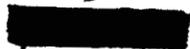


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ORIGINAL SUBMISSION

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NOTICE OF A GRAS EXEMPTION CLAIM (THIRD OF THREE COPIES)
According to FDA regulations § 170.36

SUBMITTED TO:

Office of Premarket Approval (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C St. SW
Washington DC 20204

NOTIFIER:

Brian Coyle
155 Wilson St.
Albany CA 94710
Fax & phone: 510 524-9733
Internet: bricoyle@nature.berkeley.edu

925 376 7440

1999 JUN 25 P 3: 16

NOTIFIED SUBSTANCE:

Garcinia kola, commonly called "bitter cola."

GRAS CLAIM:

Herein the undersigned, Brian Coyle, claims that the use of a approximately two (2) milliliters of watery extract of *Garcinia kola*, ("bitter cola"), added to one (1) liter of distilled spirit of palmwine, is exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act (the act) because Mr. Coyle has determined that such use is generally recognized as safe (GRAS.)

Brian M. Coyle
Manager, Pharaoh Palmier

6.19.99

date

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CONDITIONS OF USE:

The notified substance will be applied to use in the beverage Pharaoh Palmier. Pharaoh Palmier is composed of distillate of palmwine (the fermented exudate of palm hearts), distillate of grain, and distilled water, which combined in equal portions produce a beverage of 40% alcohol. To this are added FDA approved commercial flavorings, as well as the decoction of Garcinia kola.

Approximately 1 gram of Garcinia kola will be infused in 100-ml grain alcohol. Two (2) milliliters of this infusion will be added to every liter of Pharaoh Palmier.

PURPOSE OF USE:

The notified substance is used in Pharaoh Palmier for the purpose of flavor enhancement. It imparts an astringent, pleasing aftertaste. Pharaoh Palmier is a controlled alcoholic beverage that can only be sold to adults over 21 years of age. Typical consumption is 60 ml per serving.

BASIS FOR GRAS:

This use of the notified substance is determined to be GRAS based on scientific procedures.

AVAILABILITY STATEMENT:

The data and information that are the basis for the notifiers's GRAS determination will be sent to the Food and Drug Administration's (FDA) review and copying upon request.

IDENTITY OF NOTIFIED SUBSTANCE:

Chemical name: Garcinia kola seed infused extract is used in its entirety, rather than a particular chemical. However, besides crude protein, lipid, and sugar, Garcinia kola seeds are the unique source of small quantities of Kolaviron, a mixture of biflavonoids GB-1, GB-2 and kolaflavone

Chemical Abstracts Service Registry Number: NA

Enzyme Commission Number: NA

Empirical formula: Garcinia kola seed is a complete product, not a single chemical. Kolaviron is a mixture of the following biflavonoids:
GB-1 (II-3-4'-II-4"-I-5-II-5-1-7-II-7-heptahydroxy-3,8"-biflavone)
GB-2 (II-3-II-3'-I-4'-II-4"-1-5-II-5-1-7-II-7-octahydroxy-3,8"-biflavone)
Kolaflavone [garcinianin] (II-3-II-3'-II-4"-I-5-II-5-I-7-II-7-heptahydroxy-3,8"-biflavone)

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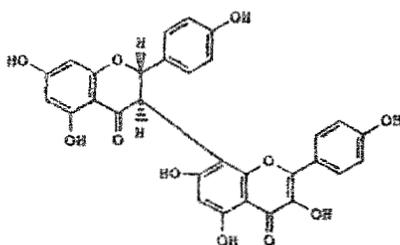
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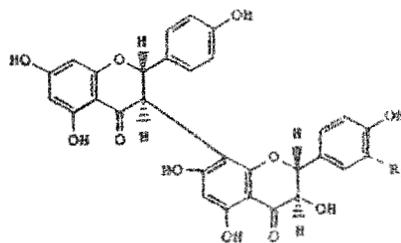
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Structural formula of Kolaviron, a constituent of *Garcinia kola*:



Kolaflavone

GB-1: R₃=H; GB-2: R₃=OH

Quantitative composition of *Garcinia kola* seeds:

Crude lipid:	7.8%.
Crude protein:	5.9%.
Mineral content, g/100 g of dry seed powder:	K, 50; Ca, 10; Mg, 17; N, 125; P, 72.
Sugar content:	18.1.
Ascorbic acid:	13.

Genus: *Garcinia*
Species: *kola*

Characteristic properties: A bitter taste like hops.

Specifications for food grade material:

Seeds of the fruit of *Garcinia kola* should be kept cool prior to being ground.

SUMMARY OF NOTIFIER'S BASIS THAT THE ABOVE USE OF NOTIFIED SUBSTANCE IS GRAS.

GRAS DETERMINATION THROUGH SCIENTIFIC PROCEDURES:

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A: Discussion of and citations to generally accepted scientific data that the notifier has relied on to establish safety, including a consideration of the probable consumption of the substance.

[REDACTED]

[REDACTED]

[REDACTED]

The data used for the establishment of the safety of *Garcinia kola* seed compounds comes from over 20 scientific studies carried out between 1982 and 1999. All of these studies used seeds from trees obtained in the forest region of West Africa.

The seeds of *Garcinia kola* have been the subject of scientific study for three reasons.

First, the seeds are widely eaten in the geographic areas where the *Garcinia kola* tree grows. Dosunmu and Johnson (2) evaluated the nutritive value of *Garcinia kola* fruit and seeds in the context of the peasant farmer's agricultural system. They found levels of toxic substances such as tannins, phytic and hydrocyanic acids, were very low. Phytic acid was determined by the method of McCance and Widdowson, hydrocyanic acid by the AOAC method, and tannins by the method of Burns. The juice of the fruit and seeds are nutritive sources of substantial ascorbic acid (vitamin C.)

The second and most significant reason for the scientific study of *Garcinia kola* seeds is that several chemical constituents have anti-hepatotoxic effects; this suggests *Garcinia kola* seeds could play a pharmacological role as a liver prophylaxis. The evidence for this implication comes from a series of studies (see heading ii, below.)

These studies isolated a set of biflavonoids that consistently exhibit potent anti-oxidant ratios. The picture emerges of a family of compounds (racemates) that inhibit liver lipid peroxidation. As Adegoke et al. (6) report, *Garcinia kola* seed achieved inhibition in a dose-dependent manner. The inhibitory activity of *Garcinia kola* was not affected by heating.

The widely observed antioxidant components of *Garcinia kola* are soluble in aqueous and ethanol media. As a consequence, the effect of minute quantities of *Garcinia kola* suspended in alcohol are beneficial for consumers of alcohol beverages such as Pharaoh Palmier (7-13.)

With no toxic byproducts, infusions of *Garcinia kola* seeds are a useful adjuvant to the diet of those who consume compounds that interfere with liver metabolism, or who suffer liver disorders. Iwu (13) reported that the seeds, used as an herbal treatment for patients with liver disease, markedly improved liver function.

The third reason for the study of *Garcinia kola* has been its potential as a replacement for hops in the brewing of lager beer in Africa. Treatment of *Garcinia kola* with methanolic lead acetate produces a yellow precipitate from which alpha acids have been confirmed to be present by thin-layer chromatography. The bitterness given to beer by hops comes from alpha acids like these. We expect this to be the flavor role of *Garcinia kola* in Pharaoh Palmier as well.

Laboratory brewing trials with *Garcinia kola* and hops gave beers with similar chemical properties. Organoleptically, *Garcinia kola* beer was as acceptable to tasters as hopped

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beer. *Garcinia kola* and hop extracts exerted similar anti-microbial effects on beer spoilage microorganisms (14-16.)

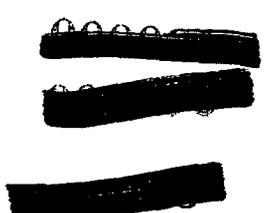
i) STUDIES ON THE CHEMICAL COMPOSITION OF *GARCINIA KOLA* SEEDS.

1. TITLE: Constituents of the seeds of *Garcinia kola*: two new antioxidants, garcinoic acid and garcinal.
AUTHORS: Terashima,-K.; Shimamura,-T; Tanabayashi,-M; Aquil,-M; Akinniyi,-J.A.; Niwa,-M.
SOURCE: *Heterocycles*. 1997. 45: 8, 1559-1566.
2. TITLE: Chemical evaluation of the nutritive value and changes in ascorbic acid content during storage of the fruit of 'bitter kola' (*Garcinia kola*).
AUTHORS: Dosunmu, M I; Johnson, E C.
SOURCE: *Food Chemistry*. 1995. 54: 1, 67-71.
3. TITLE: Chemical composition of *Cola acuminata* and *Garcinia kola* seeds grown in Nigeria.
AUTHORS: Adeyeye,-E.I.; Ayejuyo,-O.O.
SOURCE: *International Journal of food science and nutrition*. 1994. 45: 4, 223-230.
4. TITLE: High-speed counter-current chromatographic separation of biflavonoids from *Garcinia kola* seeds.
AUTHORS: Kapadia,-G.J.; Oguntimein,-B.; Shukla,-Y.N.
SOURCE: *Journal of chromatography*. 1994. 673: 1, 142-146.
5. TITLE: Flavonoids of *Garcinia kola* seeds.
AUTHORS: Iwu,-M.; Igboko,-O.
SOURCE: *Journal of Natural Products*. 1982. 45: 5, 650-651.

ii) STUDIES ON THE PROPHYLACTIC EFFECT OF *GARCINIA KOLA* SEEDS AGAINST HEPATOXICITY.

6. TITLE: Inhibitory effect of *Garcinia kola* on lipid peroxidation in rat liver homogenate.
AUTHORS: Adegoke,-G O.; Kumar,-M.V.; Sambaiah,-K.; Lokesh,-B.R.
SOURCE: *Indian Journal of Experimental Biology* 1998, 36: 9, 907-910.
7. TITLE: Natural products with hepatoprotective action.
AUTHOR: Utrilla,-M.P.
SOURCE: *Methods and Findings in Experimental and Clinical Pharmacology*, 1996. 18, Suppl. B: 11-12.
8. TITLE: Antihepatotoxic biochemical effects of kolaviron, a biflavonoid of *Garcinia kola* seeds.
AUTHOR: Braide,-V.B.
SOURCE: *Phytotherapy Research*. 1991. 5: 1, 35-37.
9. TITLE: Inhibition of drug metabolism by flavonoid extract (kolaviron) of *Garcinia kola* seeds in the rat.
AUTHOR: Braide,-V.B.
SOURCE: *Phytotherapy Research*. 1991. 5: 1, 38-40.
10. TITLE: Protective effects of *Garcinia kola* seed extract against paracetamol-induced hepatotoxicity in rats.
AUTHORS: Akintonwa-A.; Essien-A.R.
SOURCE: *Journal of Ethnopharmacology*. 1990. 29: 2, 207-211.
11. TITLE: Prevention of thioacetamide-induced hepatotoxicity by biflavanones of *Garcinia kola*.
AUTHORS: Iwu-M.M.; Igboko-O.A.; Elekwa-O.K.; Tempesta-M.S.
SOURCE: *Phytotherapy Research*. 1990. 4: 4, 157-159.

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12. TITLE: Evaluation of the anti-hepatotoxic activity of the biflavonoids of *Garcinia kola* seed.

AUTHORS: Iwu-M.M.; Igboko-O.A.; Onwuchekwa-U.A.; Okunji-C.O.

SOURCE: *Journal-of-Ethnopharmacology*. 1987, 21: 2, 127-138.

13. TITLE: Antihepatotoxic constituents of *Garcinia kola* seeds.

AUTHOR: Iwu-MM

SOURCE: *Experientia*. 1985, 41: 5, 699-700.

iii) STUDIES ON THE POTENTIAL USE OF *GARCINIA KOLA* SEEDS AS A HOP SUBSTITUTE IN BEER.

14. TITLE: A comparison of some chemical properties of *Garcinia kola* and hops for assessment of *Garcinia* brewing value.

AUTHORS: Ogu,-E.O.; Agu,-R.C.

SOURCE: *Bioresource Technology*. 1995, 54: 1 1-4.

15. TITLE: Preliminary studies on tropical hop substitutes.

AUTHORS: Aina,-J.O.; Uko,-E.E.

SOURCE: *Tropical Science*. 1991, 31: 4, 379-385.

16. TITLE: Potential use of *Garcinia kola* as hop substitute in lager beer brewing.

AUTHORS: Aniche,-G.N.; Uwakwe,-G.U.

SOURCE: *World Journal of Microbiology and Biotechnology*. Sept 1990, 6: 3, 323-327.

17. TITLE: Kolanone, a novel polyisoprenylated benzophenone with antimicrobial properties from the fruits of *Garcinia kola*.

AUTHORS: Hussain-RA; Owegby-AG; Parimoo-P; Waterman-PG

SOURCE: *Planta-Medica*. 1982, 44: 2, 78-81.

B: Discussion of reports that may appear to be inconsistent with the GRAS determination.

Because whole, natural *Garcinia kola* seeds are consumed in large quantities by many people in West Africa, scientific analyses has focused on the effect of such a diet on gastric acidity due to the presence of ascorbic acid in the seeds. There is concern that the high acidity in the product might be antagonistic for patients prone to gastrointestinal ulcers. However, studies on rats show that high concentrations of *Garcinia kola* seeds markedly inhibited gastrointestinal motility, protected against castor-oil-induced diarrhea, prolonged pentobarbital sleeping time, caused marked retardation of growth but did not affect organ weights, compared with controls (3).

The actual amount of ascorbic acid in Pharaoh Palmier will remain much lower than what is commonly found in other components of the typical American diet.

Recent analyses of nitrosatable amines in natural tropical stimulants like *Cola acuminata*, *Cola nitida* (a component of Coca Cola and other popular beverages), and *Garcinia kola* suggest that high levels of kola nut chewing promotes significant methylating activity. There is a possibility that this could be implicated in human cancer etiology where tropical nut stimulants are widely consumed. However, *Garcinia kola* is not a stimulant like the two other Colas since it does not contain caffeine or related substances (indeed,

the trees are from different families,) and show much lower levels of aliphatic amines than the other two (1).

The role of methylation in cancer formation is not proven. However, the actual amount of aliphatic amines in Pharaoh Palmier will be exceedingly low.

iv) STUDIES ON THE PHARMACOLOGICAL EFFECTS OF CHRONIC INGESTION OF GARCINIA KOLA.

1. TITLE: Nitrosatable amines and nitrosamide formation in natural stimulants: Cola acuminata, C. nitida and Garcinia kola.

AUTHORS: Atawodi,-S.E.; Mende,-P.; Pfundstein,-B.; Preussmann,-R.; Spiegelhalder,-B.

SOURCE: Food chemical toxicology, 1995. 33: 8, 625-630.

2. TITLE: Effects of diets containing seeds of Garcinia kola (Heckel) on gastric acidity and experimental ulceration in rats.

AUTHORS: Ibironke,-G.F.; Olaleye,-S.B.; Balogun,-O.; Aremu,-A.

SOURCE: Phytotherapy research. 1997, 11: 4, 312-313.

3. TITLE: Pharmacological effects of chronic ingestion of Garcinia kola seeds in the rat.

AUTHOR: Braide,-V.B.

SOURCE: Phytotherapy Research. 1990, 4: 1, 39-41.

C: The basis for concluding, in light of the data and information described above, that there is a consensus among experts that the substance is not harmful under the intended conditions of use.

We believe the data convincingly shows the unmistakable suitability of Garcinia kola as a liquor infusion. Garcinia kola has virtually no toxic effect; indeed it is safer than another tropical nut with a similar name, Cola nitida, which is a component of colas of mass consumption. (As a point of history, Cola nitida was selected for the Coca-Cola recipe from among a set of tropical flavoring candidates that included Garcinia kola, back in the 19th century.)

Research ranging from medical experimentation to bioassays suggests the most important physiological effect of Garcinia kola ingestion is as a source of protection against liver disease. This corroborates the use of Garcinia kola in traditional African medicine. ✓
Given that the physiological vector of the most pronounced negative impact of alcohol consumption is the liver, Garcinia kola is a healthful, beneficial liquor additive.

Recently, Garcinia kola has been touted as a hops replacement for beer manufacturing in Africa. All research in this domain points to Garcinia kola's entirely satisfactory and benign chemical properties.

This African product, that missed its first chance as a commercial beverage flavoring in the 19th century, should have a successful second chance in the 21st century.

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SUBMISSION END