

## Non-clinical and Clinical Evaluation of *Alternanthera sessilis* for Haemoglobin Augmentation in Anaemia

Philippines

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**Duration:** 2008-2010

**Total cost:** USD 11,000

## Summary

The major health consequences of iron deficiency anaemia (IDA) include poor pregnancy outcomes, impaired physical and cognitive development, increased risk of morbidity in children and 20% of maternal deaths. This condition also diminishes the work capacity of individuals and entire populations, leading to serious economic problems and obstacles to national development. Early treatment of this disease is necessary to restore personal health and raise national productivity levels by as much as 20% (World Health Organization, 2012). In serious cases of anaemia, blood transfusion is recommended to save the life of the patient.

Previous studies have shown that *Alternanthera sessilis* has the potential to be an alternative treatment for iron deficiency anaemia based on the results of a Phase 1 Clinical Trial (Arollado, 2010). Analysis revealed the presence of iron and vitamins A, C, B1 and B6. Its safety was confirmed since heavy metals were not detected. Further evaluation of the plant extract, when administered to the subjects in the clinical trial, revealed that there were no side

effects experienced from the formulation. This is especially significant since commercial iron preparations are often associated with unwanted effects such as gastrointestinal upsets, nausea and vomiting. In addition, biochemical parameters such as liver profile, creatinine and complete blood count of the volunteers in the Phase 1 trial appeared normal.

Since the plant is a common edible weed that grows in Philippine farmlands throughout the year, it is a convenient and readily available natural source. Propagation of the weed for the eventual commercial production of the drug requires low cost and low maintenance. This thus translates to a natural treatment which is less expensive than commercial drugs.

Based on our studies, propagation of this plant has to be initiated to provide enough material for the formulation to be used for further investigation and production. Due to its potential value as a drug, there is a need to collaborate with other agencies to commercialize and market this product.

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## Background and Justification

In 2008, the World Health Organization (WHO) reported iron deficiency as the most common and widespread nutritional disorder in the world, affecting 30% of the world's population, specifically children and women in developing countries. It is also the only nutrient deficiency that is significantly prevalent in industrialized countries. The prevalence of anaemia in the Philippines is about 19.5% based on a survey of the Food and Nutrition Research Institute of the Philippines in 2008.

Herbal medicines have now been recognized as natural alternative drugs for synthetic medicines because they are often cheaper and safer than the latter. *Alternanthera sessilis* (L.) R.Br. (Family Amaranthaceae) also known as sessile joyweed or dwarf copperleaf is a common edible weed that grows widely in Philippine farmlands (Fig. 1). Earlier investigations showed that 100 g of this weed contain minerals such as iron (1.84 mg), magnesium (314 mg), calcium (299 mg), copper (0.89 mg), zinc (2.05 mg), sodium (168 mg) and potassium (620 mg). Based on this, it could be a potential source of iron for those suffering from iron deficiency anaemia (IDA).

The aims of the project were to:

- Provide scientific proof that *A. sessilis* is a potential drug for effective haemoglobin augmentation in the clinical setting; and
- Provide a cheaper alternative treatment for patients suffering from IDA.

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## Description



Figure 1: *Alternanthera sessilis* (L.) R. Brown, a common weed in the Philippines, is being investigated as a treatment for anaemia.

The steps taken during the investigation and implementation process are outlined in Fig. 2.

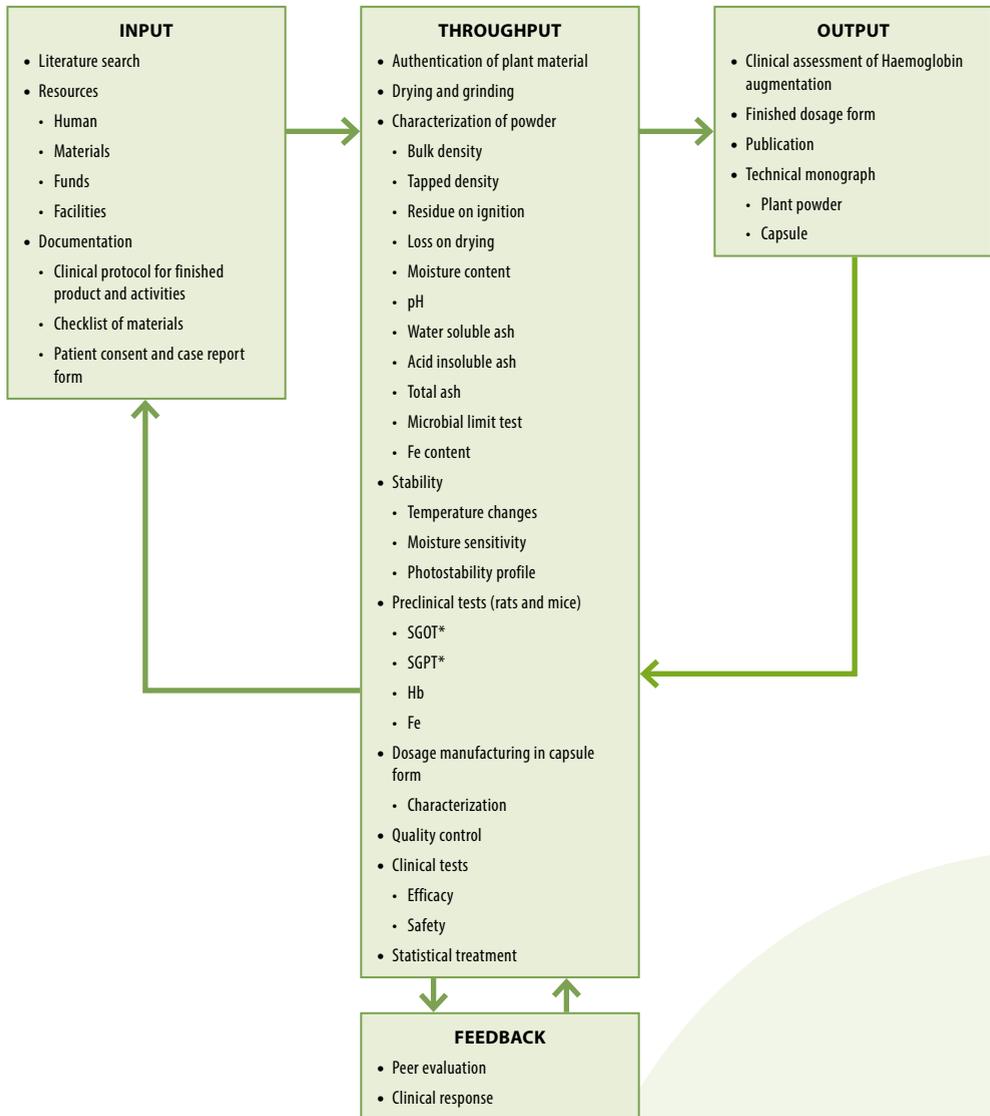


Figure 2: Conceptual framework for the research.

\*SGOT = Serum glutamic oxaloacetic transaminase and SGPT = serum glutamic-pyruvic transaminase, both of which are liver enzymes.

Samples of *A. sessilis* were collected from the island of Panay, often being bought at local markets during the main growing season. These were dried and powdered and subjected to various tests of their physico-chemical properties (Table 1) and to determine their iron content (Table 2). Results were consistent between samples and the powder shown to be stable over several months, allowing the project to move to preclinical studies.

## Results

Preclinical trials tested levels of *A. sessilis* administration to rats and mice at 100% of the dose of the standard drug (ferrous sulphate) as well as at 80, 60 and 40%. Their effects on levels of iron and haemoglobin, as well as targeted liver enzymes were all positive with no adverse effects detected.

Tests	Trial		
	First	Second	Average
Bulk density	0.3333 g/mL	0.3448 g/mL	0.3391 g/mL
Tapped density	0.4167 g/mL	0.4237 g/mL	0.4202 g/mL
Residue on ignition	0.3168%	0.3161%	0.3164%
Loss on drying	7.40%	7.43%	7.415 %
Moisture content	7.765%	6.62%	7.192%
pH	6.56	6.56	6.56
Water soluble ash	4.22%	3.59%	3.905%
Acid insoluble ash	5.425%	3.95%	4.685%
Total ash	20.11%	20.13%	20.125%

**Table 1:** Physico-chemical characteristics of powdered *A. sessilis*.

Trial	Parts per million (ppm)
1	52.15
2	51.59
3	50.57
Average	51.43

**Table 2:** Assay of powdered *A. sessilis* for iron content.

We then proceeded to the trials with human subjects. Firstly, powdered *A. sessilis* was prepared in standardised 'Lupo' capsules (Table 3) with an average iron content of 0.024mg/capsule.

SUMMARY OF EVALUATION			
Criteria	Specifications	Result	Remarks
Average weight	500 mg	465.035 mg	93.007% of target
Range	450-500 mg (+ 10% of label claim)	451.2 mg - 501.7mg	96.70 – 107.88% of average weight
Standard deviation	To be established	11.404	-
% relative standard deviation (calculated to assess the manufacturing precision)	2% maximum	2.45%	Slightly above limit (Usual for small lots)
Average iron content	Average weight x % Fe	0.024 mg/ capsule	Clinical trial : dose three times a day 3 capsules ≈ 0.072 mg 6 capsules ≈ 0.144 mg

Table 3: Summary evaluation of Lupo capsules.

Criteria	Specifications (Normal values)	Change (0 → 90 days)	Statistical Evaluation
Haemoglobin (Hgb)	12-14 g/dL (F) 14-16 g/dL (M)	↑ Increase	Significant F=13.300, p=0.000
Haematocrit (Hct)	41-50% (whole blood)	↑ Increase	Significant F=12.370, p=0.000
Red blood cells (RBC)	3.9 -5.5 x 10 <sup>6</sup> /μL	↑ Increase	Significant F=0.431, p=0.007
Mean corpuscular volume (MCV)	80-100 femtolitres/ cell	↔ Change	Not Significant
Mean corpuscular haemoglobin (MCH)	27-32 picogrammess/ cell or 1,68 - 1.92 femtomol/cell (SI-units)	↔ Change	Not Significant
Mean corpuscular haemoglobin conc. (MCHC)	25 g/dL	↔ Change	Not Significant
Blood iron concentration (serum ferritin)	15-200 ng/mL (F) 30-300 ng/mL (M)	↑ Increase	Significant F=13.158, p=0.000

Table 4: Effect of *A. sessilis* capsules on blood characteristics after 90 days.

Phase 1 clinical trials compared two groups, each consisting of 15 volunteer patients aged 18-65 years. Blood characteristics were monitored during the trial. Results after 90 days showed significant positive effects upon haemoglobin, haemocrit, numbers of red blood cells and levels of iron in the blood (Table 4).

Although the amount of iron present in one capsule is low compared to the recommended daily intake (0.024 mg compared to 15-30 mg), an increase in haemoglobin was still observed. This could be due to synergistic effects of other compounds present in the *A. sessilis*.

In addition no adverse effects were detected during a series of tests on liver and kidney function demonstrating the safety of the product.

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## Partnerships

There were no regional or international collaborators in this project. The community that sold this vegetable in the market participated in this project by providing required raw materials for payment. Since the raw materials are seasonal, cultivation of this plant is needed to sustain the required volume of samples for the project

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## Impact

This project won second prize in the National Research Council of the Philippines during a poster contest in 2009. After the project was finished, many patients with leukaemia, low platelet count, high white blood cell counts and liver disease have been using of this product continuously. Laboratory tests have confirmed the drug's positive effects.

Farmers growing this plant will be encouraged to cultivate more of it due to high existing demand for the raw material.

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## Lessons Learned

The project has great potential as it answers a basic community need. This said, as it relied upon procuring the raw plant material from the market there were times when access to materials was limited, hence the need to promote cultivation of the plant.

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## Future Plans

The plan is to study the mechanism of action of this product and continue the clinical trial with the ultimate aim of formulating *A. sessilis* extract as a commercial drug.

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## Publications

- Atienza, A.A., Arollado, E.C., Manalo, R.A.M., Tomagan. L.B. and Dela Torre G.L.T. (2016). Antioxidant Activity and Minimum Inhibitory Concentration of the Crude Methanolic Extract of *Caesalpinia pulcherrima* (L.) Swartz. *Der Pharma Chemica*, 8(17):99-104 (<http://derpharmachemica.com/archive.html>).
- Arollado E.C., Peña I.G., Dahilig V.R. (2013). Platelet Augmentation Activity of Selected Philippine Plants. *International Journal of Pharmaceutical and Phytopharmacological Research (eIJPPR)*, Res. 2013; 3 (2): 121-123.
- Arollado E.C., Peña I.G., Dahilig V.R.. (2012) Effects of *Alternanthera sessilis* (L.) R.Br. EX. DC., *Syzygium cumini* (L.) Skeels and *Averrhoa bilimbi* L. on some biochemical parameters in Alloxan-induced Diabetic mice. *Internationale Pharmaceutica Scientia*, July September 2012, Vol. 2, Issue 3.
- Arollado, E.C. (2011). Risk Evaluation of *Alternanthera sessilis* (L.) R.Br.(Family Amaranthaceae). *The UPManila Journal*, Vol 14, Issue July-Dec., 2011.
- Arollado, E.C. (2010). Safety and Hematinic Evaluation of *Alternanthera sessilis* in Animal Models. Abstracts of the 2010 FAPA Congress, Taipei, Taiwan.
- Arollado, E.C. (2010). Haemoglobin Augmentation of *Alternanthera sessilis* (L.) R.Br. in Iron Deficiency Anaemia (IDA). Abstracts of the 11th APRU Doctoral Student Conference 2010, July 12-18, 2010, Universitas Indonesia.