RECENT CHEMISTRY OF SOME INDIAN PIPER SPECIES.[1]

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Abstract: This review summarises some of our work on the chemistry of six Indian Piper species.

CONTENTS

I. Introduction

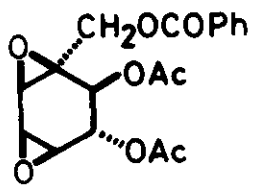
The family Piperaceae consists of four genera and contains more than 2000 species, all belonging to the tropical parts of the world. Forty-five Piper

species appear in the Flora of British India and of these, thirty-two occur in the Indian territory including the Andamans.[2]

A variety of compounds have been isolated in the few Piper species which have been investigated for their chemistry. These are aliphatic and aromatic amides,[3] cyclohexene epoxides,[4] lignans,[5,6,7] ∝-pyrones,[8,9] flavonoids[10], sesquiterpenes[11] and alkaloids.[12] The chemistry of Piper species has been reviewed earlier.[13,14] The present contribution summarises some of our work on six plants of the Piper species.

II. Piper attenuatum Ham., P. galeatum Wight., P. hookeri Hook, P. nigrum Linn. Crotepoxide, pipoxide and pipoxide chlorohydrin.

Hexane extracts of the whole plant of P. galeatum, P. hookeri and P. attenuatum afforded crotepoxide[15] (1) which is known to possess significant antitumour activity in Lewis lung carcinoma.[16] Chromatographic separation of the hexane



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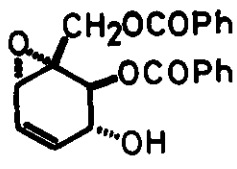

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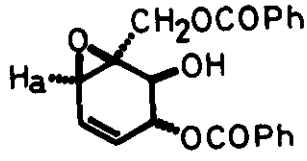

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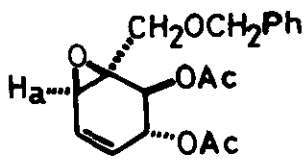
extracts of P. hookeri and P. nigrum gave colourless plates m.p. 154°, $[\alpha]_D$ - 49°, $C_{21}H_{18}O_6$ which appeared to be identical with pipoxide constituted as (2), except for the rotation, $[\alpha]_D$ + 24.5°.[17] A direct comparison including ORD showed that the compounds were identical.[15] The structure (2) was based on spectra and some chemical reactions. We found that the 60 MHz spectrum does not give clear separation of the protons. 360 MHz spectrum and decoupling experiments clearly indicated the structure (3) for pipoxide. Configuration for the epoxide was based on a comparison of the chemical shift H_a in (3) at 3.6 δ with the corresponding proton at 3.6 δ in (4), 3.68 δ in (1) and 3.47 δ in (5), 3.44 in senepoxide (6).[18] Holbert et al. have recently reported the revised structure of pipoxide as (3) by X-ray crystal structure determination and have carried out its total synthesis.[19]



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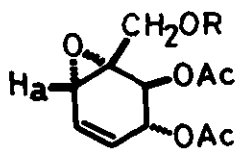
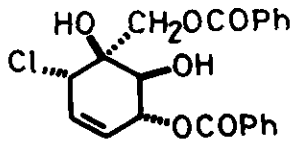


5 : R = CH_2Ph

6 : R = COPh



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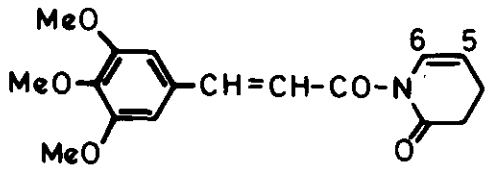
From the methanol extract of P. hookeri and P. nigrum pipoxide chlorohydrin was isolated. As it could be transformed to pipoxide on treatment with methanolic potassium carbonate[15] its structure has been revised to (7).[15,17]

III. Piper longum Linn., Piplartine

Roots of Piper longum, Linn. are widely used in the Ayurvedic System of medicine.[20] Atal and Banga first isolated[21] piplartine, $C_{17}H_{19}NO_5$. This alkaloid named piperlongumine was constituted as (8) by Chatterjee and Dutta based on



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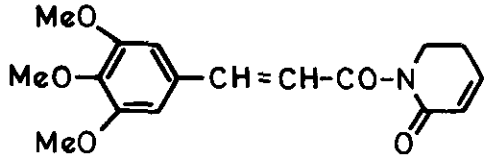

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spectral and degradation studies.[21] Our investigations showed that the double bond at the 5,6-position of the pyridone ring was incompatible with the observed NMR spectrum. Dihydropiplartine was synthesized by reaction of 3,4,5-trimethoxycinnamoyl chloride with α-piperidone. A UV difference curve between piplartine and dihydropiplartine showed λ_{max} 225 nm (ε, 11000) which is in good agreement with an α,β-unsaturated lactam chromophore. Piplartine has been assigned the structure (9) having the unsaturation at 3,4-position of the pyridone ring.[22]

IV. Piper trichostachyon C.DC.

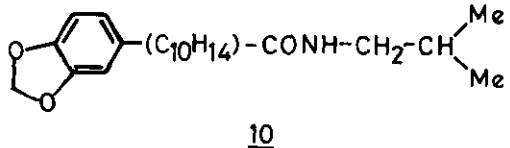
This Piper species is a twining climber growing in most of the evergreen forests of the Western Ghats of India. Earlier chemical investigations of this plant reported the isolation of a diene amide trichostachine, and also the trieneamide 1-piperettyl pyrrolidine.[23] Trichonine, the pyrrolidine amide containing a diene attached to a 15 carbon aliphatic chain has also been isolated.[24]

During the screening of medicinal plants for their biological activity[25] we examined the stems of P. trichostachyon.

Oily hexane extracts on chromatographic separation on alumina afforded four alkaloids. Two of these, piperstachine and cyclopiperstachine are isomeric and the other two which are also isomeric have been designated cyclostachine A and cyclostachine B.

1. Structure of piperstachine[26] : This analyses for $C_{22}H_{29}NO_3$ and shows UV maxima at 216, 283, 293 and 315 nm. Infra-red bands due to NH or OH, conjugated amide carbonyl, methylenedioxy and olefinic trans double bond groups are observed. The PMR spectrum accounts for all the 29 protons in the molecule. It showed 9 olefinic or aromatic protons, a methylenedioxy group, an amide NH adjacent to a methylene group, two allylic or benzylic methylenes, two saturated methylenes and an isopropyl groupings.

Double resonance studies established the following arrangement of groups : (1) The NH at 5.8 δ on irradiation changed the methylene triplet at 3.13 δ to a doublet indicating that these are adjacent. (2) The methine proton at 1.79 δ on irradiation simplified the triplet at 3.13 δ to a doublet. The methylene should therefore be spin coupled with the amide NH. (3) The allylic or benzylic methylene at 2.2 δ on irradiation simplified the saturated methylenes at $\sim$1.5 δ and also simplified the olefinic region at 6.0-6.4 δ . This data indicated a partial structure (10) for piperstachine where the $C_{10}H_{14}$ aliphatic unit contains three olefinic double bonds and four contiguous methylene groups.



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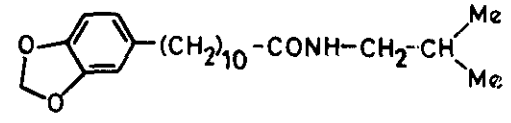

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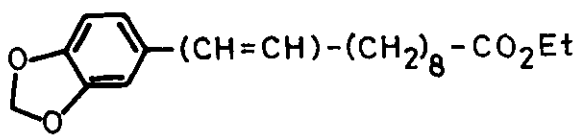
Piperstachine on hydrogenation gave the hexahydro derivative (11) the structure of which was confirmed by its synthesis.

2. Synthesis of hexahydropiperstachine (11)[26] : The chloride of ethyl hydrogen sebacate was reduced with $NaBH_4$ to the corresponding alcohol which on treatment with PBr_3 gave ethyl 10-bromodecanoate. The triphenyl phosphonium derivative

prepared from the bromoester on Wittig reaction with piperonal afforded (12). The same compound was also obtained by Wittig reaction of piperonyl-triphenyl-phosphonium bromide with methyl 9-formylnonanoate, ester exchange taking place in the presence of sodium ethoxide. Hydrogenation afforded the saturated ester (13) which was hydrolysed to the acid (14) and condensed with isobutylamine to give (11) identical with hexahydro piperstachine.



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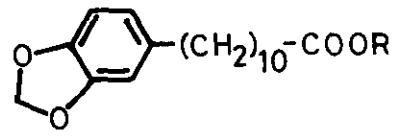
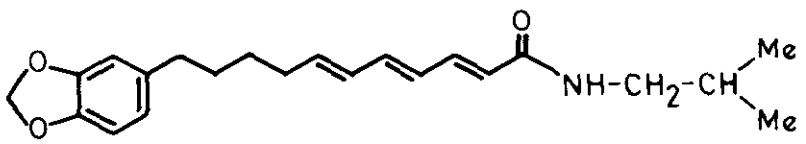


13 : R = Et
14 : R = H

3. Position and stereochemistry of the double bonds in piperstachine[26] : The PMR spectrum of piperstachine using the shift reagent $Pr(fod)_3$ indicated that the terminal carbon of one of the olefinic double bonds must be attached to the α-position of the amide carbonyl. The value of the vicinal coupling constant (15 Hz) established a trans configuration of this double bond. Piperstachine gave a Diels-Alder adduct with maleic anhydride indicating a trans-diene system of two of the three olefinic double bonds. Only three structures (15), (16) and (17) can be considered for piperstachine to fit the above data. In order to establish the



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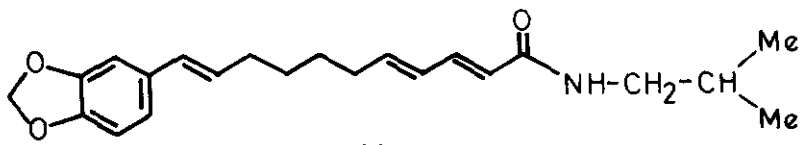

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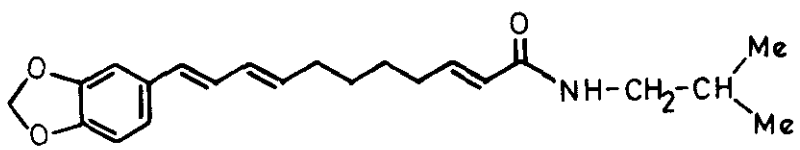

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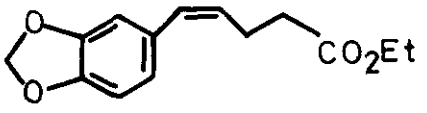
position of the olefinic double bonds and their stereochemistry, the synthesis of these compounds was undertaken.

4. Synthesis of N-isobutyl-11-(3,4-methylenedioxyphenyl)-undeca-2,4,6-*trans*, *trans*, *trans*-trienoic amide (15)[27] : Wittig reaction of piperonal with the ylid from carbethoxypropyltriphenylphosphonium bromide gave the ester (18) which on hydrolysis to the acid, reduction of the double bond and esterification gave (19). $LiAlH_4$ reduction of (19) to the alcohol and oxidation with Collins reagent



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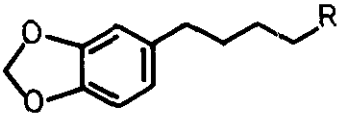
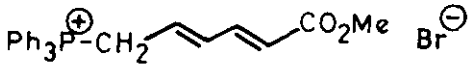


19 : R = CO_2Et
20 : R = CHO

afforded the aldehyde (20). The next step was to extend the chain to give the triene acid. Wittig condensation of (20) with the phosphonium bromide (21) obtained from methyl ω-bromo-*trans*,*trans*-sorbate gave the *trans*,*trans*,*trans*-triene ester (22). The newly generated double bond has to be *trans* since the reaction



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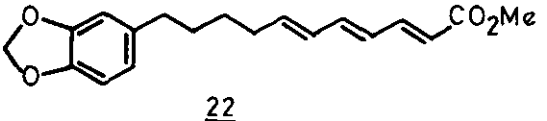

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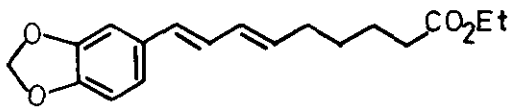
involves the condensation of a resonance stabilised phosphorane.[28] The ester (22) was hydrolysed to the acid and condensed with isobutylamine to give (15) which was found to be different from piperstachine.

5. Synthesis of piperstachine (17)[27] : Condensation of 3,4-methylenedioxy-*trans*-cinnamaldehyde with the ylid from carbomethoxypentyl-triphenylphosphonium bromide gave a mixture of the *trans*,*trans* (23) and the *trans*,*cis* (24)-diene esters in the ration of 4:6. Alkaline hydrolysis of the mixture of esters gave the acids which were separated by utilising the differential solubilities of their potassium salts in ethanol. The compounds could be distinguished, as only the acid from (23) gave the maleic anhydride adduct (25). $LiAlH_4$ reduction of (23) gave the corresponding alcohol which was best oxidised by the Pfitzner-Moffatt procedure[29]



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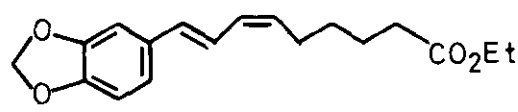

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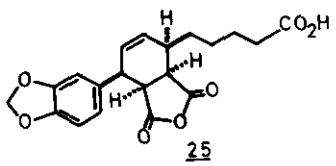
to give the aldehyde (26). Wittig reaction of (26) with carbomethoxymethylenetriphenylphosphorane yielded the triene-ester (27). This was hydrolysed to the acid (28) and then converted to the amide (17) which proved to be identical with piperstachine.



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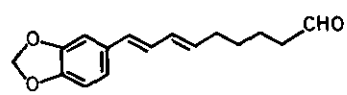

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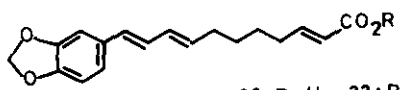
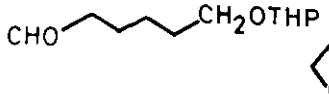


27: R=Me; 28: R=H; 33: R=Et

Another synthesis of piperstachine has recently been reported.[30] Wittig reaction of 6-(tetrahydro-2'-pyranyloxy) hexanal (29) with the phosphonium bromide (30) gave the trans,trans-diene (31) which after removal of the protecting group and oxidation gave the aldehyde (32). Wittig condensation of (32) with ethyldiethylphosphonoacetate gave the ester (33) which on hydrolysis afforded the trienoic acid (28) obtained in the previous syathesis.



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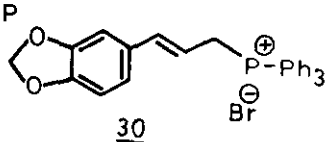

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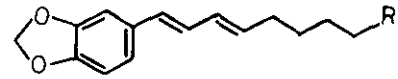
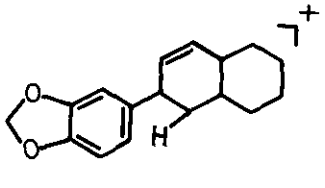


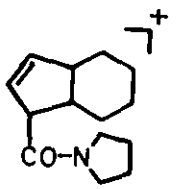
31: R = CH_2OTHP
32: R = CHO

6. Cyclostachine A[31,32] : This alkaloid $C_{22}H_{27}NO_3$ showed in the IR spectrum a tertiary amide band at 1630 cm^{-1}. Its PMR spectrum indicated a methylenedioxy group, an isolated double bond and an acylpyrrolidine moiety. The UV spectrum showed that the double bond is not conjugated with the aromatic ring. Hydrogenation gave dihydrocyclostachine A and acid hydrolysis of cyclostachine A afforded

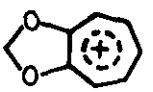
pyrrolidine. On the basis of the above data and the mass-spectral fragments (prominent ions at m/e 255, 218, 135 and 98 attributed to ions a to d) a gross hypothetical structure 34 was considered. The presence of a disubstituted double



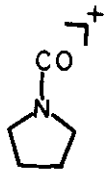
a m/e 255



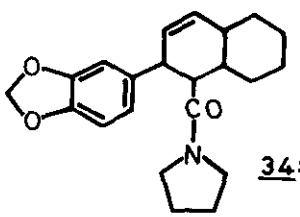
b m/e 218



c m/e 135



d m/e 98



34: M^+ m/e 353

bond was confirmed by OsO_4 oxidation to the diol and periodate cleavage to the dialdehyde. $LiAlH_4$ reduction of the alkaloid afforded the amine characterised as the crystalline sulphate. The X-ray crystal structure of this (Figure 1) showed that atoms C(7), C(8), C(9), C(10) and C(15) of the cyclohexene ring are coplanar and C(1), C(14) and C(17) are all axially disposed.[31] This is in contrast to the PMR spectrum of cyclostachine A (35) in solution showing these three substituent

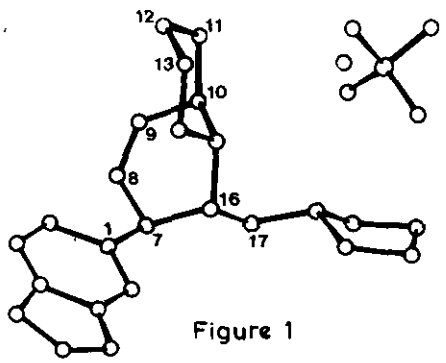
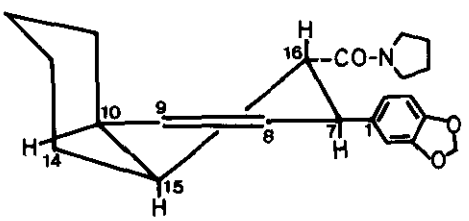


Figure 1



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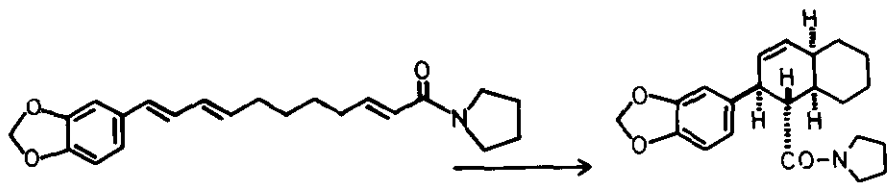
atoms equatorial, In the solid state the amine shows a conformation different, probably because of the greater volume required for the non-planar amine ring compared with the amide form and the need to proximate the sulphate ion to the

nitrogen atom for the ionic and hydrogen bonded linkage.

7. Cyclostachine B[32] : This has similar UV, IR and mass spectral fragmentation indicating that this is a stereoisomer of cyclostachine A. It was visualized that the aryl-octahydronaphthalene skeleton in 35 originates from a trienamide related to piperstachine (17). Intramolecular Diels-Alder reaction of this hypothetical precursor (36) would be expected to give two racemates.[33,34] As cyclostachine A is known to be the cis isomer, cyclostachine B could have a trans stereochemistry for the naphthalene ring as in (37). The PMR spectrum of cyclostachine B is in excellent agreement with the conformation shown.



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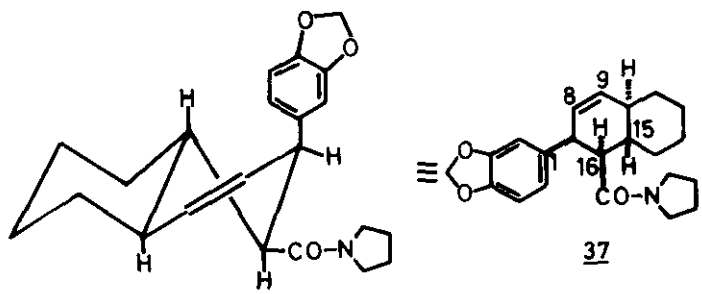
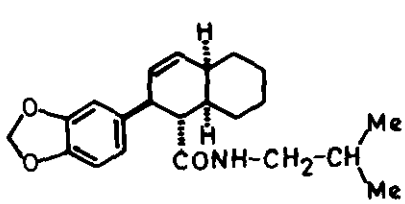


37

8. Cyclopiperstachine[32] : This alkaloid, isomeric with piperstachine has spectral properties similar to (35) and (37). The PMR and mass spectra show the presence of an isobutylamide group. The PMR spectral similarity with cyclostachine A suggested a cis fusion and the structure (38) for this alkaloid.



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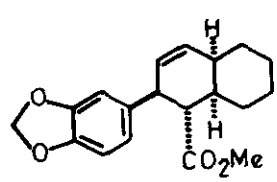
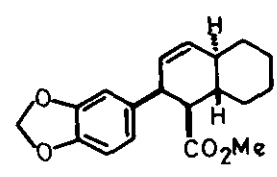
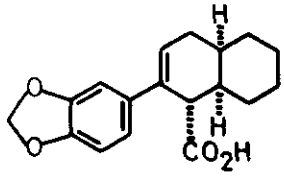


39

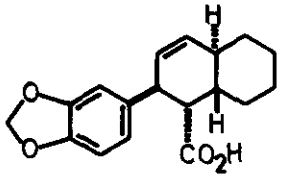


40

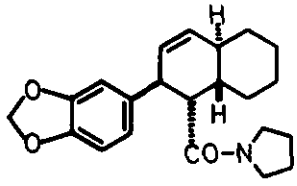
9. Synthesis of cyclostachine A, cyclostachine B and cyclopiperstachine : The ester (27) when heated in xylene gave a mixture of two compounds (39) and (40) separated by chromatography. The major product has the cis configuration. Alkaline hydrolysis of (39) and conversion to the amide gave (35), identical with cyclostachine A. Esterification of the acid with diazomethane gave (39) proving the absence of any isomerisation during hydrolysis. Under vigorous hydrolytic conditions, isomerisation took place to give the acid (41).



41



42



43

The minor ester (40) on hydrolysis to the acid was converted to the pyrrolyl-amide (37) identical with natural cyclostachine B. Vigorous alkaline hydrolysis of (40) resulted in the epimerisation at C-16 to give (42) which could be converted to the isomeric alkaloid (43). The acid obtained by mild hydrolysis of (39) on treatment with isobutylamine afforded (38) identical with natural cyclopiperstachine.

V. Pharmacological activity

Plants of the Piper species are known to be widely used in medicine and the pharmacological activity could be attributed to a variety of chemical constituents. The essential oil of P. betle Linn. has been shown to have anthelmintic activity.[35] Extracts of P. peepuloides Royle have been claimed to exhibit insecticidal and larvicidal activity in mosquito and the housefly.[36] Extracts of P. chaba Hunter. have been demonstrated to possess hypotensive and smooth muscle-relaxant properties.[37] The marked central stimulant activity of P. longum Linn. has been shown to be due to piperine.[38] P. novae-hollandiae contains amides having tumour inhibiting properties.[39] It can be seen that only a few species of this genera have been evaluated for their chemistry and pharmacology. It appears worthwhile to screen many more Piper species in order to isolate novel structures having useful medicinal properties.

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