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BLIGHIA SAPIDA; THE PLANT AND ITS HYPOGLYCINS AN OVERVIEW

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Abstract: Blighia sapida Köenig; family Sapindaceae is a multi purpose medicinal plant popular in the western Africa. It is well known for its food value and its poisonous chemical contents being hypoglycins A & B (unusual amino acids.) The hypoglycin A is more available in the fruit than hypoglycin B. Hypoglycin A have been used as glucose inhibitor therapy, thereby giving room for the plant to be used for orthodox medicinal purposes in future. Its other therapeutic values have been reported as well. The ingestion of hypoglycin A forms a metabolite called methylenecyclopropane acetyl CoA (MCPACoA) which inhibit several enzymes A dehydrogenases which are essential for gluconeogenesis. This review covers history, description, origin and uses of Blighia sapida with emphasy on the fruit and its associated biologically active component (hypoglycins) and tries to show why the plant can be used as the sources of many potential drugs in treatment of diseases, especially glucose related ones. The mechanism of hypoglycin A metabolism is also explained. The hypoglycin A potential glucose-suppressing activities warranted further studies for the development of new anti-diabetes drugs with improved therapeutic values.

KEYWORD: Blighia sapida, Sapindaceae, hypoglycins, dehydrogenases, metabolism.

Introduction

Throughout history, man has turned nature into various substances such as medicines, food and domestic aids. Medicinal plant plays a vital role in the management of various diseases (Olatunji and Atolani, 2009). *Blighia sapida* of the family sapindacae is one of nature's gifts which have been highly utilized for various purposes by man. *Blighia sapida* is both known for its food values and its poisonous properties (Morton, 1987). It is a major food in Jamaica and is noted for its high protein and fat contents (Ashurst, 1971).

It is a plant belonging to subkingdom; Tracheobionta; rosidae, order; saphindales, family; sapindacea and genus; *blighia*. It bionomical name is *blighia sapida*, the French names are aki and arbe fricassee. It Spanish names are arbol de seso and seso vegetal. Arbor del huevo and pera roja (mexico); bien me sabe or pan quesito (colombia); aki (costa Rica). In portuguese, it is castanna or castanheiro de Africa. In Nigeria, it is known as akee and ishin. It has many other dialectal names in other western Africa countries (Micheal, 1998).

Fig. 1. Photograph of *Akee* Fruit.

History

The plant has its origin in West Africa but has transversed the Atlantic making the carribean its home. Its exact date of

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arrival is unknown but it is believed that the fruit was transported to the Caribbean by slaves' ships sometimes around the 18th century. The trivial name ackee, is derived from the terms “anke and “akye fufuo” which are used to describe the fruit in west Africa. The fruit was name *Blighia sapida* in honour of the infamous captain William *Blighia* of mutiny on the Bounty who transported the fruit from Jamaica to England in 1793 (Lewis, 1965).

Description

The tree is usually densely branched and symmetrical with smooth gray bark. The tree reaching 40ft (12m) posseses evergreen (rarely decidous) alternate leaves with 3 to 5 pairs of – oblong, obovate – oblong, or elliptic leaflets, 6 to 12inches (15 – 30 cm) long, rounded at the base, short – pointed at the apex; bright – green and glossy on the upper surface, dull and paler and finely hairy on the veins on the under side. It produces bisexual male flowers, borne together in simple racemes 3 to 7in (7.5 – 17.5cm) long, fragrant, 5 petalled, white and hairy. The fruit is a leathery, pear shaped, more or less distinctly 3 – lobed capsule 2.75 to 4 inch (7 – 10cm); basically yellow, more or less flushed with bright scarlet. When the fruit is fully mature, it splits open revealing 3 cream – colored, flashy, glossy aris attached to the large, black, nearly round, smooth hard, shining seeds – normally 3 with 1 or 2 often aborted. The base of each aris is attached to the inside of the stem – end of the jacket (Morton, 1987).

Origin and Distribution

The ackee is indigenous to the forest of the Ivory Coast and Gold coast of west Tropical Africa. The fruiting tree is admired as an ornamental tree in Ghana. It was introduced to Jamaica in 1793 and was readily adopted and grown along road sides. It is being cultivated in Trinidad, Haiti, the islands of the West Indies and the Bahamas. It was apparently carried by Jamaica slaves to Parama and the Atlantic coast of Guatemala and Costa Rica. It was outlawed in Trinidad in 1900 having caused some fatalities. There are scattered trees in Surinam, Venezuela, Colombia, Ecuador Brazil and Calcutta India. The tree has been tried in the warm, moist climate of Guyana and Malaya but has never survived. At Lamao in the Philippines, it first bore fruit in 1919 (Kean and Hare, 1980).

Climate

The ackee tree is tropical to subtropical; flourishes from sea-level to an elevation of 3,000ft (900m) in Jamaica. It does not bear fruit in Guatemala city, but fruits heavily in southern Florida where young trees have been killed by winter cold (Kean and Hare, 1980).

Propagation and Culture

Ackee is propagated by seeds, cutting or grafting. Shooting is also carried out in Europe. It grows fast and requires little attention. Seedling trees begin fruiting at about 4 years, while grafted trees produce fruit in 1 – 2years. Fruiting may occur throughout the year, but principally in December through May in the Northern Hemisphere (Kean and Hare, 1980). In Jamaica, it produces fruit two times per year between January and March, and June through August (Moya, 2001).

Cultivars and Related Species

Named cultivars are not yet known. Two other species of the genus Blighia, both from tropical Africa, are B.Unjugata, which has edible leaves, and B.welwitschii, which has medicinal uses (Kean and Hare, 1980).

Season

Some flowering and fruiting occurs all

year in Jamaica. Flowering and fruiting occurs in spring and mid summer respectively in Florida. Crops are harvested February through April and July through October in Bahamas (Kean and Hare, 1980).

Food Uses

The fruit aril is edible when fully ripped. Ripped fruits are fully opened naturally. The black seeds are discarded and the arils, while still fresh and firm are best parboiled in salted water or milk and then lightly fried in butter. They are often cooked with codfish, onions and tomatoes in Jamaica (Moya, 2001). They are cooked with seasonings and eaten with rice at homes and hotels. In Africa they may be eaten raw or in soup. Canned ackee is exported primarily to the United Kingdom and Canada (CDC, 1992). Some works have been reported on its vitamin C, sugar contents (Akande, 1989) and edibility of the pulp (Rice et al, 1987). Table 1 shows the nutritional composition per 100g of the raw arils (Morton, 1987).

Content	Quantity/100g
Moisture	57.60g
Fat	18.78g
Carbohydrates	9.55g
Protein	8.75g
Fiber	3.45g
Ash	1.87g
Phosphorus	98mg
Calcium	83mg
Ascorbic Acid	65mg
Iron	5.52mg
Niacin	3.74mg
Riboflavin	0.18mg
Thiamine	0.10mg
Carotene	-

Table 1. Nutritional composition of raw *akee* aril.

Other Uses

The fruit produces lather in water and is therefore used for laundering purpose in some West Africa countries. Crushed fruits are also employed as fish poison (Duke, 1985). The seeds, because of their oil content, and the jacket because of its potash content are burned and the ashes used in making soap. The extract of the flowers is used as cologne while the pulverized bark is mixed with grounded hot peppers and rubbed on the body as stimulant. The sapwood (white or light greenish – brown) and the hearthood (reddish – brown), hard, Coarse grained, durable and termites immuned is used for construction, pilling, oars, casks and paddles (Kean, 1980).

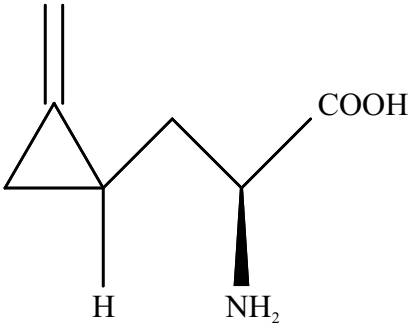
Medicinal Uses

The aqueous extract of the seed is administered as parasites expellant. The treatment is followed by a saline or oily pugative. The crushed new foliage is applied on the forehead as headache reliever. The leaf juice is employed as eye drops in opthalmia and conjunctivitis. Various preparation and combination of the extract have been made for the treatment of diseases such as dysentery, epilepsy, yellow fever (Kean and Hare, 1980) and diabetics (Gbolade, 2009). The plant has been reported to be effective against cold and pain when applied. It is as well acaricidal and insecticidal (Mitchell, 2001).

Physiochemical Properties and Associated Toxicity

For many years, it was believed that the unripe ackee fruit may be poisonous, containing a natural toxin (Hill, 1952; Hassall and Hill, 1955). Akintayo et al (2002) reported about the Chemical composition, physicochemical and functional properties of akee. Clinical and chemical studies carried on ackee revealed that it contain toxic substances called hypoglycin A (HGA) and hypoglycin B (HGB). It is known that the unripe arils contain hypoglycin A i.e. α-amino–β–(2methylene cyclopropyl) propionic acid (fig. 2) (Kean and Hare,

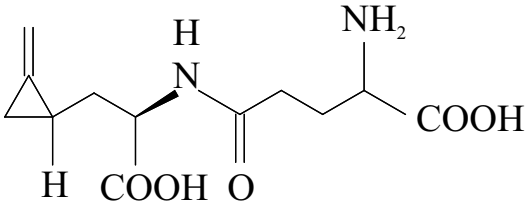
1980, Orane et al, 2006). The unripe ackee fruit contains hypoglycin A in a concentration 100 times higher than those in the ripe ackee fruit (Golden, 2002). In another study, the concentration of hypoglycin A decreased from 711 mg/100 g in raw, unripe fruit to below the limits of detection (1.2 mg/100g) in the ripe aril, as measured by ion-exchange chromatography (Chase Jr et al, 1990). The concentration of hypoglycin A in the membrane and aril is similar as the fruit matures, but the membrane contains detectable amounts (ie, about 40 ppm) of hypoglycin A even at the edible stage. (Brown et al, 1992). It is believed that the toxic substance is dispelled by light as the jacket of the riped fruit opens (Barennes et al, 2004).



Hypoglycin A

Fig. 2. Structure of Hypoglycin A (HGA)

It has been hypothesized that during fruit maturity, hypoglycin A is translocated from the arilli to the seeds of the fruit (Kean and Hare, 1980). There, it is converted to the dipeptide hypoglycin B, Fig. 3.



Hypoglycin B

Fig. 3. Structure of Hypoglycin B (HGB)

When fully ripe, the hypoglycin A reduces to about 1/10 of the original in the arils. Hypoglycin B 'is only found in the seeds of the fruit. It also possesses hypoglycemic activity but is less potent than hypoglycin A (Kean and Hare, 1980). Epidemic and victims of the illness were prominently children (Barennes et al, 2004). The death of the children was linked to ackee intoxification due to enhanced concentrations of dicarboxylic acids in the urine of the victims. In addition, other hypoglycemic compounds, including hypoglycin B and other cyclopropanoid amino acids, are found in the seed. CNS active carboxycyclopropyglycines found in the unripe fruit are reported to be potent group II metabotrophic glutamate receptor agonists (Natalini et al, 2000) and and liver function values elevator (Larson et al, 1994).

Subacute intraperitoneal administration of the lipid portion of the unriped ackee oil resulted in marked neutropenia and increase in platelets without anaemia In rats. The lung shows area of petechial haemorrphages and a dose-related perivascular and peribronchial mononuclear cell infiltration (Singh, 1992). Unripe akee fruit also contain glutamate analogs that are carboxycyclopropylglycine compounds (Natalini, 2000).

Jamaica Vomiting Sickness

HGA is considered to be responsible for the vomiting sickness, an acute condition, frequently observed in Jamaica, which is characterized by persistent vomiting and a coma (Scott, 1917, Jeliffe, 1954, Manchester, 1974 and Meda, 1999) and death within 12 hour of ingestion in severe cases (Hill, 1952; Hassall, Hill, 1955, Sherratt, 1986 and Brown et al 1992). The sickness was found predominantly in Jamaica between 1880 to 1955 (Feng, 1969). The Jamaica

vomiting sickness (JVS) is also referred to as Toxic Hypoglycemic syndrome and is associated with severe disturbances in carbohydrate and lipid metabolism. Other clinical features include abdominal pain depletion of hepatic glycogen, hypoglycemia, aciduria and severe death (Tanaka and Ikeda, 1990). Experimental analyses on animals show that HGA causes fatty degeneration of the liver (Van Holt et al, 1959). The ingestion of 12 and 24 uncooked, raw akee fruit by two adults produced vomiting and drowsiness that progressed to mild hypoglycemia and coma (Golden et al, 1984).

Poisonings may be present in 1 of 2 distinct forms. In a case, vomiting is followed by a remission period of 8 to 10 hours, followed by renewed vomiting, convulsions, and coma. The other type is characterized by convulsions and coma at the onset. Additional symptoms associated with chronic fruit ingestion include cholestatic jaundice, abdominal pain, and elevated liver function values (Larson et al, 1994). Orane and his group (2004) observed that young children in lower socio-economic group are the most vulnerable to hypoglycin toxicity, when it occurs.

Hypoglycin A Toxicity and metabolism

Onusiriuka reported that Hypoglycin A is a water – soluble liver toxin that induces hypoglycemia by inhibiting glucogenesis by limiting the activity of cofactor mimics (CoA and Camitine) that are required (Onusiruka and Ufodike, 2000). The HGA produces methylenecyclopropylacetic acid, which reduces several cofactors (eg, coenzyme A, carnitine) essential to the β-oxidation of long-chain fatty acids and inhibits the transport of longchain fatty acids into the mitochondria (Bressler et al, 1969 and Wenz et al 1981) This consequently causes conjugated carnitines-fatty acids to accumulate in the serum and urine and thereby get oxidized in the endoplasmatic reticulum of the liver (Bressler, 1976). MCPA-CoA irreversibly binds to flavin-adenine-dinucleotide (FAD) and thereby inhibits the activityof medium chain and short chain acyldehydrogenases (MCAD and SCAD), respectively. MCAD and SCAD are critical to the complete β-oxidation of fats. Hence, their inactivation will have adverse effects on blood serum short chain fatty acid concentrations, urinary hydroxyl and dicarboxylic acid concentrations, as well as plasma and urinary amino acid concentrations (Ming-tain Lai et al., 1991, 1992, 1993). There is a net reduction in the in fatty acid metabolism which resultantly causes an increased uptake of glucose, and the blockade of the substrate for hepatic gluconeogenesis leading to hypoglycemia after the depletion of NADH and hepatic glycogen stores (Bressler, 1976).

It has been discovered that it is hypoglycin A metabolite called methylene-cyclopropane acetyl CoA (MCPA–CoA) is responsible for Jamaica Vomiting Sickness (JVS). The hypoglycin A is transaminated to methylene–cyclopropyl–alanine (MCPA) and subsequently undergoes oxidative decarboxylation to form MCPA–CoA (22). α-Ketomethylenecyclopropylpropionic acid (KMCPP), an intermediate metabolite fig. 4, of HGA is first formed before the transformation to MCPA–CoA (Tanaka et al, 1972), which exerts its effect by inhibiting several coenzymes A dehydrogenases which are essential for gluconeogenesis (Von Holt et al, 1966b).

The metabolite (MCPA-CoA) contributes to the etiology of the symptoms associated with consuming unripe ackee (Von Holt et al, 1966; Tanaka, 1975; Kean, 1976).

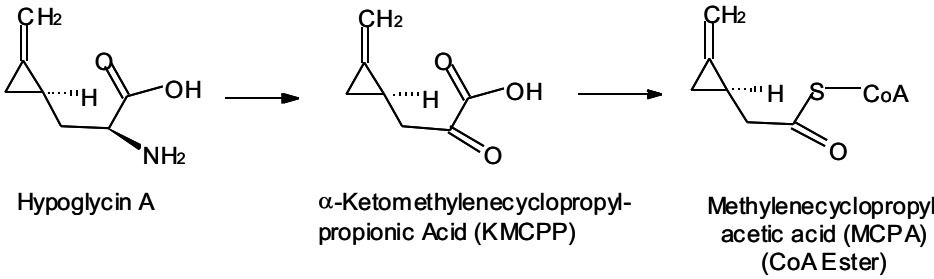


Fig 4. Metabolism of hypoglycin A

The kidneys excrete unreacted MCPA-CoA as methylenecyclopropyl-acetyl-glycine (Tanaka et al, 1972). Urine specimens from two children with akee fruit poisoning contained substantial amounts of methylenecyclopropylacetic acid as well as the medium-chain dicarboxylic acids, 2-ethylmalonate, adipate, and glutarate (Tanaka and Ikeda, 1990). Depletion of glucose reserves and the inability of cells to regenerate glucose lead to hypoglycemia (Von Holt, 1966). The ingestion of the plant is also known to be teratogenic (Persaud, 1968).

Hypoglycin A Analyses and Quantification.

Hypoglycin A analyses are difficult because of its co-elution and solubility properties identical to amino acids. However, fluorimetry, Spectrophotometry and High Performances Liquid Chromatography (HPLC) have been successfully utilized for its analyses (Sarwar and botting, 1994). HPLC provides a rapid, reliable and reproducible means of its quantification. Hypoglycin A is first derivatized using O phthalaldehyde (OPA) and phenylisothiocyanate (PITC) and subsequently analysed on a reversed-phase liquid chromatography system. The method has been successfully used to quantify and analyze hypoglycin A (McGowan,1989). HGA content of akee fruit have been determined adopting the ion exchange chromatography (IEC) method (Chase Jr, et al, 1989) and reversed phase high performance liquid chromatography with UV detection at 254 nm (RP/HPLC/UV) (Ware, 2002).

Other Metabolites In The Ackee Fruit and Biomaker.

The Ackee fruit contain a number of other metabolites such as Blighinone and vomifoliol (fig. 5). Blighinone, a sparingly soluble quinine was isolated from the arilli of the fruit (Sarwar and Botting, 1994). Vomifoliol was isolated from the leaves and stems of the plant and has been implicated in the endogenous regulation of stomata aperture (Staurt et al, 1976)

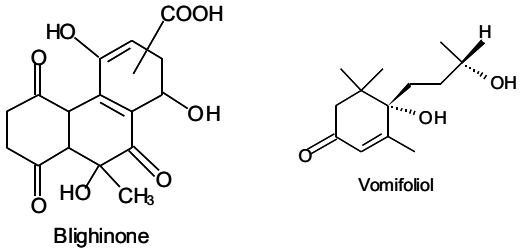


Fig. 5. Structures of blighinone and vomifoliol

Another non-proteinogenic amino acid (2S, 1'S, 2'S) 2 (2' carboxycyclopropyl) glycine (CCG) fig 6, have been isolated from the fruit of Ackee apple (Natalini, 2000). It bears resemblance with hypoglycin A with respect to the presence of clycloropane ring structure which is a rare occurrence in nature.

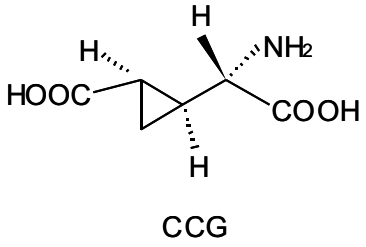


Fig. 6. Structure of (2S, 1'S, 2'S)–2–(2'–carboxycyclopropyl) glycine (CCG)

Recent research discovery on Blighia sapida extracts by Michael and his group revealed that neutrophil and platelet counts were significantly lowered ($P<0.05$) in mice treated with aqueous and lipid extracts of the unripe fruits of Blighia sapida. The percentage reduction in neutrophil and platelet counts relating to the controls for the aqueous and lipid (data in parentheses) extracts were 63.4% (59.3%) and 37.46% (32.44%) respectively after 6 weeks of treatment. The significant reduction in neutrophil and platelet numbers suggests that these extracts may be useful in disease conditions where these two blood parameters are elevated, for example chronic myeloid leukemia, essential thrombocythaemia and polythaemia (Micheal, 1998).

The detection of HGA in affected patients is not easy as a result of rapid metabolism rate, therefore the presence of the metabolite of HGA (methylenecyclopropylacetic acid) is used as a biomarker of exposure to akee fruit (Tanaka et al, 1976). The inhibition of acetyl CoA enzymes increases serum carboxylic acids and the renal excretion of dicarboxylic acids with 5-10 carbons (propionic, isobutyric, *n*-butyric, isovaleric, *n*-hexanoic, glutaric, adipic, suberic, sebacic). Adipic acid and lactic acid occur commonly in urine samples of patients poisoned with unripe akee fruit (Golden et al, 2003)

Treatment of Hypoglycin A Toxicity

There is no specific standard method of treating hypoglycemic syndrome toxicity. However supportive care such as early sugar and glucose administration is recommended for relieving the symptoms. Antiemetic is used to control vomiting, gastrointestinal decontaminants, dextrose and glucose stimulators, while Benzodiazepines is used to control seizures (Holson eMedicine). Experimental studies also suggested that methylene blue administration is a potential treatment for akee fruit poisoning, though there are no clinical data to support the efficacy of the agent during akee fruit poisoning, particularly when administered more than several hours after ingestion (Barennes et al, 2004). Fluid therapy and the administration of glucose and electrolytes is also recommended for the management of the toxicity. Patients with preexisting nutritional deficits and children may be more sensitive to the toxic effects of the fruit, therefore vitamin and nutritional supplements should be administered (Lampe, 1985 and Henry, 1998). Riboflavin and glycine administration antagonizes the effects of hypoglycin A intoxication (Duff et al, 1980). Glycine conjugates with excess dicarboxylic acids produced, due to impaired lipid metabolism while riboflavin stimulates the de novo synthesis of acyl – CoA dehydrogenases (Al-Bassam and Sherratt, 1981).

Conclusion

Ackee is an indigenous plant of the Caribbean and Jamaica. The isolation and derivatization of the toxic hypoglycins open ways for researchers to explore the interesting biological molecules found in ackee, so that its probable use as drug (such as glucose inhibitor in diabetes, etc) could be established and standardized. The ingestion of hypoglycins, the toxic constituent in unripre akee fruit should be cautioned. Other biologically active components could also be examined for their therapeutic value in the treatment of various diseases. The indiscriminate consumption of ackee fruit should stop because of the high toxin content. The plant provides the active component of

potential mainstream drugs for years to come.

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