THE ETHNOMEDICAL USE OF BLACK DRINK TO TREAT IRON DEFICIENCY ANEMIA IN BASTIMENTOS, PANAMA

by

CASSANDRA NELSON DOOLEY

(Under the Direction of Diane K. Hartle)

ABSTRACT

Iron deficiency anemia (IDA) is the most common nutritional deficiency in the world and intestinal parasites are estimated to be responsible for 30-57% of IDA cases (Yip 2001; Stoltzfus 1997). With an iron-poor diet and the high incidence of blood-sucking helminthes, the people in Bastimentos, Panama struggle with IDA. Black Drink is the ethnopharmacological answer to these pathologies. It is prepared with juice from *Citrus aurantifolia*, a cast iron vessel, and three biologically active plants, *Stachytarpheta jamaicensis*, *Hyptis suaveolens*, and *Senna spp*. The iron content and the pharmacognosy of the plants used to prepare Black Drink are investigated here. Analysis of Black Drink revealed an iron content of 2.5% indicating a dose of iron comparable to that prescribed by U.S. physicians for IDA. In Bastimentos, Panama, Black Drink is an effective, affordable, two-prong strategy for the treatment of IDA, intestinal parasite burdens, and is congruent with the popular therapeutic traditions.

INDEX WORDS: Panama, Black Drink, iron deficiency anemia, intestinal parasites, hookworm, *Stachytarpheta jamaicensis, Hyptis suaveolens, Senna spp., Citrus aurantifolia*

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DEDICATION

I dedicate this work to my Panamanian grandmother. I learned that it is possible to be a true wise woman without ever attending school, learning to read, or write. This work is in honor of her abilities as a healer and a botanist.

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I want to acknowledge my mentors from the ICBG-Maya, who gave me my first opportunity to work in the field of ethnobotany, medicinal plants, and drug discovery: Dr. Dave Puett, Dr. Elois Ann Berlin, and Dr. Brent Berlin. Next, I thank Fulbright for the chance to independently create an ethnobotanical study in Bocas del Toro, Panama. The Nutraceutical Laboratories, my major professor, Dr. Diane Hartle, and Dr. Greenspan welcomed me warmly, challenged me in the field of pharmacology, and shared enthusiasm for natural products and countless laughs with me. Finally, my friends and family provided the reassurance and emotional support to persist when I questioned my own abilities. I am deeply grateful to all of these people for their contributions to my success.

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CHAPTER 1

INTRODUCTION

Fulbright Fellowship in Panama

The author was awarded a Fulbright scholarship to study Ethnobotany in Bocas del Toro, Panama from November 2002- August 2003. Bastimentos is an Afro-Caribbean community and Salt Creek is an indigenous Ngawbe group with their own language. Three hundred botanical specimens were collected and identified at the Autonomous University of Chiriqui (UNACHI), and were deposited at the herbariums at UNACHI, University of Panama, and The University of Georgia. International partners are Botanists, Ana Karina Gomez and Dr. Rincon, Anthropologist, Luz Graciella Joly, Sociologist, Isabel Alvendas, and from the Pharmacognostic Center for the Investigation of Panamanian Flora (CIFLORPAN), University of Panama, Pablo Solis and Mahubir Gupta. Panama's Ministry of Health was also in collaboration, Nurse Jorge Chance, Nurse Brown at the Bocas del Toro Hospital.

Introduction to Black Drink

During a field class in ethnobotany and tropical ecology at the Institute for Tropical Ecology and Conservation, the author first visited Bocas del Toro, Panama in 1999. It was during this visit that Black Drink was first seen for sale in Bastimentos. The preparation was made with lime juice and a cast iron pot, with some "bush medicine" included. Black Drink, a "blood builder" was publicly recognized as an effective medicine for "Low Blood". Black Drink and "Low Blood" peeked the author's curiosity.

What is Ethnopharmacology?

Ethnopharmacology is the observation and experimental investigation of the biological activities of plant, animal, fungi, micro-organisms, and mineral substances used in the traditional medicine of past and present cultures. Other important issues in the field of ethnopharmacology, that were addressed in the execution of the field study, are preservation of local knowledge, promotion of indigenous medical systems and primary health care, intellectual property rights, and conservation of biodiversity (www.elsevier.com). In this discussion, the author explores the pharmacognosy of the plant components and the iron content of Black Drink.

Ethnomedicine in Bastimentos

In addition to the biological activity of Black Drink, this study explains the condition for which Black Drink is used, "Low Blood." Beliefs about health, particularly the desire to have blood in equilibrium, and its various qualifiers, can be found in many countries including Africa, Panama, United States, Jamaica, and Haiti. Based on this trail of ethnomedical beliefs, Black Drink represents Afro-centric ethnomedical systems and even contains plant species which are endemic to that continent. Black Drink is evidence of African cultural integrity which withstood tests of time, distance, and separation from family and country.

Iron Deficiency Anemia and Intestinal Parasites

Iron deficiency anemia (IDA) is the most common nutritional deficiency in the U.S. and the world (Yip 2001). It results from high iron needs or high iron loss. Iron deficiency anemia and intestinal parasites are two disease etiologies whose geographic distributions overlap. One reason is because hookworms, *Ascaris*, and *Trichuris*, are

endemic to the same regions and cause extensive blood loss. Infection with 100 or more worms costs the host 2.5 liters blood/year and can send an at-risk person rapidly into a state of iron deficiency anemia (Marquardt 2000). In the interest of understanding how these etiologies are synergistic, the author will discuss iron deficiency, next the intestinal parasites associated with IDA and their life cycles, and finally the relationship between the two.

Hypothesis

Black Drink, prepared in Bastimentos, Panama, is an effective ethnomedical remedy for iron deficiency anemia.

Black Drink is prepared in Bastimentos to treat anemia, or "Low Blood." The present study evaluates and validates the therapeutic value of Black Drink through iron content analysis and literature reviews of the herbal ingredients. Based on the presence and dose of elemental iron, it appears that Black Drink is an effective remedy for iron deficiency anemia. Additionally, studies on the various plant components show broad spectrum bioactivity, and even anthelminthic activity. Black Drink, an accessible, affordable, popular therapy, is validated and in accordance with tradition.

CHAPTER 2

BACKGROUND

Geography of the Area

Isla Colon and Isla Bastimentos are included in the territory of the Bocas del Toro Province on the northwestern side of Panama (Figures 2.1 and 2.2). The population of the country in 2002 was 2,942,000 people (www.paho.org). Panama is divided into provinces; each is roughly equivalent to a U.S. state. Bocas del Toro, on Isla Colon, has a population of 2,006 (over 18 years old) and 683 houses (National Census 2000). The culture is a mix of Indians, Latinos, and Afro-Caribbean people. European and American immigrants also comprise a small group called, "local foreigners." This town was virtually created by United Fruit Company.

Bastimentos village is one of many communities on the nearby island of Bastimentos (Figure 2.3). It is unique from Bocas del Toro because it has a nearly homogenous population of African descent. There are also Ngawbe Indians and Latino, or mestizo people. The dominant culture is Afro-Antillean, with customs and traditions retained from the British West Indies. Almost everyone in Bastimentos speaks "Gwaris-Gwaris," a Patois-like Jamaican English. Their second language is Spanish. A few people speak Ngawbere, the Indian language. The people live off the marine resources, tourism, and some have jobs outside of the village in Bocas del Toro, Changuinola, or Almirante (Figure 2.2).



Figure 2.1. Map of Panama delineating provinces. Note Bocas del Toro, Almirante, and Colon.



Figure 2.2. Bocas del Toro Archipelago.



Figure 2.3. Bastimentos Island. Note Juan Brown Point, which is Bastimentos village.

Another important city, which will be referred to in this study, is Colon, Panama (Figure 2.1). It is the port city on the Caribbean side of the Panama Canal, only hours away from Bocas del Toro. The ethnic make up of Colon and its surrounding towns is very similar to Bocas del Toro. Similarities exist in the traditional medicine practiced in Colon and this has been briefly explored by Linnea Angermuller in her article, "Bush Teas and Folk Remedies Used by the West Indian Populations of Colon, Republic of Panama." This appears to be the only study published on Afro-Antillean traditional medicine in Panama.

The people of Bastimentos migrated to the island in the last 150-200 years. Local legend says that the island was named Bastimentos (Island of Provisions) by Columbus when they were repairing a ship in the Bocas del Toro Archipelago. One memoir procured from a local authority says, "Around 1820, outsiders from Nicaragua, Colombia, Jamaica and the San Andres Island began to come in...Many Jamaican negroes, after the closing down of the French Canal and the completion of the railroad in 1855 became settled at Old Bank [Bastimentos] (p. 51, 52)." This may be the most accurate account of the ethnic histories of the people who now inhabit Bastimentos.

Clyde Stephens wrote "History of Hospital Point," a journal on the first medical center in the Bocas del Toro area, built by the United Fruit Company. He says that the "Colored Hospital," built after 1904, was known as such, "because a majority of the work force was imported from the West Indies, mostly from Jamaica." (Stephens, 1997) Later he mentions that in the "Laborer's House" dice games and boxing matches were held and, "Losers would row their dugouts home to Bastimentos or Bocas completely broke." (Stephens, 1997).

Socio-Economic Situation in Bastimentos and Bocas del Toro Province

In 1993, Ricardo Almanza et. al. said the Province of Bocas del Toro, Pana ma was an under-developed region in relation to Panama. He states that compared to the nation, Bocas del Toro has a lower average salary, lower quality of housing and sanitation, and lower human resources for health care. Almanza says that, "more than 50% of the homes in the province receive earnings less than \$250.00 monthly," meanwhile the cost of the most basic foods in 1990 was \$200.00/month. "More than 42,000 Bocas del Toro citizens are not satisfied in their basic needs of food, housing, education, and healthcare, among others," says Almanza.

Further, Bocas del Toro has a higher infant mortality rate and malnutrition epidemic than the Panamanian average. Infant mortality in Bocas del Toro is 2.5 times the average for Panama. Malnutrition is at 52% in the province, 2 times higher than the average in Panama (Almanza 1993).

Bastimentos has a high level of unemployment and poverty which directly influence sanitation and health. Bastimentos has a total of 127 houses. 18 houses were reported to lack potable water. 61 did not have sanitary bathroom services. 23 homes did not have televisions, 38 did not have radios. Of the 319 people over the age of 18 living in Bastimentos, 34 said they were unemployed. 154 have jobs, 40 of which said they were involved in agro- fishery work (National Census 2000). The lack of sanitary bathroom services and treated water are significant factors in disease and pathogen transmission. Similarly the low or zero earnings would prevent people from improving the sanitation in their homes or getting medical attention for themselves or their children except in dire emergencies.

Health-Care in Bocas del Toro and Bastimentos

Panama and Bocas del Toro

In Panama, the average life span for individuals born in 2002 was 77.3 years for females and 72.6 years for males. For the country of Panama there were 12.1 doctors, 2.4 dentists, and 10.7 nurses for every 10,000 inhabitants (www.paho.org). In 1990, the health care in the Province of Bocas del Toro consisted of 6 doctors, 7.5 nurses, and .8 dentists for every 10,000 inhabitants (Almanza 1990). Currently, the Bocas del Toro Hospital has 3-5 Doctors on staff, attending emergency and primary care. They have a very primitive laboratory staffed by one person which operates part-time. The hospital provides child birthing and acute care. Health cases requiring surgery or emergency medicine are sent by ambulance boat to the Hospital of Almirante or in more extreme cases, the Hospital in Changuinola.

There is one pharmacy in Bocas del Toro where citizens can buy a wide variety of medications without a doctor's prescription. In Panama, a physician's prescription is not needed to buy pharmaceutical drugs, and many are 1/10 - 1/100 of the U.S. price. Antibiotics were only recently added to the controlled drug category and can no longer be bought over-the-counter in Panama.

Bastimentos

Bastimentos has a health center which is unoccupied except for Thursday mornings when a nurse arrives to weigh children, administer vaccinations, and do consultations and minor check-ups. The stores in the village sell the basic over-thecounter pharmaceuticals such as pain relievers or anthelminthic drugs, but there is no pharmacy. Most health problems are referred to the Bocas del Toro hospital. The cost to

go the hospital from Bastimentos includes transportation (boat and taxi = 3), the cost of the prescribed medication, and perhaps any food or snacks required while enduring the remarkably long wait to see a doctor. If the patient is insured, the medication is free.

In Colon, Panama, Angermuller describes the dilemma experienced by the Afro-Antilleans, "They are extremely poor, and yet they are forced to live in an economy in which the cost of living is so high that they can barely afford the necessities. A medical consultation will cost five dollars and upwards, and modern synthetic drugs and medicines are quite beyond their reach...There is little money, and overcrowding, parasites, poor diet, and poor hygiene expose the people to a host of minor and major ills" (1968).

In Bocas del Toro and Bastimentos we are presented with a very poor population, even in comparison with the national averages for Panama, evidenced by their monthly earnings, condition of their homes, and the high incidence of infant mortality, and malnutrition. People from Bastimentos cannot easily pay the costs of health care (>\$5/visit), and therefore have developed an ethnomedical system that serves primary healthcare needs without jeopardizing their already inadequate finances.

CHAPTER 3

IRON DEFICIENCY ANEM IA

Iron-Containing Molecules in the Body

While there is only about 2.5 - 4 grams of iron in the healthy human body, this metal has a very important function and an intricate method of maintaining homeostasis. Iron is found in the red blood cells and iron stores in the liver, bone, and spleen (Seely 2003). In addition to iron's well-known role in red blood cell hemoglobin, as an oxygen/carbon dioxide carrier, iron is essential for myoglobin, cytochromes, catalase, peroxidase, and metallo-flavoprotein enzymes (Brody; Hardman 1996).

Heme proteins are the most critical compounds in the body that are reliant on adequate iron. 70% of iron is in the hemoglobin, 3.9% is in myoglobin, cytochromes, and enzymes important for energy metabolism and respiration in the mitochondria (See Table 3.1). Plasma iron represents 0.1% of the total and 25% of iron is in the ferritin stores (www.pediatriconcall.com). Hemoglobin is a protoporphyrin type IX with 4 globulins (2 alpha, 2 beta) and a ferrous iron atom at the center. Hemoglobin is exceptionally well designed for the transport, unloading, and loading of oxygen and carbon dioxide.

Hemoglobin and the iron atom at its center are recycled in the liver. The route of iron from the breakdown of hemoglobin in old red blood cells (120 days), to the reincorporation of iron in new hemoglobin molecules is via the plasma-bound iron.

	Iron Content (mg)	
	Men	Women
Hemoglobin	3050	1700
Myoglobin	430	30
Enzymes	10	8
Transport (transferrin)	8	6
Storage (ferritin and other forms)	750	300
Total	4248	2314

Table 3.1 Iron Distribution in the Adult Body (Katzung 2001).

¹Adapted, with permission, from Brown EB: Iron deficiency anemia. In: *Cecil Textbook of Medicine*, 16th ed. Wyngaarden JB, Smith LH (editors). Saunders, 1982.

²Values are based on data from various sources and assume that "normal" men weigh 80 kg and have a hemoglobin of 16 g/dL and that "normal" women weigh 55 kg and have a hemoglobin of 14 g/dL. The recycled iron can be stored as ferritin in the liver, spleen, or bone. When there is a low concentration of hemoglobin, anemia occurs.

Myoglobin is like hemoglobin but transports oxygen and carbon dioxide to and from muscle tissues, in response to contracting muscle cell needs. Cytochromes a, b, and c are involved in mitochondrial electron transport are essential for cellular energy production. Cytochrome P450, which breaks down substances for clearance by the liver, is also in this family of enzymes. Finally, the enzymes NADH dehydrogenase and succinate dehydrogenase, in the mitochondria need sufficient iron to begin the first step of the electron-transport chain (Yip 2001)

Iron Absorption and Transport

Dietary iron is taken up in the duodenum, jejunum and upper small intestine where it is actively transported into the intestinal mucosa. The ferric form of iron (Fe³⁺) must be converted (by gastric acid or citric acid) to the ferrous form (Fe²⁺), which can then be absorbed by the intestinal mucosa (Seely 2003). The iron is either bound to ferritin in the intestinal mucosal cells or bound to the plasma protein, transferrin. These two substances are instrumental in distributing iron in the cells. Ferritin is the storage form of iron and transferrin is the transport form of iron. The plasma-transferrin- Fe²⁺ complex arrives at maturing erythroid cells in the red bone marrow. The erythroid cells have transferrin receptors. The iron-transferrin complex undergoes endocytosis and recycle the transferrin and transferrin receptor (Katzung 2001).

Iron Storage

When iron is adequate in the body, iron is stored as ferritin and apoferritin in the mucosal cells of the intestine and in macrophages located in the spleen, liver, and bone.

A highly efficient method of storage, one ferritin molecule holds 4000 atoms of iron. Aggregated ferritin, less available, is called hemosiderin. Ferritin levels are detected from serum (Hardman 1996; Yip 1996; <u>www.pediatriconcall.com</u>). In the liver, ferritin is in the parenchymal cells or hepatocytes. In the bone marrow and spleen, ferritin is in the reticuloendothelial cells. Figure 3.1 summarizes iron absorption, transport, and storage in the body.

Iron Homeostasis

The body maintains a strict homeostasis on the absorption, storage, circulation, and excretion of iron. Very little iron is absorbed daily, because there is no mechanism to excrete excess iron by the body. Trace amounts of iron are excreted through sloughing of intestinal mucosal cells (which die every 3-4 days) in the feces, urine, and bile. This loss amounts to less than 1mg/day (Katzung 2001; www.pediatriconcall.com). Therefore the daily need of iron is about 1 -1.5 mg for healthy adults.

The body has a mechanism to increase or decrease iron absorption based on the levels of iron already in the body. The receptors for transferrin on cell membranes are increased or decreased depending on the need for iron by the body, as determined from cytosolic iron levels. An iron-responsive element binding protein senses the levels of iron in the plasma and controls the mRNA's that encode for transferrin receptors and ferritin (Brody; Hardman 1996). The cytosolic levels will also direct iron toward either erythropoeisis (via transferrin) or toward iron storage (via ferritin) (Katzung 2001). When iron stores are low, and iron is in high demand, the body produces more transferrin receptors. The result is more iron is available to, and absorbed



Figure 3.1. Iron Absorption, Transport, and Storage in the Body (Hardman 1996).

by the red blood cells (Hardman 1996). Increasing numbers of transferrin receptors phospholipid membrane, or high iron levels in plasma, is associated with an increase in erythropoiesis or manufacturing of red blood cells. Because the healthy body doesn't lose much iron, and the methods for regulating iron absorption are effective, the only situations which throw off this equilibrium, are increased requirements for iron, or increased losses of iron (in the form of blood) from the body.

Dietary Sources of Iron

Despite the content of iron in the diet, the actual absorption of iron in the body depends on many factors: the bioavailability of iron, the body's demand for iron, dietary enhancers or inhibitors, and even the preparation of the food. Heme iron is more bioavailable and more absorbed than nonheme iron. For example, although heme iron (from the hemoglobin and myoglobin in meats) only comprises 6 % of the diet, it is 30% of the absorbed iron (Yip 2001). Foods high in iron are organs, brewer's yeast, wheat germ, egg yolk, oyster, dried beans, and some fruits. See Table 3.2 for more foods that increase the bioavailability of dietary iron. Foods lows in iron are milk, milk products, and nongreen vegetables (Hardman 1996).

Nonheme iron, "accounts for most of the iron in the diet, usually more than 85%" according to <u>Present Knowledge in Nutrition</u>. Absorption of nonheme iron is significantly increased by citric acid and meat (by increasing gastric acid secretion). The acid reduces ferric iron to ferrous iron, the form easily absorbed in the small intestine. Conversely, there are substances such as phosphates, phytates, bran, tea polyphenols, and antacids that inhibit iron absorption. Phosphates and phytates are plentiful in cheap, calorie rich foods such as grains and those

 Table 3.2. Foods that Increase the Bioavailability of Iron or Enhancers

Food (enh	nancer)	Degree of effect
Meat, poul	try, and fish	+++
Orange, pi	neapple, and guava	+++
Beer		++: //
Banana, m	nango, and melon	++-
Carrot, pot tomato, ca	tato, beet root, pumpkin, broccoli, cauliflower, bbage, and turnip	++.
Salad (lett	uce, tomato, green pepper, and cucumber)	+
Soy sauce		+
Attention:	The availability of iron in breast milk is high com	pared with that in other kinds of m
Note:	The number of plus signs (+) indicates the degr	ee of enhancing effect, e.g., guava

ote: The number of plus signs (+) indicates the degree of enhancing effect, e.g., guavas, oranges, and pineapples are foods that greatly increase the availability of nonheme iron in foods.

you would find in the diets of impoverished people (Hardman 1996; Havel 1989). Ray Yip says that, "In developing countries the prevalence of IDA for women in childbearing age ranges from 20% - 40% because of diets low in bioavailable iron or food from animal sources," the problem being that, "foods with greater iron bioavailability are also more expensive" (2001).

RDA of Iron

In the healthy adult human, there are 2.5-5 grams of iron and children have 55 mg/kg body weight of iron (www.pediatriconcall.com). Recommended daily allowances (RDA), "have been established for people who daily consume 30-90 g of meat, poultry, fish, or foods containing 25 – 75 mg of ascorbate after preparation". Values are shown in Table 3.3: 10 mg per day for adult males, 15 mg per day for females, and 10 mg per day for post-menopausal women. Pregnant and lactating females require 15 mg/day. Infants of six months, children, and adolescents need 10-15 mg per day (Havel 1989).

Of these numbers, the iron actually absorbed from the diet is 1-5 mg or 1mg/day for men and 1.4 mg/day for women (Hardman 1996). Absorption of dietary iron varies according to iron stores. As mentioned previously, homeostasis of iron is carried out by up or down-regulation of transferrin and ferritin receptors on cell surfaces. By this mechanism, men absorb less iron per day because their iron stores are greater than those of women. Further, an anemic person, with low iron stores and low hemoglobin, can absorb 50% more nonheme iron than a person with adequate iron stores (Yip 2001).

Iron Deficiency Anemia (IDA)

IDA is defined as a concentration of hemoglobin in the red blood cells lower than the cutoff defined by the World Health Organization (Nestel 2002). It is a microcytic,

use of outer		
Subject	RDA	
Adult Male	15 mg/day	
Adult Female	15 mg/day	
Post-Menopausal Female	10 mg/day	
Pregnant/Lactating Female	15 mg/day	
Infants, Children, Adolescents	10-15 mg/day	

Table 3.3 RDA values based on a diet containing 30 - 90 g of meat or 25 - 75 mg ascorbate.

hypochromic condition of the red blood cells (RBC), meaning they are smaller and have less red color (less hemoglobin) than normal RBC's. Iron deficiency advances in stages starting with decrease iron stores and ultimately ending in changes to the RBC's and iron deficiency anemia. Figure 3.2 gives comparisons between the stages and the various indicators of iron levels. The first stage of iron deficiency is depletion of iron stores; the second is iron-deficient erythropoeises. As iron requirements continue to be unquenched, all of the iron stores have been used, the iron in the hemoglobin (or "functional iron") is depleted. The final stage is iron deficiency anemia. When hemoglobin is less than 40 g/L, very severe anemia results, the body can no longer compensate for the decreased oxygen-carrying capacity and acidosis occurs (Yip 2001). The various symptoms and health consequences are elaborated in the following sections.

Prevalence of IDA

IDA is the most common nutrient deficiency in the United States and worldwide, affecting mainly older infants, young children, and women of childbearing age (Yip 2001). The World Health Organization states that IDA affects 94 million people on our continent (PAHO). The more common, iron deficiency is estimated to affect 2 billion in the world, mostly in developing countries (UN 2000). In Latin America alone, 40% are pregnant women and 50% are children. In the Caribbean region of Latin America, 52% of pregnant women are anemic according to the WHO in 1992 (www.hki.org; Epstein web).

Causes of IDA

Causes of iron deficiency can be grouped into four categories: low dietary intake of iron, gastrointestinal blood loss, poor absorption of iron in the body, and increased iron requirements. Inadequate dietary levels of vitamins B12, folic acid, vitamins A, C, E, or trace elements contribute to development of IDA. Malaria and hemoglobinopathies also

			0	
Iron Stores Erythron Iron	Normal	Iron Depletion	Iron-Deficient Erythropoiesis	Iron-Deficienc Anemia
RE marrow Fe	2-3+	0-1+	0	0
Transferrin μg/100 ml (μM)	330 ± 30 (59 ± 5)	360 (64)	390 (70)	410 (73)
Plasma ferritin, µg/l	100 ± 60	20	10	<10
Iron absorption, %	5-10	10-15	10-20	10-20
Plasma iron µg/100 ml (µM)	115 ± 50 (21 ± 9)	115 (21)	<60 (<11)	<40 (<7)
Transferrin saturation, %	35 ± 15	30	<15	<10
Sideroblasts, %	40-60	40-60	<10	<10
BBC protoporphyrin μg/100 ml RBC (μmol per liter RBC)	30 (0.53)	30 (0.53)	100 (1.8)	200 (3.5)
Erythrocytes	Normal	Normal	Normal	Microcytic/ hypochromic

Figure 3.2. Sequential Changes (from left to right) in the Development of Iron Deficiency in the Adult (Hardman 1996).

decrease iron levels. Dr. Lokeshwar points out that many other factors are involved in the development of IDA; poor health facilities, poor socioeconomic status, degree of urbanization, ethnic background, prevalence of hook worm and other worm infestations, and even repeated bacterial infection (www.hkiorg.; www.pediatriconcall.com). *Symptoms of IDA in Adults and Children*

Largely due to the decreased availability of oxygen to the hemoglobin, cytochromes, and mitochondrial enzymes, the known consequences of iron deficiency and IDA are on tissue and cardiac health, physiological growth, productivity, maternal and fetal mortality, cognitive development and attention span. Mild anemia, or iron deficiency, is nearly asymptomatic because the body compensates for the reduced oxygen delivery (and carbon dioxide evacuation) to the tissues through various mechanisms.

IDA is expressed symptomatically through pallor, fatigue, dizziness, and exertional dyspnea. The tissues are not properly oxygenated and may suffer from ischemic damage. The chronic effects of IDA threaten cardiac health; tachycardia, increased cardiac output, and vasodilation (Katzung 2001). Another behavioral manifestation of iron deficiency is very well-known but not explained, termed "pica" which involves ingestion of mud or clay, laundry starch, and ice (www.pediatriconcall.com).

IDA triples the risk of maternal mortality (Brentlinger 2003). Other symptoms of IDA are a 10 – 30% decreased work capacity, decreased ability to maintain body temperature and immune function, and decreased cognitive performance (Havel 1989, Assessing the problem.). Doctors Lokeshwar and Shah attribute behavioral changes in iron deficient patients to the decreases of aldehyde oxidase and MAO, responsible for the

breakdown of serotonin, 6-hydroxyindole compounds and catecholamines, respectively (www.pediactriconcall.com). IDA increases risk of lead poisoning (because IDA increases absorption of heavy metals), and some studies point to IDA as cause of preterm birth, low birth-weight babies, and even fetal mortality (Yip 2001).

In children IDA has been associated with apathy, short attention span, irritability, and reduced ability to learn (Havel 1989). It has also been observed to, "delay child development" and in preschoolers, it reduces visual distinction abilities (www.hki.org). Rats that were depleted of iron in the brain after weaning sustained irreversible damage. The consequences of iron depletion at that early stage of development could not be remedied for the lifetime of the rat despite continuous iron supplementation (www.pediatriconcall.com).

Those At-Risk for Developing Iron Deficiency

Increased iron requirements and increased blood loss are the causes of iron deficiency anemia (see Figure 3.3). The people most at risk for developing iron deficiency anemia are pregnant women, infants, adult females, and adolescent females, in that order (Hardman 1996). Pregnant and lactating females have higher requirements for iron as well as growing children (Katzung 2001). Pregnant women will need 680 mg more than their normal requirements of iron over the course of pregnancy. The majority of iron stores in the fetus are developed in the third trimester. This is limited in cases where the mother is iron deficient, and babies are also iron deficient upon birth (pediatriconcall.com). Preterm babies are not born with the normal iron stores and are very vulnerable to iron deficiency. Feto-maternal hemorrhaging is said to occur in nearly 50% of pregnancies that result in fetal blood loss.



Figure 3.3 Factors Contributing to IDA. Adapted from <u>www.hki.com</u> and www.pediatriconcall.com

Pre-menopausal women need more iron because they lose 30 mg iron every month in menstrual blood loss. 10% of pre-menopausal women are further iron depleted due to excessive menstrual bleeding (Yip 2001). Adolescents, experiencing increased growth, require increased red blood cells and therefore have a higher iron requirement. Helminth infestations cause substantial blood loss to the host, and when coupled with other barriers for getting enough iron, intestinal parasites rapidly deplete the host's iron. Drug Treatment for IDA

A person with IDA can absorb 50-100 mg of iron daily because their iron stores are low and receptors for transferrin and ferritin are up-regulated. Feosol or ferrous sulfate is 20% iron and is considered the treatment of choice for iron deficiency anemia. Other forms of iron supplementation are ferrous fumarate and ferrous gluconate, shown in Table 3.4. Treatment regimens are 200 mg per day for adults and 100 mg per day for children. However, in extreme cases of IDA, up to 480 mg per day has been used to achieve rapid results (Hardman 1996). This treatment is continued for 3-6 months in order to restore hemoglobin iron levels and iron stores (Katzung 2001). For children dosage is 1.5-2.0 mg/kg body weight 3 times a day (www.pediatriconcall.com). Response to treatment should be almost immediately evident in the hemoglobin levels and the patient will feel an increase in energy, but iron stores will not be sufficient for months afterward with iron supplementation. Fortification of foods is achieved with ferrous sulfate and elemental iron (Yip 2001).

Iron Toxicity and Free Radicals

Iron toxicity in the adult is possible but requires enormous quantities of iron. The lethal dose of iron is 200-250 mg/kg. The "Tolerable Upper Intake Level (UL)" is 45

Table 3.4. Percentage and Amount of Iron in Some Commonly Used Iron Tablets (www. Pediatriconcall.com).

Preparation	Iron compound (mg) per tab	Elemental iron (mg) per tab	% of iron given
Ferrous fumarate	200	66	33
Ferrous gluconate	300	36	12
Ferrous sulphate (7H ₂ O)	300	60	20
Ferrous sulphate (anhydrous)	200	74	37
mg/day of iron, based on the occurrence of gastrointestinal side effects (Yip 2001). The main victims of iron toxicity are children who overdose on 10 or more iron tablets. The symptoms of overdose manifest largely in the gut as necrotizing gastroenteritis, vomiting, abdominal pain, bloody diarrhea, shock, lethargy, and dyspnea. The remedy for iron toxicity is bowel irrigation, administration of deferoxamine (to bind iron and clear it), and phlebotomy (Katzung 2001).

The Fenton Reaction is responsible for the production of an oxidative free radical hydroxyl group from the highly reactive iron ion. The high levels of iron are believed to cause oxidative damage to the endothelium, resulting in "premature cell aging." This conclusion was presented based on correlates between serum ferritin levels and chronic diseases such as cancer and coronary heart disease. Upon investigation of the epidemiological literature, however, Yip, in 2001 states that evidence to support this theory is very weak. The only strong evidence is that humans with hemochromatosis are predisposed to develop hepatic carcinoma. However this study showed that these individuals had a normal incidence of coronary heart disease. The author points out that serum ferritin "functions as an acute reactant and becomes elevated with inflammatory processes" and this may be responsible for the relationship found between iron and inflammatory diseases (Yip 2001). Much more investigation into this concept is necessary to discover if high serum iron causes these chronic diseases, or if it is merely a symptom in the disease process.

The Case of Iron Deficiency in Bastimentos, Panama

Iron deficiency and IDA are common health problems in Bastimentos and Bocas del Toro. The Hospital of Bocas del Toro reported that for 2002, there were 342 cases of

anemia of 12,000 patients. Anemia was the fifth most common illness. Because the people of Bastimentos are poor, it is very unlikely that they, and particularly their children eat 30-90 g of meat, poultry or fish daily. The RDA based on a developed country's standard cannot be applied to this population who has a very high incidence of malnutrition and infant mortality. People in Bastimentos eat fish, beef, pig, and sea turtle. Fish, hotdogs, and chicken are the most common. In general, meat portions in Bastimentos are very small in comparison to the standard American servings. Foods such as yucca, rice, pasta, and bread dwarf the size of the meat servings.

CHAPTER 4

BLOOD-SUCKING INTESTINAL PARASITES

Intestinal Parasites that Cause IDA

A number of intestinal parasites have been shown to cause IDA: *Necatur americanus* (hookworm), *Ancylostoma duodenale* (hookworm), *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and *Schistosoma haematobium* (flukes). R. Stoltzfus advises, "...if we are serious about meeting the current global objective of reducing anemia by one-third, hookworm-related blood loss cannot be ignored" (Stoltzfus 1997). The problem of intestinal parasitosis is insidious with devastating affects on health worldwide. *Trichuris, Ascaris*, and hookworms (*Necatur americanus* and *Anclyostoma duodenale*) account for a global loss of 39 million disability-adjusted life years (DALY's) (World Bank, 1993, Chan et al. 1994; Chan, 1997; de Silva, Chen & Bundy, 1997a). The World Bank has said that helminth infections are the main cause of disease for children age 5-14 years old in developing countries (World Bank 1993).

It is commonly accepted that worms cause loss of iron via blood loss, but current studies attempt to understand the extent to which this disease process affects different ages, classes, genders, and the average impact of worms on hemoglobin levels. The bloodsucking worms cause an interdependent set of symptoms including iron deficiency, decreased appetite, decreased nutrient absorption, and low birth weight babies. These babies then grow up to be relatively small women who then give birth to low birth weight infants. As illustrated in Figure 4.1, intestinal parasites set off a vicious



Figure 4.1. How Parasites Cause/Aggravate Malnutrition and Retard Development (Holland 2002).

cycle of malnutrition, stunted growth and cognitive deficits, and even infant and maternal mortality. To add injury to insult, the worms often act synergistically with other intestinal parasites, bacteria and viruses to further incapacitate the healthy functioning of the body (Stephenson 2002). In <u>Parasitology & Vector Biology</u>, authors state that, "In nearly all helminthoses there is a mixture of a half dozen or more" (Marquardt 2000).

Hookworm-related IDA depends on iron stores, intensity and duration of infection, and diet (Fleming 1982). With high iron stores, and high levels of bioavailable-iron in the diet, a light infection of hookworm may be insignificant. The groups most jeopardized by helminthoses are pre-menopausal women, children, and pregnant mothers because their iron stores are usually significantly lower than those of post-adolescent men. Infection with intestinal parasites can easily escalate asymptomatic iron deficiency to iron deficiency anemia. In schoolchildren, Stoltzfus asserts that eradication of hookworm would reduce IDA by 35% and severe anemia by 73% (Stoltzfus 1997). IDA can be caused by severe worm infection, but when we consider a synergistic effect, of worms with other causes of blood loss such as hemorrhaging or GI bleeding, low bioavailability of dietary iron, and increased requirements of iron in cases such as pregnancy, IDA is a much more pervasive and challenging disease to eradicate. Hookworm Prevalence and Geographical Distribution

Hookworm affects approximately 25% of the world's population in tropical and sub-tropical countries (www.healthlink.mcw.edu). It is estimated that 60,000 die annually as a result of hookworm infection (www.cdc.gov/epo/mmwr). *A. duodenale* is found in subtropical Europe, Asia, South America, and Africa. *Necatur americanus* is found in tropical U.S., Central and South America, Africa, Orient, and Australia

(Marquardt 2000). It is believed that hookworm prevalence is as high as 80% in rural, unsanitary, humid, tropical areas, and that this helminth has a life span of 2-5 years (Stephenson 1987; Stoltzfus 1997; www.cdc.gov/epo/mmwr).

Hookworm Life Cycle

Hookworms, *N. americanus* and *A. duodenale*, hatch out of eggs in the feces from an infected individual. To contract the parasites, the skin must come into contact with vegetation or soil that houses the larvae. They penetrate the skin (commonly of the feet) and travel to the lungs via the blood. From the lungs, the larvae crawl up the bronchi and trachea, where they are coughed and swallowed, thereby entering the intestines. In the small intestines, the worms mature to adults, mate, and feed (Slot 2000). The life cycle is illustrated in Figure 4.2.

The larvae in the soil are viable for 3-4 weeks (www.cdc.gov/epo/mmwr). One female *A. duodenale* releases 10-30 thousand eggs daily and 1 female *Necatur americanus* produces and releases 5 – 10 thousand eggs into the environment daily (Marquardt 2000). In the case of one person, with 100 worms, this comes to over 180 million eggs released into the environment annually. One can imagine the considerable contamination of the soil with hookworm eggs and the difficulty in eradication of hookworm when the environment is practically filled with larvae.

Effects and Symptoms of Hookworm in the Human

Diagnosis of hookworms is through number of eggs in stool, the presence of iron deficiency anemia, and fatigue (Marquardt 2000). Some of the possible symptoms are: an itchy rash where the worm penetrated the skin, asthma, lung congestion, or



Figure 4.2. Life Cycle of the Hookworms (Beck 1971).

pneumonia-like symptoms. Most common however, are symptoms in the gastrointestinal tract which include: abdominal pain, diarrhea, weight loss, loss of appetite and excessive gases (Slot 2000).

Ascaris lumbricoides and Trichuris trichiura

A. *lumbricoides* infects 29% of preschoolers and 35% of school-age children worldwide (Michael et al. 1997). *Ascaris* is said to have a prevalence of 1-12% in people who live in rural Georgia (Marquardt 2000). The eggs of *A. lumbricoides* enter the host through the mouth and travel down the trachea to the lungs, where, like hookworm, they are coughed up and swallowed. The eggs hatch into larvae in the small intestine and exit the body via the feces. The reproducing adults migrate to the liver, at which point they return to the lungs to be coughed up and re-enter the cycle (Marquardt 2000). This intestinal parasite causes lung diseases and/or pneumonia. *A. lumbricoides* causes anemia via decreasing appetite and nutrient absorption, not through blood-feeding per se (Stephenson 2002). *T. trichiura* lives in the large intestine. It is contracted when the eggs are eaten. *Trichuris* causes anemia in severe infestations via bloody diarrhea which is an inflammatory response to the worm.

Iron and Blood Lost to Intestinal Parasites

As seen in Figure 4.3, hookworms feed on the blood and tissue of the mucosa in the upper small intestine, and shift position every 4-6 hours (Stoltzfus 1997). The worms lacerate the capillaries of the lamina propria and blood is ingested by the worm, or leaks at the site. *Necatur americanus* secretes anti-coagulant substances to facilitate feeding that are not detected by the immune system (Viaene 2000).



Figure 4.3. Sagittal Section of a Hookworm Feeding in the Intestine of the Host (Marquardt 2000). The worm pinches off a mouthful of intestinal mucosa and swallows with the esophagus.

The majority of the blood is lost to ingestion by hookworms, however some blood flows around the worm and can be reabsorbed later in the digestive tract. Bleeding continues, even after the worm moves sites, due to the anti-coagulants secreted at the feeding site (Hotez & Cerami 1983). In addition to iron lost to the parasites, they ingest plasma and the nutrients contained therein (Pawlowski, Schad & Stott 1991).

Necatur americanus infection results in a blood loss of 0.01 – 0.04 ml/worm/day and *A. duodenale* causes blood loss of 0.05 – 0.3 ml/worm/day. For a person with a load of 100 hookworms, they can lose more than 2.5 liters of blood in a year (Marquardt 2000). *A. duodenale* feeds on 2 -10 times more blood than *N. americanus*, while *Trichuris* removes 1/10 the blood consumed by hookworms (Stoltzfus 1997). *T. trichiura* is responsible for .005mL/day/worm in adults. A study of Venezuelan children showed a daily loss of .8-8.6 ml in children compared to uninfected children who only lost 0.2 to 1.5 ml per day (Roche et al. 1957). Blood and iron losses are estimated in Table 4.1.

Infection with hookworm in children increases with age, leveling off at 15-20 years old. Intensity of hookworm actually is greater in adulthood. *A. lumbricoides* and *T. trichiura* are different because they reach maximum prevalence and intensity of infection during adolescence, and decrease in adult years (Stoltzfus 224). Children are more vulnerable to helminthoses because prevalence and intensity of hookworm infection are high in this group (Stoltzfus 1997).

Impact of Intestinal Parasites on Hemoglobin

High hookworm loads (measured by egg count per gram of fecal material) result in high blood loss in feces and lower hemoglobin counts. Egg counts found in stool samples are directly proportional to hemoglobin counts (Stoltzfus 1997). One study

	Number of	ml blood	Calculated iron	Calc. blood	Calc. iron
	worms	loss/day	lost in mg/day	loss ml/year	lost mg/year
<i>N</i> .	1	0.01 -	0.008	3.65 - 14.6	1.26 - 5.05
americanus		0.04			
<i>A</i> .	1	0.05 - 0.3	0.06	18.25 –	6.31 - 37.89
duodenale				109.50	
<i>N</i> .	32	1.3	0.45	475	164
americanus					
<i>A</i> .	11	2.2	0.76	803	277
duodenale					
Trichuris	"moderate	0.46	0.16	167.9	58.4
	load"				

Table 4.1 Iron and Blood Losses Caused by N. americanus, A. duodenale, and Trichuris

Adapted from Marquardt 2002, Holland 2002, Stoltzfus 1997

showed that for every additional 1000 eggs/gram of stool, there was 0.825 mg/g of hemoglobin excreted in the stool (Stoltzfus et al. 1996). Of pregnant women treated for anemia in Chiapas, Mexico, 50% were infected with *N. americanus*. These women had significantly lower hemoglobin counts than non-infected, anemic, mothers. Of the hospital population, 1.9% harbored hookworm, while 50% of the anemic mothers harbored the parasite (Brentlinger 2003; <u>www.165.158.1.110</u> PAHO). Hookworm infected mothers displayed hemoglobin of 4.1 g/dl while non-infected anemic mothers had hemoglobin levels of 7.0g/dL (Brentlinger 2003). In a study of Zanzibari school children, higher hookworm infection led to more children with iron deficiency, IDA, and severe IDA (see Figure 4.4).

The worms continue to ingest blood and may increase in numbers, little by little depleting the host of iron in the blood. Hookworm, *Ascaris*, and *Trichuris* blood loss can double or triple a person's RDA for iron. In preschoolers a light infection of 40 hookworms caused a daily blood loss of .55 mg³, equaling the daily iron requirement of .56 mg. Stoltzfus remarks, "If children in many environments cannot meet this normal requirement, they certainly cannot offset a blood loss that doubles their requirement for absorbed iron" (1997).

Hookworms During Pregnancy

"Infection in pregnancy," Rebecca Stoltzfus states, "is particularly disastrous to iron status because iron demand is already very high in pregnancy" (1997). Women who are pregnant or lactating cannot spare the iron depleted by these intestinal helminthes. Intestinal parasitosis increases infant and mother mortality and morbidity (Crompton 2002). In the article, "Hookworm Infection and Anemia in Adult Women in Rural



Figure 4.4. Hookworm-Related IDA in School Children (Stoltzfus 1996)

Chiapas, Mexico," authors point out that an increase in parasite infection in pregnant mothers is correlated with decreased iron and decreased fetal growth. Authors recommend that anthelminthics be administered to mothers in 2nd and 3rd trimesters of pregnancy due to the risks to fetal and maternal health (Brentlinger 2003).

Anthelminthics Reverse IDA

Studies show that de-worming programs alone can raise hemoglobin concentrations in children and pregnant women (Crompton 2002). Anthelminthics also increase growth (weight and height) of the host. In a study of 853 Haitian children, of which 42% had *Trichuris*, 29% *Ascaris*, and 7% hookworm, treatment with Albendazole and Ivermectin resulted in significant weight and height increases for all groups (Beach et al 1999). In a study of Zanzibari and Nepalese who had iron-poor diets and low iron stores, the authors estimated that from 31 – 57% of moderate to severe cases of anemia could be attributed to hookworms (see Table 4.2). A study undertaken to test the effect of anthelminthic treatment on hemoglobin levels in children and adults, found that with the anthelminthic there was an average increase of 4.1g/L hemoglobin. Significant restoration of iron and hemoglobin in the host was observed when the worm load was simply decreased (Stoltzfus 1997). The overwhelming mandate made by the authors is that de-worming programs should be carried out in areas where anemia is a significant health problem.

Anthelminthic Drugs (See Table 4.3)

The discovery and development of modern pharmaceutical anthelminthics began in the 1940's (Campbell 1986). Intestinal helminthes need neuromuscular coordination in order to stay in any one location, to move for molting, feeding, and mating purposes.

Table 4.2 from Stoltzfus 1996.

	Type of Anemia*				
Population Group	Iron Deficiency Anemia	 Moderate to Severe Anemia 			
Zanzibari schoolchildren	41%	57%			
Zanzibari men	31%	31%			
Zanzibari nonpregnant women	19%	56%			
Nepalese pregnant women ^b	29%	41%			

⁴ Iron deficiency anemia is defined as protoporphyrin > 80 μ mol/mol heme and hemoglobin < 110 g/L in pregnant women and schoolchildren or <120 g/L in nonpregnant women or < 130 g/L in men. Moderate to severe anemia is defined for all groups as hemoglobin < 90 g/L.

Table 4.3 Anthelmenthic Drugs and Mechanisms

Drug class	Mode of action	
Phenothiazine	Interruption of microtubular function (?)	
Benzimidazoles	Interruption of microtubular function	
Imidazoles, quaternary ammonium salts, pyrimidines, pyridines	Cholinergic ganglionic blockers	
Avermectins	Chloride channel opener at GABA-mediated inter- neuron	
Organophosphates	Acetylcholinesterse inhibitors	
Piperazine	Hyperpolarization of muscle membrane (chloride channel opener; GABA-agonist)	
Piperazine derivative, diethylcarbamazine	Opsonization for immune destruction	
Antimonials	Inhibition of phosphofructokinase	
Arsenicals	Bind to sulfhydryl proteins	
Naphthalene sulfonic acid	DHFR or protein kinase or pyridine nucleotide utilization inhibition	
Isothiocyanate	Glucose transport, synthesis into glycogen and cata- bolism inhibition	
Cyanine dyes	Glucose transport or oxidative metabolism inhibition	
Substituted phenols and salicylanilides	Uncouple electron-transport-associated phosphoryla- tion	

Table I. Proposed Mode of Action for Antinematodal Drugs

They also have to break down carbohydrates to maintain energy levels and finally the integrity of microtubules is important for cell division, and cell-to-cell movement (Rew 1996). These physiological requirements serve as important targets in the action of existing anti-nematodal drugs and the search for new ones. In addition to those three physiologic requirements, other possible anthelminthic drug targets are larval development, adult sex pheromones, insect growth regulators, and decreasing gastric acid secretion, making the environment inconducive for parasitism (Rew 1996; Hall 1984)

The drugs for *A. duodenale, N. americanus, Trichuris*, and *Ascaris* are virtually identical. Sites of action for the commonly used anthelminthic drugs are glucose transport, glycogen metabolism, phosphofructokinase, fumarate reductase, oxygen uptake, ATPase, acetylcholinesterase, cholinergic and GABAergic neurons, and muscle membranes (Campbell 1986). Three major classes of anthelminthic drugs are Benzamidazoles, Imidazoles, and Ivermectin. Others are organophosphates, piperazine, diethylcarbamazine, salicylanilides, substituted phenols, antimonials, arsenicals, naphthalene sulfonic acid, and isothiocyanate (Rew 1986).

The anthelminthic drugs of choice for hookworm infection are the Benzimidazoles. Members of this drug group are Mebendazole, Albendazole, Thiabendazole, Fenbendazole, Oxfendazole, Oxibendazole, Febantel, and Triclabendazole (www.worminfo.org). The Benzimidazoles work against adults and larvae by inhibiting microtubule polymerization in the hookworms, while not affecting the mammalian protein (Hardman 1996). The action on the microtubule polymerization decreases egg hatching, larval development, glucose metabolism, and fumarate reductase. This leads to the worm's death by starvation (Rew 1996).

The second group of anthelminthic drugs is the Imidazoles, or Levamisole-like drugs. These include imidazothiazoles and tetrahydropyrimidines. Examples are Levamisole, Tetramisole, Pyrantel, Oxantel, Morantel. These drugs act as cholinergic agonists at the neuromuscular acetylcholine receptor. "It interferes with carbohydrate metabolism, fumarate reductase, and succinate oxidation. The net result is paralysis and expulsion of the worms" (www.worminfo.org).

The third group is Macrocyclic lactones which include Ivermectin, Avermectin, Doramectin, Abamectin, Moxidectin, Milbemycin, Eprinomectin, Selamectin. These also cause paralysis and death of the intestinal helminth. The drug acts by blocking interneurons and excitatory motor neurons via GABA receptor complex which increases the permeability of the cell to chloride ions (www.worminfo.org; Kass 1984). The worm loses locomotor activity, recovers, and then loses total locomotor activity (Rew, 1986). Intestinal parasites in Bastimentos

Bocas del Toro and Bastimentos have significant health problems resulting from helminthoses. "Roundworms, hookworms, and whipworms thrive in human communities in which poverty is entrenched and clean drinking water, sanitation, health care, and health awareness are inadequate" (Crompton 2002). This is exactly the set of conditions in Bastimentos, Panama. The Hospital of Bocas del Toro reported that for 2002, there were 348 cases of intestinal parasites in their report, "Principal Causes of Morbidity of 12,000 Attended Patients in 2002." The environmental conditions in Bastimentos, Panama perpetuate parasitic infections. In Bastimentos, there is neither water purification nor treatment. The drinking and bathing water comes from an uncovered holding tank in the ground. Chickens, dogs, horses, and pigs roam freely in Bastimentos.

After rains, the tap water is brown. Drinking water is also collected from rain water which drains off of the roofs. This may be cleaner water, except that the roofs rust and many times birds (vultures) are on the roofs, defecating, eating, etc...According to the 1990 Census, nearly half of the homes had unsanitary bathrooms. Many homes are built over the bay. This is a site of "black water" because sewage pipes from homes drain directly into the water. There is one sidewalk in Bastimentos and most paths are mud. The quantity of viable nematode eggs in the soil is probably very high, given that 5 - 30 thousand eggs are produced by a single female intestinal helminth (Marquardt 2001).

CHAPTER 5

ETHNOMEDICAL SYSTEM IN BASTIMENTOS, PANAMA

Ethnomedicine in Bastimentos

In Bastimentos, Panama the Afro-Antillean people have a variety of health practices and beliefs to address primary health care concerns. Many of these practices are related with African traditional medicine, with humoral concepts of disease and healing, customs and beliefs from the British West Indies, and even biomedical information. The people of Bastimentos live in a province of Panama that is poor, malnourished, with high rates of infant mortality and therefore use traditional medicine to achieve acceptable states of health in the least expensive manner possible. This ethnomedical explanatory model is outlined, focusing primarily on concepts relevant to Black Drink; humoral qualities of the blood, equilibrium, and the folk classification of anemia as "Low Blood".

The blood as an indicator of health and disease is found in other ethnicities: African-Americans, Haitian-Americans, Mexican Americans ("sangre debil"), Southern White Americans, and Jamaicans, people from Bahamas, and the Cape Verdean Islands (Snow 1974, Snow 1983) and Africa. Finally, based on the geographic appearance and uncanny similarities between those health beliefs in cultures with African influence, Black Drink could represent an ethnomedical system that, originating in Africa, crossed the Atlantic Ocean and arrived in the Americas with the slaves. Bush Medicine Due to necessity and tradition, the Afro-Antilleans of Panama have a rich tradition of medicinal plant use in primary health care. "Bush tea" is the most common mode of ingestion of medicinal plants. Bush tea is considered an inexpensive, tasty, beverage that has the benefit of preventing and curing illness (Angermuller 1968).

Medicinal Plant Knowledge in Bastimentos

The knowledge and use of bush medicine is pervasive, regardless of age or gender. There are a substantial number of medicinal plants that are very commonly used and known by everyone, or "common knowledge". Conversely, there is more specific medicinal plant knowledge held by the bush doctors. Linnea Angermuller, in her article, "Bush Teas and Folk Remedies Used by the West Indian Population of Colon, Republic of Pana ma," also observed that medicinal plant knowledge is common, "among all elements of society" (1968). According to Dr. Pablo Solis at the University of Panama, mothers hold the vast majority of medicinal plant knowledge in the family unit. His studies were conducted with the Afro-Antillean community of Nombre de Dios, Panama. Bush Doctors in Bastimentos

In Bastimentos there are bush doctors or authorities in the village who make medicine and sell it for \$3-\$5/bottle to locals and foreigners. The medicines are for specific ailments and often involve a precise recipe with three or more herbs and various processes i.e. steeping, boiling, cutting, and mixing with other substances. Black Drink is prepared and sold by bush doctors to locals and foreigners.

Role of Humors in Bastimentos Ethnomedicine

In accordance with the humoral system, medicinal herbs, as well as ailments, are ascribed qualities of "hot" or "cold". The Greek humors are blood (hot, moist), phlegm (cold, moist), yellow bile (hot, dry), and black bile (cold, dry) (Foster 1994). The humoral values are metaphorical, not literally referring to temperature. In <u>Hippocrates' Latin</u> <u>American Legacy</u>, the author reveals that the use of the humoral system in Latin America is used to validate empirical knowledge, or to explain why a treatment works on a disease state but is not a treatment in itself. In Latin America the wet/dry distinction is not used to explain disease.

The goal is to achieve balance and equilibrium of the humors. Imbalance of hot and cold caused by activities, exposure to substances, or going from one extreme to the other rapidly can predispose a person to illness or cause illness. Healing is conducted according to the "principle of opposites," and attempts to bring the humors into balance. For example, a "hot" illness (caused by imbalance of the humors) is treated effectively with a "cooling" remedy. Blood is the most important of the humors in African-American, African-Haitian, African-Panamanian, and African-Jamaican beliefs (Snow 1974; Laguerre 1978; Angermuller 1968; Lowe 2001).

Blood: The Most Important Humor

Panama

In Panama as well as in other ethnomedical explanatory models of African origin, the quality of the blood is an extremely important determinant of health. Blood can be high, low, too much, too little, thick, thin, hot, cold, dirty, or clean (Snow 1974). Any of these extremes results in illness, with the goal of a blood in equilibrium. Medicinal plants, diet, and other measures are prescribed to treat imbalances of the blood (Angermuller 1968). The quality of the blood is not the cause of illness; rather it is an

explanation for why there is illness (Foster 1994). Angermuller describes the concept of blood in Colon, Panama.

The West Indians believe that the blood may be heated or cooled by drinking or eating. "Hot" blood is bad for a person, as is thick blood, and many bush teas are drunk to keep the blood "cool." Hot blood may cause skin rash, "fine heats" which break out on the skin. It is believed that the old folk live long because of their reliance on teas and herbs in keeping their blood clean and cool...It is believed that a good purge will clean the blood of its impurities, preventing disease (1968).

Africa

The role of blood and humoral medicine in health and illness has a history traceable to Africa. In Sidama, Ethiopia, balance and equilibrium are thought to indicate good health. Imbalances in digestion, evacuation, and "blood levels" are considered to cause disease. Vecchiato reported that some informants believed that hepatitis was caused by too much blood in the body (Vecchiato 1998). In another publication he states that the Sidama believe that lack of nutrition decreases blood resulting in tuberculosis and other disease states. The solution is to increase food intake and the quantity of (raw) blood in the diet. One cure for a patient with tuberculosis is they have to vomit out the "bad" blood (Vecchiato 1997).

A concept found commonly in ethnomedical systems of African influence is that sexually transmitted diseases are caused by violating sexual taboos. The person has "bad" or "dirty" blood afterward. In Botswana, Tswana ethnomedicine holds that sexual intercourse is the mode that blood is mixed and the transmission of "bad" blood occurs.

Primarily a woman can cause disease by transmitting "hot" or "dangerous" blood if she is pregnant, menstruating, windowed, lost a child, or recently given birth. On the other hand, a man can cause disease with "bad" blood if he has had sexual intercourse with someone other than his wife (Haram 1991).

In the Mpumalanga Province in South Africa, "dirty" or "bad" blood is associated with sexually transmitted diseases and sexual practices considered taboo in traditional African culture (website <u>www.aegis.com</u>; Reddy). In Zimbabwe, people believe that "mixing of blood" causes AIDS through violating principles of purity, coolness, balance, and social harmony. STD's are believed to be caused by an accumulation of "dirt" which hatches out of the infected organs and invades the body via the blood (Kraft 1993). *Haiti*

The beliefs found in Africa could easily have been transported across the Atlantic to the Americas with slaves, a testimony to the integrity of this ethnomedical system. Indeed many similarities exist and the importance of blood imbalances in disease states is pervasive. In Haitian-American medicine, disequilibrium of hot and cold and blood (volume, quality, color, and movement) are considered two of the six causes of illnesses. In Ethnicity and Medical Care, Michael Laguerre says that, "By far the most dangerous types of illnesses are believed to be caused by irregularities in the blood system, and beliefs about the blood are extensive among Haitians." Further, Weidman has called blood, "the central dynamic in Haitian understandings of bodily functioning and pathological processes." (1978). Laxatives are used to treat "dirty" or "cold" blood and are believed to clean the blood and GI tract. "Dirty" blood results in skin eruptions and venereal disease (Laguerre 1981).

United States

There is striking similarity between the ethnomedicine of the Afro-Antilleans of Panama and lower class African-Americans in the United States. Only those beliefs pertinent to the discussion of Black Drink are examined. In African-American traditional medicine (also found among Southern whites) Loudell Snow found that "The blood is the focus of most attention, and there is concern with its generation and volume, the circulation, purity, and viscosity...it is in constant flux" (1974). She says that in this system blood is considered good, bad, clean, dirty, thick, thin, high, low, sweet, or bitter. Extremes are dangerous and equilibrium indicates health. The term of "bad" blood signifies venereal disease. Lower-class African-Americans also use teas for babies as well as laxatives to clean out the "cold" (Snow 1974).

"Low Blood" is Not Low Blood Pressure' (Snow 1974)

Commonly confused with low blood pressure, low blood is conceptually allied with anemia in Panama, Haiti, and among lower class African Americans in the U.S. In Colon, Panama, Afro-Antilleans drink "iron beer" and stout to "build" the blood (Angermuller 1968). In Haitian ethnomedicine, "weak" blood is treated with red remedies and pregnant mothers are advised to eat them to "build up the baby's blood." They believe that "thin blood" causes pallor and weak blood causes physical or mental weakness. The treatments are red meat, sugar beets, and/or syrup made of cow legs and sugar (Laguerre 1981).

Loudell Snow's studies with lower class African Americans can be used to extrapolate some ethnomedical beliefs of Afro-Antilleans in Panama. In the United States, the terms of high or low blood can refer to quantity of blood or location of blood

in the body. The cause of "low" blood is acid or astringent foods such as lemon juice, vinegar, pickles, or Epson salts which are believed to "cut" the blood. The symptoms are lassitude, fatigue, and weariness. Conversely, "high" blood is conceptually allied with polycythemia and caused by too much rich food. The symptoms are dizziness, palpitations, headache, and vision problems. The cures are mentioned above as substances that "cut" the blood (Snow 1976).

The African-American ethnomedical treatments for low blood, or "blood builders" are red foods such as beets, wine, grape juice, liver, blood sausage, and water in which a nail has been allowed to rust. The <u>Textbook of Black-Related Diseases</u> said that Voodoo remedies for anemia included raw liver and "blood pie" (Jordon 1975). These remedies work by opening the pores to sweat out the excess or opening the bowels to purge it out (Snow 1974; 1976).

"Low Blood," is a source of confusion between patients and physicians because it is misunderstood as low blood pressure. Because blood is in a state of constant flux, diagnosis that lasts a lifetime doesn't make sense to people who believe that blood in equilibrium is essential for health. If a patient is told he/she has high blood pressure, medication may be discarded because cheaper, shorter (3-9 days), easier, natural remedies are available at home. The patient believes that dietary changes (lemon juice or vinegar) will "bring down the blood." Further, if a patient is diagnosed as anemic ("Low Blood") and with high blood pressure ("High Blood"), he/she will think the physician is a fool, as the two conditions are mutually exclusive according to their ethnomedical system (Snow 1974).

CHAPTER 6

ETHNOMEDICAL USE OF BLACK DRINK FOR IDA

Black Drink Recipe and its Use in Bastimentos

Black Drink is famous in Bastimentos and unique to this community. The steps

for preparing Black Drink (See Figures 6.1- 6.4) are:

- 1. 100 limes are squeezed into a cast iron pot
- 2. Broken pieces of old cast iron pots are added
- 3. The mixture is allowed to sit for 9 days
- 4. On the 9th day, 3 medicinal herbs are added to the mixture:
 - a. 3 roots (113.97 g) of "Dandelion" or Senna spp.
 - b. leaves (05.52 g) of "Vervine" or Stachytarpheta jamaicensis
 - c. 3 roots (10.42 g) of "Pignut" or Hyptis suaveolens
 - d. leaves (12.03 g) of "Pignut" or Hyptis suaveolens
- 5. The mixture is boiled for more than 4 hours, to reduce the amount of water
- 6. Black Drink is mixed 1:1 with red wine



Figure 6.1. Bottle of Black Drink.



Figure 6.2. Senna spp.



Figure 6.3. Vervine or Stachytarpheta jamaicensis

Ethnobotany of Plants in Black Drink

The plants in Black Drink were identified by Botanists, Ana Gomez, R. Rincon, and Alex Espinosa. *H. suaveolens* is in the Lamiaceae family. *S. jamaicensis* is in the Verbenaceae family. *C. aurantifolia* is in the Rutaceae family. Lime is native to Asia and cultivated in tropical and sub-tropical countries (Germosen-Robineau 1997). *Senna spp.* is in the Caesalpinioideae family. This plant was not identified by botanists because it is a foreign species to Panama. For the purposes of this study, and to the best knowledge of the author, this plant is *Senna occidentalis*.

Ethnobotanical Uses of Hyptis suaveolens

The plants used in Black Drink have various ethnobotanical uses in the Caribbean, Africa, the Americas, and the Orient. *Hyptis suaveolens* is called "spikenard" in the United States. In William Grime's, <u>Ethnobotany of the Black Americans</u>, he sites the use of *H. suaveolens* by an African rootwoman, who he claims introduced the plant from Africa as a cure for smallpox (<u>www.mamiwata.com/Hoodoo.html</u>). In Jim Duke's Phytochemical and Ethnobotanical Database, he reports the ethnobotanical uses of *H. suaveolens* are: catarrh, dermatosis, lactagogue, stimulant, sudorific, headache, stomachache, analgesic, antispasmodic, antisuperofic, aperitif, bechic, bilious, cancer, carminative, cold, colic, constipation, depurative, dyspepsia, epistaxis, expectorant, fever, flu, gall, intestines, lactogogue, liver, malaria, menorrhagia, nausea, pacifier, palsy, poison (veterinary), refrigerant, insect repellant, rheumatism, spasm, stomachic, tea, tumor, uteritis, and yellow fever (www.ars-grin.gov/duke). LAMIACEAE



Figure 6.4. Hyptis suaveolens (Missouri Botanical Gardens)

In Jamaica, *H. suaveolens* is used to treat abscesses, ulcers, boils, and appetite. It treats the bowels, cases of diarrhea, dysentery, and constipation. Jamaicans also use it for colds, as a febrifuge, for fever, skin diseases, and urinary disorders (Lowe 2001). *H. suaveolens* is used in western Kenya and Guinea Bissau, Africa as a mosquito repellent (Seyoum et al. 2002). The essential oil from the leaves and flowers are used in Cameroon, Mali, and South India (Ngassoum, MB et al. 1999). In another province of Panama, the Darien, *S. jamaicensis* and *Hyptis* are used together for fever in children (www.ars-grin.gov/duke/dictionary/tico/s.html).

Ethnobotanical Uses of Citrus aurantifolia

According to Duke's USDA databases the worldwide ethnobotanical uses for *C*. *aurantifolia* are as follows: headache, stomachache, cough, dermatosis, dysentery, gonorrhea, neuralgia, yaws, antiseptic, aperitif, bactericide, bilious, catarrh, cold, cystitis, depurative, diarrhea, dropsy, dysmenorrheal, emetic, empacho, epistaxis, erysipelas, fever, flu, insomnia, liver, newborns, ophthalmia, pneumonia, purgative, refrigerant, rheumatism, scorpion, scurvy, soap, sores, sorethroat, stomachic, thrush, urogenital, venereal, vermifuge, witchcraft, and yellow fever (www.ars-grin.gov/duke).

Lime is used in Jamaican ethnomedicine and in Nigeria for the treatment of typhoid fever (Lowe 2001; Evans et al. 2002). It is also in the pharmacopoeia of Indonesian medicine (Limyati 1998). According to TRAMIL, *C. aurantifolia* is used in Haiti and English and Spanish-speaking countries of the Caribbean for asthma, fever, conjunctivitis, cold, cough, and diarrhea (TRAMIL). In a study of 802 patients in a

Puerto Rican hospital, 39% used lime as a sedative and 17% used it for gastrointestinal disorders (Hernandez et al. 1984).

Ethnobotanical Uses of Stachytarpheta jamaicensis

Some ethnobotanical uses for *S. jamaicensis* are listed in Table 6.1. In Jamaica, the plant is used for asthma, for blood, and as a blood purifier. It treats colds, diabetes, epilepsy, and eye ailments. It is also used for fever, high blood pressure, nervous diseases, sores, urinary disorders, and as a vermifuge. It acts as an emetic, enema, and a tonic (Lowe 2001). In Trinidad and Tobago *S. jamaicensis* is used in traditional medicine and in ethnoveterinary medicine as a lactagogue (Chariandy et al. 1999). It is also a medicinal plant used in Hong Kong (Arthur 1953). It is also used in Taiwanese folk medicine to treat liver disease and rheumatism (Shinne-Ren 1976).

According to authors of "Pharmacological and Chemical Evaluation of *Stachytarpheta jamaicensis* (Verbenaceae)," the plant is used as a vermifuge (Haiti, Bahamas, Salvador, Trinidad, Jamaica), an emetic and purgative (Bahamas, Puerto Rico, Mexico), for diarrhea (Costa Rica, Panama, Dominican Republic), for flu (Bahamas, Trinidad, Jamaica), febrifuge (Mexico, Panama, Trinidad), as an emenagogue and sudorific (Mexico), a sedative (Cuazao), antidiabetic and hypertension treatment (Dominican island), and an abortive in the Bahamas (Rodriguez 1996).

Duke's Ethnobotanical databases document its use as an abortive, to treat malaria, rhinosis, sores, headache, alopecia, amenorrhea, anodyne, asthma, boils, bronchitis, bruises, cardiac conditions, cataract, chest-colds, coughs, diarrhea, dropsy, dysentery, eczema, erysipelas, fever, flu, gonorrhea, inflammation, itch, nausea, nerves, poison, rash, rectitis, rheumatism, rhinitis, skin, sores, sprain, stomach, syphilis, tumors, venereal

disease, vermifuge, vitiligo, and yellow fever. In ethnomedical systems, it acts as a cathartic, depurative, emetic, emmenagogue, lactagogue, pressor, purgative, sedative, and sudorific (www.ars-grin.gov/duke).

Ethnobotanical Uses of Senna spp. or Cassia spp.

In Senegal, Africa *Senna occidentalis* is a pharmacologically active medicinal plant (Le Grand 1989). *Senna spp.* is used in Africa and in the Orient. It is considered a Sudanese medicinal plant and is used in India also (El-Tahir et.al 1999). The seeds of *Cassia tora* and *Cassia obtusifolia* are used as purgatives in Chinese, Japanese, and Taiwanese ethnomedical systems (Shoji et al. 1969). The popular purgatives in Japan are *Senna folium, Cassia angustifolia*, or *Cassia acutifolia* (Yoneda et al. 1997) In Africa, the leaves, roots and whole plant treat impetigo, ulcers, helminthiasis and as a purgative (Chidume 2002).

 Table 6.1 Ethnobotanical Uses of Stachytarpheta jamaicensis (Taylor 2002)

ETHNOB	SOTANY: WORLDWIDE USES of Stachytarpheta jamaicensis
Amazonia	Asthma, fever, stomach pain
Bahamas	Abortifacient, asthma, bronchitis, chest cold, emetic, itch,
	puerperium, skin, sore, vermifuge
Belize	Boils, colds, cough, fever, flu, heart, intestinal parasites, liver,
	nervousness, neuralgia, sores, stomachache
	Allergies, amenorrhea, amoebas, antacid, anthelmintic,
	antidiarrheal, antiemetic, antirheumatic, antitussive,
	antisyphilitic, arthritis, bronchitis, bronchial catarrh, cathartic,
Brazil	chest pains, cholagogue, colds, constipation, contusions,
	cough, cuts, debilitation, diaphoretic, digestive, diuretic,
	dropsy, dysentery, dyspepsia, eczema, emetic,
	emmenagogue, erysipelas, expectorant, febrifuge, fever, flu,
	gastritis, gastrointestinal disorders, hemorrhoids, hepatitis,
	hepatoprotective, high blood pressure, hoarseness, hydropsy,
	liver, lung, rheumatism, skin, sore, stimulant, stomach,
	stomachache, sudorific, tea, tonic, tumor, ulcer, urinary
	complaints, venereal disease, vermituge, worms, wounds,
	Vellow level
Cuba	Abornive, anticatarrinal, anticiabetic, CINS depressant, diuretic,
Guba	emmenagogue, emetic, hypotensive, hypothermic, lactation,
	Cathartia drapay amotia ammanagagua any inclas nonyo
Haiti	califatilo, diopsy, effetic, effinienagogue, erysipeias, fierve,
	Abartifaciant discontario, fourier inflammation, required
India	Abornacient, uysentery, iever, initalitination, meumatism,
Jamaica	Emmenadoque intestinal worms
Malava	Abortive malaria rhinosis sore
Mexico	Amenorrhea anodyne gonorrhea nerve sudorific synhilis
	vellow fever
Samoa	Boil, nausea, rhinitis, sore
South	
America	Antheimintic, antifertility, emmenagogue, vermituge
Trinidad	Boil, chest colds, collyrium, cough, depurative, dysentery,
	eczema, fever, flu, heart attack, lactagogue, ophthalmia,
	purgative, rash, rectitis, stomach, vermifuge, vitiligo, worms
West	Anthelmintic, childbirth, dysmenorrhea, emmenagogue,
Indies	lactagogue, parasites, vermifuge, worms
CHAPTER 7

GENERAL METHODS

The author bought 3 bottles of Black Drink from a vendor and bush doctor in Bastimentos, Panama, June 28, 2003. The ethnomedical preparation cost \$ 2.50/ bottle. Plants were collected in Bastimentos, Panama. Botanical identifications were determined by botanists, Ana Gomez and Rafael Rincon at the Autonomous University of Chiriqui, PÀ and by Alex Espinosa, Botanist at the University of Panama. Both *H. suaveolens* and *Senna spp.* could not be easily identified because they are foreign species. The National Herbarium of Panama had no record of these plants occurring in Panama and no matching herbarium specimens. *Senna spp.* could not be identified to species name. For the purposes of this study, properties of the genera and related species are discussed. It is likely that the plant is *Senna occidentalis*. Samples of Black Drink were analyzed by Inductively Coupled Plasma Emission Spectroscopy at the University of Georgia. Literature reviews were carried out on the pharmacognosy of the botanical parts of Black Drink using databases such as Medline and Chemical Abstracts SciFinder.

CHAPTER 8

RESULTS

Iron Analysis

The iron content of Black Drink was analyzed by Inductively Coupled Plasma Emission Spectroscopy. The samples of Black Drink showed an iron content of 2.502%. Pharmacognosy of the Plants in Black Drink

The pharmacognosy of the plants present in Black Drink; *C. aurantifolia, H. suaveolens, S. jamaicensis*, and *Senna spp.* have been investigated thoroughly in the case of *Senna* and inadequately in the case of lime. However, these plants show biological activity in cells, rats, humans, and are commonly used medicinal plants other areas of the world such as Africa, Asia, the Middle East, and Mexico. The biological activities of the 4 plant substances in Black Drink are found in Appendix 1. Phytochemicals and Biological Activities in Black Drink. Each of these plants contains hundreds of phytochemicals and the possible combinations and synergistic actions can only be imagined. Here it is proposed that Black Drink is prepared with these plant species in order to expel gastrointestinal parasites through increased intestinal peristalsis, nematicidal phytochemicals, and decreasing gastric acid. Additionally, analgesic and anti-diarrhea activities may counteract gastrointestinal irritation caused by the iron content.

Lime or *Citrus aurantifolia*

Lime has been suggested as a treatment for iron deficiency anemia because the high content of ascorbic acid significantly increases absorption of nonheme iron in the small intestine (Diaz 2003). Concentrated lime juice extract was found to inhibit the proliferation of a tumor cell line (Gharagozloo 2002). *Citrus aurantifolia* shows antibacterial and anti-fungal activity (Ebana 1991).

<u>Senna spp</u>. or Dandelion

The *Senna spp.* in Figure 8.1 contains various compounds that increase colonic motility and result in rapid propulsion; sennosides, anthraquinones, and rhein. These plants have a lengthy record of use by humans, with first historical mention by Arab physicians in the 9th or 10th century. J. Lemni states that, "senna introduced in medical practice by the Arabians remains during 10 centuries one of the most used laxatives" (1988). Sennosides, when administered to dogs, decrease the colonic motility temporarily and induce a greater number of giant contractions with high amplitudes. The authors note that a liquid feces always accompanies the giant contractions (Fioramonti 1988). In rats, administration of sennosides resulted in reducing the time for large intestinal transit from more than 6 hours to 20-30 minutes. When sennosides were given with their natural metabolites; sennidins A + B, rhein-9-anthrone, and rhein, large intestinal transit was 50-70 minutes in the rat. Partial antagonist activity against *Senna*, was displayed by indometacin, loperamide, and calcium-channel antagonists such as verapamil (Leng-Peschlow 1988).

Dr. Nnochiri in, <u>Medical Parasitology in the Tropics</u>, states that most anthelminthics work by, "paralyzing the worms in the gastrointestinal tract causing them to lose their grip on the mucosal wall and to be removed by peristalsis or purgation before

they recover " (1975). The rapid propulsion in the colon, caused by *Senna* spp. (Figure 8.2) and its metabolites, may be functioning in this manner, to clear the worms rapidly before they regain ability to reattach. *Senna spp.* increases gastrointestinal motility via



Figure 8.1. Scanned Image of the *Senna spp*. in Black Drink

smooth muscle contraction and decreases nociception (Chidume 2002). According to Duke's Phytochemical Database, the plant has analgesic and anthelminthic action due to mannitol. One related species, *Cassia tora*, has three compounds that act as laxatives and five phytochemicals which act as purgatives (www.ars-grin.gov/duke).

<u>Hyptis suaveolens</u> or Pignut

H. suaveolens inhibits the growth of chloroquine-sensitive and chloroquineresistant strains of *Plasmodium falciparum*. It contains six phytochemicals which act as analgesics. It is also an anthelminthic and a laxative due to alpha-phellandrene and pcymene, respectively. *H. suaveolens* is a nematicide and has spasmogenic properties (www.ars-grin.gov/duke). At a dose of 1mL per animal, *Hyptis suaveolens* was toxic to mice, and stimulated guinea pig ileum. It also stimulated rat limb flow at a dose of .1mL (Feng 1962).

The essential oil of *H. suaveolens* contains a monoterpene cyclic ether, cineole, or eucalyptol. 1,8-cineole is used to treat airway diseases with infection, and is found in decongestants and antitussives. It is also used as a percutaneous enhancer, is anti-microbial, anti-inflammatory, and analgesic. In one study conducted with rats, the authors concluded that the compound 1,8-cineole is gastro-protective because it decreased gastric secretory volume and gastric acid output in a dose-dependent manner (Santos 2001). This compound increases liver CYP450 when it is inhaled. It increases the metabolism, and clearance, of other drugs (Madhava 1986).

H. suaveolens was studied for its activity against the nematode, *Meloidogyne incognita*. Authors stated, "Bioassay of the crude extract of *H. suaveolens* leaves showed that the plant possessed strong nematicidal properties." Shown in Table 8.1, authors

Time of Exposure (initiates)											
Treatment	10	20	30	40	50	60	80	Correlation coefficient			
Crude extract							100%				
Whole oil	41.66	73.11	98.20					0.997			
D-	17.33	25.55	36.00	49.11	67.00	84.30		0.992			
limonene											
Menthol	45.11	62.88	83.60	99.00				0.998			

Table 8.1. Effect of crude extract, whole oil of *Hyptis suaveolens*, and its two constituents on the mortality (%) of *Meloidogyne incognita* larvae during 80 minutes of exposure. Each value is averaged from 10 replicates (Babu and Sukul 1990). **Time of Exposure (minutes)**

found that the crude extract of the leaves killed 100% of *Meloidogyne incognita* larvae in 80 minutes. The essential oils, menthol and D-limonene, were more effective, killing 100% larvae in 30 minutes. Menthol killed 99% larvae within 40 minutes and D-limonene killed 84% in 60 minutes (See Figure 8.2). They concluded that monoterpenoids such as menthol and D-limonene are more effective nematicidals than monoterpenoids with higher numbers of carbons (Babu 1990, 1118).

Stachytarpheta jamaicensis or Vervine

Vervine contains verbascoside and ipolamyide iridoids, alkaloids, triterpenes, flavonoids, and chlorogenic acid (Vela 1997; Arthur 1953). *S. jamaicensis* contains a compound called hispidulin which is, "100-fold more potent than theophylline in preventing aggregation and in increasing cAMP levels in platelets" (Bourdellat 1988, 5). *S. jamaicensis* was said to be, "of pharmaceutical value because of its high content of [anti-inflammatory compounds called] chlorogenic acids (Costa 1960)."

Dr. Duke's Phytochemical and Ethnobotanical Databases shows that the plant acts as an analgesic (<u>www.ars-grin.gov/duke</u>). In, "Pharmacological Screening of West Indian Plants," authors found that *S. jamaicensis* expresses ganglionic blocking action in guinea pig ileum and was toxic to mice at .1mL dose (1962). The water extract also stimulated rat limb flow at a dose of .1mL. The ethanol extract of *S. jamaicensis* showed mouse toxicity at a dose of .1 mL per animal, and also stimulated guinea pig ileum at that dose (Feng 1962). Another study by A. Lagarto Parra et al. found that the LD50 in mice was 2035.12 mg of plant/kg (2001, 398). Dopamine has been isolated in *S. jamaicensis* and is believed to be responsible for the strong pressor effect displayed in dogs that had been anaesthetized with pentobarbitone sodium and given *S. jamaicensis* (Durand 1962).



Figure 8.2 Mortality of menthol, D-limonene, and whole oil on *Meloidogyne incognita* larvae (Babu and Sukul 1990).

Verbascoside (acteoside) is a compound found in *S. jamaicensis*. It is responsible for analgesic, muscular relaxant, and laxative properties (Rodriguez 1996). Li Ji et. al. report that this compound inhibits tumor cells, microsomal lipid peroxidation, autoxidation of lineolic acid, is a ROS scavenger, and repairs oxidative damage in DNA bases (1997). They stated that verbascoside inhibited human gastric adenocarcinoma cellular growth by 53.2% and there was a 75% decrease of tumorigenicity for treated cells compared to controls (Ji 1997).

In a study on the anthelminthic activity of *S. jamaicensis*, the 2mg of plant leaf extract, in 100 uL of Locke's solution, inactivated 95% *Strongyloides stercoralis* larvae in 128.2 hours (See Figure 8.3). This action is comparable, if not more effective, than that of the popular antinematodal pharmaceutical, Thiabendazole (See Table 8.2). Initially, *S. jamaicensis* inactivated 100% of larvae, activity similar to that of Levamisoke (Robinson 1990).

A closely related species of *S. jamaicensis*, *Stachytarpheta cayenensis* has been shown to act as an antacid, a laxative, and it inhibits gastric ulcers via protection of the gastric mucosa. It did not show toxicity at a dose of 2 g/kg⁻¹, but did depress the central nervous system of rats and mice for four hours. "The extract reduced basal gastric acidsecretion, and secretion induced by histamine and bethanechol." Administration of the extract (.06 to 0.5 g/kg⁻¹) into the duodenum produced a dose-dependent response, inhibiting gastric acid secretion and increased pH values up to 5.8. The authors believe that the extract may inhibit the histaminergic acid secretion through cAMP, proton pump, or H2 receptors (Vela 1997).



Figure 8.3. Inactivation of larvae by *S. jamaicensis*

Plant Extract/	Inactivation Time (h	Relative Activity ^a		
Commercial Drug	It ₅₀ (95% FL)	It ₉₅ (95% FL)	lt ₅₀	It ₉₅
Thiabendazole	73.9 (70.9 - 102.5)	122.7 (76.7 - 124.5)	1.00	1.00
Albendazole	34.9 (28.4 - 49.5)	69.5 (33.4 - 70.3)	2.11	1.77
Levamisoleb	< 1.0	<1.0	>73.90	>122.70
Vervine	81.5 (57.8 - 93.0)	128.2 (68.3 - 135.7)	0.91	0.96

Table 8.2. S. jamaicensis, or Vervine, Compared to Popular Anthelminthic Drugs.

Other studies show it exerts an anti-diarrheal affect (Almeida 1995). A fraction of *S. cayenensis*, containing phenylethanoid glycoside acteoside (verbascoside) and iridoid ipolamiide, showed the strongest biological activity in comparison to other plant fractions of the plant, as an anti-inflammatory and analgesic (Elfrides 1997). One study, "Tapping an Amazonian Plethora: Four Medicinal Plants of Marajo Island, Brazil," found that *S. cayenensis* contains bioactive triterpenoid esters and catechins. The authors stated that *S. cayenensis*, "has been little studied although it contains highly active principles and as such it has great potential for further development (1993).

CHAPTER 9

DISCUSSION AND CONCLUSIONS

The "Morbidity Report" from the Bocas del Toro Hospital attests to the prevalence of IDA and intestinal parasites in the communities of Bocas del Toro and Bastimentos. Based on these high numbers and the environmental conditions conducive for transmission of parasitic diseases, it is likely that a significant portion of IDA cases are caused by intestinal parasites. Perhaps through a mixture of orally transferred information and trial and error, the bush doctors of Bastimentos have developed Black Drink, an ethnopharmacolgically effective remedy for the dual health risk of IDA and intestinal parasitosis.

The reasons that people develop IDA are high iron requirements or excessive blood loss. Women, pre-menopausal and pregnant, and children are at high risk for developing IDA. In Bastimentos, this is coupled with a diet low in bioavailable iron. The pervasive presence of blood-sucking helminthes pushes at-risk people into iron deficient and iron deficiency anemic states rapidly. Parasite-related IDA depends on a number of factors such as length of infection and worm load, iron stores in the host, and environmental exposure to eggs and larvae.

Bocas del Toro and Bastimentos have a high level of poverty, malnutrition, unsanitary disposal of waste, and infant mortality. Complicating matters, there is limited health care access. To survive under such conditions, people in developing countries

attend to primary health care with inexpensive, natural resources: medicinal plants, home remedies, and even element-derived medicines, as in the case of Black Drink.

Given the long history of intestinal parasitosis in humankind, we have an equally substantial history of chemotherapy of the helminthes, particularly those which are visible, and anti-worm remedies date back beyond the time of Aristotle and Chinese medical records. In the 1850's, anthelminthics were prepared by pharmacists with a laxative and a tonic. *Artemisia* and *Chenopodium* are plant antinematodals that were used popularly. Powdered rust of iron was even mentioned in old texts as an anthelminthic but it was the action the rust had on iron deficiency that appeared effective to the treating physician (Campbell 1986). Black Drink is a comparable pharmaceutical invention, an attempt to control parasite-related IDA.

Iron Dose

With an iron content of 2.5%, Black Drink is an effective treatment for IDA. Goodman and Gillman say that "...reduced iron (metallic iron, elemental iron) is as effective as ferrous sulfate..." (Hardman 1996). Elemental iron, converted to the more bioavailable oxidation state by lime juice is absorbed in the small intestine.

A dose of 5 - 30 ml of Black Drink would contain a quantity of iron nearly identical to iron supplementation recommended by biomedical physicians for IDA. Western medical physicians prescribe 1.5 - 2.0 mg iron / kg body weight 3 times a day for children and 4 - 6 mg iron/ kg body weight for adults. For a child weighing 50 pounds, this comes to 135.78 mg iron daily. For a 130 pound adult, the iron dose is 354 mg daily. In severe IDA cases, they may prescribe up to 480 mg iron per day. Treatment

continues for 3 - 6 months afterward, however, to build up iron stores (www.pediatriconcall.com).

Initiation of treatment with Black Drink should result in increased energy and a daily increase in hemoglobin. In the following week and a half, an increase in reticulocytes should be seen. Over one month of treatment with Black Drink at the abovementioned dose, hemoglobin would normalize. It is not clear if Black Drink can rebuild iron stores. Gastrointestinal effects are experienced at a dose of 45 mg of elemental iron but the toxic dose is 200-250 mg/ kg body weight. Therefore, Black Drink should be taken cautiously, particularly by children, and with attention to gastrointestinal reaction.

Phytochemical Actions

It is proposed here that the plant components in Black Drink decrease worm load in the host while simultaneously raising hemoglobin levels. The modes of action are through intestinal peristalsis, nematicidal properties, and decreasing gastric acid secretion, making the small intestine inhospitable to the parasites. *H. suaveolens* and *S. jamaicensis* have shown nematicidal activity *in vivo*. *S. jamaicensis* shows anthelminthic activity comparable to the anthelminthic Levamisole; and the essential oils of *H. suaveolens* killed 100% larvae within 40 minutes. *Hyptis suaveolens* decreases gastric acid secretion and *S. jamaicensis* may act by inhibiting gastric acid secretion. Finally, lime has nine nematicidal compounds (Lowe 2001).

Senna spp serves as a laxative which likely has anthelminthic function. Senna spp. speeds intestinal transit time, possibly clearing nematodes before they have a chance to recover from the nematicidal effects of *S. jamaicensis, H. suaveolens* and perhaps *C*.

aurantifolia. Chidume says of *C. tora*, a relative of *Senna spp*., that the traditional use of the plant in Africa as an anthelminthic purgative is justifiable (2002).

The plants show a range of other bioactivities that may or may not have effects on IDA or hookworms. However, the analgesic affects, decreased nociception, anti-oxidant and anti-diarrheal properties may well buffer the high level of iron in Black Drink. Further investigation is needed into the possible anthelmintic activity of the phytochemical constituents to assess if they have any action on adult hookworms, *Trichuris*, or *Ascaris*. The plant components are used, to cure a variety of illnesses, by people in many parts of Africa, Asia, the Americas, and the Caribbean. Overall, the plants in Black Drink are interesting leads for research and development.

Black Drink also fits the requirements for drugs according to E.S. Turner, who says, historically, in attempts to find cures to diseases, "remedies were esteemed according to whether they were rare, complex, or unpleasant. A drug which combined all three qualities was irresistible." (Turner 1958) Black Drink tastes horrible, is rare, prepared by bush doctors, with common and uncommon medicinal plants included, and in numbers of three. It has a laxative affect due to the *Senna spp.*, necessary for healthy equilibrium. Black Drink is a medicine with strong ties to traditional African ethnomedical beliefs and practices. Because the condition, "Low Blood," is well understood, the use of Black Drink may result in better patient compliance and trust.

IDA has devastating health consequences including infant and maternal mortality, permanent cognitive and growth abnormalities, and a host of less severe symptoms such as decreased energy and productivity. Black Drink may be one of the most practical strategies to combat this health threat for people living in poor, rural areas with

inadequate health-care. It appears that Black Drink is a successful, affordable, two-prong treatment for IDA and for helminthiasis in Bastimentos, Panama.

Future Work: Ministry of Health in Bocas del Toro and Bastimentos

Control of Iron Deficiency

- 1. Administer iron supplements starting with high-risk groups
- 2. Increase dietary intake of bioavailable iron and decrease inhibitors
- 3. Food fortification with iron
- 4. Health care personnel should support those ethnomedical practices that improve patient compliance or health.
- 5. Improve laboratory technology in effort to diagnose IDA and worm infestations.
- 6. Doctors should ask about the use of laxatives and home remedies
- 7. Using the numbers 3, 6, 9 and recommending medicinal plants might be of advantage in earning patient trust and compliance.
- 8. Be familiar with the folk terminology of blood, its qualifiers (particularly

"Low/High"), and the importance of equilibrium.

Helminth Control in Bastimentos

- 1. Water treatment
- 2. Prevent transmission of intestinal parasites
 - a. sanitary disposal of human waste
 - b. wearing shoes
 - c. using cement walkways
- 3. Periodic anthelminthics and iron supplements should be administered to at-risk groups (children and pregnant women).

Educational campaigns to the public should include:

- 1. The connection of intestinal parasites and IDA i.e. "Worms cause 'Low Blood.""
- 2. Parasites and their transmission
- 3. Water treatment
- 4. IDA
- 5. Sanitary disposal of waste
- 6. Foods high in iron
- Bush doctors should recommend to anemic patients, to seek anthelminthic drugs and increase dietary iron.

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APPENDIX A. (www.ars-grin.gov/duke.html)

PHYTOCHEMICALS AND BIOLOGICAL ACTIVITIES IN BLACK DRINK

Chemicals and their Biological Activities in: Citrus aurantiifolia (CHRISTM.)

SWINGLE (Rutaceae) -- Lime

1,4-CINEOLE Fruit 180 ppm;

No activity reported.

1,8-CINEOLE *Fruit* 70 ppm;

(-)-Chronotropic 87 nl/ml; (-)-Inotropic; Acaricide; Allelopathic; Allergenic; Anesthetic; Anthelmintic; Antiacetylcholinesterase IC50=41 ug/ml; Antiallergic; Antibacterial 50 ppm; Antibronchitic; Anticariogenic; Anticatarrh; Anticholinesterase; Antifatigue; Antihalitosic; Antiinflammatory; Antilaryngitic; Antinociceptive; Antipharyngitic; Antirheumatic; Antirhinitic; Antiseptic; Antisinusitic; Antispasmodic; Antistaphylococcic; Antitussive; Antiulcer; Candidicide; Carcinogenic; Choleretic; CNS-Stimulant; Convulsant; Counterirritant; Cytochrome-P450-Inducer; Decongestant; Degranulant 0.3 ul/ml; Dentifrice; Edemagenic inj; Expectorant; FLavor *FEMA 1-200*; Fungicide; Gastroprotective; Gram(+)icide; Gram(-)icide; Hepatotonic; Herbicide IC50=78uM; Hypotensive; Inflammatory inj; Insectifuge; Irritant; Myorelaxant; Nematicide; Neurotoxic; P450-Inducer; Perfume; Pestic ide; Rubefacient; Secretogogue; Sedative; Spasmogenic; Surfactant; Testosterone-Hydroxylase-Inducer; Trichomonicide LD100=1,000 ug/ml

2,2-DIMETHYL-5(-1)-METHYL-1-PROPENYL)TETRA-HYDROFURAN *Plant 30 ppm*;

No activity reported.

2,6,6-TRIMETHYL-2-VINYL-TETRAHYDROPYRAN *Fruit* 16 ppm; No activity reported.

5-METHOXY-PSORALEN *Fruit*:

Antimutagenic; Antipsoriac; Antitumor; Antivitiligic; Cancer-Preventive; Carcinogenic?; Fungicide; Melaninogenic; Melatoninogenic; Photodermatitigenic **ALPHA,ALPHA-P-TRIMETHYLBENZYL-ALCOHOL** *Fruit* 60 ppm; No activity reported.

ALPHA-ALPHA-P-TRIMETHYL-BENZYL Plant:

No activity reported.

ALPHA-BERGAMOTENE Fruit 50 - 250 ppm

No activity reported.

ALPHA-BISABOLENE Fruit 250 - 400 ppm

No activity reported.

SWINGLE (Rutaceae) -- Lime

ALPHA-LINOLENIC-ACID Fruit 190 - 1,615 ppm

5-Alpha-Reductase-Inhibitor; Antiaggregant; Antihypertensive; Antiinflammatory *IC50=42 uM*; Antileukotriene-D4; Antimenorrhagic; Antimetastatic; Antiprostatitic; Cancer-Preventive; Hypotensive; Immunostimulant 0.12 *ml/man/day*; Lymphocytogenic 0.5 ug/ml; Propecic; Prostaglandin-Synthesis-Inhibitor 39.5 g/day/hmn; Vasodilator

ALPHA-P-DIMETHYL-STYRENE Fruit 50 ppm;

No activity reported.

ALPHA-PHELLANDRENE Fruit 20 ppm;

Antibacterial; Antistaphylococcic; Dermal; Emetic; FLavor *FEMA 10-130*; Fungicide; Insectiphile; Irritant; Laxative; Perfumery; Pesticide **ALPHA-PINENE** *Fruit* 80 - 240 ppm

Allelochemic; Allergenic; Antiacne; Antibacterial; Antifeedant; Antiflu; Antiinflammatory; Antispasmodic; Antiviral; Cancer-Preventive; Coleoptophile; Expectorant; FLavor *FEMA 15-150*; Herbicide *IC50=30 uM*; Insecticide *0.82*

uM/fly; Insectifuge *50 ppm*; Insectiphile; Irritant; P450-2B1-Inhibitor *IC50=0.087 uM*; Perfumery; Pesticide; Sedative; Spasmogenic; Tranquilizer; Transdermal **ALPHA-TERPINENE** *Fruit 80 ppm*;

Acaricide; ACE-Inhibitor 100 ug/ml (weak activity); Aldose-Reductase-Inhibitor 100 ug/ml; Antiacetylcholinesterase IC50=1.0 mM; Antinitrosaminic;

Antispasmodic; FLavor *FEMA 1-40*; Insecticide 0.86 *uM/fly*; Insectifuge; P450-2B1-Inhibitor *IC50=0.76 uM*; Perfumery; Pesticide; Spasmogenic

ALPHA-TERPINEOL Fruit 30 - 590 ppm

ACE-Inhibitor 100 ug/ml (weak activity); Aldose-Reductase-Inhibitor 100 ug/ml; Allelopathic; Antiacne; Antibacterial *MIC*=800-1,600 ug/ml; Anticancer; Anticariogenic; Antiseptic; Cicatrizant *ED50*=240 ug/g mus; FLavor *FEMA 5-40*; Insecticide 1.29 uM/fly; Motor-Depressant; Nematicide *MLC*=1 mg/ml; Perfumery; Pesticide; Sedative; Termiticide *IC100*=5 mg/g; Vulnerary *ED50*=240 ug/g mus

ALPHA-THUJENE Fruit 40 ppm;

No activity reported.

BERGAMOTTIN Fruit:

Calcium-Antagonist 20 ug/ml gpg; Cytochrome-P450-Inhibitor **BERGAPTEN** *Fruit*:

Antiaggregant; Antiapertif; Anticonvulsant; Antihistaminic 25 mg/kg ipr mus; Antiinflammatory; Antijet-lag; Antileukodermic; Antimitotic 5-25 ug/ml; Antiplatelet; Antipsoriac; Antispasmodic; Antitumor; Calcium-Antagonist; Cancer-Preventive; Carcinogenic; Clastogenic; CNS-Depressant; DME-Inhibitor IC50=96 uM; Hypotensive; Insecticide; Lipolytic; Molluscicide; Mutagenic; Pesticide; Phototoxic; Piscicide

BETA-BISABOLENE *Fruit* 90 ppm;

SWINGLE (Rutaceae) -- Lime

Abortifacient; Antirhinoviral *IC50=1,800?*; Antiulcer *IC57=100 mg/kg*; Antiviral *IC50=1,800?*; Perfumery; Stomachic

BETA-PHELLANDRENE Fruit 90 ppm;

Expectorant; Fungicide; Perfumery

BETA-PINENE *Fruit* 90 - 1,190 ppm

Allergenic; Antiinflammatory; Antiseptic; Antispasmodic; Candidicide; FLavor *FEMA 15-600*; Herbicide; Insectifuge; Irritant; Perfumery; Pesticide; Spasmogenic

BETA-TERPINEOL *Fruit* 70 ppm;

Insectifuge; Perfumery; Pesticide

BORNEOL Fruit 60 ppm;

(-)-Chronotropic 29 ug/ml; (-)-Inotropic; Allelochemic; Analgesic; Antiacetylcholine; Antibacterial MIC=125-250 ug/ml; Antibronchitic; Antiescherichic MIC=125 ug/ml; Antifeedant; Antiinflammatory; Antiotitic; Antipyretic; Antisalmonella; Antispasmodic ED50=0.008 mg/ml; Antistaphylococcic MIC=250 ug/ml; Antiyeast; Candidicide; Choleretic; CNS-Stimulant; CNS-Toxic; FLavor FEMA < 1; Fungicide; Hepatoprotective; Herbicide IC50=470 mM IC50=470 uM; Inhalant; Insect-Repellent; Insectifuge; Irritant; Myorelaxant; Nematicide MLC=1 mg/ml; Perfumery; Pesticide; Sedative; Tranquilizer

CAMPHENE Fruit 50 - 80 ppm

Allelopathic; Antilithic?; Antioxidant; Expectorant; FLavor *FEMA 15-175*; Hypocholesterolemic?; Insectifuge; Pesticide; Spasmogenic

CARYOPHYLLENE Fruit 30 - 250 ppm

Aldose-Reductase-Inhibitor; Antiacne; Antiasthmatic; Antibacterial; Anticariogenic *MIC*=>1,600 ug/ml; Antiedemic; Antifeedant 500 ppm; Antiinflammatory *IC50*=100 uM; Antispasmodic; Antistaphylococcic; Antistreptococcic; Antitumor; Candidicide; FLavor *FEMA* 20-200; Fungicide; Insectifuge; Irritant; Perfumery; Pesticide; Sedative; Termitifuge

CITRONELLAL Fruit 140 ppm;

Acaricide; Allergenic; Antibacterial; Antiseptic *3.8 x phenol*; Antistaphylococcic; Antistreptococcic; Candidicide; Embryotoxic; FLavor *FEMA* <1; Fungicide; Insectifuge; Irritant; Motor-Depressant; Mutagenic?; Nematicide *MIC 1 mg/ml*; P450-2B1-Inhibitor *IC50=1.56 uM*; Perfumery; Pesticide; Sedative *ED=1 mg/kg*; Teratogenic

DECANAL Fruit 9 - 10 ppm No activity reported. DECANOL Fruit 6 ppm; Nematicide MLC 100-700 ug/ml; Pesticide DECYL-ACETATE Fruit 10 ppm; FLavor FEMA <1-1 DIMETHOXYCOUMARIN Fruit: Chemicals and their Biological Activities in: Citrus aurantiifolia (CHRISTM.)

SWINGLE (Rutaceae) -- Lime

No activity reported. **DODECANAL** *Fruit 1 ppm*; FLavor *FEMA 1-100*; Irritant **FENCHOL** *Fruit 120 ppm*; No activity reported. **FOLUENE** *Plant*: No activity reported. **FURFURAL** *Fruit 1 ppm*; Antiseptic; FLavor *FEMA 1-30*; Fungicide; Insecticide; Irritant; **GAMMA-SELINENE** *Fruit 20 ppm*;

No activity reported.

GAMMA-TERPINENE Fruit 60 - 2,170 ppm

Acaricide; ACE-Inhibitor 100 ug/ml (weak activity); Aldose-Reductase-Inhibitor 100 ug/ml; Antiacetylcholinesterase IC23=1.2 mM; Antifeedant; Antioxidant; FLavor FEMA 1-40; Insectifuge; Irritant; Perfumery; Pesticide

GERANIAL Fruit 10 - 680 ppm

Antibacterial; AntiEBV *IC50=16 uM*; Antiviral; Pesticide

GERANYL-ACETATE Fruit 30 - 310 ppm

Allergenic; FLavor *FEMA 1-20*; Insectiphile; Perfumery; Sedative

ISOIMPERATORIN *Fruit*:

Antitumor-Promoter *IC94=50 ug/ml*; Artemicide *ED50=6->100 ug/ml*; Calcium-Antagonist; Cytochrome-P450-Inhibitor 2 *nM*; Cytotoxic (Breast) *ED50=6.56 ug/ml*; Cytotoxic (Colon) *ED50=>10 ug/ml*; DME-Inhibitor *IC50=46 uM*; Pesticide

ISOPIMPINELLIN *Fruit*:

Antiappetant; Antifeedant; Antiinflammatory *100 ppm*; Antilipogenic; Antimitotic *5-25 ug/ml*; Antitubercular; Calcium-Antagonist; Cancer-Preventive; Diuretic *125 mg/kg*; Fungicide; Insecticide; Molluscicide; Mutagenic; Pesticide; Piscicide

LIMONENE Fruit 4,700 - 7,500 ppm

Acaricide $LC100=8 \, uM$; AChE-Inhibitor; Allelochemic; Allergenic 1/20thcarene; Antiacetylcholinesterase $IC22-26=1.2 \, mM$; Antialzheimeran?; Antibacterial; Anticancer; Antifeedant; Antiflu; Antilithic; Antimutagenic; Antiseptic; Antispasmodic $ED50=0.197 \, mg/ml$; Antitumor; Antitumor (Breast); Antitumor (Pancreas); Antitumor (Prostate); Antiviral; Cancer-Preventive; Candidistat; Chemopreventive; Detoxicant; Enterocontractant; Expectorant; FLavor; Fungiphilic; Fungistat; Herbicide $IC50=45 \, uM$; Insecticide $0.37 \, uM/fly$; Insectifuge; Irritant; Nematicide $IC=100 \, ug/ml$; Ornithine-Decarboxylase-Inhibitor ~750 mg/kg (diet); P450-Inducer; Pesticide; Photosensitizer; Sedative $ED=1-32 \, mg/kg$; Transdermal

LINALOL *Fruit* 9 - 20 ppm No activity reported.
Chemicals and their Biological Activities in: Citrus aurantiifolia (CHRISTM.)

SWINGLE (Rutaceae) -- Lime

MALIC-ACID Fruit 2,000 ppm;

Antiatherosclerotic; Antibacterial; Antioxidant Synergist; Antiseborrheic; Antiseptic; Antitubercular; Antitumor; Bacteristat; Bruchiphobe; Hemopoietic; Laxative?; Mycobactericide; Pesticide; Sialogogue MALONIC-ACID *Fruit*:

Irritant

METHYL-HEPTENONE *Fruit* 1 ppm;

No activity reported.

MYRCENE *Fruit* 70 - 1,030 ppm

ACE-Inhibitor *100 ug/ml*; Aldose-Reductase-Inhibitor; Allergenic; Analgesic; Antibacterial; Anticonvulsant; Antimutagenic; Antinitrosaminic; Antinociceptive *10-20*

Chemicals and their Biological Activities in: Citrus aurantiifolia (CHRISTM.)

SWINGLE (Rutaceae) -- Lime

mg/kg ipr mus 20-40 mg/kg scu mus; Antioxidant; Antispasmodic; FLavor FEMA 0.5-9; Fungicide; Hypothermic; Insectifuge; Irritant; P450-2B1-Inhibitor *IC50=0.14 uM*; Perfumery; Pesticide NERAL Fruit 40 - 460 ppm Antibacterial; Antispasmodic; Pesticide; Termiticide LD100=5 mg/gNERYL-ACETATE Fruit 1 - 310 ppm Antiflu; Antiviral; FLavor FEMA 1-15; Perfumery; Pesticide **NERYL-FORMATE** *Fruit* 20 ppm; FLavor *FEMA 5-15*: Perfumery NONANAL Fruit 20 ppm; No activity reported. **NONANE** *Fruit* 6 ppm; No activity reported. NONANOL Fruit 1 - 10 ppm No activity reported. **NOOTKATONE** *Fruit* 1 ppm; Antiulcer 20 mg/kg orl rat; FLavor FEMA 3-50; Perfumery OCTANAL Fruit 30 - 80 ppm No activity reported. **OCTANOIC-ACID** Fruit 2 ppm; Candidicide; FLavor FEMA 3-20; Fungicide; Perfumery; Pesticide **OCTANOL** *Fruit* 1 ppm; No activity reported. **OXALIC-ACID** Fruit: Acaricide; Antiseptic; CNS-Paralytic; Fatal; Hemostatic; Irritant; Pesticide; Renotoxic: Varroacide **P-CYMENE** *Fruit* 50 - 1,160 ppm Analgesic; Antiacetylcholinesterase *IC40=1.2 mM*; Antibacterial; Antiflu; Antirheumatalgic; Antiviral; FLavor FEMA 12-250; Fungicide; Herbicide *IC50=50 uM*; Insectifuge; Irritant; Laxative; Pesticide; Sedative; Trichomonicide LD100=50 ug/ml**PERILLALDEHYDE** Fruit: Acaricide; Antibacterial MIC=500->1,000 ug/ml; Antimelanomic IC50=120 *uM/l*; Antiproliferative; Antiseptic; Candidicide *MIC=500 ug/ml*; Fungicide *MIC=250-500 ug/ml*; Mutagenic; Nematicide *MLC=1 mg/ml*; Sedative; Vibriocide 250 ug/ml **PHLOBOTANNIN** *Fruit*: No activity reported. **POLYHYDROXYPHLOBAN** Fruit: No activity reported. **QUINIC-ACID** Fruit: Choleretic

Chemicals and their Biological Activities in: Citrus aurantüfolia (CHRISTM.)

SWINGLE (Rutaceae) -- Lime

SABINENE Fruit 160 ppm; Perfumery SUGARS Fruit 17,400 ppm; No activity reported. TERPINEN-1-OL Fruit 70 ppm; No activity reported. TERPINEN-4-OL Fruit 166 ppm; Allelopathic; Antiacetylcholinesterase *IC21-24=1.2 mM*; Antiacne; Antiallergic; Antiasthmatic; Antibacterial; Antioxidant; Antiseptic; Antispasmodic; Antitussive; Antiulcer; Bacteriostatic; Diuretic 0.1 ml/rat; Fungicide; Herbicide *IC50=200 mM IC50=22 uM*; Insectifuge; Irritant; Nematicide *MLC=1 mg/ml*; Pesticide; Renoirritant; Spermicide *ED100=0.015*; Vulnerary **TERPINOLENE** Fruit 60 - 120 ppm Allelochemic; Antifeedant; Antinitrosaminic; Deodorant; FLavor FEMA 15-60; Fungicide; Perfumery; Pesticide THYMYL-METHYL-ETHER Fruit 2 ppm; No activity reported. **TRIDECANE** *Fruit* 2 *ppm*; No activity reported. UNDECANE Fruit 3 ppm; No activity reported. **XANTHYLETIN** *Plant*: DME-Inhibitor *IC50=57.5 uM*

1,7-DIHYDROXY-5-METHOXYCARBONYL-3-METHYLXANTHONE *Plant*:

No activity reported.

4,4',5,5'-TETRAHYDROXY-2,2'-DIMETHYL-1,1'-BIANTHRAQUINONE *Leaf*:

No activity reported.

4-O-BETA-D-MANNOPYRANOSYL-D-MANNOPYRANOSE *Seed*: No activity reported.

6-O-ALPHA-D-GALACTOPYRANOSYL-D-MANNOPYRANOSE *Seed*: No activity reported.

ACHROSINE *Plant*:

No activity reported.

ALOE-EMODIN Seed:

Antibacterial *MIC*=2-64 ug/ml; Antiherpetic; Antileukemic; Antisalmonella; Antiseptic; Antistaphylococcic; Antitumor 1 ug/ml; Antiviral; Arylamine-N-Acetyltransferase-Inhibitor; Calcium-Antagonist (*strong activity*); Candidicide *MIC*=25-250 ug/ml; Cathartic; Cytotoxic 20 ppm; Fungicide *MIC*=25-250 ug/ml; Genotoxic; Laxative; Mutagenic; Pesticide; Purgative *ED50*=>59.6 mg/kg orl *mus*; Termitifuge; Topoisomerase-II-Inhibitor 1 mM IC50=741 uM/ml; Tuberculostatic

ALPHA-3-SITOSTEROL Plant:

No activity reported.

ANTHRAQUINONES Root 19,000 ppm;

Antilithic; Bird-Repellent; Carcinogenic; Laxative; Litholytic; Toxic

ANTHRONES Root 45,000 ppm;

No activity reported.

APIGENIN-C-GLYCOSIDE Plant:

No activity reported.

BETA-SITOSTEROL-ALPHA-GLUCOSIDE Seed:

No activity reported.

BIANTHRAQUINONE *Plant*:

No activity reported.

CAMPESTEROL Seed:

Antioxidant *IC37=10 uM*; Hypocholesterolemic

CASSIOLLIN Plant:

No activity reported.

CHRYSAROBIN Seed 2,500 ppm;

Allergenic; Antipsoriac; Antitrichophytotic; Cytotoxic *1 ug/ml*; Emetic; Fungicide; Irritant; Keratolytic; Mutagenic; Pesticide **CHRYSOPHANOL** *Leaf*: *Root*:

Antibacterial; Antiseptic; Calcium-Antagonist 5/6 aloeemodin; Candidicide; Cathartic; Hemostat; Pesticide; Pigment; Purgative *ED50=>500 mg/kg orl mus*; Termitifuge

EMODIN Root:

Allergenic; Antiaggregant; Antibacterial; Anticytomegalovirus ED50=1.1 ug/ml; Antifeedant; Antiinflammatory 15 mg/kg; Antileukemic; Antilymphomic; Antimutagenic; Antineoplastic; Antiplaque ED50=1.1 ug/ml; Antisarcomic; Antiseptic; Antispasmodic; Antisprout; Antitumor (Breast); Antiulcer 15 mg/kg; Antiviral EC50=1.1 ED50=1.1 ug/ml; Cathartic; CNS-Depressant 15 mg/kg ipr mus; Cytotoxic CD50=2.6 ug/ml; Genotoxic; Gonadotropic; Hypolipidemic; Immunostimulant; Immunosuppressant; Leucocytogenic; Mutagenic; Pesticide; Prostaglandin-Synthesis-Inhibitor IC50=23 uM/ml; PTK-Inhibitor; Purgative ED50=>500 mg/kg orl mus; Styptic; Topoisomerase-II-Inhibitor 1 mM IC50=7 uM/ml; Trichomonicide; Vasodilator

FUNICULOSIN Plant:

No activity reported.

GAMMA-SITOSTEROL Plant:

No activity reported.

GUM Seed:

No activity reported.

HELMINTHOSPORIN Seed:

No activity reported.

ISLANDICIN Seed:

No activity reported.

JACEIDIN-7-RHAMNOSIDE *Plant*:

No activity reported.

MATTEUCINOL-7-RHAMNOSIDE Leaf:

No activity reported.

MUCILAGE Seed 360,000 ppm;

Cancer-Preventive; Demulcent

O-ALPHA-D-GALACTOPYRANOSYL-(1-6)-BETA-D-

MANNOPYRANOSYL... Plant:

No activity reported.

O-ALPHA-D-MANNOPYRANOSYL-(1-4)-O-BETA-D-

MANNOPYRASONYL... Plant:

No activity reported.

OXYMETHYLANTHRAQUINONE Root 3,000 ppm; Seed 2,500 ppm;

No activity reported.

PHYSCION *Root*:

Antiseptic; Calcium-Antagonist 5/6 aloeemodin; Cathartic; Pesticide; Purgative ED50=>500 mg/kg orl mus

PHYSCION-1-BETA-D-GLUCOPYRANOSIDE Flower: No activity reported. **PHYSCION-DIANTHRONE** Seed: No activity reported. **QUERCETIN** *Root* : 11B-HSD-Inhibitor; 5-Lipoxygenase-Inhibitor IC50 (uM)=4; Aldose-Reductase-Inhibitor 100 uM 4 ug/ml IC50=0.344 uM IC50=0.84 ug/ml cow; Allelochemic IC82=1 mM; Allergenic; Analgesic; Antiaflatoxin IC50=25 uM IC50=7.5 ppm; Antiaggregant 30 uM IC50=55 uM; Antiallergic IC50=14 uM; Antialzheimeran; Antianaphylactic; Antiarthritic; Antiasthmatic; Antiatherosclerotic; Antibacterial; Anticarcinomic (Breast) IC50=1.5 uM; Anticariogenic ID50=120 ug/ml; Anticataract; Anticolitic 400 mg/man/3x/day; Anticomplementary; AntiCrohn's; Anticystitic 1,000 mg/day/4 weeks; Antidermatitic; Antidiabetic; Antielastase *IC50=0.8 ug/ml*; Antiencephalitic; Antiescherichic; Antiestrogenic; Antifeedant *IC52*=<*1,000 ppm diet*; Antifibrosarcomic; Antiflu; Antigastric; Antigonadotropic; AntiGTF ID50=120 ug/ml; Antihepatotoxic; Antiherpetic 48-150 ug/ml; Antihistaminic IC50=<10 uM; AntiHIV; Antihydrophobic; Antihypertensive; Antiinflammatory 20-150 mg/kg; Antileishmanic IC50=64; Antileukemic 5.5-60 uM IC50=10 uM IC50=>10 ug/ml; Antileukotriene; Antilipoperoxidant IC67=50; Antimalarial IC50=1-6.4 ug/ml; Antimelanomic; Antimetastatic; Antimutagenic ID50=2-5 nM; Antimyocarditic; Antinitrosaminic; Antinociceptive; Antioxidant 4.7 x Vit. E ED50=2.3 uM IC47=10 uM IC96=300 *ppm*; Antipancreatitic; Antiperiodontal; Antipermeability; Antiperoxidant; Antipharyngitic; Antiplaque; Antiplasmodial *IC50=13-64*; AntiPMS 500 mg/2x/day/wmn; Antipodriac; Antipolio; Antiproliferant 10 nM; Antiprostanoid; Antiprostatitic: Antipsoriac: Antiradicular *IC50=4.6 uM*: Antispasmodic: Antistreptococcic *ID50=120 ug/ml*; Antithiamin; Antithrombic; Antitrypanosomic *IC50=13*; Antitumor *10 uM*; Antitumor (Bladder); Antitumor (Breast); Antitumor (Colon); Antitumor (Lung); Antitumor (Ovary); Antitumor (Skin) 20 uM; Antitumor-Promoter; Antiulcer; Antiviral 48-150 ug/ml IC50=10 *uM*; Apoptotic 20-60 *uM*; ATPase-Inhibitor; Bacteristat 10 mg/ml; Bradycardiac; Calmodulin-Antagonist; cAMP-Phosphodiesterase-Inhibitor; Cancer-Preventive; Candidicide; Capillariprotective; Carcinogenic 40,000 ppm (diet) mus; Catabolic; COMT-Inhibitor; Copper-Chelator; COX-2-Inhibitor <40 uM; Cyclooxygenase-Inhibitor; Cytochrome-P450-1A2-Inhibitor; Cytotoxic ED50=70 ug/ml IC82=100 ug/ml; Deiodinase-Inhibitor; Diaphoretic?; Differentiator 5.5 uM; Estrogenic 10% genistein; Fungicide; Glucosyl-Transferase-Inhibitor ID50=120 ug/ml; Hemostat; Hepatomagenic 5,000 ppm (diet) rat; Hepatoprotective; HIV-RT-Inhibitor *IC50*=<*1 ug/ml*; Hypoglycemic *100 mg/kg orl rat*; Inotropic; Insulinogenic; Juvabional; Larvistat 8,000 ppm diet; Lipoxygenase-Inhibitor IC11=1.25 mM IC50=0.1-5 uM; MAO-A-Inhibitor; Mast-Cell-Stabilizer; Metal-Chelator (Copper); Metalloproteinase-Inhibitor *IC50*=>42 uM; MMP-9-Inhibitor 20 uM;

Mutagenic; NADH-Oxidase-Inhibitor; NEP-Inhibitor *IC50=>42 uM*; Neuroprotective 5-25 uM; NO-Inhibitor *IC>50=125 uM*; NO-Synthase-Inhibitor 5-50 uM; Ornithine-Decarboxylase-Inhibitor <10 uM; P450-Inducer 5 uM; P450-Inhibitor 50-100 uM; Pesticide; Phospholipase-Inhibitor; Plasmodicide; Proliferant; Prostaglandin-Synthesis-Inhibitor 40 ug/ml; Protein-Kinase-C-Inhibitor; PTK-Inhibitor 0.4-24 uM; Quinone-Reductase-Inducer 13 uM 6 uM; Teratologic;

Topoisomerase-I-Inhibitor *IC50=12.8 ug/ml IC50=42 uM*; Topoisomerase-II-Inhibitor *IC50=1-6.9 ug/ml IC50=23-40 uM*; Tumorigenic 0.1% diet orl rat/yr; Tyrosinase-

Inhibitor *ID50=70 uM*; Tyrosine-Kinase-Inhibitor; Vasodilator; Xanthine-Oxidase-Inhibitor *IC50=>0.4 ug/ml*

RHEIN Seed:

Antibacterial; Anticarcinomic; Anticariogenic; Anticytomegalovirus ED50=1.1ug/ml; Antineoplastic; Antiplaque ED50=0.6 ug/ml; Antiseptic; Antitumor; Antiviral EC50=1.1 ED50=0.61 ug/ml; Calcium-Antagonist 9/10 aloeemodin; Candidicide; Cathartic; Cytotoxic CD50=3.4 ug/ml; Fungicide; Pesticide; Proteinase-Inhibitor; Purgative ED50=97.5 mg/kg orl mus

TANNIC-ACID Seed:

Aldose-Reductase-Inhibitor *IC50=1.8 ug/ml*; Allergenic; Antianacarditic (*Rhus*); Antibacterial; Anticariogenic; Anticolitic; Antidecubitic; Antidermatotic; Antidiarrheic; Antidote *For Heavy Metals*; Antidysenteric; Antiencephalitic; Antienteritic; Antifeedant 2-4% diet; Antigargantitic; Antigingivitic; Antihemorrhoidal; Antiherpetic; AntiHIV *IC90=200 ug/ml*; Antimutagenic; Antinitrosaminic; Antiobesity (*Antinutrient*); Antiophidic; Antioxidant *IC56=30 ppm*; Antipharyngitic; Antipolio; Antirhinitic; Antiseptic; Antistomatitic; Antitonsilitic; Antiulcer; Antiviral; Astringent; Cytotoxic *15 ug*; Detoxicant; Emetic; FLavor *FEMA 1-1,000*; Hemostat; Hepatotoxic; Immunostimulant; Pesticide

XANTHORIN Seed:

No activity reported.

Wild Hops

1,1,3-TRIMETHYLDECAHYDROCYCLOPROPAZULENE *Plant* 140 ppm; No activity reported. 1,3,3-TRIMETHYLBICYCLO{2.2.1}-HEPTAN-2-OL Plant 80 ppm; No activity reported. 1,4-DIMETHYL,1,2,3,3A,4,5,6,7-OCTAHYDROAZULENE Plant 195 ppm; No activity reported. **1,8-CINEOLE** *Plant* 130 - 4,555 ppm (-)-Chronotropic 87 *nl/ml*; (-)-Inotropic; Acaricide; Allelopathic; Allergenic; Anesthetic; Anthelmintic; Antiacetylcholinesterase IC50=41 ug/ml; Antiallergic; Antibacterial 50 ppm; Antibronchitic; Anticariogenic; Anticatarrh; Anticholinesterase; Antifatigue; Antihalitosic; Antiinflammatory; Antilaryngitic; Antinociceptive; Antipharyngitic; Antirheumatic; Antirhinitic; Antiseptic; Antisinusitic; Antispasmodic; Antistaphylococcic; Antitussive; Antiulcer; Candidicide; Carcinogenic; Choleretic; CNS-Stimulant; Convulsant; Counterirritant; Cytochrome-P450-Inducer; Decongestant; Degranulant 0.3 ul/ml; Dentifrice; Edemagenic inj; Expectorant; FLavor FEMA 1-200; Fungicide; Gastroprotective; Gram(+)icide; Gram(-)icide; Hepatotonic; Herbicide *IC50*=78 *uM*; Hypotensive; Inflammatory *inj*; Insectifuge; Irritant; Myorelaxant; Nematicide; Neurotoxic; P450-Inducer; Perfume; Pesticide; Rubefacient; Secretogogue; Sedative; Spasmogenic; Surfactant; Testosterone-Hydroxylase-Inducer; Trichomonicide *LD100=1,000 ug/ml* 2,5-DIMETHYL-3-METHYLENE-1,5-HEPTADIENE Plant 125 ppm; No activity reported. 2,6-DIMETHYL-6-(4-METHYL)BICYCLO{3.1.1}-HEPT-2-ENE Plant 110 ppm; No activity reported. 3,7-DIMETHYL-1,6-OCTADIEN-3-OL Plant 180 ppm; No activity reported. 3-CYCLOHEXEN-1-CARBOXALDEHYDE Plant 840 ppm; No activity reported. 4,11,11-TRIMETHYL-8-METHYLENE-BICYCLO{7.2.0}-UNDEC-4-ENE **Plant** 3,320 ppm; No activity reported. 4-METHYL-1-(1-METHYLETHYL)-3-CYCLOHEXEN-1-OL Plant 260 ppm;No activity reported. 5ALPHA-ANDROST-2,11-DIONE Plant 390 ppm; No activity reported. 5ALPHA-ANDROST-9(11)-EN-12-ONE Plant 270 ppm; No activity reported. 5BETA,8BETA,H-9BETA,H-10ALPHA-LAB-14-ENE Plant 435 ppm; No activity reported.

Wild Hops

ALPHA-CADINOL Plant 125 ppm;
No activity reported.
ALPHA-CARYOPHYLLENE Plant 480 ppm;
No activity reported.
ALPHA-CARYOPHYLLENE-ALCOHOL Plant 85 ppm;
No activity reported.
ALPHA-CYMENE Plant 250 ppm;
No activity reported.

ALPHA-PHELLANDRENE Plant 285 ppm;

Antibacterial; Antistaphylococcic; Dermal; Emetic; FLavor *FEMA 10-130*; Fungicide; Insectiphile; Irritant; Laxative; Perfumery; Pesticide

ALPHA-PINENE Plant 215 ppm;

Allelochemic; Allergenic; Antiacne; Antibacterial; Antifeedant; Antiflu; Antiinflammatory; Antispasmodic; Antiviral; Cancer-Preventive; Coleoptophile; Expectorant; FLavor *FEMA 15-150*; Herbicide *IC50=30 uM*; Insecticide *0.82 uM/fly*; Insectifuge *50 ppm*; Insectiphile; Irritant; P450-2B1-Inhibitor *IC50=0.087 uM*; Perfumery; Pesticide; Sedative; Spasmogenic; Tranquilizer; Transdermal **ALPHA-TERPINENE** *Plant 130 ppm*;

Acaricide; ACE-Inhibitor 100 ug/ml (weak activity); Aldose-Reductase-Inhibitor 100 ug/ml; Antiacetylcholinesterase IC50=1.0 mM; Antinitrosaminic; Antispasmodic; FLavor FEMA 1-40; Insecticide 0.86 uM/fly; Insectifuge; P450-2B1-Inhibitor IC50=0.76 uM; Perfumery; Pesticide; Spasmogenic

ALPHA-TERPINEOL Plant 110 ppm;

ACE-Inhibitor 100 ug/ml (weak activity); Aldose-Reductase-Inhibitor 100 ug/ml; Allelopathic; Antiacne; Antibacterial *MIC*=800-1,600 ug/ml; Anticancer; Anticariogenic; Antiseptic; Cicatrizant *ED50*=240 ug/g mus; FLavor *FEMA 5-40*; Insecticide 1.29 uM/fly; Motor-Depressant; Nematicide *MLC*=1 mg/ml; Perfumery; Pesticide; Sedative; Termiticide *IC100*=5 mg/g; Vulnerary *ED50*=240 ug/g mus

BETULINIC-ACID Root:

Anthelmintic; Antibacterial; Anticancer; Anticarcinomic; Antiedemic; AntiHIV 14.8 uM EC50=2.0 ug/ml IC50=6.5 ug/ml; Antiinflammatory; Antileukemic; Antimalarial IC50=19-26 ug/ml; Antimelanomic; Antinociceptive;

Antiplasmodial; Antitumor; Antiviral *14.8 uM*; Apoptotic; Cytotoxic *16.4 uM 50-100 ppm*; Phospholipase-A2-Inhibitor; Prostaglandin-Synthesis-Inhibitor *200 ug/ml IC50=101 uM*

ELEMENE Plant 260 ppm;

No activity reported.

GAMMA-TERPINENE Plant 175 ppm;

Acaricide; ACE-Inhibitor 100 ug/ml (weak activity); Aldose-Reductase-Inhibitor 100 ug/ml; Antiacetylcholinesterase IC23=1.2 mM; Antifeedant; Antioxidant; FLavor FEMA 1-40; Insectifuge; Irritant; Perfumery; Pesticide

Wild Hops

LIMONENE Plant 390 ppm;

Acaricide *LC100=8 uM*; AChE-Inhibitor; Allelochemic; Allergenic *1/20th carene*; Antiacetylcholinesterase *IC22-26=1.2 mM*; Antialzheimeran?; Antibacterial; Anticancer; Antifeedant; Antiflu; Antilithic; Antimutagenic; Antiseptic; Antispasmodic *ED50=0.197 mg/ml*; Antitumor; Antitumor (Breast); Antitumor (Pancreas); Antitumor (Prostate);

Antiviral; Cancer-Preventive; Candidistat; Chemopreventive; Detoxicant; Enterocontractant; Expectorant; FLavor; Fungiphilic; Fungistat; Herbicide *IC50=45 uM*;

Insecticide 0.37 uM/fly; Insectifuge; Irritant; Nematicide IC=100 ug/ml; Ornithine-Decarboxylase-Inhibitor ~750 mg/kg (diet); P450-Inducer; Pesticide; Photosensitizer; Sedative ED=1-32 mg/kg; Transdermal

LINALOL Plant 80 ppm;

No activity reported.

MENTHOL *Plant*:

Allergenic; Analgesic; Anesthetic 2,000 ppm; Antiacetylcholinesterase IC50=2.0 mM; Antiaggregant IC50=750; Antiallergic; Antiasthmatic; Antibacterial; Antibronchitic; Antidandruff; Antihalitosic; Antihistaminic; Antiinflammatory; Antineuralgic; Antiodontalgic; Antipruritic; Antipyretic; Antirheumatic; Antiseptic 4 x phenol; Antisinusitic; Antispasmodic ED50=0.01 mg/ml; Antivaginitic; Antivulvitic; Bradycardic 65 mg/3 x day/woman; Bronchomucolytic; Bronchomucotropic; Bronchorrheic; Calcium-Antagonist; Carminative; Choleretic; Ciliotoxic; CNS-Depressant; CNS-Stimulant; Congestant; Convulsant; Counterirritant; Decongestant? 11 mg/man; Dermatitigenic; Diaphoretic; Enterorelaxant; Expectorant; Gastrosedative; Irritant; Myorelaxant; Nematicide MLC=1 mg/ml; Neurodepressant; Neuropathogenic 40-100 mg/day/rat; Nociceptive; Perfumery; Pesticide; Refrigerant; Rubefacient; Termiticide; Vibriocide

THUJANE Plant 325 ppm;

No activity reported.

(Verbenaceae) -- Brazilian Tea

6-HYDROXYLUTEOLOL-7-GLUCURONIDE Plant: No activity reported. APIGENOL-7-GLUCURONIDE Plant: No activity reported. CHLOROGENIC-ACID Plant:

Aldose-Reductase-Inhibitor IC50=1.8 uM rat (strong activity); Allelochemic; Allergenic; Analgesic; Antiatherosclerotic; Antibacterial; Anticancer (Colon); Anticancer (Forestomach); Anticancer (Liver); Anticancer (Skin); Anticarcinogenic; AntiEBV; Antifeedant; Antigenotoxic; Antigonadotropic; Antihemolytic 10 uM; Antihepatotoxic; Antiherpetic; Antihistaminic; AntiHIV; Antihypercholesterolemic; Antihyperthyroid; Antiinflammatory; AntiLegionella; Antileukotriene; Antimelanogenic; Antimutagenic; Antinitrosaminic; Antioxidant IC53=200 ppm IC80=12 uM; Antiperoxidant IC50=36 uM; Antipolio; Antiradicular 10 uM 9 x quercetin; Antiseptic; Antisunburn; Antithyroid; Antitumor; Antitumor (Colon); Antitumor (Forestomach); Antitumor (Liver); Antitumor (Skin); Antitumor-Promoter *IC25=10 uM*; Antiulcer; Antiviral; Autotoxic; Cancer-Preventive; Cholagogue; Choleretic; Clastogenic; CNS-Active; CNS-Stimulant 1/6 Caffeine; Collagen-Sparing; Diuretic; Fungicide; Hepatoprotective; Histamine-Inhibitor; Immunostimulant; Insectifuge; Interferonogenic; Juvabional; Larvistat; Leukotriene-Inhibitor; Lipoxygenase-Inhibitor *IC23=5 mM*; Metal-Chelator; NO-Genic; Ornithine-Decarboxylase-Inhibitor; Oviposition-Stimulant; Pesticide; Sunscreen; Sweetener; Vulnerary **DOPAMINE** *Plant*:

Adrenergic; Antilactagogue; Antimyocontractant; Antineurogenic; Antiparkinsonian; Antiprolactin; Antishock; Antithyreotropic; Cardiotonic; Diuretic; Hypertensive; Inotropic; Myocontractant *10 uM*; Natriuretic; Neurotransmitter; Priapistic; Sympathomimetic; Teratogenic; Vasoconstrictor; Vasodilator

LUTEOLOL-7-GLUCURONIDE Plant: No activity reported. STACHYTARPHINE Plant: No activity reported. TARPHETALIN Plant: No activity reported.