CHAPTER I

INTRODUCTION
In the recent years, there has been a revival of interest in medicinal plants. This is due to researches which have revealed therapeutic properties hitherto unknown in certain plants. Intensive research is being carried out in advanced nations of Europe and in America. The importance of such researches in tropical countries like India can not be overlooked.

A knowledge of chemical constituents of plants is desirable not only for the discovery of new therapeutic agents but also because such information may lead us to newer sources of economically useful materials like gums, tannins, oils and intermediates for synthesis of complex compounds.

Gentinales is one of the many orders in the classification of plant kingdom. It has about 12,000 species distributed in five large families and about 150 species in six smaller ones. Some of the species belonging to this order are of great economic importance. Coffea arabica serves as a source of coffee, whereas Cinchona, Rauwolfia, Vinca and Uncaria are drug yielding genera. Rubber can be obtained from Fulbinia elastica and Cryptostegia grandiflora. American Indians have used many species of Asclepias genus
(milkweed genus) for their fibre requirements. Species of Gentiana, Stapelia, Vinca, Coleusmum and Oleander are planted for ornamental flowers. Poisonous constituents occur in many species of family Loganiaceae and in Strychnos and Nerium.

Rubiaceae is one of the important families of the order Gentinales$^2$. It is comprised mostly of trees and shrubs and some climbers. Leaves are opposite or whorled, usually with conspicuous, persistent stipules. Intraxylary phloem is absent. The inflorescence varies from one large flower to many small flowers in one head. Calyx lobes are 4 or 5, Corolla 4 or 5 united petals, mostly with radial symmetry but tending to bilateral symmetry in some cases. Stamens 4 or 5 and are epipetalous. Ovary, with a few exceptions, is inferior, of 2 carpels and one to many anatropous ovules. Fruit is fleshy or dry.

There are about 500 genera and 6500 species in family Rubiaceae. One of the genus of this family is Mitragyna. Some plants of this genus are considered to be of therapeutic value in fever, colic and muscular pain besides being useful in expulsion of worms. The leaves of M. speciosa, according to Holmes$^4$ are said to be used as substitute for opium, while Hooper$^5$ mentions them to be antiopiate. The bark and root of M. parvifolia are said to be useful in fever and colic$^6$. 
Following ten species of the genus *Mitragyna* are known:

(a) *Mitragyna hirsuta* Havil

(b) *M. parvifolia* (Roxb.) Korth.

(c) *M. javanica* Koord and Valeton

(d) *M. rotundifolia* (Roxb.) O. Kuntze synonym
   *M. diversifolia* (Hook F.) Havil

(e) *M. speciosa* Korth

(f) *M. tubulosa* Havil

(g) *M. rubrostipulacea*

(h) *M. stipulosa*

(i) *M. ciliata*

(j) *M. innermis* (Willd.) O. Kuntze.

Of the ten species mentioned above, 3 species viz.,
*M. parvifolia*, *M. rotundifolia* and *M. tubulosa* grow wild
in India. *M. parvifolia* grows abundant in Kerala,
Maharashtra, Uttar Pradesh, Bengal, Bihar and Madhya Pradesh.

Its vernacular names are:

<table>
<thead>
<tr>
<th>Language</th>
<th>Hindi</th>
<th>Bengali</th>
<th>Marathi</th>
<th>Gujarati</th>
<th>Telegu</th>
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<tbody>
<tr>
<td></td>
<td>Kaim, Kalim, Kadassa</td>
<td>Gulikadama</td>
<td>Kalamb, Kuddam</td>
<td>Kadamb</td>
<td>Mirakadambe</td>
</tr>
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</table>
Mitragyna parvifolia is a medium to large deciduous tree with rounded crown, found throughout the greater part of India, ascending up to a height of 1200 m in the outer Himalayas. Bole is often short, fluted or butterssed. The bark is grey, smooth and exfoliating in scales. The leaves are variable, stipulate, elliptical, suborbicular or obovate in shape. Flowers are in globose head, greenish yellow in colour and fragrant. Capsules are oblong; seeds are minute and winged.

The tree is scattered in deciduous forests and develops best in well drained soil. It can tolerate stiff and badly drained soils and often grows gregariously in low lying areas around river banks and swamps, where it remains stunted. In the Deccan Peninsula it is found on black cotton soil and alluvial soil near rivers. In the early stages of growth the tree withstands a certain amount of shade but demands light later on. It is fairly drought hardy.

Mitragyna genus has been extensively investigated for its alkaloidal content. It is known to contain indole and oxindole alkaloids and their N-oxides, the presence of
oxindole alkaloids being of special interest. The oxindole alkaloids are limited to the genera *Gelsemium*, *Oreocarpis*, *Aspidosperma*, *Rauwolfia*, *Vincas*, *Ucarias*, and *Mitragyna* and represent only 5-6% of total known alkaloids. It is interesting to note that the alkaloidal pattern varies with the geographical source. The presence of N-oxides in *Mitragyna* has also been widely reported.

**OXINDOLE ALKALOIDS**

The oxindole alkaloids were isolated for the first time from the roots of *Gelsemium sempervirens* Ait. Several reviews throw light on the chemistry of oxindole alkaloids. The oxindole alkaloids can be classified as:

(a) Oxindoles of *Gelsemium* type

(b) Oxindoles of *Secoyohimbane* and *Heteroyohimbane* types

(a) **Oxindoles of Gelsemium type**

The oxindole alkaloids obtained from *Gelsemium sempervirens* Ait. are gelsemine, gelsemicine, gelseidine and gelsevirine. The structure of gelsemine was revealed after exhaustive degradation and by application of X-ray crystallography, mass spectrometry (CMR), PMR and biogenetic studies.
Gelsemine

Gelsemicine and gelsedine are secondary bases isolated from residual alkaloids of *G. sempervirens*.\textsuperscript{19} The structure of gelsemicine was established by X-ray crystallography\textsuperscript{20} and gelsedine was shown to be 11-demethoxy gelsemicine by Wenkert et al.\textsuperscript{21}

Gelsemicine $R = \text{H}$

Gelsedine $R = \text{OCH}_3$
Gelsevirine is a tertiary base left after recovery of secondary bases from the residual alkaloids of \textit{G. sempervirens}. Initial data was reported by Schwartz and Marion\textsuperscript{19} but spectroscopic studies by Wenkert \textit{et al.}\textsuperscript{16} indicated that the presence of two methoxyl groups reported by Schwartz and Marion\textsuperscript{19} was erroneous.

![Gelsevirine]

Gelsevirine

(b) Oxindoles of Secoyohimbane and Heteroyohimbane types

The alkaloids that have been isolated from \textit{Aspidosperma}, \textit{Mitragyna}, \textit{Ouropaaria}, \textit{Rauwolfia}, \textit{Vinca} and \textit{Uncaria} all bear a structural resemblance to each other. They possess the same basic framework and may be regarded as derived from tryptophan via its decarboxylation product\textsuperscript{22-24} tryptamine and secologanin, a C-10 unit of terpenoid origin. These oxindoles can be conveniently classified into two structural classes\textsuperscript{25}:

(i) Tetracyclic structures of the 17-18 secoyohimbane type or corynantheidine type.
(ii) Pentacyclic structures of heteroyohimbane type or ajmalicine type.

(I) Pentacyclic heteroyohimbanes - akuammigine
(II) Tetracyclic heteroyohimbanes - corynanthdeine
(III) Pentacyclic oxindoles - pteropodine
(IV) Tetracyclic oxindoles - rotundifoline

Secologanin

I
Pentacyclic heteroyohimbane
R = H, OH or MeO

II
Tetracyclic heterohohimbane
R = H, OH or MeO
R' = Et or Vinyl
III
Pentacyclic oxindole
\[ R = H, \text{ OH or MeO} \]

IV
Tetracyclic oxindole
\[ R = H, \text{ OH or MeO} \]
\[ R' = \text{Et or Vinyl} \]

The oxindoles can exist as isomers depending on the orientation of \( H \) at C-3 and C-20.

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<thead>
<tr>
<th></th>
<th>C-3H</th>
<th>C-20H</th>
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<tbody>
<tr>
<td><strong>allo</strong></td>
<td>( \alpha )</td>
<td>( \alpha )</td>
</tr>
<tr>
<td><strong>epiallo</strong></td>
<td>( B )</td>
<td>( \alpha )</td>
</tr>
<tr>
<td><strong>normal</strong></td>
<td>( \alpha )</td>
<td>( B )</td>
</tr>
<tr>
<td><strong>pseudo</strong></td>
<td>( B )</td>
<td>( B )</td>
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III and IV can exist as A or B isomers in which the lactam carbonyl lies either below (A) or above (B) the plane of C-D rings.
Arndt\textsuperscript{26} identified carpanaubine among the alkaloids of \textit{Aspidosperma rigidus} Rusby. Subsequently, carpanaubine and isocarpanaubine were found to be associated with rauvoxine and rauvoxinine - an isomeric pair of oxindole alkaloids first isolated from the leaves of \textit{Rauvolfia vomitoria} Aitz\textsuperscript{27,28}.

Many oxindole alkaloids have been isolated from \textit{Vincetoxicum} species. Vinine, an alkaloid obtained from \textit{V. pubescens} Urv.\textsuperscript{29} has been proved to be identical with carpanaubine\textsuperscript{30}. Mitraphylline has been isolated from \textit{V. rosea} Reichb.\textsuperscript{31} while herbaline - a dihydropentaacyclic oxindole has been found to be present in \textit{V. herbacea} Waldst. et Kt\textsuperscript{32,33}.

Two isomeric bases A-4 and A-5 were isolated from \textit{V. herbacea}\textsuperscript{33,34} and these were subsequently proved to be identical with majdine and isomajdine\textsuperscript{33,35} which were isolated from \textit{V. major} L. by Russian workers\textsuperscript{30}. Kaul and Trojanek\textsuperscript{36} have confirmed the presence of majdine in \textit{V. major} L. and that the alkaloid V (C\textsubscript{23}H\textsubscript{26}N\textsubscript{2}O\textsubscript{3}) isolated with majdine is related to it\textsuperscript{37}. Elegantine\textsuperscript{38} isolated from \textit{V. elegantissima} Hort. and herbaverine from \textit{V. herbacea}\textsuperscript{39} have the same molecular formula as alkaloid V. Vinerine, vineridine\textsuperscript{40,41} and erycinine\textsuperscript{42} are three isomeric oxindoles (C\textsubscript{22}H\textsubscript{26}N\textsubscript{2}O\textsubscript{2}) isolated from \textit{V. erecta} Regl. et Schmalh.
I. Oxindoles of secovohimbane type

Rhynchophylline and isorhynchophylline, the oxindoles of *Mitragyna* possess the normal B and A configuration as in rhynchophylline the lactam carbonyl lies above the plane of C/D ring and in isorhynchophylline below the C/D ring. Assignment of stereochemistry at C-7 is based on pKa, isomerization, C D data and is supported by TLC evidence and by PMR spectra.

![Oxindole A](image1)

![Oxindole B](image2)

Beckett et al. have carried out Mass spectroscopy of a number of tetracyclic oxindoles and the main Mass spectral fragments were found to be independent of stereochemistry. Tameien et al. have given a full synthesis of rhynchophyllol and isorhynchophyllol.

The 9-hydroxy bases rotundifoline and isorotundifoline have the same configuration at C-15 and C-20 but are isomeric at C-3 and/or C-7. In rotundifoline the phenolic
group undergoes a strong intramolecular hydrogen bonding with $N_b$ and hence does not respond to reactions of phenolic group, whereas isorotundifoline which does not undergo such bonding gives positive reaction for phenolic compounds. Based on PMR studies, rotundifoline and isorotundifoline have been assigned B and A configuration respectively\textsuperscript{43}. This assignment has been supported by TLC evidence\textsuperscript{46}.

Rynchocephylline and ciliaphylline are an interconvertible pair of isomeric oxindole alkaloids ($C_{23}H_{30}N_2O_5$) which been isolated from \textit{M. ciliata} Aubrev. et Pellegr\textsuperscript{47,48}. The physicochemical data and PMR studies indicate that these isomers are rynchocephylline type with an extra methoxyl group in the aromatic ring\textsuperscript{43}. Thus rynchoceoline and ciliaphylline are \textit{normal} A and \textit{normal} B methoxy oxindoles respectively. Specionoxeine and isopecionoxeine are similar oxindoles ($C_{23}H_{26}N_2O_5$) isolated from \textit{M. speciosa}\textsuperscript{43}. They have been assigned 9 methoxy \textit{normal} A (isopecionoxeine) and 9 methoxy \textit{normal} B (pecionoxeine) configuration.

Corynoxine, corynoxin and isocorynoxine have been isolated from \textit{Pseudocinchona africana} A Chev. Corynoxine is a \textit{normal} A oxindole and related to rynchocephylline as a vinyl analog\textsuperscript{11}. On the basis of spectral and degradative studies it has been suggested that corynoxine is an isomer of rynchocephylline and isorhynchocephylline\textsuperscript{49}. Equilibration
studies indicated that it should have allo or epiallo configuration. The C-18 methyl triplet at 100 MHz FMR indicated an axial C-20 ethyl group. Moreover, corynoxine has been synthesised from corynantheidine, indole of allo configuration.

II. Oxindoles of heterocyclohexane type

The pentacyclic oxindoles are true oxindoles. The chemical and physical data pertaining to its structure is supported, in many cases, by the data on their corresponding indole alkaloids. Bindra has compiled the formulae, melting points, UV, IR, (α)D and pKa data of many such oxindoles.

Mitrphylline and isomitrphylline are oxindoles of normal B and A series. The orientation of hydrogen at C-15 (α), C-19 (β) and C-20 (β) has been confirmed by partial synthesis from ajmalicine. Formosamine and isoformosamine (earlier known as uncarines A and B) are also oxindoles of normal series. Their FMR, pKa and CD data have been reported. Pteropodine, isopteropodine, speciophylline and uncarine F are for isomeric interconvertible oxindoles earlier known as uncarines C, D, E and F respectively. Their structures are well established.
THE ALKALOIDAL N-OXIDES

Amine oxide is a general term and includes all compounds having a general formula:

\[
\begin{align*}
R' \\
\downarrow \\
R - N \rightarrow O \\
\downarrow \\
R''
\end{align*}
\]

or

\[
\begin{align*}
R' \\
\downarrow \\
R - N \rightarrow O \\
\downarrow \\
R''
\end{align*}
\]

Where \( R, R' \) and \( R'' \) are either alkyl or aryl groups. This definition, however, excludes such compounds which have the \( N \rightarrow O \) attached to heteroatoms such as \( N \) or \( O \).

\( N \)-oxides may be derived from tertiary amine functions which are attached to aliphatic, alicyclic or aromatic moieties or which form a heterocyclic ring system. Because of resonance stabilization the \( N \)-oxides of compounds having tertiary amine nitrogen as a part of heterocyclic ring system have more stable \( N \rightarrow O \) bond and hence are more stable\(^{55}\).

Amine \( N \)-oxides have been prepared in the laboratory by oxidation with hydrogen peroxide, peracetic, perbenzoic and monoperoththalic and \( m \)-chloroperbenzoic acids\(^{56-58}\). The \( N \)-oxides can be reduced to their bases by the action of zinc and sulphuric acid, sulphurous acid, alkali or a redox polymer comprising of 2-methyl - 5-vinyl pyridine and \( M \)-di-isopropanyl benzene\(^{59,60}\).
Initial studies on some alkaloidal N-oxides like atropine-N-oxide and strychnine N-oxide showed that the N-oxides have the same activity as the alkaloid but are much less toxic. In some instances it was found that the route of administration is an important factor as far as activity is concerned. Morphine subcutaneous is 11-22 times more potent than morphine-N-oxide intraperitonially\textsuperscript{61}. The pharmacological effects of tropane alkaloids and their N-oxides have also been compared\textsuperscript{62,64}. Some pyrrolidizine alkaloid-N-oxides are reported to be possessing anticancer activity\textsuperscript{65,66}.

It has been proposed that N-oxides are artifacts but at the same time it has been proved in certain instances that N-oxides are not artifacts but occur naturally. Phillipson and Handa studied the variation in the ratio of alkaloid : alkaloid N-oxide in different strains of three species of \textit{Nicotiana}\textsuperscript{69} and found that the N-oxide content varied between 10.5 and 24\% of the tertiary base.

\textbf{ALKALOIDS OF MITRAGYNA}

Field\textsuperscript{70} was the first to isolate an alkaloid Mitraversine from the leaves of \textit{M. diversifolia} (Syn. \textit{M. rotundifolia}). Subsequently, Raymond-Hamet\textsuperscript{71} isolated alkaloid mitraphylline from bark of this plants. Rhynchophylline, rotundifoline and Mitragynol base have been also isolated from \textit{M. rotundifolia}\textsuperscript{72,73}. 
In 1907 Hooper\(^5\) and in 1921 Field\(^70\) investigated \textit{M. parvifolia} and \textit{M. parvifolia} and \textit{M. speciosa}. Hooper succeeded in isolating one alkaloid which was not named. Field did not succeed in isolating any alkaloid from \textit{M. parvifolia} though he isolated mitragynine from \textit{M. speciosa}. Ing and Raisin\(^74\), as well as Hendrickson\(^75\) succeeded in isolating mitragynine and rhynochophylline and stipulatine from \textit{M. Speciosa}. Seaton \textit{et al.}\(^76\) isolated isorhynochophylline from \textit{M. rubrostipulacea}, whereas Beckett \textit{et al.}\(^47,48\) isolated oiliaphylline, isorhyncho-
phylline, rhynocholine and mitraciliatine from \textit{M. stipulosa} and \textit{M. oiliata}. According to Shellard and Phillipson\(^77\) rhynochophylline and isorhynochophylline are present in \textit{M. rotundifolia}.

In 1965 Beckett \textit{et al.}\(^78,79\) isolated and characterised mitragynine and speciofoline from \textit{M. stipulosa}. It was proposed that speciofoline is an isomer of rotundifoline. They reported the presence of other alkaloids which were subsequently identified as mitraphylline, isomitraphylline and speciophylline a new isomer of mitraphylline\(^80\). They have also reported UV, IR, NMR and isomerisation data of mitraphylline, isomitraphylline and speciophylline and the proposed stereochemistry of these oxindoles was found to be in agreement with that of other oxindoles\(^22,51,82-85\). Beckett and co-workers\(^86\) have also investigated indole
alkaloids of *M. speciosa* and succeeded in isolating ajmalicine, corynantheidine speciogynine, paynantheine and speciociliatine. The last three were described for the first time. Speciociliatine was found to be similar to mitraciliatine.

The leaves of *Mitragyna javanica* var. *microphylla* Kord and Valeton, which are sometimes used as substitute for those of *M. speciosa* were investigated for the first time by Shellard and co-workers. Of the six alkaloids isolated by them, three were new—javaphylline, mitrajavine and Pa6. The known alkaloids were mitraphylline, isomitraphylline and ajmalicine. The NMR spectrum of javaphylline was qualitatively similar to that published by Lee et al., who had also studied CD and ORD data.

The alkaloids of *M. hirsuta* Havil were studied by Shellard et al. They isolated four known alkaloids—mitraphylline, isomitraphylline, rhynchophylline and isorhynchophylline as well as a new alkaloid hirsutine from *M. hirsuta*. Trager et al. have shown hirsutine to be a pseudoisomer of corynantheine on the basis of spectral data, CD and ORD curves.

Shellard and Phillipson in 1964 isolated and characterised rotundifoline, isorotundifoline, rhynchophylline and isorhynchophylline from the leaves of *M. parvifolia*. They observed that earlier workers had mistaken *M. rotundifolia* to be *M. parvifolia*, as the alkaloids
obtained by them were of a different sequence. Shellard et al.\textsuperscript{92} isolated akuammigine, an indole alkaloid in addition to pteropodine, isopteropodine, speciophylline and Gu 23 from the leaves of \textit{M. parvifolia} growing in Maharashtra state of India. Akuammigine, earlier had been isolated from \textit{Picrodima nitida} by Henry\textsuperscript{93} and its structure was deduced by Robinson and Thomas\textsuperscript{94} and by Shamma and Moss\textsuperscript{83} while pteropodine and isopteropodine were earlier isolated from \textit{Uncaria pteropoda}\textsuperscript{95,96}. Beecham et al.\textsuperscript{97} isolated identical alkaloids from \textit{U. ferrea} D.C. and designated them as Uncarines C, D, E and F. Johns and Lamberton\textsuperscript{98} have referred speciophylline as uncarine D.

The leaves of \textit{M. parvifolia} growing in Burma, Cambodia and Ceylon have been examined for their alkaloids\textsuperscript{99}. The alkaloidal pattern was somewhat similar to that of the leaves obtained from Kerala but rotundifoline and isorotundifoline were absent. Dihydrocorynantheine and hirsutine (both indole) and rhynchophylline and isorhynchophylline were found to be present in the Burmese leaves. Dihydrocorynantheine was isolated for the first time from \textit{Mitragyna} species. Rhynchophylline and isorhynchophylline were the two oxindoles isolated from the Cambodian leaves. No indole alkaloid could be isolated from these leaves. The Ceylonese leaves were found to contain akuammigine (indole) and rhynchophylline, isorhynchophylline, pteropodine and isopteropodine (all oxindoles).
In 1968 Shellard et al.\textsuperscript{100} isolated the alkaloids from the leaves of \textit{M. parvifolia} growing in Lucknow, Dehradun, Bihar and West Bengal. They observed that of the three sources examined only Dehradun leaves had any indole alkaloid, (3-\textit{joseajmalicine} a pseudoisomer of akuammigine). The isomeric oxindole pair of mitraphylline and isomitraphylline was a common feature of all the three sources. Later they\textsuperscript{101} made a comprehensive study of the bark of \textit{M. parvifolia} growing in Burma, Cambodia, Ceylon, Dehradun, Lucknow, Kerala and Maharashtra. It was noted that only the Burmese bark had any indole alkaloid (hirsutine in traces) but the oxindoles alkaloids were common to all, except the Kerala sample. They also suggested a possible biogenetic pathway and conformations for these alkaloids, the latter being based on works of Thomas\textsuperscript{102}, Battersey and others\textsuperscript{51,52, 103-115}.

The distribution of alkaloids in young plants of Ceylonese \textit{M. parvifolia} was studied by Shellard and Houghton\textsuperscript{116}. They isolated two new alkaloids \( \Delta^{15} \) hirsutine (designated as hirsuteine) and corynoxeine (\( \Delta^{13} \) rhyncho-phylline). The former is an indole and the latter an oxindole. They have also suggested possible biogenetic pathways in roots and leaves. They also studied the distribution of alkaloids in young plants of \textit{M. parvifolia} from Uttar Pradesh and have suggested a possible biogenetic
pathway in roots. They found that the young leaves contained two different alkaloidal sequences, the closed E ring allo-epiallo sequence and the closed E ring normal - pseudo sequence.

Shellard and Houghton\textsuperscript{121} fed \textsuperscript{14}C tetrahydralcalstonine and \textsuperscript{14}C akuammignite into the xylem of young Ceylonese plants and observed that additional alkaloids formed due to feeding of radioactive alkaloids. They also proposed biogenetic pathways of closed E and open E ring Mitragyna alkaloids. In a further study\textsuperscript{122} using \textsuperscript{14}C alkaloids they observed that pteropodine in the leaves got converted into mitraphylline, while mitraphylline was converted into rhynchophylline and corynocyteine.

The alkaloidal patterns in the leaves from Burma, Ceylon and Maharashtra have been studied with a view to examine a possible relationship between pseudo alkaloids and normal oxindole alkaloids\textsuperscript{123,124}. Shellard and Lala\textsuperscript{125}, who studied the alkaloidal pattern in the leaves, stem, bark and root of \textit{M. parvifolia} from Kerala, observed three distinct alkaloidal sequence in the plant. These were:

\begin{itemize}
  \item[(a)] \textit{allo - epiallo} series of closed E ring alkaloids
  \item[(b)] \textit{normal - pseudo} series of closed E ring alkaloids
  \item[(c)] \textit{normal - pseudo} series of E seco alkaloids
\end{itemize}
In 1975, Hemingway et al.\textsuperscript{126} succeeded in isolating 9-hydroxyrhynchophylline type oxindole alkaloids from \textit{M. parvifolia} and \textit{M. speciosa}. These were mitrafoline, speciofoline, isomitrafoline and isospiciofoline.

Phillipson and Hemingway isolated speciophylline N-oxide from \textit{Unaria bernaysii}\textsuperscript{127}, while Shellard et al.\textsuperscript{128} isolated rhynchophylline and isorhynchophylline N-oxides. The 'base line alkaloid' which was observed in alkaloids of \textit{M. parvifolia} was subsequently shown to be composed of N-oxides of akuammigine, speciophylline, uncarine F and dihydrocorynantheidol\textsuperscript{129}.

Phillipson and Hemingway\textsuperscript{25} have reviewed chromatographic (TLC and GLC) methods of separation and UV and mass spectra characteristics of some sixty oxindoles.

Shellard and Alam carried out quantitative determinations of \textit{Mitragyna} bases using UV measurements\textsuperscript{130,131}, colorimetry\textsuperscript{132,133} and densitometry\textsuperscript{134}, and found densitometry to be more reliable\textsuperscript{135}.

Stereochemistry and TLC behaviour of \textit{Mitragyna} oxindoles has been correlated\textsuperscript{136}, and effect of methoxy substitution and configuration on TLC and GLC behaviour has also been investigated by Shellard and co-workers\textsuperscript{137-140}. 
The influence of stereochemistry on Mass spectra of corynantheidine group and related oxindole alkaloids has been studied by Beckett et al.\textsuperscript{141}

The total alkaloids isolated from leaves of \textit{M. parvifolia} obtained from Madhya Pradesh are reported to show significant analgesic, antipyretic and anti-convulsant properties\textsuperscript{142}.
### TABLE I

**Distribution of Alkaloids in the Bark and Leaves of *M. parvifolia* of different Geographical sources**

<table>
<thead>
<tr>
<th>Geographical source</th>
<th>Indole Alkaloids</th>
<th>Oxindole Alkaloids</th>
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<tr>
<td></td>
<td>Leaves</td>
<td>Bark</td>
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<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Burma</td>
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<tr>
<td>Dihydrocosyrnantheine</td>
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<td>Geylon</td>
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<td>Bihar and Bengal</td>
<td>-</td>
<td>(Not examined) Mitra-phylline</td>
<td>(Not examined)</td>
<td>Uncarine F</td>
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<tr>
<td>Dehra- Dun</td>
<td>3-isoajamaline</td>
<td>-</td>
<td>Mitra-phylline</td>
<td>Isomitraphylline</td>
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<tr>
<td>Lucknow</td>
<td>-</td>
<td>-</td>
<td>Mitra-phylline</td>
<td>Isomitraphylline</td>
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</table>

Maharashtra Akuammigine - Pteropodine  Pteropodine

Isopteropodine  Isopteropodine

Specio-phylline  Specio-phylline

Uncarine F  Uncarine F
The literature survey revealed that the alkaloidal sequence in the leaves of *M. parvifolia* varies with the geographical source. The leaves obtained from Maharashtra and Uttar Pradesh have also been studied and it has been observed that the sequence of alkaloids differs. Since Madhya Pradesh is geographically situated between these two states, it would be of interest to study whether the alkaloidal sequence is identical or different from those of Maharashtra or Uttar Pradesh. Further, it would be of interest to study the alkaloidal N-oxides and their relationship with corresponding tertiary bases as the leaves of *M. parvifolia* have not been examined from this angle. These investigations may also throw some light on the biogenetic aspect of the alkaloids of *M. parvifolia*.

The plants of various species of *M. parvifolia* have not been described in detail in literature and there is atleast one reference where the identity of *M. rotundifolia* was confused with that of *M. parvifolia*. In view of this, it was proposed to study the anatomy of the leaves as well.

The investigations on the leaves of *M. parvifolia* were, therefore, carried out on the following lines:

1. Macroscopic and microscopic examination.
2. Proximate analysis.
(3) Successive solvent extraction and qualitative tests for plant constituents.

(4) Isolation and characterisation of alkaloids.

(5) Study of the alkaloidal pattern over a period of 12 months.

(6) Isolation and characterisation of alkaloidal N-oxides and their pattern.
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