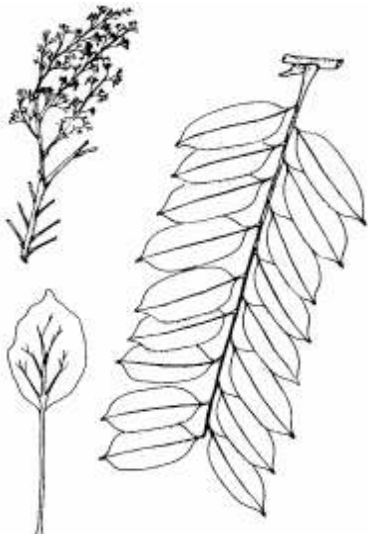
Technical Data Report

for

SIMAROUBA

Simarouba amara



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Simarouba

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Family: Simaroubaceae

Genus: *Simarouba*

Species: *amara, glauca*

Synonyms: *Quassia simarouba, Zwingera amara*, *Picraena officinalis*, *Simarouba medicinalis*

Common Names: Simarouba, gavilan, negrito, marubá, marupá, dysentery bark, bitterwood, paradise tree, palo blanco, robleceillo, caixeta, daguilla, cedro blanco, cajú-rana, malacacheta, palo amargo, pitomba, bois amer, bois blanc, bois frene, bois negresse, simaba

Parts Used: Bark, wood, leaves

Simarouba is a medium-sized tree that grows up to 20 m high, with a trunk 50 to 80 cm in diameter. It produces bright green leaves 20 to 50 cm in length, small white flowers, and small red fruits. It is indigenous to the Amazon rainforest and other tropical areas in Mexico, Cuba, Haiti, Jamaica, and Central America.

The leaves and bark of Simarouba have a long history of use as a natural medicine in the tropics. Simarouba was first imported into France from Guyana in 1713 as a remedy for dysentery. When France suffered a dysentery epidemic from 1718 to 1725, simarouba bark was one of the few effective treatments.[1] French explorers "discovered" this effective remedy when they found that the indigenous Indian tribes in the Guyana rainforest used simarouba bark as an effective treatment for malaria and dysentery—much as they still do today. Other indigenous tribes throughout the South American rainforest use simarouba bark for fevers, malaria, and dysentery, as a hemostat to stop bleeding, and as a tonic.

Simarouba also has a long history in herbal medicine in many other countries. In Cuba, where it is called *gavilan,* an infusion of the leaves or bark is considered as astringent, digestive, anthelmintic, and emmenagogue. It is taken internally for diarrhea, dysentery, malaria, and colitis; it is used externally for wounds and sores. In Belize the tree is called *negrito* or *dysentery bark*. There the bark and, occasionally, the roots are boiled in water to yield a powerful astringent and tonic used to wash skin sores and to treat dysentery, diarrhea, stomach and bowel disorders, hemorrhages, and internal bleeding. In Brazil it is employed much the same way against fever, malaria, diarrhea, dysentery, intestinal parasites, indigestion, and anemia. In high dosages it is reported to be emetic, diuretic, and soporific. In Brazilian herbal medicine, simarouba bark tea has long been the most highly recommended (and most effective) natural remedy against chronic and acute dysentery.

After a 200-year documented history of use for dysentery, its use for amoebic dysentery was finally validated by conventional doctors in 1918. A military hospital in England demonstrated that the bark tea was an effective treatment for amoebic dysentery in humans.[2] The Merck Institute reported that simarouba was 91.8% effective against intestinal amoebiasis in humans in a 1944 study[3] and, in 1962, other researchers found that the seeds of simarouba showed active anti-amoebic activities in humans.[4] In the 1990s scientists again documented simarouba's ability to kill the most common dysentery-causing organism, *Entamoeba histolytica,*[5] as well as two pathogenic diarrhea-causing bacteria, *Salmonella* and *Shigella*.[6]

The main active group of phytochemicals in simarouba are called *quassinoids,* which belong to the triterpene chemical family. Quassinoids are found in many plants and are well known to scientists. The antiprotozoal and antimalarial properties of these chemicals have been documented for many years. Several of the quassinoids found in simarouba, such as ailanthinone, glaucarubinone, and holacanthone, are considered the plant's main therapeutic constituents and are the ones documented to be antiprotozal/anti-amoebic, antimalarial, and even toxic to cancer and leukemia cells.

The Indians in the Amazon have also treated malaria with simarouba bark for centuries. Scientists first looked at simarouba's antimalarial properties in 1947, when they determined a water extract of the bark (as well as the root) demonstrated strong activity against the malaria-causing organism *Plasmodium gallinaceum* in chickens.[7] This study showed that doses of only 1 mg of bark extract per kg of body weight exhibited strong antimalarial activity. When new strains of malaria with resistance to our existing antimalarial drugs began to develop, scientists began studying simarouba once again. Studies published between 1988 and 1997 demonstrated that simarouba and/or its three potent quassinoids were effective against malaria *in vitro* as well as *in vivo*.[5,8–13] More importantly, the research indicated that the plant and its chemicals were effective against the new drug-resistant strains *in vivo* and *in vitro.* While most people in North America will never be exposed to malaria, between 300 and 500 million cases of malaria occur each year in the world, leading to more than one million deaths annually. Having an easily-grown tree in the tropics where most malaria occurs could be an important resource for an effective natural remedy; it certainly has worked for the Indians in the Amazon for ages.

It will be interesting to see if North American scientists investigate simarouba as a possibility for North America's only malaria-like disease: the newest mosquito-borne threat, West Nile virus. It might be a good one to study because, in addition to its antimalarial properties, clinical research has shown good antiviral properties with simarouba bark. Researchers in 1978 and again in 1992 confirmed strong antiviral properties of the bark *in vitro* against herpes, influenza, polio, and vaccinia viruses.[14,15]

Another area of research on simarouba and its plant chemicals has focused on cancer and leukemia. The quassinoids responsible for the anti-amoebic and antimalarial properties have also shown in clinical research to possess active cancer-killing properties. Early cancer screening performed by the National Cancer Institute in 1976 indicated that an alcohol extract of simarouba root (and a water extract of its seeds) had cytotoxic actions against cancer cells at very low dosages (less than 20 mcg/ml).[16] Following up on that initial screening, scientists discovered that several of the quassinoids in simarouba (glaucarubinone, alianthinone, and dehydroglaucarubinone) had antileukemic actions against lymphocytic leukemia *in vitro* and published several studies in 1977 and 1978.[17–19] Researchers found that yet another simarouba quassinoid, holacanthone, also possessed antileukemic and antitumorous actions in 1983.[20] More recently, in 1993, researchers in the UK cited the antitumorous activity of two of the quassinoids, ailanthinone and glaucarubinone, against human epidermoid carcinoma of the pharynx.[5] A later study in 1998 by U.S. researchers demonstrated the antitumorous activity of glaucarubinone against solid tumors (human and mouse cell lines), multi-drug-resistant mammary tumors in mice, and antileukemic activity against leukemia in mice.[21]

Simarouba is the subject of one U.S. patent so far and, surprisingly, it's not for its antimalarial, anti-amoebic, or even anticancerous actions. Rather, water extracts of simarouba were found to increase skin keratinocyte differentiation and to improve skin hydration and moisturization.[22] In 1997, a patent was filed on its use to produce a cosmetic or pharmaceutical skin product. The patent describes simarouba extract as having significant skin depigmentation activity (for liver spots), enhancing the protective function of the skin (which maintains better moisturization), and having a significant keratinocyte differentiation activity (which protects against scaly skin).[23]

While at least one scientific research group attempts to synthesize one or more of simarouba's potent quassinoids for pharmaceutical use, the plant remains an important natural remedy in the herbal pharmacopeias of many tropical countries and in the rainforest shaman's arsenal of potent plant remedies. Natural health practitioners outside of South America are just beginning to learn about the properties and actions of this important rainforest medicinal plant and how to use it in their own natural health practices.

Documented Properties and Actions: Amoebicide, analgesic, anthelmintic, antibacterial, antidysenteric, antileukemic, antimalarial, antimicrobial, antitumorous, antiviral, astringent, cytotoxic, emmenagogue, febrifuge, skin hydrator, stomachic, sudorific, tonic, vermifuge

Main Phytochemicals: Ailanthinone, benzoquinone, canthin, dehydroglaucarubinone, glaucarubine, glaucarubolone, glaucarubinone, holacanthone, melianone, simaroubidin, simarolide, simarubin, simarubolide, sitosterol, tirucalla

Traditional Remedy: For diarrhea or dysentery, the traditional remedy calls for preparing a standard decoction with the bark. A teacup full (about 6 ounces) is taken 2–3 times daily. Five to ten ml of a bark tincture can be substituted if desired.

Contraindications: None reported. Reported side effects at high dosages (approx. three times the traditional remedy) include increased perspiration and urination, nausea, and/or vomiting.

Drug Interactions: None reported.

WORLDWIDE ETHNOBOTANICAL USES

Country	Uses
Amazonia	Dysentery, emetic, fever, hemostat, purgative, tonic
Belize	Astringent, bowel disorders, diarrhea, dysentery, excessive menstruation, hemorrhage, internal bleeding, skin, sores, stomach disorders, tonic
Brazil	Anemia, anthelmintic, bitter tonic, diarrhea, dysentery, dyspepsia, fever (intermittent), febrifuge, hemorrhage, inappetite, intestinal parasites, malaria, tonic
Cuba	Anthelmintic, astringent, colitis, diarrhea, digestive, dysentery, emmenagogue, malaria, sores, wounds
Dominican Republic	Colic, diarrhea, gonorrhea, malaria
El Salvador	Amoebiasis, intoxicant, stomachic
Haiti	Ache (body), anemia, anodyne, dysentery, dyspepsia, emetic, emmenagogue, fever, purgative, rheumatism, skin, sudorific
Mexico	Amoebicide, dyspepsia, fever, malaria
Peru	Fever, malaria, diarrhea, dysentery, emetic, flatulence, stomach pains
Elsewhere	Colds, diarrhea, dysentery, emetic, fever, hemostat, malaria, purgative, soap, tonic

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Ethnomedical Information on Simarouba (Simarouba amara)

Plant Part / Location	Documented Ethnic Use	Type Extract / Route	Used For	Ref #
Bark French Guiana	For diverse medications.	Not stated	Various	K01504
Bark Amazonia	Used for fever. Used for malaria, dysentery and tonic. Used as an emetic, hemostat, and purgative.	Decoction / Oral Tincture / Oral Decoction / Oral	Human Adult	L04137
Root Brazil	Used to stop diarrhea. Used as an anthelmintic.	Hot H2O Ext / Oral Not stated / Oral	Human Adult	A06732
Rootbark French Guyana	Used for dysentery, malaria, and as a tonic.	Infusion / Oral	Human Adult	J12967
Leaf Cuba	Used as an astringent, digestive, anthelmintic and emmenogogue for diarrhea, dysentery, malaria and colitis.	Not stated / Oral	Human Adult	ZZ1022
Leaf Haiti	Used for skin affections.	H2O Ext / Oral	Human Adult	T13846
Bark / Wood Cuba	Used for wounds and sores. Used as an emmenagogue.	Not stated / External H2O Ext / Oral	Human Adult Human Adult	ZZ1022 W02855
Bark Belize	Used as an astringent and tonic for dysentery, diarrhea, stomach and bowel disorders, hemorrhages and internal bleeding.	Hot H2O Ext / Oral	Human Adult	ZZ1019
Bark Belize	Used for skin sores.	Not stated / External	Human Adult	ZZ1019
Bark Brazil	Used for intermittent fevers, diarrhea, dysentery, intestinal parasites, tonic, hemorrhages, dyspepsia, and anemia.	Hot H2O Ext / Oral	Human Adult	ZZ1013
Bark Brazil	Bitter, dyspepsia, anemia and fevers.	Decoction / Oral	Human Adult	ZZ1099
Bark + Root Brazil	Used for bleeding diarrhea.	Decoction / Oral	Human Adult	ZZ1099
Bark Brazil	Used for acute and chronic dysentery, bitter tonic, febrifuge, diarrhea, inappetite, and dyspepsia.	Infusion / Oral	Human Adult	ZZ1007
Root Peru	Used for stomach pains and flatulence.	Infusion / Oral	Human Adult	ZZ1093

Presence of Compounds in Simarouba (Simarouba amara)

Compound	Chemical Type	Plant Part	Plant Origin	Quantity	Ref #
Ailanthinone	Triterpene	Fruit Not stated Fruit	Panama Bolivia Panama	Not stated Not stated Not stated	T14116 L09232 T13729
Benzoquinone, 1-4: 2-6-dimethoxy:	Quinoid	Bark Bark	Not stated Not stated	Not stated Not stated	A06083 A12193
Canthin-6-one, 5-hydroxy:	Indole Alkaloid	Rootbark Bark	Guyana Not stated	00.17% Not stated	L00487 ZZ1047
Glaucarubine, 2'-acetyl:	Triterpene	Rootbark Bark	Guyana Not stated	Not stated Not stated	M01027 ZZ1047
Glaucarubolone	Triterpene	Plant Seed	Not stated	Not stated	ZZ1095
Glaucarubinone	Triterpene	Not stated Fruit Fruit Rootbark	Bolivia Panama Panama Guyana	Not stated Not stated Not stated Not stated	L09232 T13729 T14116 M01027
Glaucarubinone, 13-18-dehydro:	Triterpene	Rootbark Bark	Guyana Not stated	Not stated Not stated	M01027 ZZ1047
Glaucarubinone, 2'-acetoxy:	Triterpene	Fruit	Panama	Not stated	T13729
Glaucarubinone, 2'-acetyl:	Triterpene	Fruit Rootbark Bark	Panama Guyana Not stated	Not stated Not stated Not stated	T14116 M01027 ZZ1047
Holacanthone	Triterpene	Fruit Bark	Panama Not stated	Not stated Not stated	T14116 T13729
Melianone	Triterpene	Rootbark Bark	Not stated Not stated	Not stated Not stated	M00099 ZZ1047
Melianone, 20-anhydro:	Triterpene	Rootbark Bark	Not stated Not stated	Not stated Not stated	M00099 ZZ1047

Compound	Chemical Type	Plant Part	Plant Origin	Quantity	Ref #
Simaroubidin	Triterpene	Entire Plant Bark	Not stated Not stated	Not stated 500 ppm	A00035 ZZ1047
Simarolide	Triterpene	Bark	Not stated	Not stated	ZZ1047
Simarubin	Triterpene	Bark	Not stated	10,000 ppm	ZZ1047
Simarubolide	Triterpene	Bark	Not stated	Not stated	ZZ1047
Sitosterol, beta:	Steroid	Seed Not stated Rootbark	Not stated Bolivia Not stated	00.03% Not stated Not stated	K01504 L09232 M00099
Tirucalla-7-24-dien, 3-21-dioxo:	Triterpene	Rootbark	Not stated	Not stated	M00099
Tirucalla-7-24-dien, 3-oxo:	Triterpene	Rootbark	Not stated	Not stated	M00099
Tirucalla-7-24-diene, 3-21-dioxo:	Triterpene	Seed Bark	Not stated Not stated	00.014% Not stated	K01504 ZZ1047
Tirucalla-7-24-diene, 3-oxo:	Triterpene	Seed Bark	Not stated Not stated	00.0147% Not stated	K01504 ZZ1047

Biological Activities for Extracts of Simarouba (Simarouba amara)

Plant Part - Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested	Ref #
Bark Not stated	Antitumor Activity	Fraction: Glaucarubinone	Cell Culture	Not stated	Active		AH1009
Bark Bolivia	Anticrustacean Activity	MEOH Ext	Cell Culture	LD50= 7.38 ppm	Active	*Artemia salina* (Assay system is intended to predict for antitumor activity.)	L09232
Root Costa Rica	Cytotoxic Activity	ETOH-H2O (1:1)Ext	Cell Culture	ED50 < 20 mcg/ml	Active	Ca-9kb	X00001
Dried Bark	Cytotoxic Activity	H2O Ext	Cell Culture	10.0%	Active	Hela Cells	T09507
Seed El Salvador	Cytotoxic Activity	H2O Ext	Cell Culture	ED50 < 20 mcg/ml	Active	Ca-9kb	X00001
Bark Not stated	Cytotoxic Activity	Fractions: Glaucarubinone & Alianthinone	Cell Culture	Not stated	Active	Human epidermoid carcinoma of the nasopharynx	AH1005
Bark Not stated	Cytotoxic Activity Antitumor Activity	Fractions: Glaucarubinone & Alianthinone	Cell Culture	Not stated	Active		AH1009
Bark Not stated	Cytotoxic Activity	Fraction: Glaucarubinone	Cell Culture	Not stated	Active	Murine solid tumor cells Human solid tumor cells MDR murine mammary tumor	AH1004
Bark Not stated	Cytotoxic Activity Antileukemic Activity	Fraction: Holacanthone	Cell Culture	Not stated	Active		AH1011
Bark Not stated	Antileukemic Activity	Fraction: Glaucarubinone	Cell Culture	Not stated	Active	Murine leukemia	AH1004
Bark Not stated	Antileukemic Activity	Fraction: Glaucarubinone	Cell Culture	Not stated	Active	Murine leukemia	AH1010
Bark Not stated	Antileukemic Activity	Fraction: Dehydro-glaucarubinone	Cell Culture	Not stated	Active	Murine lymphocytic leukemia P388	M01027

Plant Part - Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested	Ref #
Bark	Antiviral Activity	H2O Ext	Cell Culture	Not stated	Active	Virus - herpes (unspec) Virus - influenza (unspec) Virus - poliovirus (unspec) Virus - vaccinia	K10864
Dried Bark Brazil	Antiviral Activity	H2O Ext	Cell Culture	10.0%	Strong Activity	Virus - herpes Type 2 Virus - influenza A2 Virus - poliovirus II Virus - vaccinia	T09507
Bark Mexico	Antiamebic Activity	Hot H2O Ext	Oral Human	Not stated	Active	3/7 cases cured - treatment for 7 days. *Entamoeba histolytica*	A00750
Seed Not Specified	Antiamebic Activity	H2O Ext	Oral Human	Not stated	Active	Intestinal amoebiasis *Entamoeba histolytica* 91.8% effective:	A00035
Dried Stem Panama	Antiamebic Activity	Butanol Ext CHCL3 Ext Ether Ext H2O Ext MEOH Ext	Not stated Not stated Not stated Not stated Not stated	IC50= 6.89 mcg/ml IC50= 2.9 mcg/ml IC50= 114 mcg/ml IC50= 52.5 mcg/ml IC50= 6.2 mcg/ml	Active	*Entamoeba histolytica*	M18314
Bark Guatemala	Antibacterial Activity	EtOH-H2O (50%)Ext	Agar Plate	50.0 mcl/plate	Active Active Inactive	*Salmonella typhosa* *Shigella flexneri* *E. coli*	K24899
Dried Rootbark French Guyana	Lipid Profile Alteration	H2O Ext	Cell Culture Keratinocytes	10.0 mcg/ml	Active	Cholesterol sulphate, cholesterol and ceramide content increased in treated cultures. Results significant at P < 0.01 level.	J12967
Dried Rootbark French Guyana	Skin Moisturizing Effect	H2O Ext	External Human Adult Female	Dose 0.2%	Active	20 volunteers were treated twice daily for one month with a lotion containing the extract.	J12967
Dried Rootbark French Guyana	Transglutaminase Stimulation	H2O Ext	Cell Culture Keratinocytes	25.0 mcg/ml	Active	Cell culture was treated for 4 days with extract. Results significant at P < 0.05 level.	J12967

Plant Part - Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested	Ref #
Wood	Antimalarial Activity	CHCL3 Ext CHCL3 Ext H2O Ext H2O Ext H2O Ext	Oral Chicken SC Chicken Oral Chicken SC Chicken SC Chicken	25.0 mg/kg 1.5 mg/kg 500.0 mg/kg 100.0 mg/kg 3.0 mg/kg	Strong Activity	*Plasmodium gallinaceum*	A00785
Bark + Twigs	Antimalarial Activity	CHCL3 Ext CHCL3 Ext	Oral Chicken SC Chicken	32.0 mg/kg 5.0 mg/kg	Strong Activity	*Plasmodium gallinaceum*	A00785
Bark + Twigs	Antimalarial Activity	H2O Ext H2O Ext	Oral Chicken SC Chicken	200.0 mg/kg 20.0 mg/kg	Inactive Weak Activity	*Plasmodium gallinaceum*	A00785
Branches	Antimalarial Activity	CHCL3 Ext CHCL3 Ext H2O Ext H2O Ext	Oral Chicken SC Chicken Oral Chicken SC Chicken	60.0 mg/kg 48.0 mg/kg 1.64 gm/kg 410.0 mg/kg	Inactive Inactive Inactive Inactive	*Plasmodium gallinaceum*	A00785
Branches	Antimalarial Activity	CHCL3 Ext H2O Ext	SC Chicken SC Chicken	50.0 mg/kg 60.0 mg/kg	Inactive Inactive	*Plasmodium gallinaceum*	A00785
Dried Fruit Panama	Antimalarial Activity	CHCL3 Ext	Not stated	Not stated	Active	*Plasmodium falciparum* (chloroquine resistant)	T13729
Dried Fruit Panama	Antimalarial Activity	MEOH Ext MEOH Ext	Not stated Oral Mouse	IC50= 0.05 mcg/ml 900 mg/kg	Active Active	*Plasmodium falciparum* *Plasmodium berghei*	T14116
Part Not Specified Guatemala	Antimalarial Activity	MEOH Ext CHCL2 Ext	Mice	Not stated	Active	*Plasmodium berghei* - chloroquine-susceptible and -resistant	AH1002

Biological Activities for Compounds of Simarouba (Simarouba amara)

Compound Tested	Activity Tested For	Test Model	Dosage	Result	Notes/Organism tested	Ref #
Ailanthinone	Antiamebic Activity	In vitro	Not Stated	Active	*Entamoeba histolytica*	AH1005
Ailanthinone	Antimalarial Activity	Cell Culture	Not Stated	Active	*Plasmodium falciparum:* chloroquine-resistant. Inhibited protein synthesis and nucleic acid synthesis in human erythrocytes infected with *P. falciparum.*	AH1006
Ailanthinone	Antiprotozoal Activity	In vitro	Not Stated	Active	*Toxoplasm gondii*	AH1005
Ailanthinone	Antimalarial Activity	In vitro	Not Stated	Active	*Plasmodium falciparum*	AH1005
Glaucarubione	Antiamebic Activity	In vitro	Not Stated	Active	*Entamoeba histolytica*	AH1005
Glaucarubione	Antiprotozoal Activity	In vitro	Not Stated	Active	*Toxoplasma gondii*	AH1005
Glaucarubinone	Antimalarial Activity	In vitro	Not Stated	Active	*Plasmodium falciparum*	AH1005
Glaucarubinone	Antimalarial Activity	Cell Culture	Not Stated	Active	*Plasmodium falciparum:* chloroquine-resistant. Inhibited protein synthesis and nucleic acid synthesis in human erythrocytes infected with *P. falciparum.*	AH1006
Glaucarubinone	Antimalarial Activity	In vitro	Not Stated	Active	*Plasmodium berghei.*	AH1007
Glaucarubinone	Antimalarial Activity	Mice	Not Stated	Active	*Plasmodium berghei.*	AH1007
Glaucarubinone	Antimalarial Activity	In vitro	IC=0.006 mcg/ml	Active	*Plasmodium falciparum*	AH1008
Holacanthone	Antimalarial Activity	Cell Culture	Not Stated	Active	*Plasmodium falciparum:* chloroquine-resistant. Inhibited protein synthesis and nucleic acid synthesis in human erythrocytes infected with *P. falciparum.*	AH1006
Simarolide	Antimalarial Activity	In vitro	IC=0.01 mcg/ml	Active	*Plasmodium falciparum*	AH1008

Literature Cited - Simarouba

A00035	EFFICACY AND TOXICITY OF SIMAROUBIDIN IN EXPERIMENTAL AMOEBIASIS .CUCKLER,AC: SMITH,CC: FED PROC 8 : 284- (1944) (MERCK INST THERAPEUTIC RES RAHWAY NJ USA)
A00750	PRESISTENT CARRIERS OF ENTAMEBA HISTOLYTICA. SHEPHEARD,S: LILLIE,DG: CANTAB,MA LANCET 1918 : 501- (1918) (MONT DORE MILITARY HOSP BOURNEMOUTH ENGLAND)
A00785	SURVEY OF PLANTS FOR ANTIMALARIAL ACTIVITY. SPENCER,CF: KONIUSZY,FR: ROGERS,EF: SHAVEL JR,J: EASTON,NR: KACZKA,EA: KUEHL JR,FA: PHILLIPS,RF: WALTI,A: FOLKERS,K: MALANGA,C: SEELER,AO: LLOYDIA 10 : 145-174 (1947) (RES LAB MERCK + CO,INC RAHWAY NJ USA)
A06083	NOTE ON THE ISOLATION OF 2,6-DIMETHOXYBENZOQUINONE FROM THE BARK AND WOOD OF SOME SIMAROUBACEAE AND MELIACEAE. POLONSKY,J: LEDERER,E: BULL SOC CHIM FR 1959 : 1157- (1959) (INST BIOL PHYS CHIM PARIS FRANCE)
A06732	BRAZILIAN ANTHELMINTIC PLANTS. PECKOLT,G: REV FLORA MED 9 7: 333- (1942) (NO ADDRESS GIVEN)
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T14116	PLANTS AS SOURCES OF ANTIMALARIAL DRUGS, PART 6: ACTIVITIES OF SIMAROUBA AMARA FRUITS. O'NEILL,MJ: BRAY,DH: BOADMAN,P: WRIGHT,CW: PHILLIPSON,JD: WARHURST,DC: GUPTA,MP: CORREYA,M: SOLIS,P: J ETHNOPHARMACOL 22 2: 183-190 (1988) (DEPT PHARMACOGNOSY SCH PHARM UNIV LONDON LONDON WC1N 1AX ENGLAND)
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AH1010	ANTITUMOR PLANTS. IV. CONSTITUENTS OF SIMAROUBA VERSICOLOR. GHOSH,PC: LARRAHONDO,JE: LEQUESNE,PW: RAFFAUF,RF: LLOYDIA. 40 4: 364-9 (1977)
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Clinical Abstracts

Antimicrob Agents Chemother 1997 Jul;41(7):1500-3
In vivo and in vitro antiplasmodial activities of some plants traditionally used in Guatemala against malaria.
Franssen, F. F., et al.
We present an evaluation of the antiplasmodial and cytotoxic effects of four plants commonly used in Guatemalan folk medicine against malaria. Methanol extracts of Simarouba glauca D. C., Sansevieria guineensis Willd, Croton guatemalensis Lotsy, and Neurolaena lobata (L.)R.Br. significantly reduced parasitemias in Plasmodium berghei-infected mice. Dichloromethane fractions were screened for their cytotoxicities on Artemia salina (brine shrimp) larvae, and 50% inhibitory concentrations were determined for Plasmodium falciparum in in vitro cultures. Both chloroquine-susceptible and -resistant strains of P. falciparum were significantly inhibited by these extracts. Of all dichloromethane extracts, only the S. glauca cortex extract was considered to be toxic to nauplii of A. salina in the brine shrimp test.

J Ethnopharmacol 1996 Aug;53(2):65-74
Simarouba amara extract increases human skin keratinocyte differentiation.
Bonte, F., et al.
An aqueous extract of Simarouba amara was studied for its activity on the differentiation of human skin keratinocytes. Submerged and air-exposed treated keratinocyte cultures displayed a more highly differentiated histoarchitecture, with presence of ultrastructural differentiated elements, than untreated controls. Immunohistochemistry of involucrin and activation of transglutaminase activity provided further evidence for the increase in corneocyte envelope formation observed ultrastructurally. Lipid analysis of air-exposed cultures revealed an increase in the cholesterol sulphate, cholesterol and ceramide contents. After 4 weeks of treatment on the hemiface of volunteers, the capacitance and transepidermal water loss evaluation revealed the potential interest of this extract for improvement of skin hydration. Electron microscopic examination of the corneocyte envelope on tape strips confirmed its actions. Taken together these data demonstrated that an aqueous extract of S. amara increases human keratinocyte differentiation.

J Ethnopharmacol 1988 Feb-Mar;22(2):183-90
Plants as sources of antimalarial drugs, Part 6: Activities of Simarouba amara fruits.
O'Neill, M. J., et al
Extracts prepared from Simarouba amara fruits collected in Panama have been found to be active against Plasmodium falciparum in vitro and against Plasmodium berghei in mice. Four active quassinoids have been identified as ailanthinone, 2'-acetylglaucarubinone, glaucarubinone and holacanthone.

J Ethnopharmacol 1990 Aug;30(1):55-73
Plants used in Guatemala for the treatment of gastrointestinal disorders. 1. Screening of 84 plants against enterobacteria.
Caceres, A., et al.
Gastrointestinal disorders are important causes of morbidity in developing countries. Natural healing is the traditional way of treating these diseases in Guatemala. Ethnobotanical surveys and literature reviews showed that 385 plants from 95 families are used in Guatemala for the treatment of gastrointestinal disorders. The activity of 84 of the most commonly used plants was screened in vitro against five enterobacteria pathogenic to man (enteropathogenic Escherichia coli, Salmonella enteritidis, Salmonella typhi, Shigella dysenteriae and Shigella flexneri). Results indicate that 34 (40.48%) plants inhibit one or more of the enterobacteria tested. The most commonly inhibited bacterium was S. typhi (33.73%) and the most resistant was E. coli (7.35%). The plants of American origin which exhibited the best antibacterial activity were: Byrsonima crassifolia, Diphysa robinioides, Gnaphalium stramineum, Guazuma ulmifolia, Psidium guajava, Sambucus mexicana, **Simarouba glauca**, Smilax lundelii, Spondias purpurea and Tagetes lucida. These results indicate a scientific basis for use of these medicinal plants for attacking enterobacterial infections in man.

Antimicrob Agents Chemother 1988 Nov;32(11):1725-9
Use of microdilution to assess in vitro antiamoebic activities of Brucea javanica fruits, Simarouba amara stem, and a number of quassinoids.
Wright, C. W., et al.
A microdilution technique for the assessment of in vitro activity against Entamoeba histolytica was devised and validated with metronidazole. The test was used to detect the antiamoebic activities of plant extracts prepared from the traditional remedies Brucea javanica fruits and Simarouba amara stems. The activity was associated with quassinoid-containing fractions. The 50% inhibitory concentrations for some quassinoids against amoebae were determined by using the microdilution method. These concentrations ranged from 0.019 micrograms.ml-1 for bruceantin, the most active quassinoid, to greater than 5 micrograms.ml-1 for glaucarubol, the least active compound tested. These results are discussed with reference to the known activities of these compounds against Plasmodium falciparum. Overall, the activities of the quassinoids against both protozoa are similar. The microdilution technique will be useful in the search for novel antiamoebic drugs.

Experientia 1978 Sep 15;34(9):1122-3
The isolation and structure of 13,18-dehydroglaucarubinone, a new antineoplastic quassinoid from Simarouba amara.
Polonsky, J., et al.
An investigation of the Guyana plant Simarouba amara Aubl. (Simaroubaceae) for antineoplastic quassinoids led to isolation and structural determination of the new quassinoids 2'-acetylglaucarubine (1a) and 13,18-dehydroglaucarubinone (2). The previously known 2'-acetylglaucarubinone (3a) and glaucarubinone (3b) were also obtained. The new quassinoid 2 was found significantly to inhibit growth of the murine lymphocytic leukemia P388.

Oncol Res 1998;10(4):201-8
Anticancer activity of glaucarubinone analogues.
Valeriote, F. A., et al.
A series of glaucarubinone analogues, obtained from natural sources as well as synthesized by us, were studied both in vitro and in vivo. The focus of the in vitro assessment was to define solid tumor-selective compounds by quantitating differential cytotoxic activity between murine and human solid tumor cells and either murine leukemia or normal cells. Subsequent in vivo studies were aimed at determining the therapeutic efficacy of these analogues against the murine models. Structure-activity analysis con-sequent to both the in vitro and in vivo studies demonstrated that few changes could be made in the parent glaucarubinone structure (outside of the C-15 position) without abrogating either cytotoxicity or potency. How-ever, significant changes could be made at the C-15 position which modified, either enhanced or diminished, in vitro differential cytotoxicity, potency, human solid tumor selectively, and differential cytotoxicity to a MDR-expressing murine mammary tumor.

C R Acad Sci III 1987;304(6):129-32 [Therapeutic trials of experimental murine malaria with the quassinoid, glaucarubinone]
Monjour, L., et al.
Prevention and treatment of malaria are endangered by the appearance of chemoresistance against the common anti-malarial drugs by Plasmodium falciparum. Today, only a quinoline derivative, mefloquine, is a safe and effective agent against P. falciparum. An in vitro antiplasmodial activity having been found for the quassinoid glaucarubinone we tested its in vivo therapeutic action on mice infected with a P. berghei strain. At low doses, glaucarubinone retarded mortality by exerting a partial, temporary, inhibition of parasitaemia; its toxicity, however, precludes, further applications at the present time.

J Eukaryot Microbiol 1993 May-Jun;40(3):244-6
Quassinoids exhibit greater selectivity against Plasmodium falciparum than against Entamoeba histolytica, Giardia intestinalis or Toxoplasma gondii in vitro.
Wright, C. W., et al.
The in vitro activities of a series of quassinoids against Plasmodium falciparum, Entamoeba histolytica, Giardia intestinalis and Toxoplasma gondii have been compared with their in vitro cytotoxic effects against KB cells (human epidermoid carcinoma of the nasopharynx). All of the compounds tested were more toxic to KB cells than to G. intestinalis, but four (ailanthinone, bruceine D, brusatol and glaucarubinone) were slightly less toxic to KB cells than to E.histolytica. Glaucarubinone was similarly more toxic to intracellular T. gondii than to KB cells but ailanthinone was

more selective (36 times more toxic to T. gondii than to KB cells). All of the compounds were more toxic to P. falciparum than to KB cells; the most selective quassinoids--glaucarubinone, bruceine D, ailanthinone and brusatol--were found to have toxicity/activity ratios of 285, 76, 48 and 32 respectively. These results suggest that quassinoids have a selective action on P. falciparum. Further studies to elucidate the basis for this are in progress.

Biochem Pharmacol 1989 Dec 15;38(24):4367-74
In vitro studies on the mode of action of quassinoids with activity against chloroquine-resistant Plasmodium falciparum.
Kirby, G. C., et al.
Using the incorporation of [3H]isoleucine or [3H]hypoxanthine into acid-insoluble products as indices of protein- and nucleic acid-synthetic activity, respectively, it was shown that seven plant-derived quassinoids with differing chemical substitutions all inhibited protein synthesis more rapidly than nucleic acid synthesis in human erythrocytes infected with Plasmodium falciparum, in vitro. Five quassinoids (ailanthinone, bruceantin, bruceine B, glaucarubinone and holacanthone) were effective within 30 min at doses 10 times their 48 hr in vitro IC50 values. Chaparrin and glaucarubol differed in that they did not inhibit protein synthesis during the time course of these experiments when applied at 10 times their in vitro IC50 values. When these compounds were used at 209 and 114 times their respective IC50 values, their observed effects were identical to those of the other quassinoids studied. The time (t50) at which nucleic acid synthesis was reduced to 50% of control was directly proportional to the t50 for protein synthesis, suggesting that failure of nucleic acid synthesis is a consequence of inhibition of protein synthesis. It is concluded that in the malaria parasite, as in eukaryote models, quassinoids are rapid and potent inhibitors of protein synthesis, and that this is most likely due to effects upon the ribosome, rather than upon nucleic acid metabolism.

Antimicrob Agents Chemother 1986 Jul;30(1):101-4
Plants as sources of antimalarial drugs: in vitro antimalarial activities of some quassinoids.
O'Neill, M. J., et al.
Fourteen quassinoids, obtained from simaroubaceous plants, were tested for in vitro antimalarial activity. All of these inhibited the incorporation of
[3H]hypoxanthine into Plasmodium falciparum in vitro at concentrations below 0.41 microgram ml-1. The two most potent quassinoids, bruceantin and simalikalactone D, showed 50% inhibitory concentration values of 0.0008 and 0.0009 microgram ml-1, respectively. The results are compared with the antiamoebic, antileukemic, and cytotoxic activities of these compounds reported in the literature.

J Ethnopharmacol 1988 Feb-Mar;22(2):183-90
Plants as sources of antimalarial drugs, Part 6: Activities of Simarouba amara fruits.
O'Neill, M. J., et al.
Extracts prepared from Simarouba amara fruits collected in Panama have been found to be active against Plasmodium falciparum in vitro and against Plasmodium berghei in mice. Four active quassinoids have been identified as ailanthinone, 2'-acetylglaucarubinone, glaucarubinone and holacanthone.

Life Sci 1998;63(7):595-604
Mode of action of the anticancer quassinoids--inhibition of the plasma membrane NADH oxidase.
Morre, D.J., et al.
A plasma membrane-associated NADH oxidase of transformed cells was shown to be inhibited by nanomolar and subnanomolar concentrations of the antitumor quassinoid, glaucarubolone. The inhibition was seen with plasma membrane vesicles of HeLa cells at two log orders less glaucarubolone than with plasma membrane vesicles of rat liver. Assignment of a drug-binding site to the external surface of the HeLa cell plasma membrane was supported by findings where full activity of the glaucarubolone in the inhibition of NADH oxidase activity of isolated plasma membrane vesicles and of growth of HeLa cells was given on a molar glaucarubolone basis by an impermeant conjugate of glaucarubolone in which the glaucarubolone moiety was linked via the C-15 hydroxyl to amino polyethyleneglycol (ave Mr 5,000). The activity of the conjugate, and to a lesser extent, of free glaucarubolone was modulated by the redox environment of the cells and of the plasma membrane vesicles. Activity, both in the inhibition of NADH oxidase activity and in the inhibition of growth, was enhanced by oxidizing conditions in the presence of oxidized glutathione compared to reducing conditions in the presence of reduced glutathione.

Life Sci 1998;62(3):213-9

Effect of the quassinoids glaucarubolone and simalikalactone D on growth of cells permanently infected with feline and human immunodeficiency viruses and on viral infections.

Morre, D. J., et al.

Growth of Crandall feline kidney cells permanently infected with feline immunodeficiency virus was inhibited by the anti-cancer quassinoid glaucarubolone whereas growth of uninfected cells was not inhibited. Similar results were obtained for human MOLT-4 cells infected with HIV-1. The results suggest that cell lines permanently infected with either the feline or the human lentivirus exhibit growth response characteristics to the quassinoids in common with other cell lines malignantly transformed. In addition the quassinoids may delay viral infection suggesting some commonality between the mechanism responsible for inhibition of the growth of the transformed phenotype and viral infection.

J Nat Prod 1983 May-Jun;46(3):359-64

Plant anticancer agents XXV. Constituents of Soulamea soulameoides.

Handa, S. S., et al.

Three simaroubolides, glaucarubolone (1), holacanthone (2), and isobrucein A (3) were found to be responsible for the cytotoxic and antileukemic activities observed for extracts of the wood stem, stem bark, and twigs of Soulamea soulameoides. Other cytotoxic constituents isolated include a coumarinolignan cleomiscosin A (4) and the hydroxy canthin-6-one derivative 5. Picrasin B (6) was also obtained, but was not active.

Am J Trop Med Hyg 1981 May;30(3):531-7

Antimalarial activity of quassinoids against chloroquine-resistant Plasmodium falciparum in vitro.

Trager, W., et al

The growth of Plasmodium falciparum in vitro was markedly inhibited by certain quassinoids (the bitter principles from plants of the family Simaroubaceae). The most active compound, simalikalactone D, gave complete inhibition at 0.005 microgram/ml. Glaucarubinone an soularubinone were equally effective at 0.006 microgram/ml, whereas chaparrinone and simarolide had little effect even at 0.01 microgram/ml. These relative activities are parallel to the antineoplastic activities of these materials.

Lloydia 1977 Jul-Aug;40(4):364-9

Antitumor plants. IV. Constituents of Simarouba versicolor.

Ghosh, P. C., et al.

beta-Sitosterol, epilupeo, amarolide-11-acetate, amarolide-2,11-diacetate, ailanthinone and glaucarubinone have been isolated from S. versicolor. The cytotoxic and antileukemic activities of extracts of this plant are due chiefly to glaucarubinone.