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A REVIEW OF THE CHEMISTRY AND PHARMACOLOGY OF KAVA (*PIPER METHYSTICUM* FORST.)

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INTRODUCTION

Yaqona, or kava (or awa), as it is known outside much of Fiji and the name used from hereon, was used in many South Pacific countries before first arrival of Europeans in the 18th Century. The kava plant, botanical name Piper methysticum Forst., family Piperaceae, and the drink prepared from it are at present most widely used both socially and ceremonially. In the past, however, it occupied a very central place in the lives of the people, having both ritualistic and magico-religious importance.

The many European travellers to the Pacific in the past 2 centuries have produced an enormous amount of literature on kava (see Singh, 1986), much of which is ethnographic in nature. However, in the past 125 years important chemical and pharmacological work have been carried out and these will be summarized in this report. A small section on the effects of drinking kava as reported in the literature is also included to put in perspective some of the reasons why there has been such an enormous amount of interest in this plant and beverage.

Effects of Drinking Kava

There is some considerable disagreement as to the taste and effect of the kava drink. Consider some typical reports.

In 1903, Emerson wrote: "While tramping in the woods I have often moistened my tongue with a piece of awa chipped from some root, and experienced relief from thirst by its pleasant, cooling, aromatic, numbing effect on the mucous membrane of the tongue."

According to Te Rangi Hiroa (1930), a Polynesian from New Zealand who often drank kava, "It is cooling, refreshing, and stimulating without being

intoxicating . . . Used in moderation, it is probably the best drink for a tropical climate."

On the other hand, other reports talk of great bitterness and a burning taste in the mouth. For instance, Ellis (1828) wrote: "If an opinion of its taste might be formed by a distortion of their countenance after taking it, it must be a most nauseous doser," while Churchill (1916) observed: "Polynesians do not praise kava for its taste, it is the odour which appeals to their sense of pleasure."

However, the first effect of drinking kava probably is a numbing and astringent effect on the tongue and, to a lesser extent, the inner lining of the mouth. Titcomb (1948) quotes two Hawaiians, one of whom reported that, "there is a peculiar bitterness with a feeling of thickness in the mouth, so that one does not taste the deliciousness of food after chewing or drinking awa," and the other: "If you chew a piece in your mouth, it is sour, and very bitter. The mouth will not taste food that is eaten after."

A little while after drinking, kava is found to reduce fatigue, to allay anxiety and to produce a generally pleasant, cheerful and sociable attitude, although some other quite different physiological effects, some bordering on intoxication, have been noted in various parts of Oceania. For instance, "It gives a pleasant, warm and cheerful, but lazy feeling, sociable, though not hilarious or loquacious; the reason is not obscured" (Hocart, 1929); "It refreshes the fatigued body and brightens and sharpens the intellectual faculties" (Lewin, 1931); "The head is affected pleasantly; you feel friendly, not beer sentimental; you cannot hate with kava in you. Kava quiets the mind; the world gains no new color or rose tint" (Lemert, 1967).

Compare these reports with other accounts from various locations outside Western Polynesia. Morrison, who visited Tahiti between 1788 and 1791, wrote: "Kava almost immediately deprives them of the use of their limbs and speech, but does not touch the mental faculty, and they appear in a thoughtful mood and frequently fall backwards before they have finished eating" (Morrison, 1935).

Titcomb (1948) quotes a report by a Hawaiian, written in the last century: "There is no admiration for the body and face of an awa drinker whose eyes are sticky, and whose skin cracks like the bark of the kukui trees of Lilikoi in unsightliness."

Consider also Torrey's (1848) description of kava drinking in the Marquesas: "Copious draughts cause a dizziness and a horribly distorted countenance. They lose the use of their limbs, and fall and roll about on the ground, until the stupefication wears away."

Thus there are obvious differences in the pharmacological effects observed by various writers. Some reasons that may be advanced in form of an explanation of the differential effects include the following:

(a) Different varieties of Piper methysticum were used in different societies.

(b) Related to the above factor could also be differences in soil and climatic variations.

(c) The plant may be used in different states of freshness or maturity. For instance, the green root or stem, is reputed to provide the much stronger drink.

(d) Effects may vary according to whether or not drinkers combine kava consumption with eating. Drinkers often assume that combination of feasting with kava injestion may result in less debilitating effects.

(e) The accounts of missionaries and explorers may have exaggerated the deleterious effects of kava drinking.

(f) Different psychological attitudes towards kava drinking may affect the responses to injestion of the drug. Those who expect or desire intoxicating effects are more likely to experience them.

(g) Additives which might have been added to the drink could have produced some of the more extreme effects. The practice of adding extracts of Yaqoyaqona (Piper puberulum), often with a malicious intent, is still practised in some places in Fiji.

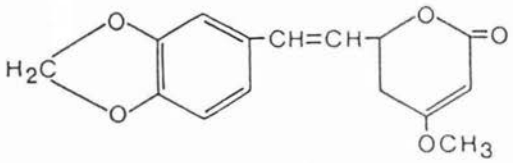
CHEMISTRY

The reported physiological effects of kava drinking have prompted numerous chemical investigations over the past 125 years in the search for the biologically active constituents. These investigations have resulted in the isolation of 2 series of closely related compounds which are either substituted 5,6-dihydo-α-pyrones (Fig. 1) or substituted α-pyrones (Fig. 2).

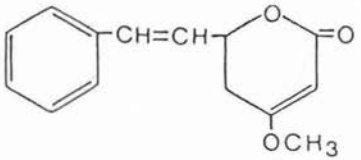
The first chemical studies of any note were those of Gobley (1860), O'Rorke (1860) and Cuzent (1861) who almost simultaneously reported the isolation of the first of these compounds, now called methysticin, and previously also known variously as kavakin, kawakin, kavatin and kanakin. In 1874, Notting and Kopp reported a second neutral crystalline material whose isolation was later repeated by Lewin (1886) and who named this compound yangonin (Fig. 2). A little later, the isolation of dihydromethysticin was achieved by Winzheimer, in 1908.

The appearance of Lewin's monograph in 1886 was followed by extensive chemical investigation on the kava plant with the notable publication of a series of papers by Borsche and his co-workers (listed in Singh, 1986). This work covered the isolation of 2 new constituents, kawain and dihydrokawain and their structural elucidation together with that of the 3 previously known components, methysticin, yangonin and dihydromethysticin.

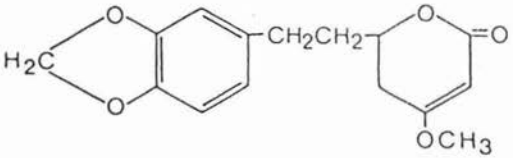
More recently four new compounds have been added to the α-pyrone series with the isolation of 5,6-dehydromethysticin, 11-methoxyyangonin and 11-methoxynoryangonin (Mors, Magalhaes and Gottlieb, 1962), and desmethoxy-yangonin (Klohs, Keller and Williams, 1959) (Fig. 1) together with the isolation of 2 pigment materials, flavokawin A and flavokawin B. The



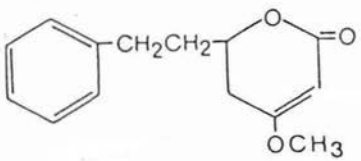
Methysticin



Kawain

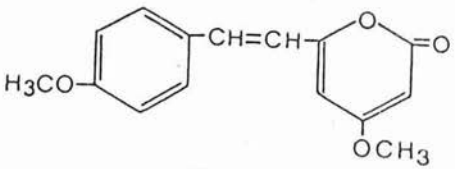


Dihydromethysticin

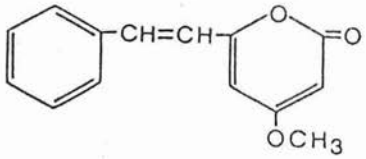


Dihydrokawain

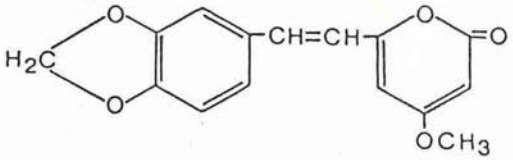
FIG. 1



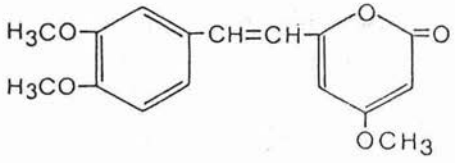
Yangonin



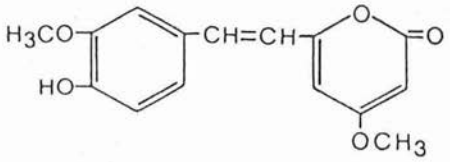
Desmethoxyyangonin



5.6-Dehydromethysticin



11-Methoxyyangonin



11-Methoxy-nor-yangonin

FIG. 2

structures of these pigments have been established by synthesis to be substituted chalcones (Hansel, Ranft and Bahr, 1963). According to Shulgin (1973) these pigments, which are otherwise biologically inactive, might provide an explanation for the skin discoloration observed with chronic drinkers of the beverage.

Attempts to determine the relative amounts of the various constituents present in the intact plant have yielded uncertain results being largely due to the different separation procedures employed. Young et al. (1966) used spectrophotometric analytical techniques while Klohs et al. (1959) assayed the fractions obtained from column chromatographic separations. On the basis of the available data in the literature (Hansel, Sauer & Rimpler, 1966; Hansel & Klaproth, 1966; Hansel, Ranft & Bahr, 1963; Sauer & Hansel, 1967; Young et al. 1966), the proportion of each component present has been classified by Shulgin (1973) as being major, minor or trace, as follows:

major (present to 1% or more):

dihydrokawain, kawain and methysticin

minor (present 0.1% to 1%):

5,6-dehydromethysticin, desmethoxyyangonin, dihydromethysticin, flavokawin A and yangonin

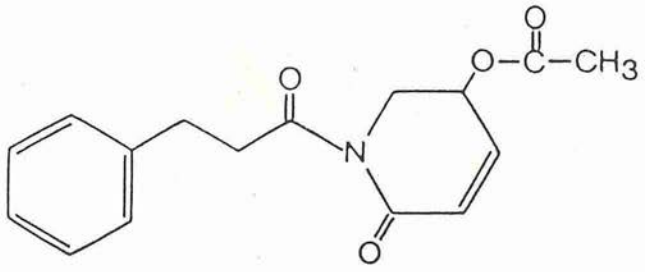
trace (present 0.01% to 0.1%):

flavokawin B, 11-methoxynoryangonin and 11-methoxyyangonin

Despite ealier reports (Lavialle, 1889; Winzheimer, 1908; Scheuer and Horigan, 1959) that alkaloids were present in the roots in concentrations of up to 0.22%, all attempts to isolate them were unsuccessful until 1970 when 2 amides in trace amounts (0.002%) were reported by Achenbach and Karl. More recently, the isolation and structural determination of a novel

alkaloid, pipermethystine (Fig. 3), a major constituent (0.17%) of the leaves, has been achieved by Smith (1979). This compound is also present in small amounts in the stems and roots of the plant, but is unstable on standing and to most separation techniques. Hence, the difficulty is its detection previously.

In an effort to assign biological activity to one or other portion of the molecule, a number of structural modifications of the active constituents have been carried out. Pharmacological assays of the analogues in various test systems suggest certain structure-activity relationships (Klohs, 1967). For instance, shortening or lengthening of the two-carbon bridge between the rings of the dihydrokawain molecule (Fig. 1) decreases the fungistatic activity of this compound. Elimination of the 2-carbon bridge generally leads to a decrease in biological activity, as measured by the compound's ability to provide the test animal with protection against convulsions which may be induced by strychnine. On the other hand, the introduction of hydrogen in the pyran 5-6 position of the yangonin molecule leads to the appearance of some narcotic effects in the compound (Werny and Hansel, 1963). For more detailed accounts of the chemistry and structure-activity relationships, reviews by Keller and Klohs (1963), Hansel (1968) and Shulgin (1973) should be consulted.



Pipermethystine

FIG. 3

PHARMACOLOGY

The first pharmacological evaluation of the kava pyrones was published in 1886 in Lewin's monograph but because only very small quantities of the pure compounds, methysticin and yangonin, were at his disposal, his data must now be considered with some caution. In any case, they are worth noting here. Methysticin was found to be inactive when injected intraperitoneally in doses of up to two grams in both warm- and cold-blood animals. Yangonin, which was available in even smaller quantities, could be tested only in two frogs in oral doses of 0.05 g with no observable effects.

The bulk of Lewin's experiment was carried out on the resin remaining after the crystallization of methysticin and yangonin. It produced paralysis in frogs and exhibited a local anaesthetic action. In experiments with a bat, a sparrow and a pigeon, it caused the loss of use of the wings and the animals appeared to be deeply sedated. Subcutaneous administraiton of the material in cats resulted in a deep sleep with obvious local anaesthetic activity but when given orally, only salivation and vomiting were noted.

Borsche and Blount (1933) came to the conclusion that none of the kava pyrones known at that time, i.e. methysticin, dihydromethysticin, yangonin, dihydrokawain and kawain, possessed the biological activities reputed to be present in the crude preparation. The possibility that the active principle might be present in the unsaponifiable fraction could not be substantiated as the low solubility of the fraction did not allow for biological testing. In a pharmacological investigation carried out about

this time by Schubel (1924), the kava resin was found to have a weak narcotic action, to paralyze sensory nerves and to first stimulate, then paralyze smooth muscles. The hydrolysis products of this resin also showed similar actions. The local anaesthetic action was attributed to compounds containing benzoic and cinnamic acid residues. In experiments in the isolated frog heart, Schubel showed that incubation of the kava root with human saliva increased the potency of the kava extract. He considered the increase in activity to be due to the enzymatic breakdown of starch in the root which in turn led to a more efficient extraction of the active materials. However, Schubel was unable to demonstrate any pharmacological activity when the pure compounds yangonin and methysticin were administered to rabbits, pigeons or frogs.

Van Veen (1938) used pigeons, monkeys and rice birds to follow the active principles of kava in his isolation procedures. Preliminary results indicated that rice birds were overly sensitive to the crude extracts and monkeys to be too resistant. Pigeons were thereafter used for routine assays. Eight to fifteen minutes after administration of the extract, the pigeons became sleepy and atactic; a deep sleep then set in, lasting from two to ten hours. The birds appeared to be fully recovered upon awakening. Monkeys required three to five times the dose used in pigeons. An effective dose caused initial loss of limb control, followed by sleep within fifteen to thirty minutes which lasted for fifteen hours or longer. Van Veen found that purified fractions gave a maximal effect when administered in an oil or lecithin-water emulsion and consequently proposed that chewing the root and admixing saliva (as in a traditional method of kava preparation) only served to bring about emulsification and thus promote activity.

Van Veen also isolated an active fraction from which he reported a crystalline material and which he called "marindinin" after Marind-Anim district in New Guinea, now known as Kolepom. Later, he demonstrated that marindinin was a slightly impure form of dihydrokawain, a compound claimed by Borsche to be physiologically inactive. Van Veen also tested the purified dihydrokawain and showed that the physiological activity he had earlier demonstrated was indeed due to this refined material and not to an impurity.

More recently, work in several laboratories has confirmed the activities of the kava pyrones. Hansel and Beiersdorff (1958) showed that dihydrokawain and dihydromethysticin both appeared to be active in causing sleep in white mice and white rats when administered orally by a stomach tube as an emulsion. Klohs et al. (1959) studied the effects of yangonin, kawain, dihydrokawain, methysticin, dihydromethysticin and desmethoxy-yangonin for their effects on the central nervous system as measured by their ability to antagonize strychnine-induced convulsions in mice, to potentiate barbiturate sleep time, and to promote fall out from roller cages. Dihydromethysticin appeared to be the most active and, contrary to previous reports, dihydrokawain the least active.

Meyer, Oberdorf and Seifen (1960) have reported that dihydrokawain and dihydromethysticin had sedative effects when administered intraperitoneally or orally to mice, rats, rabbits and cats. Higher doses led to a marked atactic phase followed by loss of the righting reflex. When administered to mice as peanut oil solutions, both dihydrokawain and dihydromethysticin produced sedation, hypothermia and a corresponding reduction in total oxygen consumption. In unanaesthetized rabbits blood pressure was only

slightly reduced (Meyer, 1962). These findings could not be duplicated by Keller and Klohs (1963) and are reminiscent of the contradictory evidence of Borsche and Van Veen as mentioned earlier.

More recently, Meyer (1967) demonstrated that the most characteristic central nervous action of all kava pyrones was their ability to produce a mephenesin-like muscular relaxation in all species of laboratory animals. The pyrones have also proved to be considerably more effective than mephenesin in protecting mice from convulsions and death caused by toxic doses of strychnine. Thus, these compounds might represent a new group of potent centrally acting skeletal muscle relaxants, possibly the first of natural origin. Larger doses produced ataxia and an ascending paralysis without loss of conciousness, followed by complete recovery, being reminiscent of the effect of kava drink on humans. In doses causing muscular relaxation, the pyrones did not posses a curare-like action on the neuromuscular function (Meyer and Kretzchmar, 1966). Death after large oral or intraperitoneal doses was the result of respiratory failure. In addition, the pyrones reduced the oedema produced by formalin, serotonin, dextran and carrageenin indicating an anti-inflammatory action. Contractions of isolated ileum or uterus produced by histamine, barium ions, acetylcholine, bradykinin, serotonin or nicotine were inhibited by the pyrones in concentrations $1:10^6$ to $1:10^5$ (Meyer, 1967).

The local anaesthetic actions of the pyrones originally observed by Lewin (1886), Schubel (1924) and others early this century have later been re-investigated. In one study most of the kava pyrones inhibited frog heart contraction (Meyer and May, 1964). These actions were compared with those of cocaine which showed a similar protection against ventricular

fibrillation through its local anaesthetic effectiveness. More recently, Singh (1983) examined the effects of whole kava extract on muscle contractility and neuromuscular transmission using twitch tension and electrophysiological techniques. He found that the extract caused muscle paralysis by mechanisms similar to local anaesthetics like lignocaine.

The antimicrobial and antifungal properties of some of the pyrones have been investigated (Hansel, Weiss and Schmidt, 1966; Hansel, 1968). A large number of Gram positive, Gram negative, pathogenic and non-pathogenic bacteria were found to grow uninhibited in nutrients containing the pyrones, indicating they are not bacteriostatic in nature. However, some of the pyrones showed remarkable fungistatic properties against a wide genera of fungi including some which are pathogenic to humans.

Since the bulk of the pharmacological work has concentrated on the water-soluble pyrones, Buckley, Furgiuele and O'Hara (1967) investigated the biological activity of the water-soluble fractions of kava (obtained by steam distillation). They found that the 2 fractions so obtained contained biologically active materials which were relatively free of any pyrones. These materials suppressed spontaneous activity in test animals and at higher doses led to muscular relaxation previously seem with the pyrones. In addition, one of the 2 fractions exhibited an anti-serotonin activity similar to that of dihydromethysticin.

Although the effect of regular kava drinking on the skin has been noted in many reports, there has been but one attempt (Frater, 1958) to understand the pharmacological basis for it and to search for a cure. The lesion in question, called kani in Fijian, requires regular (almost daily) consumption of kava before it apppears, taking from a few months to a year

or more. The skin becomes dry and covered with scales, especially the palms of the hands, the soles of the feet and the forearms and shins. Frater came to the tentative conclusion that kani was caused by an interference by kava of the normal uptake and assimilation of some members of B group vitamins. Thus, the condition could be reversed, even in the most serious cases, by a reduction in kava consumption and a balanced diet.

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