chronic Diseases; University of Calgary; [3]403 Stone Place; [4] University of Alberta Faculty of Medicine and Dentistry

What is A4+?

A4+ is composed of extracts from three plants:

- **Ratio of 80:10:10**
- **Distinct chemical fingerprints** →
- **Peruvian origin**
- **Patent protected**

Curcuma longa:

Curcumin, Tumerone, Furanodiene, Curzerene

Cordia Lutea:

Flavanol glycosides, Quercetin, Rutin

Annona Muricata:

Kaemferol, Acetogenins

Clinical reports

Clinical studies of A4+ in Chronic Hepatitis C:

A pilot study of 6 patients given 20 grams a day of A4+ for 4 weeks showed:

- **Improvement in anorexia, fatigue, nausea and depression**
- **No changes in biochemical markers or HCV RNA titers**

Further study of 10 patients treated with A4+ for 4 weeks:

- **Improvement in quality of life and symptom scores (Figures 1 and 2)**
- **Significant increase in prothrombin and serum cholinesterase levels**
- **No change in serum bilirubin, AST, ALT, albumin, or echo-texture of the liver**

Indications

- **A4+ was approved by the Natural Health Product Directorate of Health Canada (license NPN 80033347) in July 2012 as a hepato-protectant**
- **Potential uses include:**
  - **Alleviate liver disease-associated sickness behaviors such as fatigue, malaise, low-mood and nausea**
  - **Dyspepsia and indigestion**
  - **May be beneficial in NASH, hepatitis, cirrhosis and immune deficiencies**
  - **Adjunct to other treatments for liver disease**
  - **Ameliorate symptoms associated with liver and GI toxins, for example alcohol and chemotherapy**

Acknowledgements

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Toxicology

A4+ had a no observed adverse effect level (NOAEL) of 2000 mg/kg.

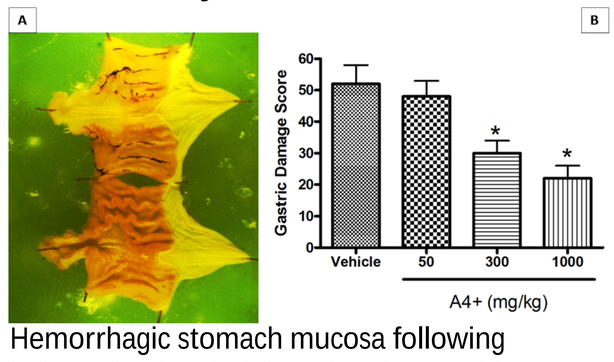
It showed no evidence of toxicity in:

- **A 28-day repeated-dose test (125 mg/kg -2000mg/kg)**
- **A micronucleus study for cytotoxicity and genotoxicity**

Efficacy data

Animal and in vitro tests have shown efficacy for:

- **Anti-inflammatory activity**
- **Anti-oxidant activity**
- **Anti-viral activity against Hepatitis C**
- **Improving sickness behaviour in a model of chronic liver disease**
- **Gastric Mucosal Protection in NSAID induced ulceration**



Hemorrhagic stomach mucosa following indomethacin administration, in a positive control animal. (B) Mucosal ulceration score of rats treated orally with A4+ at doses of 50, 300 or 1000 mg/kg 4 hours prior to indomethacin. There were significant reductions in hemorrhage at doses above 300 mg/kg. *p<0.05 versus the vehicle-treated group.

Clinical reports

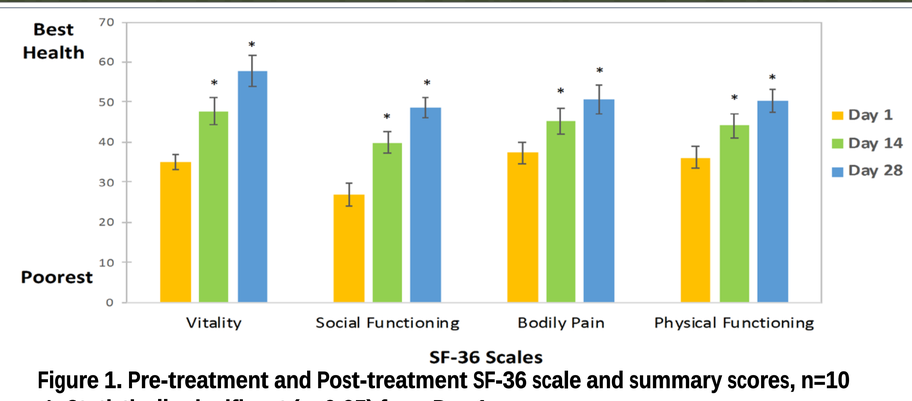


Figure 1. Pre-treatment and Post-treatment SF-36 scale and summary scores, n=10
***=Statistically significant (p<0.05) from Day 1**

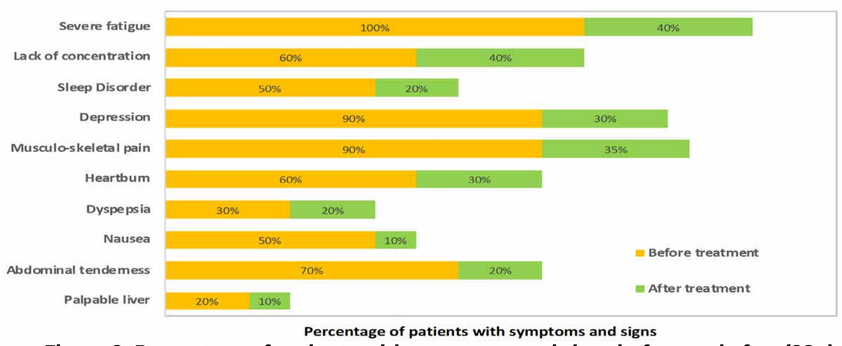


Figure 2. Percentage of patients with symptoms and signs before and after (28 days) treatment with A4+, n=10

Summary and Conclusions

Preclinical Studies	Clinical Studies
Potent anti-inflammatory/oxidant activity	Improvements in all indices of quality of life
Protection against immune mediated hepatitis	Improvement in symptoms and signs of chronic liver disease
Improved sickness behaviour in a model of chronic liver disease	Some improvements in liver function tests
Anti-viral activity against Hepatitis C	No reduction of HCV RNA titers in preliminary clinical studies
Protected rat gastric mucosa from the ulcerogenic effects of NSAIDs	Positive results in individual patients with various liver disorders

References

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