QUASSIA : A Review

Quassia

Quassia amara

Family: Simaroubaceae

Synonyms: Quassia amarga, Picrasma excelsa, Quassia alatifolia, Quassia officinalis, Simarouba officinale

1/ Common names: [1, 2, 3, 4, 5, 6, 7, 8, 9]

English: Amargo, Bitter-ash, Bitter-wood, Jamaican bark, Jamaican Quassia, Picrasma, Quassia wood, Ruda, Simaruba, Surinam Quassia, Surinam Wood.

German: Quassiaholz, Fliegenholz, Simarubabaum.

French: Bois de Quassia, Bois amer, Quinine de Cayenne, Quassia de Cayenne.

Spanish: Guabo, Guavo, Hombre Grande, hombrón, Palo de Cuasia, Palo Muñeco.

Portuguese: Leno de Quassia, Murupa, Marupa, Marauba, Pau amarelo, Pau Quassia, Quassia de Caiena, Quina de Caiena.

Guyana Creole: Bitter bush, Quashie, Bitters.

Guyana Patamona: Ya-ko-yik, Ya-ku-yik.

Suriname Creole: Kwasibita, Kwasi bita, Kwasi bita bluem knoppen.

Suriname Sranan: bitterhout.

French Guyana Creole: Couachi, Quinquina de Cayenne.

Various: Crucete, Gorzkla, Kashshing, Kyassia, Quassie, Quina, Wewe Gifi.[1, 4, 5, 7]

2/ Used Parts [1, 4, 5, 7]: Trunk wood, roots, bark, stems, leaves, flowers and seeds.

3/ Botany [2, 3, 5, 6, 8]

Quassia amara is a member of the family Simaroubaceae, including around 150 species (essentially tropical and subtropical) in approximately 25 genuses.
Simaronbaceae is a small family with bitter compounds in the wood, bark and seeds. The leaves in this family are spread and feathered and the flowers usually have scales at the feet of the fumitory.
Quassia amara is a shrub or small tree growing mainly on sandy soils in lowland and highland forests and along the riverbanks.
This shrub grows 4 to 6 m in height. All parts are exceedingly bitter.
The leaves are alternate, 5 to 16 cm long, pointed at the apex narrowed toward the base.

The leaf midrib (rachis) is conspicuously winged and the stem, stalks and nerves are often red. The flowers are bright red with five lanceolate petals, which never fully expand but remind mostly closed together forming a spirally twisted cylinder, 2.5 to 4.5 cm long, from which ten stamens protrude, borne in showy racemes 10 to 30 cm long.
The fruit is on aggregate of five black, elliptic or obovate drupes 8 to 15 mm long, attached to a fleshly red receptacle, each containing a small seed. The wood is yellow-white.

4/ Origin and distribution [2, 3, 6]

Simaroubaceae, a pan tropical family, consists of six subfamilies with 32 genera and more than 170 arborous or shrubby species in tropical America, Africa, Asia, Malaysia and Northeastern Australia.
Plants in the genus Quassia are native to northern South America, and Quassia amara is indigenous to Northern Brazil and the Guyanas and it also grows in Venezuela, Columbia, Argentina, Panama and Mexico.
This small tree is used and marketed interchangeably with Picrasma excelsa that is also called Quassia.
P. excelsia is much taller (up to 25 meters) than Q. amara and occurs in the tropics of Jamaica, the Caribbean and the West Indies.

5/ Industrial use

The wood extract of Picrasma excelsa is commercially used in flavoring of aperitifs, liqueurs, soft drinks and baked goods.
Brewers have used it in the past as wood chips as a substitute for hops.
Quassia amara bark is universally employed as a bitter stomachic, it is also used to denature alcohol.

6/ Ethnobotanical use [1, 3, 4, 6, 7, and 9]

In the Amazon rainforest, Quassia is used in much in the same manner as quinine bark, for malaria and levers. The plant grows in lower areas (where quinine does not grow) and contains many of the same antimalarial phytochemicals contained in quinine.
In Suriname in Peru and more generally in all South-America it is used for the treatment of fevers.
In the same manner, seeds of plants of the same family are used in Indonesia for their antipyretic properties.
Quassia wood was an important export article of Suriname in the early 1900s, essentially as an antipyretic. In Suriname, bitter wood is still used against fever: a stick 5cm long and 1cm wide is steeped in 1 liter water or large bottle of vermouth, and small cupful is taken three times a day to prevent fever.
In French Guyana, the Guyana Patamona use to make infusions with roots, bark, stems, wood, leaves, flowers or a combination of the same, for the prevention and treatment of malaria and fevers.
For the same indications, indigenous prepare an alcohol extract called “quassine” with chips of wood macerated in water, gin, vermouth or cognac.
Another wide indication for Quassia is anorexia: it is used as a bitter stomachic to stimulate appetite and digestion, by increasing the secretion of digestive juices.
It used to be considered also as an emetic (Indonesia), a mild laxative and purgative (Indonesia, Brazil).
It is also widely used as an antiparasitic, especially in diarrheal and dysentery caused by amoeba. (Brazil, Guyana).
Quassia possesses a very well-known antiparasitary activity on intestinal worms, and is used in this indication in numerous countries such as Mexico, Brazil, Nicaragua, Guyana (bark macerated in rum or in infusion into water) and more generally in Latin America. It can be used orally, but also rectally in this indication.
The antiparasitary properties of Quassia have also topical applications.
Infusion of Quassia is commonly used for the prevention and treatment of pediculosis, as well in Argentina as in Brazil or Guyana.
The same preparation is also used to eradicate the cutaneous parasites like Agouti lice (Guyana) or smallpox (Guyana).
One of the popular used in Brazil are snake bites.
In the same country, a leaf decoction is used in bathing for measles and as month rinse after extraction.
The insecticide properties of Quassia have also to be highlighted.
Boiling pieces of wood of Quassia in water, one obtains a spray effective against many insects. Such popular remedies are used in Guyana, in Suriname but also in Brazil. It is also used in Guyana as a repellent against mosquitoes.

Tab.1 Ethnobotanical use of Quassia amara around the world

Country	Ailment treated / Properties and actions
Brazil	Diarrhea, Digestive, Dysentery, Dyspepsia, Flatulence, Gonorrhea
Caribbean region	Fever, Digestive complaints, Tonic
Chile	Appetizing, Blood purifier, Digestive, Fever, Intestinal parasites, tonic, Tuberculosis
Costa Rica	Diabetes mellitus, Diarrhea, Fever.
Guatemala	Constipation, Diabetes mellitus, Hypertension, Nervousness
Guyana	Appetizing, Digestive, Diarrhea, Dysentery, Fever, malaria, Intestinal, Parasites, Blood purifier, Pediculosis, tonic
Mexico	Dyspepsia, Enema, Fever, Gallbladder disorders, Intestinal parasites, liver disease, Stomachic, Tonic, Vermicide
Nicaragua	Anemia, Astringent, Bites, Intestinal parasites, Malaria, Strings, Tonic, Worms
Nigeria	Antianemic, Antibiotic, Malaria, Stomachic
Panama	Cure-all, febrifuge, Fever, Hyperglycemia, Liver disorders, Malaria Snakebite
Thailand	Antipyretic
Turkey	Astringents, Diarrhea, Digestive, Diuretic, Dysentery, fever, Malaria, Tonic
Venezuela	Diuretic, Dysentery, Fever, Laxative, Tonic, Vermifuge.
Others	Cancer, carcinoma, Fever, Intestinal parasites, snake bites.

In Europe, Quassia amara is registered in the British Pharmacopoeia, but also in the Pharmacopeias of Belgium, Denmark, France, Germany, Norway, Spain, Switzerland and Sweden.
Further, the Egyptian Pharmacopeia mentions it.
All the afore-mentioned Pharmacopeia authorized it, except the French one (!)
In the British Pharmacopeia, the recommended dose is between 120 and 500 mg (2 to 8 grains).
Indications are as a bitter stomachic to stimulate the appetite, and it can be prescribed with iron salts.
Infusion of Quassia (1 to 20 of cold water) is recommended as an enema for the expulsion of intestinal worms, and orally together with 0,502 of magnesium sulphate in the same indication.
Infusion of Quassia is also used as a lotion for pediculosis.

In said pharmacopeia, are listed the following formulas:

Concentrated infusion of Quassia (BP). Inf. Quass.Conc.
1 in 12,5; prepared by maceration with cold water. It contains 21 to 24% v/v of alcohol.
Dose: 2 to 4 nil. (30 to 60 minims).

Enema Quassia (B.P.C. 1949)
Fresh infusion of Quassia, undiluted.
Dose: 600 mil. (20 fl. 02)

Ext. Quass. (8.P.C.1949). Extract of Quassia
Prepared by maceration till percolation with cold water and evaporating the percolate to the consistence of a soft extract.
Protect from moisture.
Dose: 200 to 300 mg. (3 to 5 grains)

Fresh infusion of Quassia (B.P.) Inf. Quass. Rec
Quassia 1 g and cold water 100 ml. infused in covered vessel for 15 minutes, and strained.
Dose: 15 to 30 ml (0.5 to 1 fl. 02)

Infusion of Quassia (B.P) Inf.Quass. Concentrated infusion of Quassia
12,5 ml, water to 100 ml. It should be used within 12 hours, of its preparation. When infusion of Quassia is prescribed, fresh infusion of Quassia may be dispensed.
Dose: 15 to 30 ml (0,5 to 1 fl. 02)

Mist. Quass. Acid. (N.W.F.1947)
Infusion of Quassia 120 m. dilute hydrochloric acid 10 m; chloroform water to 0.5 fl. 02.
Dose: 15 ml (0.5 fl. 02)

Mist. Quass. Alk. (N.W.F. 1947)
Infusion of Quassia 120 m. Sodium bicarbonate 10 gr, chloroform water 0.5 fl.02
Dose: 15 ml (0.5 fl. 02)

Tinct. Quass. (B.P.1948) . Tincture of Quassia
Prepared by macerating Quassia 10g. with alcohol (45%) 100 mil.
Dose: 2 to 4 ml (30 to 60 minims).

In the natural medicine of USA and Europe, Quassia is used as a bitter tonic for stomach, gallbladder and for digestive disorders (increasing the flow of bile, digestive juices and saliva); as a laxative; as an amoebicide, insecticide and expel intestinal worms.

It is frequently found as a component in various herbal medicines sold in Europe to stimulate digestive, liver and biliary functions.
In England is also used a water extract of wood in topical way against scabies, lice and other cutaneous parasites.

7/ Chemical composition [3, 6, 8, 10, 11]

Quassia contains a great number of active ingredients, and phytochemicals in all its parts.

These active ingredients include alkaloids, triterpenes and bitter principles.
The bitter principles of Quassia wood are quassinoids (triterpenoid compounds), present in amounts of ~0, 25 %, from which 0,1-0,15 % are quassin, neoquassin, 18 hydroxy-quassin and Simalikalactone D.

Other quassinoids present in the wood ace: isoquassin, parain, quassimarin, quassinol and quassol.

Chemically, quassinoids are seco-triterpene-δ-lactones mostly found in the family Simaroubaceae.

Quassinoids are the major components responsible for the biological and pharmacological activities in this family.

At that time, more than 170 quassinoids have been insolated and characterized.
In Quassia, most of the quassinoids belong to type C-20, i.e. with twenty of carbon, (quassin, neoquassin, 18-hydroxy-quassin, isoquassin, parain, quassinol, quassol) whilst Simalikalactone D is of type C-25 and quassimarin C-27.

Quassinoids are biosynthetically related to triterpenes, and share the same metabolic precursors.
As it can be deduced from quassinoids of the structure-activity relationship, the most potent quassinoids possess cyclic systems with pentacyclic ring, with a lactone function and a cyclic methylen-oxygen bridge linking C-8 and C-13 or C-11.

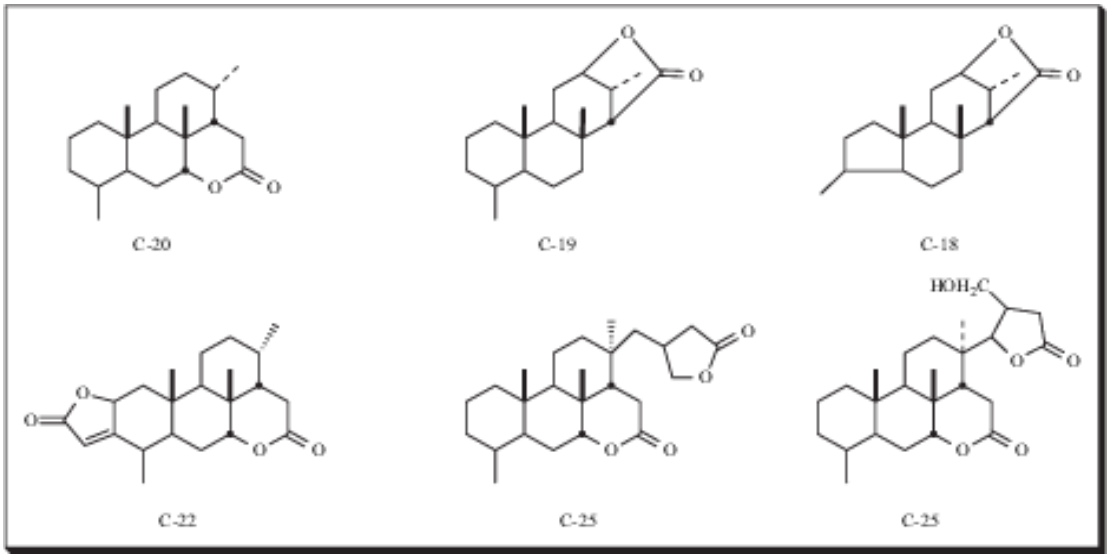

Fig 1- Skeleton of quassinoids.

Later[40] was discovered in Quassia amara the presence of indole alkaloids of the family of beta-carbolines, namely 1-vinyl- 4,8-dimetroxy-beta-carbolene, 1-methoxycarbonyl-beta-carboline and 3-methylcantin-2,6-dione.

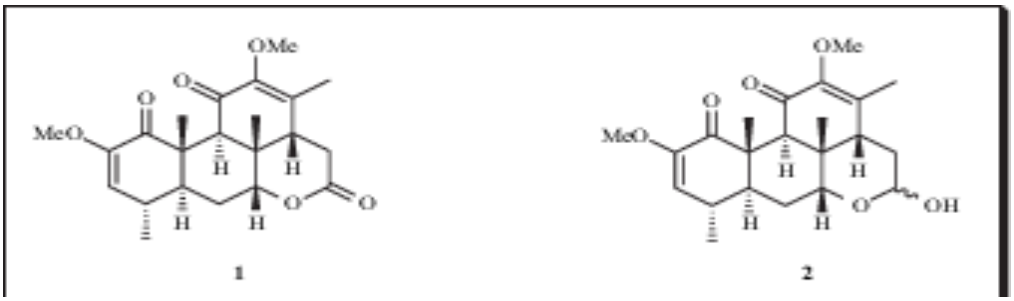

Fig.2 – Structure of quassin [1] and neoquassin [2]

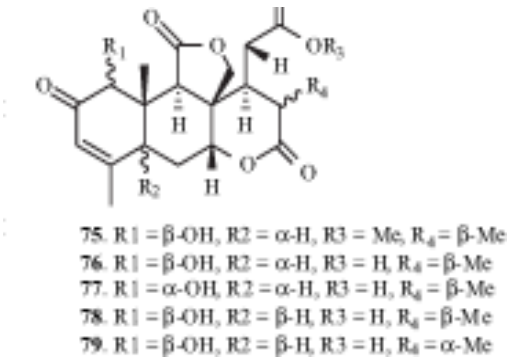

Fig. 3 – Structure of quassimarin

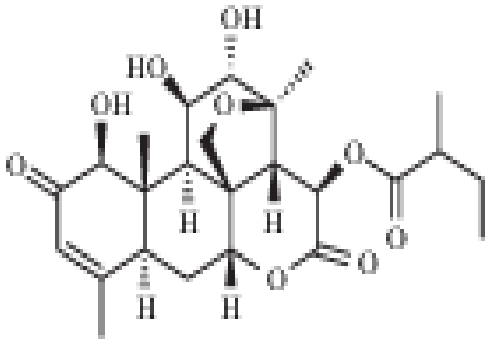

Fig. 4 – Structure of Simalikalactone D

8/ Biological activities and Clinical Investigation

- **Antiparasitary properties**

Antimalarial activity (Plasmodium)

An ancient private study (1947) in USA did not find any activity of water extract Quassia at 1.10 g/kg on the strain Plasmodium gallinaceum [12] whilst a more recent study (1999) reported a strong activity of two alcoholic extracts of Quassia on mice infected by Plasmodium berghei at doses of 100 and 2000 mg/kg [13]
Referring to the active ingredients responsible for this activity, various studies reported the in vitro antimalarial activity of Simalikalactone D [14, 15, and 16] on Plasmodium falciparum with the following concentrations:
IC50 = 0,0008 – 0,0009 mcg/ml [15] and IC100 = 0,005 mcg/ml [16], the latter in resistant strains of plasmodium falciparum.
Consequently, Simalikalactone D is much more potent than chloroquine in the same conditions.
It was demonstrated that the mechanism of action is through inhibition of protein synthesis. [17]
All quassinoids investigated in this study the protein synthesis more rapidly than the synthesis of nucleic acid in the human erythrocytes infected by P.falciparum, the inhibition of nucleic acid being observed following the defect of protein synthesis.
This antiplasmodial activity in vitro was also reported with extracts in water, in ethanol and in dichloromethan of Quassia africana [18] and with various other extracts and quassinoids of plants of the family Simaroubaceae. [19, 20]

Amoebicide activity
According to our knowledge, there is no report of a potential amoebicide action of Quassia amara, in spite of its traditional use in this indication.
However, there are various studies demonstrating this type of activity with various plants of the family Simaronbaceae and various quassinoids from the same. [19, 20]

Activity on pediculosis
Various clinical studies conducted with Quassia supported its traditional use as a natural insecticide, resulting to be an effective treatment for pediculosis in humans.
One of these studies reported can efficacy of 99% in 454 patients with only two topical applications with an interval of one week. [21]

In another study realized in double-blind vs. placebo, in 148 children with pediculosis, those treated with Quassia extract reported a minor number of new cases, demonstrating a preventive effect against lice. [22]
In parallel, a water extract of Quassia demonstrated to possess a good efficacy as an aphicide. [23]

Activity on insects
An interesting study conducted in India reported the efficacy of various extracts of Quassia on various types of insects including mosquitoes. [24]
Another study [25] permitted to verify these results.
As a result of other studies [26], quassin resulted to be responsible (or one the responsible) for this activity.

- **Antiviral properties**

Some quassinoids possess antiviral properties.
Simalikalactone D results to be active in vitro in concentrations between 0,2 and 20 µg/ml on Poliomyelitis, Semliki forest virus, herpes simplex virus type-1 (HSV-1) and Vesicular Stomatitis Virus (VSV). In concentrations of 0,2 µg/ml it was able to reduce the viral population by 99%. [27]
The same happened with quassin. [27]
In the same study, quassin resulted to be active in concentrating between 0,2 µg/ml and 20 µg/ml on the strain HIV III B, as well as Simalikalactone D.
These data confirm another report [28] claiming the antiviral activity of a water extract of Quassia at the doses of 50 µg in cultures of lymphoblastoid cells infected by HIV.

- **Anti-inflammatory properties**

Quassia amara extracts were evaluated as regards their analgesic and antiedematogenic properties in the carrageenan induced paw edema in mice. [2]
Although the oral administration of the extracts did not result to have a significant efficacy, interesting results were obtained with the intraperitoneal injection of the same, as well at anti-inflammatory as analgesic and sedative levels.
Interestingly, some quassinoids showed a promising anti-inflammatory activity in studies in vivo, [29] Thus, brusatol at dose of 0,25 mg/kg was as effective as indomethacin at the dose of 10 mg/kg.
Brucein B also showed interesting anti-inflammatory properties in the same study.
In another clinical study [30], Samaderine X and B showed a significant anti-inflammatory activity, inhibiting the volume of exudate by 79% and 78% respectively at a dose of 1 mg/kg.
On the other hand [31], it was discovered that brucein B was potent inhibitor of leukocyte-endothelial cell adhesion, suggesting that it could possess an interesting anti-inflammatory activity.

- **Antitumor properties**

It was reported [32] that Quassia extract, more especially probably quassimarin, would possess an antitumor activity on P388 cells in leukemia. At the concentration of 200 mg/kg the same extract should display a percentage of inhibitions of 81 % [33]. The

same investigators designed a study to predict the antitumor activity of the same extract on the inhibition of crown gall tumor in Agrobacterium tumefaciens. The product resulted to be active at a dose of 2 mg/ml.
Quassimarin and Simalikalactone D resulted to be active and possess antitumor properties [34] in cultures of human tumor KB, A-549, HCF 8, CAKI-1, MCF-7 and SK-MEL-2 cells, with ED 50 = 0,26 ± 0,012 g/ml

- **Anti-ulcer activity**

In a study comparing the anti-ulcer activity of four Quassia extracts [35], the investigators demonstrated that at the dose of 100 mg/kg by oral way, said extracts were active to inhibit as well the ulcer provoked by indomethacin / betanechol as gastric wound induced by hypothermal retention stress. Although not being so efficient, in lower doses these extracts increased the free gastric mucosa inhibited by indomethacin. Further, at the same concentration of 100 mg/kg by peritoneal way, the extracts under investigation reduced the content of gastric juice, increased the values of PH and diminished the acid secretion.
Moreover, a significant increase was observed in prostaglandin synthesis, inhibited by indomethacin.
Another study demonstrated that quassinoids, either orally or IM were efficient in the prophylaxis and treatment of peptic ulcers, such as gastric or duodenal ulcer, in rats. [36]

- **Other activities**

Antifertility effect

With methylic extract of an African variety of Quassia (Nigeria) it was demonstrated that the latter, at a dose of 100 mg/kg orally in male rats, resulted in a reduction in the weight of testis, epididymis, and seminal vesicles, with an increased of the anterior pituitary gland. [33] These observations were accompanied by a decrease in sperm count, and decreased levels of by a decreased in sperm count, and decreased levels of FSH, LH and testosterone.
The same authors reported in another study [37] that the same extract provoked an inhibition of secretion of testosterone as well basal as LH-stimulated.
Another Indian study [38] corroborated these observations with IM injections of a Quassia extract in male rats.
After 15 days treatment, it was observed a reduction in the weight of testis and epididymis, a decrease in sperm account, motility and viability, but contrarily with the other study, there was no effect on the seminal vesicles, nor on prostate, the prostatic acid phosphatase activity, citric acid levels and seminal vesicle fructose concentrations being unchanged.
It was deduced from the first study [33] that quassin was the one responsible for this activity.

Gastrointestinal effect

A study from Costa Rica [35] reported that oral intake of an aqueous extract of Quassia (500 to 1000 mg/kg) by mice was susceptible of increasing the intestinal movement in the same. The results being significant only with the highest dose.

9/ Toxicity of Quassia and quassinoids.

Further to its traditional use for centuries, there are fortunately a great number of studies as regards the toxicological innocuity of Quassia and related quassinoids.

It is well known, that Quassia extracts display a high toxicity orally by insects, but also by frogs. [24]
As regards mammals, although no study was conducted in humans, there are various valuable studies in mice.

In the study conducted in Brazil to evaluate the anti-ulcer activity of various Quassia extracts [35], no toxic effect was reported, nor the death of any animal, included using doses as high as 5000 mg/kg orally and 1000mg/kg intraperitoneally.

In the afore mentioned study from Costa Rica, [39] no sign of Quassia orally till a dose of 1000 mg/kg, confirming the Brazilian data, but nevertheless the same aqueous extract induced symptoms of acute toxicity, with recovery at 24 hours, in mice submitted to an intraperitoneal injection of 500 mg/kg and was lethal when the injection was 1000 mg/ kg which is in contradiction with the results of the Brazilian study.

The Indian study [38] focused on the antifertility effect of Quassia, did not detect any change in the biological parameters, i.e. the levels of hemoglobin, bilirubin, SGPT, SGOT, protein and urea.

A Microwell cytotoxicity assay using Artemia salina (brine shrimp) [40] reported the lack of toxicity of quassin at this level.

In the study of sub acute and sub chronic toxicity of Quassia, an Italian study most be highlighted, in which two groups of rats aged approximately 2 years old (10 rats in each group, were given dried Quassia extract dissolved in water or water alone by gavage in doses of 50 mg/kg/day 6 days/week for 8 weeks).
All the rats were killed and the heart, liver, adrenals and spleen were weighed. Body weights for the test and control animals were similar and remained roughly constant through out the study. Hematology tests revealed very little difference between the two groups. There were no significant differences in organ weights between groups either. However two of the control and one of the tests rats died during the second week of the study, which the authors claim, was probably as a result of the inflammatory process of the bronchi which was found at post mortem.
This could have been a result of the gavage method of dosing.

In the same work, was evaluated the reproductive and developmental toxicity of the same Quassia.
Pregnant rats were given dried Quassia extract at 100 mg/kg/day during the second half of pregnancy and through out the lactation period. The dosing period began at different times for each of the three rats in the test group i.e. at day 7, day 6 and day 5 before littering. No dosing details are given for the controls.

The numbers of pups in each litter were as follows: 14, 8 and 12 in the three control animals and10, 6 and 10 in the animals dosed on days 7, 6 and 5 before littering respectively. It would appear that there is a slight reduction in the number of pups in the dosed groups but the significance of this is nuclear. The weights of the pups in each litter were recorded at days 1, 7, 14 and 21 after birth. There were no significant differences in weights between test and control litters.

Njar et al [37] have studied the effect of Quassia amara on the steroido-genesis in rat Leydig cells in on in-vitro system. The crude methanol extract of the stem wood of Quassia amara at graded doses (50-250 µg/ml) inhibited both the basal and LH-stimulated testosterone secretion from rat Leydig cells in a concentration-dependent fashion. Quassia and the alkaloid 2-methoxycanthin-6-one were isolated from the Quassia extract, and the two isolated components were studied in the same way as described above for the extract, and quassin proved to be the bioactive agent. Again, both the basal and the LH-stimulated testosterone production by the Leydig cells were inhibited in a dose related manner with doses from 5 ng/ml and up to 25 ng/ml of the isolated Quassia. The inhibition of testosterone production was shown not to be caused by cytotoxic of the Quassia extract or of the isolated Quassia.

In continuation of the above study, another Indian staff of investigators have studied antifertility activity of Quassia amara in male rats.
Quassia amara stem wood crude methanol extract and two compounds isolated from the extract, quassin and the alkaloid 2-methoxycanthin -6-one were studied. The Quassia extract was given with the drinking water to made Wistar strain albinos rats (200-220g), five per group at doses corresponding to 1000 and 2000 mg per kilo body weight for eight weeks, then killed and examined as described below. A second set of groups of rats, also five per groups, similarly treated as above, were subject to a recovery period of eight weeks without further treatment.
The isolated quassin and 2- methoxycanthin- 6-one were applied in the same way as the Quassia extract, at doses corresponding to 0,1, 1,0 and 2,0 mg per kg body weight. The control rats (five per groups) received phosphate buffer saline. All rats had free access to food and water.
After the eight weeks of treatment the final body weight of the dosed groups did not differ significantly from the control groups, not either after the further eight weeks recovery period.
The study demonstrated that the crude methanol extract of the stem wood of Quassia amara significantly reduced the weight of the tests, epididymis and seminal vesicle and significantly increased of the tests, epididymis and seminal vesicle and significantly

increased that of the anterior pituitary gland. Epididymal sperm count serum levels of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FS4) were significantly reduced when the rats were treated with the extract.
All these changes seemed to be restored completely eight weeks after withdrawal from the eight weeks of treatment.
Furthermore, the basal and L4.stimulated testosterone secretion from Leydig cells isolated from rats pre-treated with the extract was inhibited.
The viability of the Leydig cells was unchanged after the treatment (no lethal effect on the cells of the treatment). All the effects were shown at all three dose levels and no dose-relationship was demonstrated.
Quassin produced quantitatively and qualitatively biological actions similar to the Quassia extract while the effects of 2-methoxycanthin- 6-one did not seem to differ from those of the control and the authors concluded that quassin appears to be the antifertility principle of Quassia amara.
All these data were taken into account by the scientific committee on food on the European Union, when this latter gave his opinion as regards the food use of quassin. Although asking for more studies, the committee extended the authorization of quassin as a component in foods. (52)
On the other hand, and this is not of minor importance Quassia has the status of "Generally Recognized as Safe" (GRAS) from the FDA. [9]

BIBLIOGRAPHY

1. DeFilipps, R.A., S.L. Maina, and J. Crepin. 2004. Medicinal Plants of the Guianas (Guyana, Surinam, French Guiana). www.mnh.si.edu/biodiversity/bdg/medicinal. p263-264.
2. Toma W, Gracioso JS, Hiruma-Lima CA, Andrade FDP, Vilegas W, Souza Brito ARM, Evaluation of the analgesic and antiedematogenic activities of Quassia amara bark extract. J.Ethnopharmacol 85 (2003) 19-23.
3. www.raintree.com/amargo. 2008
4. www.raintree.com/amargo. 2006
5. www.puralibre.com/html/eng_quassia.html 2008
6. Fernand VE. Initial characterization of crude extracts from *Phyllantus amarus Scum. And Thonn.* And *Quassia amara L.* using normal phase thin layer chromatography. Thesis . Faculty of Louisiana State University, USA, 2003.
7. www.herbdatanz.com/bitters_picture_monograph2.htm 2008
8. www.bba.de/oekoland/oeko3/quassia.htm 2008
9. www.naturaldatabase.com/S(vaptwt55got13045w5fnjm55)/nd 2008
10. Guo Z, Vangapandu S, Sindelar SW, Walker LA, Sindelar RD. Biologically active quassinoids and their chemistry: potential leads for drug design. Current Med Chem (12) 173-190, 2005.
11. www.//userpage.fu-berlin.de/~kayser/seite2.htm 2006
12. Spencer CF, Koniuszy FR, Rogers EF, Shavel JR, Easton NR, Kaczka EA, Kuehl Jr FA, Phillips RF, walti A, Folkers K, Malanga C, Seeler AO, Survey of plants for antimalarial activity. Res. Lab. Merck+Co Inc, Rahway NJ, USA. 145-174, 1947
13. Ajaiyoeba EO, Abalogu UI, Krebs HC, Oduola AM, In-vivo antimalarial activities of Quassia amara and Quassia undulate plant extracts in mice. J Ethnopharmacol (67)3:321-325. 1999
14. Cabral JA, McChesney JD, Milhous WK, A new antimalarial quassinoids from Simaba guianensis. J Nat Prod 56(11):1954-1961. 1993

15. O'Neill MJ, Bray DH, Boardman P, Phillipson JD, Warhurst DC, Peters W, Suffness M. Plants as sources of antimalarial drugs: in-vitro antimalarial activities of some quassinoids. Antimicrob Agents Chemother 30(1):101-104. 1986
16. Trager W, Polonsky J. Antimalarial acivity of quassinoids against chloroqine-resistant Plasmodium falkciparum in-vitro. Am J Trop Med Hyg 30(3):531-537. 1981.
17. Kirby GC, O'Neill MJ, Philippson JD, Warhurst DC. In-vitro studies on the mode of action of quassinoids with activity against chloroqine-resistant Plasmodium falciparum. Biochem Pharmacol 38(24):4367-4374. 1989.
18. Mbatchi SF, Mbatchi B, Banzouzi JT, Bansimba T, Nsonde Ntandou GF, Ouamba JM, Berry A, Benoit-Vical F. In-vitro antiplasmodial activity of 18 plants used in Congo Brazaville traditional medicine. J Ethnopharmacol 104:168-174. 2006.
19. Schwikkard S, van Heerden FR. Antimalarial activity of plant metobolites. Nat Prod Rep 19:675-692. 2002.
Gillin FD, Reiner DS, Suffness M. Bruceantin, a potent amoebicide from a plant, Brucea antidysenterica. Antimicrob Agents Chemother 22(2):342-345. 1982.
20. Wright CW, O'Neill MJ, Philippson JD, Warhurst DC. Use of microdilution to assess in-vitro antiamoebic activities of Brucea javanica fruits, Simarouba amara stem, and a number of quassinoids. Antimicrob Agents Chemother 32(11):1725-1729. 1988.
21. Jensen O, Nielsen AO, Bjerregaard P. Pediculosis capitis treated with Quassia tincture. Acta Derm Venereol 58(6):557-559. 1978.
22. Ninci ME. Prophylaxis and treatment of pediculosis with Quassia amarga. Rev Fac Cien Med Univ Nac Córdoba 49(2):27-31. 1991.
23. Roark RC, Some promising insecticidal plants. Econ Bot 1:437-445. 1947.
24. Evans DA, Raj RK, Extracts of Indian plants as mosquito larvicides. Indian J Med Res 88(1):38-41. 1988.
25. Evans DA, Raj K, Larvicidal efficacy of quassin against Culex quinquefasciatus. Indian J Med Res 93:324-327. 1991.
26. Evans DA, Kaleysa RR, Effect of quassin on the metabolism of catecholamines in different life cycle stages of Culex quinquefasciatus. Indian J Biochem Biophys 20(4):3600-3603. 1992.
27. Apers S, Cimanga K, Van den Bergehe D, Van Meenen W, Longanga AO, Foriers A, Vlietinck A, Pieters L, Antiviral activity of simalikalactone D, a quassinoids from Quassia Africana. Planta Med 68(1):20-24. 2002.
28. Abdel-Malek S, Bastien JW, Mahler WF, Jia Q, Reinecke MG, Robinson Jr WE, Shu YH, Zalles-Asin J, Drugs leads from the Kallawaya herbalists of Bolivia. Background, rationale, protocol and anti-HIV activity. J Ethnopharmacol 50:157-166. 1996.
29. Hall H, Lee KH, Imakura Y, Okano M. Anti-inflammatory agents III: Structure-activity relationships of brusatol and related quassinoids. J Pharm Sci 72(11):1282-1284. 1983.
30. Kitagawa I, Mahmud T, Yokota KI, Nakagawa S, Mayumi T, Kobayashi M, Shibuya H, Chem Pharm Bullk 44:2009. 1996.
31. Utoguchi N, Nakata T, Cheng HH, Ikeda K, Makimoto H, Mu Y, Nakagawa S, Kobayashi M, Kitagawa I, Mayumi T. Brucein B, a potent inhibitor of leukocyte-endothelial cell adhesion. Inflammation 21(27):223-233. 1992.
32. Kupchan SM, Streelman DR, Quassimarin, a new antileukemic quassinoids from Quassia amara. J Org Chem 41:3481. 1976.
33. Raji Y, Bolarinwa AF, Antifertility activity of Quassia amara in male rats – In vivo study. Life Sci 61(11):1067-1074. 1997.
34. Xu Z, Chang FR, wang HK, Kashiwada Y, McPhail AT, Bastow KF, Tachibana Y, Cosentino M, Lee KH, Anti-HIV agents 45(1) and antitumor agents (2) Two new sesquiterpenes, leitneridanins A and B, and the cytotoxic and anti-HIV principles from Leitneria floridana. J Nat Prod 63(12):1712-1715. 2000.
35. Toma W, Gracioso JS, Andrade JDP, Hiruma-Lima CA, Vilegas W, Souza Brito ARM. Antiulcerogenic activity of four extracts obtained from the bark wood of Quassia amara L. Biol Pharm Bull 25(9):1151-1155. 2002.

36. Tada H. Novel anti-ulcer agents and quassinoids. US Patent #4,731,459. 1988.
37. Njar VCO, Alao TO, Okogun JI, Raji Y, Bolarinwa AF, Nduka EU, Antifertility activity of Quassia amara: quassin inhibits the steroidogenesis in at Leydig cells in-vitro. Planta Med 61(2):180-182. 1995.
38. Parveen S, Das S, Kundra CP, Pereira BM, A comprehensive evaluation of the reproductive toxicity of Quassia amara in male rats. Reprod Toxicol 17(1):45-50. 2003.
39. Garcia J, Gonzalez M, Gonzalez Camacho SM, Pazos Sanou L, Pharmacologic activity of the aqueous wood extract from Quassia amara (Simaroubaceae) on albinos rats and mice. Rev Biol Trop 44(45):47-50. 1997.
40. Solis PN, Wright CW, Anderson MM, Gupta MP, Philippson JD, A microwell cytotoxicity assay using Artemia salina (brine shrimp). Planta Med 59(3):250-252. 1993.
41. Cao R, Peng W, Wang Z, Xu A, Beta-carboline alkaloids: biochemical and pharmacological functions. Curr Med Chem 14(4):479-500. 2007.
42. Ang KKH, Holmes MJ, Higa T, Hamann MT, Kara UAK, In-vivo antimalarial activity of the beta-carboline alkaloid manzamine A. Antimicron Agents Chemother $$8&):1645-1649. 2000.
43. Costa EV, Pinheiro ML, Xavier CM, Silva JR, Amaral AC, Souza AD, Barison A, Campos FR, Ferreira AG, Machado GM, Leon LL. A pyrimidine-beta-carboline and other alkaloids from Annona foetida with antileishmanial activity. J Nat Prod 69(2):292-294. 2006.
44. Moura DJ, Richter MF, Boeira JM, Henriques JAP, Saffi J, Antioxidant properties of beta-carboline alkaloids are related to their antimutagenic and antigenotoxic activities, Mutagenesis 22(4) :293-302. 2007.
45. Tse SY, Mak IT, Dickens BF, Antioxidative properties of harmane and beta-carboline alkaloids, Biochem Pharmacol 42(3):459-464. 1991.
46. Ichikawa M, Yoshida J, Ide N, Sasaoka T, Yamaguchi H, Ono K, Tetrahydro-beta-carboline derivatives in aged garlic extract show antioxidant properties. J Nutr 2006
47. Pari K, Sundari CS, Chandani S, Balasubramanian D, Beta-carbolines that accumulate in human tissues may serve a protective role against oxidative stress, J Biol Chem 275(4):2455-2462. 2000.
48. Yoon JW, Kang JK, Lee KR, Lee HW, Han JW, Seo DW, Kim YK, Beta-carboline alkaloid suppresses nf-kappaB transcriptional activity through inhibition of IKK signaling pathway, J Toxicol Environ Health A 10(68):23-24. 2005.
49. Greten FR, Arkan MC, Bollrath J, Hsu LC, Goode J, Miething C, Göktuna SI, Neuenhahn M, Fierer J, Paxian S, van Rooijen N, Xu Y, O'Cain T, Jaffee BB, Busch DH, Duyster J, Schmid RM, Eckmann L, Karin M, NF-kappaB is a negative regulator of Il-1beta secretion as revealed by genetic and pharmacological inhibition of IKKbeta. Cell 130(5):918-931. 2007.
50. Barbetti P, Grandolini G, Fardella G, Chiappini I, Indole alkaloids from Quassia amara. Planta Med 53(3):289-290. 1987.
51. Margaria R, Analisi dei gruppi lattinici di una quassina greggia. Communication to "Comité pour l'étude des boissons alcooliques aromatisées » de la Ferdervini, Milan, 1-10. 1963.
52. European Commission. Opinion of the Scientific Committee on Food on quassin. 2002.