The narcotic pepper - The chemistry and pharmacology of Piper methysticum and related species

Details

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Kava-kava is the name given to a drink prepared from the rhizomes of the plant, Piper methysticum. The generic name Piper comes from the Latin for pepper, and the species methysticum from the Greek μ θ ν σ τ ι κ ο ζ meaning intoxicant. It has thus become widely known as the intoxicating or narcotic pepper, or Rauschpfeffer.

The drink is made by soaking the pulverized roots of the plant in water to produce a cloudy, amber liquid. It has apparently been used for centuries throughout Western Polynesia, including Tonga, Samoa, and as far west as Tahiti where it is known as ava, or angooner. In the Marquesas Island group the plant has been identified as Piper latifolium, but this is probably synonymous with P. methysticum; there, the native name is avavahai. It is found in the Caroline Islands of Micronesia, and in many scattered locations throughout eastern Melanesia, including New Britain, New Ireland, New Hebrides, and Fiji (where it is referred to as yagona). The groups that migrated south from Melanesia to New Zealand (the Maori) found a closely related and superficially similar plant Piper excelsum, but from this no satisfactory drink could be made. The related species, P. betle, is only found much further west in Indonesia, and is discussed below in conjunction with several additional Piper species. The use of Kava-kava was first described by James Cook and the first descriptions of the chemistry and pharmacology were reported by Lewin in 1886 . An excellent bibliography that lists nearly a hundred references of early historical and ethnographic accounts of Kava-kava usage has appeared, and a recent review of its chemistry is also available.

There is no agreement whatsoever on the pharmacological classification of the drink, Kava-kava. These uncertainties are evident from references such as Cutting's Handbook of Pharmacology which lists Kava-kava under the general heading of psychotomimetics, but then states that it" produces gentle stimulation, then depression ". The equally authoritative text, Goodman and Gilman's "The Pharmacological Basis of Therapeutics" avoids any classification by listing the plant as a material that is "used for subjective effects". Lewin has Classified it as a hypnotic.

It is classified here as an excitant, as it has found its primary use as an adjunct to social meetings, and serves the same role as coffee in the Kaffeeklatsch, or the alcohol in the cocktail party. Pharmacologically it can lead to a seemingly natural sleep, and indeed the animal studies that have been conducted on the several compounds that have been isolated from it, show muscular relaxation and a protection from induced convulsion more

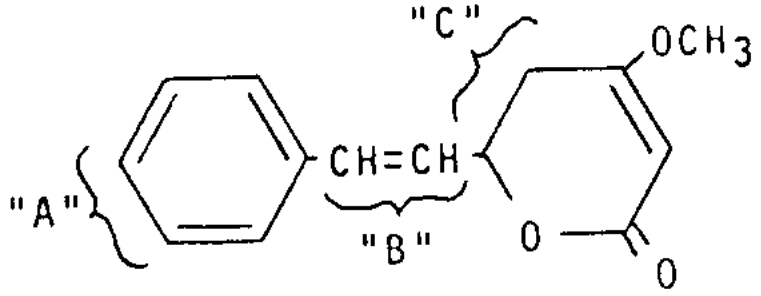
characteristic of a sedative. The use is, however, social rather than individual, and leads to conviviality rather than to escape. Kava-kava contains no alcohol, although the use of alcoholic beverages has to some extent displaced it in modern usage.

Early missionary reports strongly suggest that it was a narcotic substance (and so appropiately condemned) as they describe physical impairment related to its use. This apparent paralysis seems to be adequately accounted for by the associated habit of sitting cross-legged during the lengthy Kava-kava ceremonies. More recent reports describe it as" a refreshing, astringent drink which produces nothing more than a tingling sensation in the mucous membrane of the mouth and a short-lived numbness of the tongue ". Two distinctly different methods of preparing the Piper methysticum rhizome for the final drink concoction have been well documented.

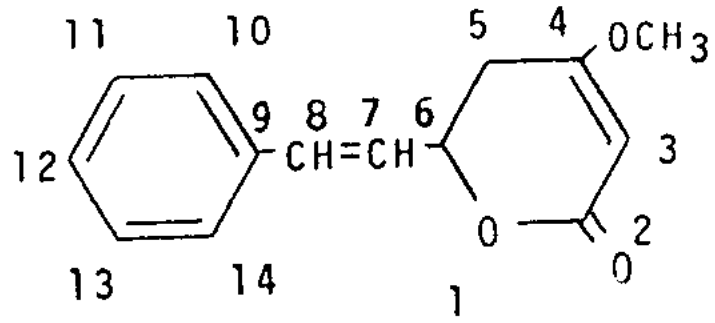
One, often called the "Tonga method" although it was the principal method used in Samoa as well, consists in having young men or women chew the root until it was fine and fibrous. Efforts were made to keep the material as free of saliva as possible, and none of the juices were swallowed. The chewed cud was then soaked in water, and after a period of time decanted and drunk. The chewer experiences anaesthesia of the tongue and of the inner lining of the mouth, a loss of taste for an extended period, stiffness of various mouth muscles contributing to difficulties in articulation, but apparently there were no central effects. With preparation of the drug in this manner, there is claim of narcotic effects, with reports of visual and auditory changes, and a generalized euphoriant effect involving improved appetite, loss of fatigue, and a benign social attitude. Larger doses appeared to lead to muscular inco-ordination, and a drunkenness that leads to a stuporous sleep.
A second method of preparation, sometimes called the "Fiji method" and the procedure most widely practised today, involves the use of a mechanical pounding and pulverizing of the root, and the extraction of the residue with water. The effects produced by this procedure are claimed to be more of a stimulant and socially relaxing nature, hardly suggesting the narcotic-like consequences mentioned above. It is possible that the action of the saliva may well induce some chemical transformation in the plant material, but this is unexplored, and the entirety of present pharmacological knowledge is based on material produced solely by this latter process.

A complete description of contemporary preparation ceremonies and the associated protocols of use are given by Holmes. An ethnographic description of its uses in Fiji has recently appeared in an excellent review, and a complete review of both plant description and general social use has been prepared by Steinmetz.

The structures of the isolates from Kava-kava can be organized about a general skeleton of an arylethylene-α-pyrone of the generalized structure shown in (I), wherein "A" can represent some degree of substitution (hydrogen, hydroxyl, methoxyl, or methylenedioxy), "B" is either a vinyl unsaturation or the dihydro-counterpart, and "C" can represent the inclusion of a second double bond in the pyrone ring. The numbering system shown in (Ia) is widely accepted.

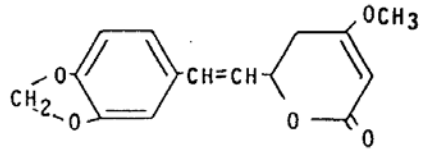


(I)

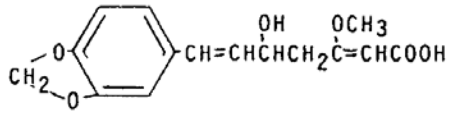


(Ia)

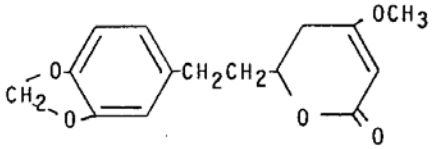
The first substance isolated from Piper methysticum was methysticin (II), also known as kavatin, kavahin, and kanakin. The chemical name for methysticin can follow emphasis either upon the heterocyclic nature of the pyrone ring or upon the aliphatic acid nature of the lactone system. In the former aspect, the IUPAC has recommended the name 5,6-dihydro-4-methoxy-6-[3',4'-(methylenedioxy)styryl]-2H-pyran-2-one. The Chemical Abstracts indexing has followed the latter path, using 5-hydroxy-3-methoxy-7-[3,4-methylenedioxyphenyl]-2,6-hepta- dienoic acid - lactone. This open-chain structure name (IIa) emphasizes the biosynthetic origins of this class of compounds.



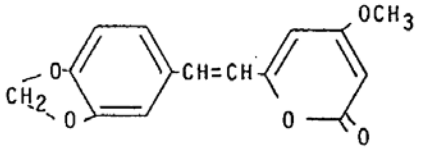
(II) METHYSTICIN



(IIa)



(III) DIHYDROMETHYSTICIN

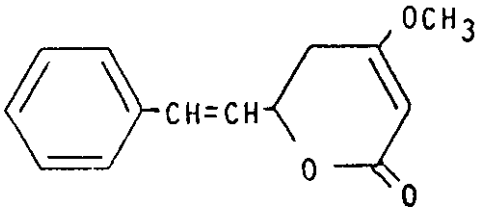


(IV) 5,6-DEHYDROMETHYSTICIN

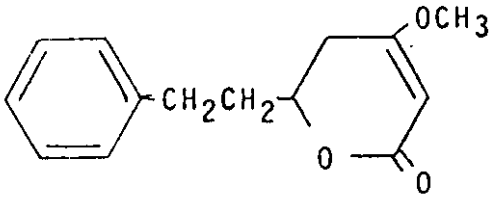
The ethylenic dihydroanalog dihydromethysticin (III) was isolated almost 50 years later by Winzheimer. The completely conjugated analogue, 5,6-dehydromethysticin (IV) has recently been observed as a component of Kava-kava.

The corresponding unsubstituted phenyl analogues of this series were uncovered by Borsch and co-workers who reported the unsubstituted counterparts of methysticiu as components of Kava-kava. The precise analogue to methysticin is kawain (V) also known as kavain and gonosan. The dihydroderivative (dihydrokawain, VI) and the dehydro-analogue (desmethoxyyangonin, VII) are both exactly comparable to the methysticin hydrogenation family above. This last name is classically more acceptable than the more obvious term dehydrokawain, as the monomethoxy-pyrone yangonin was one of the first compounds isolated from Kava-kava and along with methysticin is one of the major components. It was originally assigned the γ-pyrone structure VIII but this was successfully challenged some 10 years ago on theoretical grounds, and the correct structure IX, in complete harmony

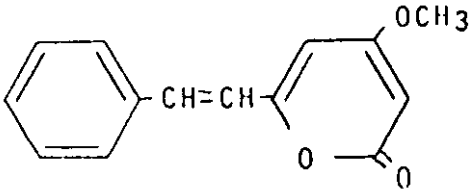
with the other γ-pyrones of this group, was confirmed by synthesis.



(V) KAWAIN



(VI) DIHYDROKAWAIN

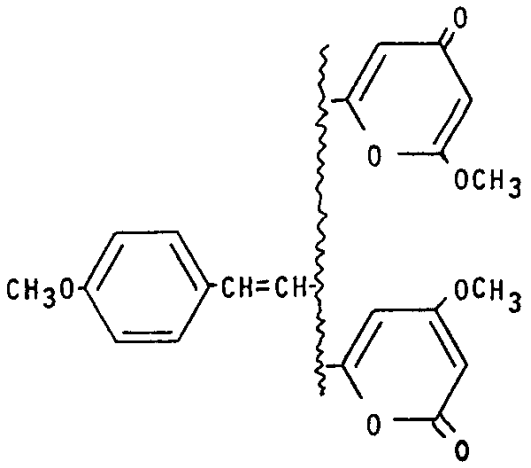


(VII) DESMETHOXYYANGONIN

Yangonin serves as the basis for two additional substances isolated from Kava-kava, both of which have been established synthetically as possessing the α-pyrone ring. These are the meta-methoxy analogue 11-methoxyyangonin (X) and the phenolic counterpart 11-methoxy-nor-yangonin (XI). These substances show a structural resemblance to the parent methylenedioxy compound methysticin in a manner completely analogous to examples within the essential oil family. Anethole (XII, 4-OCH ₃), methyl-isoeugenol (XII, 3,4-(OCH ₃) ₂), isoeugenol (XII, 3-OCH ₃-4-OH), and isosafrole (XII, 3,4-OCH ₂O) are exact analogues of yangonin, 11-methoxyyangonin, 11-methoxynoryangonin, and methysticin, resp. It is certainly possible that their origins employ common biosynthetic pathways.

Two pigment materials have been isolated from the rhizomes of Piper methysticum by chromatographic techniques. One, called Flavokawin A was initially obtained in 0.04% yield; the other, Flavokawin B, in one tenth this amount. The structures of these have been established by synthesis to be substituted chalcones that bear an obvious biogenetic relationship to the styrylpyrones. Flavokawin A has proved to be 2'hydroxy-4-4'-6'-trimethoxychalcone (XIII) and Flavokawin B is 2'-hydroxy-4'-6' dimethoxychalcone (XIV). These yellow pigments provide an explanation for the skin discoloration observed with chronic exposure to Piper methysticum extracts, but they appear to be without biological

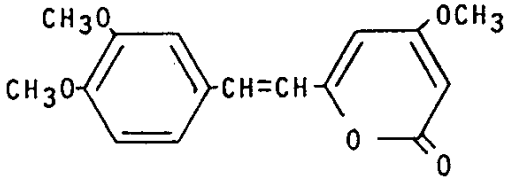
activity.



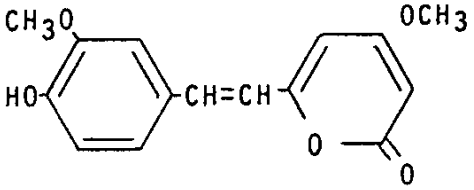
(VIII)

(IX)

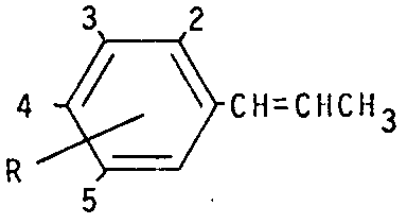
YANGONIN



(X) 11-METHOXYYANGONIN



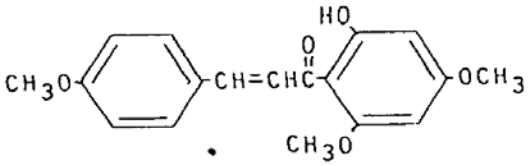
(XI) 11-METHOXY-nor-YANGONIN



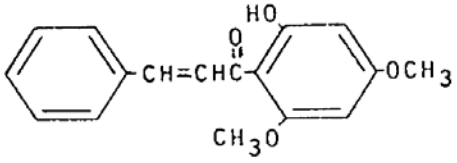
(XII)

Two additional chalcones have been reported as components of a New Guinea Piper species, both closely related to Flavokawin B. These are the respective demethylated resorcinols pinostrobinchalcone (XV) and alpinetinchalcone (XVI). These latter two compounds are present in the plant in amounts comparable to the major chalcone,

Flavokawin A.

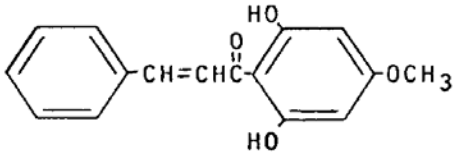


(XIII) FLAVOKAWIN A

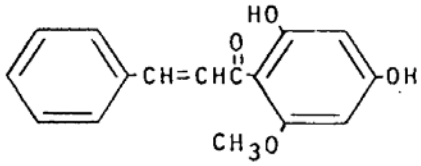


(XIV) FLAVOKAWIN B

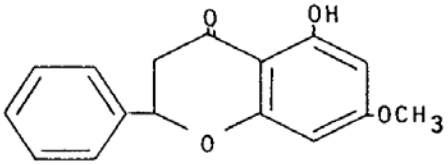
PLATE 6



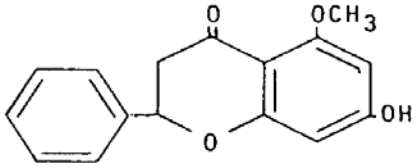
(XV) PINOSTROBINCHALCONE



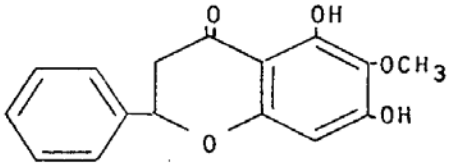
(XVI) ALPINETINCHALCONE



(XVII) DIHYDROTECTOCHRYSIN



(XVIII) ALPINETIN



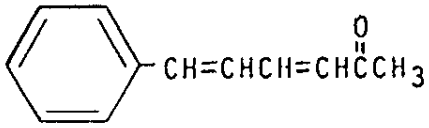
(XIX) DIHYDROOROXYLIN A

A number of other related flavanones have also been observed in this same New Guinea species, and it is entirely possible that at least two of them might have arisen

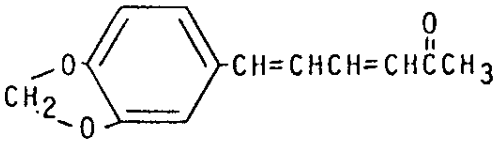
through a chemical modification of these above-mentioned chalcones as a consequence of isolation. Dihydrotectochrysin (XVII) is the cyclization product of pinostrobinchalcone (XV), and alpinetin (XVIII) is related similarly to alpinetinchalcone (XVI). Both of these compounds, regardless of their origins within the isolation procedures employed, represent several tenths of a per cent of the total plant extract.

A third flavanone has been observed, dihydrooroxylin A (XIX) but no corresponding chalcone has as yet been reported.

Yet another style of component of Piper methysticum is illustrated by the structures of two conjugated diene ketones, cinnamylidineacetone (XX) and 3,4-methylenedioxy-cinnamylidineacetone (XXI). These two compounds ouldc theoretically arise as artifacts, through hydrolysis and decarboxylation, from kawain and methysticin, respectively, but this source has been excluded through appropiate experiments. The general structure of a carbonyl group conjugated through olefins to an aromatic ring is suggestive of piperine, the major alkaloid of most peppers of food use (v.i.).

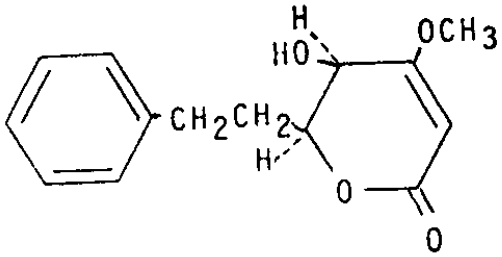


(XX) CINNAMYLIDINEACETONE



(XXI) METHYLENEDIOXYCINNAMYL-IDINEACETONE

A novel alcohol has been reported present in unspecified amounts, and a structure has been proposed (XXII). This is the hydroxyl analogue of dihydrokawain (VI) and is probably related through reduction and hydration to desmethoxyyangonin (VII). As it is optically active, it is presumably natural, and not an artifact of isolation. The presence of alkaloid components in Kava-kava are suggested but no details are as yet available. A recent report has compiled the various physical properties of many of these chemicals, both singly and in combination.



(XXII)

The determination of the relative amounts of these various components present in the intact plant is difficult, as different separation procedures lead to different analyses. Klohs has assayed the actual isolates from the column chromatography separations of various fractions; Young has used spectrophotometric techniques for the analysis of these

fractions. A clear separation into major, minor, and trace contributions may be made as follows:

Present to 1% or more Ref: 26,27
Dihydrokawain (VI)
Kawain (V)
Methysticin (II)
Present 0,1% to 1% Ref: 21,22,26,27
Yangonin (VIII)
Dihydromethysticin (III)
Desmethoxyyangonin (VII)
Flavokawin A (XIII)
Pinostrobinchalcone (XV)
Dihydrotectochrysin (XVII)
Alpinetinchalcone (XVI)
Alpinetin (XVIII)
Dihydrooroxylin A (XIX)
Present 0,01% to 0,1% Ref: 15,19,21
1l-Methoxy-nor-yangonin (XI)
11-Methoxyyangonin (X)
Flavokawin B (XIV)

A number of structural modifications of the basic mythysticin molecule have been synthesized in an effort to assign biological activity to one or another portion of the molecule. These analogues have been assayed pharmacologically in micro-organism systems as well as in test animals, and certain structure-activity relationships are apparent. Shortening or lengthening of the two-carbon bridge between the rings of the molecule dihydrokawain (VI) decreased the effectiveness of this chemical as a fungistatic agent. Elimination of the 2-carbon bridge (B, in I) generally leads to a decrease in biological activity, as measured by the capability of the compound to protect a test animal against the convulsive effects of strychnine. This was found to be true through extensive modifications of the substitution pattern on the aromatic ring (A, in I). Included in these studies was the trimethoxy- structure found in the oil isoelemicin (XII, R = 3,4,5-OCH_3) and the alkaloid mescaline. Maintaining the methylenedioxy ring of methysticin but instituting extensive changes in the chemical nature of the ethylene bridge between the two rings has led to no increase in potency.

The unnatural dihydro-analogue of kawain (dihydropyrone, with the styrene double bond intact), and the tetrahydro-counterpart have been synthesized but no measure has been made of their comparitive activities. A similar hydrogenation study has been conducted with yangonin (IX) and it appears that some narcotic effects appear with the introduction of hydrogen in the pyran 5,6-position.

Homologues of mythysticin have been studied as well. The substitution of a variety of groups on the tertiary carbon connecting the ethylene link with the dihydropyrone ring, yielded compounds without pharmacological interest. On the other hand, the replacement

of the methoxy- group of methysticin with an ethoxy group (ethysticin) seems to provide an active material that has been studied in man (v.i.).

Extensive animal studies have been conducted, not only on the many isolated chemicals but on the total extract of P. methysticum itself. One of the most common pharmacological measurements has been the inhibition of the convulsions induced by strychnine or by electroshock. The skeletal relaxant, mephenesin, has usually been used as a comparative measure of activity.

This central activity of the Kava-kava family of compounds has recently been extensively studied . Increased dosages of several of the pyrones led to ataxia and paralysis, but without a loss of consciousness, in a manner more reminicent of mephenisin than of curare. In most animal species muscular ataxia is noted at drug levels of about 10 mg/Kg with the intravenous route, and at perhaps 100 mg/Kg by the oral route.

With oral administration, absorption from the gut is extremely rapid for kawain (V) and dihydrokawain (VI) as the biological effects (protection against maximal electroshock seizure) were maximum in about 10 minutes. Methysticin (II) and its dihydro- derivative (III) were quite a bit more potent, but were more slowly absorbed (about 45 minutes being required for maximum effectiveness). The effective levels of dihydromethysticin and dihydrokawain (VI) via an intraperitoneal route (in protection against electroshock seizure) are 25 mg/Kg and 60 mg/Kg resp. This is some 2 1/2 times more effective than the oral route. The dihydro- derivatives of both kawain and methysticin have also showed effects in the inhibition of frog heart contraction. These actions have been compared with those of cocaine which shows a similar protection against ventricular fibrillation through its local anaesthetic effectiveness. Anaesthetic action as measured by protection of the rabbit cornea has again been shown to be characteristic of these dihydroderivatives as well as of their unsaturated parents.

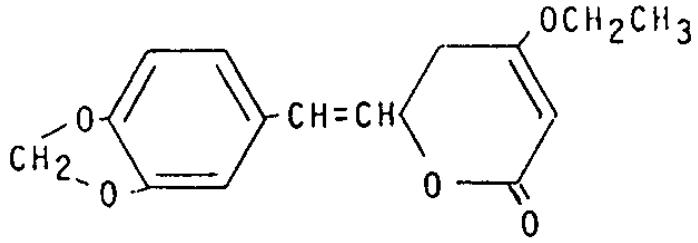
Yangonin (IX) and desmethoxyyangonin (VII) are relatively ineffective orally as anticonvulsive agents (employing strychnine as a challenge drug) but they appear to possess biological activity comparable to the other related alpha-pyrones when administered parenterally. Further, it has been observed that the oral administration of yangonin and dehydroyangonin in combination with other pyrones, led to a marked increase in over-all potency. This possible potentiation might explain the unsatisfactory comparisons between the pharmacology of the total root of Piper methysticum and of the several isolated components. It has been reported that a recombination of isolated chemicals does indeed reconstitute the observed biological response found with the extract of the entire root, whereas none of the individual compounds appeared to be similarly active. Recent studies in the mouse have shown that the several pyrones found in Piper methysticum and especially methysticin itself are effective in protection against strychnine-induced convulsion. This component, as well as kawain appear to be effective antispasmatics in studies with guinea pig ilium preparations , and these two chemicals can account for the entire plant extract potency in this test.

A report has appeared indicating that a water-soluble fraction of kava-kava (obtained by steam distillation) contains biologically active materials, and that this fraction was shown to be relatively free of any pyrone material. It suppresses spontaneous activity in test animals, and at higher doses leads to a muscular relaxation similar to that seen from the earlier-mentioned pyrones. Chemically this fraction is unexplored, but its separation into various distinct fractions has been described . Extracts of the complete root of P. methysticum have been reported to be fungistatic. The active components are the dihydropyrones, and dihydrokawain appears to be especially active against a test Aspergillus species.

Many reports have appeared that describe the action of the total extracts of the plant in man. A thorough bibliography of historic usage has been mentioned earlier , and the Kava-kava ceremony as it is observed at the present time has been recently described within the cultures both of Samoa and of Fiji .

On the contrary, clinical reports that might suggest potential medical virtue of either the plant extracts themselves or of the isolated individual components as chemical entities, are almost unknown. The main effort in this latter direction has been the exploration of the Kava-kava principles as possible anti-epileptics. The administration of the crude root-substance, at levels of 6 grammes/day gave some degree of protection against seizure, as did the employment of 1 gramme/day of an alcoholic extract. However, after a period of several weeks of chronic usage, there was a distinct discoloration of the skin of the subjects, and efforts were directed to the study of the component chemicals .
Studies of dl-dihydromethysticin were similarly conducted as possible anti-epileptics. At chronic levels of 1200 mg/day there was some control of grand mal seizures, but no sign of improvement in the incidence of Petit Mal epilepsy. Again, as with the total root extract, after a period of a month of chronic usage there were signs of accumulation (conjunctival erythema) and indications of gastric and intestinal distress.

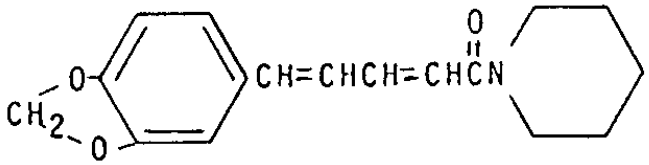
Acute studies of dl-methysticin (II) and the pharmacologically promising homologue dl-ethysticin (532-Riker, XXIII) have been reported. At single dosages of 800 mg there was little if any activity noted. "No significant changes of blood-pressure, pulse rate, grip-strength, hand steadiness, or pupil size occurred. The subjective responses were equally divided between stimulant, placebo, and sedative reports."



(XXIII) ETHYSTICIN

The only report that compares directly the human responses of the natural (d) isomer of compounds found in plant sources to their synthetic counterparts, is a paper describing electro-encephalographic activity modifications. DL-dihydromethysticin, d-dihydromethysticin (III) and dihydrokawain (VI, of unspecified optical activity) have been compared at acute oral levels of 160 mg. (200, for dihydrokawain). There were minimal

changes in the EEG tracings but subjects reported a "mild sedation" with all three compounds. These authors have concluded that no further studies with this plant material are justified.



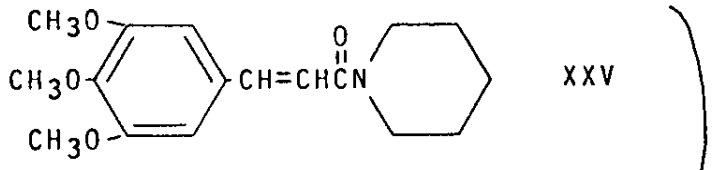
(XXIV) PIPERINE

A number of interesting and closely related compounds have been described in plants that are also widely known as peppers. The table spice commonly employed as a condiment is derived primarily from the plant Piper nigrum, black pepper. A distinct form known as " long pepper " was employed by preference through the classical times and during the Middle Ages. This latter is today essentially nonexistent, but is known to be closely related to two allied plants, Piper longum found in the Philippines west to Ceylon and Southern India, and Piper officinarum, a climbing shrub found primarily in Java. The racemic mixture of dihydromethysticin is synthetic. The natural forms of both dihydromythesticin and methysticin itself are the dextrorotatory isomers.

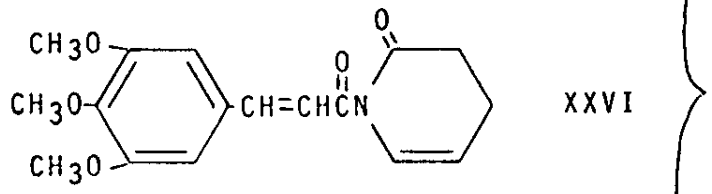
The principal substance responsible for the sharp taste of pepper is the alkaloid piperine (XXIV) which has been known through isolation and synthesis for nearly a hundred years. Points of similarity between piperine and methysticin (II) are evident: the presence of the 3,4-methylenedioxyring, and the presence of the styrene nature of conjugated unsaturation.

A number of Piper spp., although not of known central activity, have nonetheless been found to contain substances that possess structures that resemble both of these compounds. Many of these plants have been studied due to their involvement and reputation in the Ayurvedic system of Indian medicine. Piper longum, mentioned above as Indian long pepper, is a plant material that has been used for the treatment of asthma and chronic bronchitis. A major alkaloid, piplartine, was isolated and described by Atal. Initially its structure was thought to be a piperidide of trimethoxycinnamic acid (XXV) but the same chemical appears to have been reisolated subsequently, given the name piperlongumine (piperlangumine), reanalysed to show a fifth oxygen atom, and assigned the structure of a piperidone amide (XXVI) [47,48]. A recent report supports a structure with an isomeric double-bond position (XXVII) but encourages a return to the original (and simpler) naming of piplartine. The Chattergee group has also reported the isolation of a minor component, piperlunguminine (XXVIII). which appears to be an open chain amide of piperic acid, in

which isobutylamine replaces piperidine.



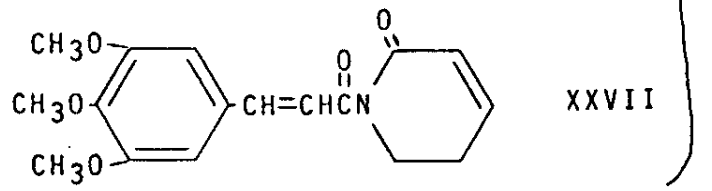
XXV



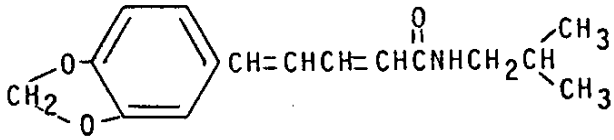
XXVI

PIPLARTINE

(PIPERLANGUMINE)

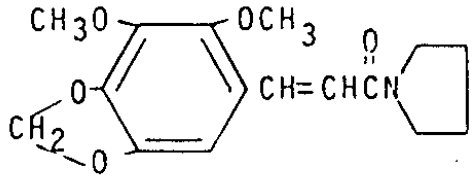


XXVII

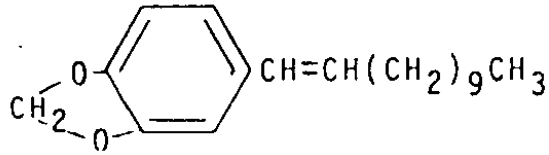


(XXVIII) PIPERLUNGUMININE

Piper peepuloides is yet another pepper plant employed in the Ayurvedic system of medicine, and has been found to contain the closely related cinnaminamide, peepuloidin (XXIX) . As with all the styryl compounds in the Piper species, the aromatic ring substitution pattern is the same as that found in the propenyl essential oils. Just as the afore-mentioned amides from Piper longum are related to isoelemicin (XII, 3,4,5-$(OCH_3)_3$) so peepuloidin is assigned the substitution pattern of isodillapiole (XII, 2,3-$(OCH_3)_2$-4,5-(OCH_2O)). A homologue of isosafrole, pipataline (XXX) is yet another styrenelike component of P. peepuloides.

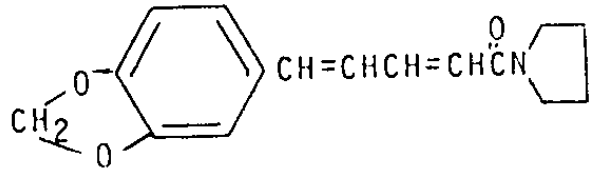


(XXIX) PEEPULOIDIN



(XXX) PIPATALINE

Another pyrrolidine amide alkaloid closely related to peepuloidin has been discovered in the pepper species, Piper trichostachyon . This is trichostachyon (XXXI) the transvinylog of the styrene ethers. None of these styrene amides have been explored pharmacologically.



(XXXI) TRICHOSTACHYON

Piper excelsum has been mentioned earlier as a New Zealand pepper, which in no manner could serve as a substitute for Piper methysticum in the preparation of an intoxicating drink. The Maori are reported to employ the plant for the preparation of a treatment of headache, but its chemistry and pharmacology remain unexplored. Piper plantagiveum has been mentioned as being found in the West Indies and Mexico, and as serving as a course of a Kava-kava-like narcotic.

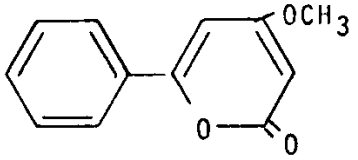
Piper betle is the source of Betel, a dried leaf preparation that has been extensively used in Southeast Asia both topically as well as internally. The term Betel (leaf of the pepper Piper betle) must not be confused with Betel Nut (seed of the palm, Areca catechu) which is an entirely separate and unrelated abuse drug. Betel (the leaf) has often served as a wrapping for the Betel Nut, which is usually encountered thinly sliced and mixed with some slaked lime. The internal use of Betel is as a source of sharpness in the flavouring of Betel Nut. The leaves, known as Sirih in Malayan, provide an oil that contains a number of phenolic substances, many of which are allylphenols . Chavicol (4-hydroxyallyl-benzene) is a major component and is strongly antiseptic. Hydroxychavicol (allylpyrocatechol, 3-4-dihydroxyallylbenzene) is present (and contains the carbon skeleton of safrole) as is its 4-methyl ether, chavibetol, which is classically known as " betel phenol ". Although the use of Betel is almost incidental to the use of Betel Nut, there have been some preliminary studies made into its pharmacological properties.

A second large Genus of peppers are those associated with the chili pepper, the Capsicum spp. Most of these have found use as foods and flavourings, but one report suggests that the addition of pepper pods of Capsicum annuum to Kava-kava has been intentional, to strengthen its effects and suggesting a relationship to the Betel of Indonesia. Another report describes the use of peppers as a "stimulant and excitant" by the Kakusi Indians of British Guiana . Since these New World peppers have been clearly identified as a species of Capsicum a careful search in this Genus for alkaloids or pyrones would certainly be warrented.

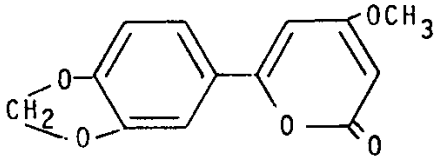
A number of the compounds that have been described as comprising the Piper methysticum plant are known from other areas of the botanical world. 11-Methoxy-yangonine (X), mentioned above as a minor component of the Kava-kava root, had previously been observed as a component of the Brazilian Rosewood Aniba firmula . One of the earliest compounds isolated from Aniba firmula was desmethoxy-yangonin (VII) and was originally called 5,6-dehydrokavain due to its clear relationship to kawain. This isolation was the first description of this chemical from natural sources and predates its

observation in the Piper group. The chemical itself had first been synthesized fully two decades before either of the observations of its natural occurrence.

An interesting family of chemicals, the phenylcoumalins, also occurs in the rosewood. These are the analogues of desmethoxy-yangonin and dehydromethysticin, lacking only the vinyl group that connects the two ring systems. 4-Methoxy-phenylcoumalin (XXXII) can be related directly to desmethoxy-yangonin (5,6-dehydrokawain, VII) and this has been isolated as a major component of Aniba duckei.



(XXXII) 4-METHOXYPHENYLCOUMALIN



(XXXIII) 4-METHOXYPARACOTOIN

The 4-methoxyparacotoin analogue (XXXIII) has been described in conjunction with the isolation of desmethoxyyangonin from this species. This methylenedioxy counterpart of methoxyphenylconmalin (XXXII) appears to be biogenetically related to the methysticin group. A complete review of all these interrelated pyrones has recently appeared. The rosewood (Aniba firmula) which has no reputation for central activity, must not be confused with the woodrose (Argyreia nervosa) which is an exceptionally active psychotomimetic.

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