PART-IV
Chemical Constituents of
Morinda citrifolia
Section 1: A brief review of phytochemicals reported from different *Morinda* species

The genus *Morinda* comprises about 80 species, distributed exclusively in tropical climate zones [1]. Most common species are: *M. citrifolia* L.; *M. coreia* Ham; *M. lucida* Benth; *M. morindoides* (Baker) Milne Redh; *M. tinctoria* Roxb.; *M. officinalis* How.; *M. elliptica* Ridl.; *M. angustifolia*; *M. parvifolia* and *M. umbellata* L. All these species have been used in traditional medicine for prevention and treatment of different diseases. Among them, *M. citrifolia* has a long tradition as a medicinal plant in India, Tropical Asia and the Pacific Islands. All the parts of the plant, *M. citrifolia* have folk uses including treatment of boils and cures, abscesses, inflammations of various origins, fungal infections, constipation, diabetes, gastric ulcers, intestinal worms, menstrual cramps, high blood pressure, and even cancers [2-4]. Noni juice, made from *M. citrifolia* fruits has become a popular tonic in recent years since it is reputed to be use for prevention of several life style related diseases, such as diabetes, hypertension and arteriosclerosis [5]. Products derived from the fruits of *Morinda citrifolia* (noni) have gained much popularity worldwide as food supplements for maintenance of good health and are nowadays available in health food stores and on the internet. The plant is widely cultivated in French Polynesia (Tahiti) and Hawaii to meet the huge need of the people.

Similarly, *M. morindoides* syn. *Gaertneria morindoides* Bak., commonly called Nkongabalulu, Kongobololo or Nkama mesu in the Democratic Republic of Congo, is a popular medicinal plant in Africa. A decoction of the leaves is used in treatment of various diseases including malaria, amoebiasis, haemorrhoids, intestinal worms, gonorrhoea and rheumatic pains [6].

*M. coreia* (Thai name: Yo-Paa) is grown is Thiland. The bark and wood of the plant are used as antifever, menstrual disorders and anti malarial agent in Thai (Isarn) traditional medicine [7].

*M. elliptica* (locally know as “Menkudu kecil” in Malaysia) is grown wild throughout Malay Peninsula. Traditionally different parts of the plant are used for different ailments including loss of appetite, headache, cholera, fever and
haemorrhoids. The pounded leaves are applied externally upon the spleen and wound and upon the body after childbirth [8].

*M. lucida* Benth is used as traditional medicine in the Gulf of Guinea for treatment of malarial fever [9].

The roots of *M. officinalis* are used in traditional medicine in North East Asia to treat impotence, menstrual diseases and inflammatory diseases such as rheumatoid arthritis and dermatitis over 2000 years [10].

Three review articles are available on noni (*M. citrifolia*) in respect to phytochemistry and pharmacology but detailed information on the chemical constituents of this plant was not provided [11–13]. The present investigator provided a list of chemical constituents isolated from different Morinda species in **Table 4.1** to highlight the type of chemical compounds present in them.
Table 4.1. List of phytochemicals reported from different *Morinda* species

<table>
<thead>
<tr>
<th>Str. No.</th>
<th>Name and Structure</th>
<th>Source</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>[A]</td>
<td><strong>Iridoids</strong></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>Asperulosidic acid</td>
<td><em>M. citrifolia</em></td>
<td>[14-17]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. citrifolia</em></td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. coreia</em></td>
<td>[19]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. elliptica</em></td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. officinalis</em></td>
<td>[21]</td>
</tr>
<tr>
<td>2</td>
<td>Deacetylasperulosidic acid</td>
<td><em>M. citrifolia</em></td>
<td>[16][22]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. officinalis</em></td>
<td>[21]</td>
</tr>
<tr>
<td>3</td>
<td>Asperuloside</td>
<td><em>M. citrifolia</em></td>
<td>[18]</td>
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<tr>
<td></td>
<td></td>
<td><em>M. coreia</em></td>
<td>[19]</td>
</tr>
<tr>
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<td><em>M. elliptica</em></td>
<td>[20]</td>
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<td></td>
<td></td>
<td><em>M. officinalis</em></td>
<td>[21]</td>
</tr>
<tr>
<td>4</td>
<td>Deacetylasperuloside</td>
<td><em>M. citrifolia</em></td>
<td>[23]</td>
</tr>
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<td></td>
<td></td>
<td><em>M. coreia</em></td>
<td>[19]</td>
</tr>
<tr>
<td>5</td>
<td>Aucubin</td>
<td><em>M. citrifolia</em></td>
<td>[24]</td>
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</table>
6  Scandoside methyl ester  \textit{M. citrifolia}  [22]

\begin{center}
\includegraphics[width=0.3\textwidth]{scandoside}
\end{center}

7  6-O-Acetylsandoside  \textit{M. coreia}  [19]

\begin{center}
\includegraphics[width=0.3\textwidth]{acetylsandoside}
\end{center}

8  9-\textit{epi}-6\textalpha-Methoxygeniposidic acid  \textit{M. citrifolia}  [22]

\begin{center}
\includegraphics[width=0.3\textwidth]{methoxygeniposidic}
\end{center}

9  Rhodolatouside  \textit{M. citrifolia}  [25]

\begin{center}
\includegraphics[width=0.3\textwidth]{rhodolatouside}
\end{center}

10  6\textalpha-Hydroxyadoxoside  \textit{M. citrifolia}  [23]

\begin{center}
\includegraphics[width=0.3\textwidth]{hydroxyadoxoside}
\end{center}
<table>
<thead>
<tr>
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<th>Species</th>
<th>Reference</th>
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<td>Yopaaoside C</td>
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<tr>
<td>12</td>
<td>6β, 7β-Epoxy-8-epi-splendoside</td>
<td><em>M. citrifolia</em></td>
<td>[23][26]</td>
</tr>
<tr>
<td>13</td>
<td>6-epi-Dihydrocornin</td>
<td><em>M. citrifolia</em></td>
<td>[23]</td>
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<tr>
<td>14</td>
<td>Loganic acid</td>
<td><em>M. citrifolia</em></td>
<td>[25]</td>
</tr>
<tr>
<td>15</td>
<td>Monotropein</td>
<td><em>M. officinalis</em></td>
<td>[21]</td>
</tr>
</tbody>
</table>

![Chemical Structures]

**Natural Products Chemistry**
16 10-O-Acetylmonotropein  
\[
\text{M. coreia} \quad [19]
\]

17 Citrifoside  
\[
\text{M. citrifolia} \quad [27]
\]

18 Morofficinaloside  
\[
\text{M. officinalis} \quad [21]
\]

19 Citrifolinin B (isolated as C-10 epimeric mixture, a & b, 5:4).  
\[
\text{M. citrifolia} \quad [23] \quad \text{M. citrifolia} \quad [28]
\]

20 Morindolide  
\[
\text{M. officinalis} \quad [21]
\]
<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
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<td>Umbellatolide A</td>
<td><em>M. umbellata</em></td>
<td>[29]</td>
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<tr>
<td>22</td>
<td>Umbellatolide B</td>
<td><em>M. umbellata</em></td>
<td>[29]</td>
</tr>
<tr>
<td>23</td>
<td>Tinctoroid</td>
<td><em>M. tinctoria</em></td>
<td>[30]</td>
</tr>
<tr>
<td>24</td>
<td>Iridoid derivative</td>
<td><em>M. citrifolia</em></td>
<td>[31]</td>
</tr>
<tr>
<td>25</td>
<td>Citrifolinoside A (=Yopaaoside B)</td>
<td><em>M. citrifolia</em></td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. coreia</em></td>
<td>[19]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. elliptica</em></td>
<td>[20]</td>
</tr>
</tbody>
</table>
Gaertneroside

\[ \text{M. morindoides} \quad [32][33] \]

6'-O-Acetylgaertneroside

\[ \text{M. morindoides} \quad [32][33] \]

3'-Methoxygaertneroside

\[ \text{M. morindoides} \quad [32,33] \]

6'-O-Acetyl-3'-methoxy gaertneroside.

\[ \text{M. morindoides} \quad [33] \]
30 Dehydrogaertneroside \[ M. morindoides \] [32]

31 Citrifolinin A (=Dehydromethoxy gaertneroside) \[ M. citrifolia \] [23]
\[ M. citrifolia \] [34][35]
\[ M. morindoides \] [32][33]

32 Morinipticoside \[ M. elliptica \] [20]

33 Gaertneric acid \[ M. morindoides \] [32]
34 6β,7β- Epoxygaertneroside  
\[ \text{M. morindoides} \quad [32] \]

35 6β,7β- Epoxy-3"-methoxy-gaertneroside  
\[ \text{M. morindoides} \quad [32] \]

36 Citrifolinoside  
\[ \text{M. citrifolia} \quad [35][36] \]
\[ \text{M. coreia} \quad [19][35] \]
\[ \text{M. elliptica} \quad [20] \]

37 Citrifolinin A-1  
\[ \text{M. citrifolia} \quad [37] \]
### Review on Different *Morinda* Species

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Species</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>Oruwacin</td>
<td><em>M. lucida</em></td>
<td>[38]</td>
</tr>
<tr>
<td>39</td>
<td>Secoxyloganin</td>
<td><em>M. coreia</em></td>
<td>[19]</td>
</tr>
<tr>
<td>40</td>
<td>Borreriagenin (=Morindacin)</td>
<td><em>M. citrifolia</em></td>
<td>[23,26,35]</td>
</tr>
<tr>
<td>41</td>
<td>4-epi-Borreriagenin</td>
<td><em>M. citrifolia</em></td>
<td>[16]</td>
</tr>
</tbody>
</table>

### Anthraquinonoids

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Species</th>
<th>References</th>
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<tr>
<td>42</td>
<td>Tectoquinone (=2-Methylantraquinone)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td><em>M. lucida</em></td>
<td>[40]</td>
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<tr>
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<td></td>
<td><em>M. officinalis</em></td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. umbellata</em></td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td>Compound</td>
<td>Species</td>
<td>References</td>
</tr>
<tr>
<td>---</td>
<td>----------------------------------------------</td>
<td>--------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>43</td>
<td>2-Formylanthraquinone</td>
<td><em>M. citrifolia</em></td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. lucida</em></td>
<td>[40]</td>
</tr>
<tr>
<td>44</td>
<td>1-Hydroxyanthraquinone</td>
<td><em>M. citrifolia</em></td>
<td>[42]</td>
</tr>
<tr>
<td>45</td>
<td>2-Hydroxyanthraquinone</td>
<td><em>M. umbellata</em></td>
<td>[41]</td>
</tr>
<tr>
<td>46</td>
<td>2-Hydroxymethyl anthraquinone</td>
<td><em>M. parvifolia</em></td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. citrifolia</em></td>
<td>[44]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. umbellata</em></td>
<td>[41]</td>
</tr>
<tr>
<td>47</td>
<td>1-Hydroxy-2-methylanthraquinone</td>
<td><em>M. citrifolia</em></td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. elliptica</em></td>
<td>[45]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. citrifolia</em></td>
<td>[44]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. lucida</em></td>
<td>[40]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. umbellata</em></td>
<td>[41]</td>
</tr>
<tr>
<td>48</td>
<td>2-Hydroxy-1-methoxyanthraquinone</td>
<td><em>M. officinalis</em></td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. citrifolia</em></td>
<td>[47]</td>
</tr>
<tr>
<td>No.</td>
<td>Compound</td>
<td>Species</td>
<td>Reference</td>
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<tr>
<td>-----</td>
<td>-----------------------------------------------</td>
<td>--------------------------</td>
<td>-----------</td>
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<tr>
<td>49</td>
<td>2-Methoxyanthraquinone</td>
<td><em>M. officinalis</em></td>
<td>[46]</td>
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<tr>
<td></td>
<td></td>
<td><em>M. umbellata</em></td>
<td>[41]</td>
</tr>
<tr>
<td>50</td>
<td>2-Formyl-1-hydroxyanthraquinone</td>
<td><em>M. citrifolia</em></td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. elliptica</em></td>
<td>[45]</td>
</tr>
<tr>
<td>51</td>
<td>1-Methoxy-2-methylantraquinone</td>
<td><em>M. umbellata</em></td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. lucida</em></td>
<td>[40]</td>
</tr>
<tr>
<td>52</td>
<td>Alizarin (=1,2-Dihydroxyanthraquinone)</td>
<td><em>M. citrifolia</em></td>
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<td></td>
<td></td>
<td><em>M. umbellata</em></td>
<td>[41]</td>
</tr>
<tr>
<td>53</td>
<td>Alizarin -2- methylether</td>
<td><em>M. umbellata</em></td>
<td>[41]</td>
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</tbody>
</table>
Review on Different *Morinda* Species

54 Alizarin-1-methylether

55 Rubiadin (=1,3-Dihydroxy-2-methylantraquinone)

56 Rubiadin 1-methylether

57 Damnacanthal (=3-Hydroxy -1-methoxy - 2-formylantraquinone)

58 Nordamnacanthal
59  Damnacanthol -3-O-β-D-primeveroside  
\[ \text{M. citrifolia} \]  
\[
\begin{array}{c}
\text{O} \\
\text{OMe} \\
\text{CH}_2\text{OH} \\
\text{O} \\
\text{O} \\
\text{Glc(6\epsilon-1)Xyl} \\
\end{array}
\]

60  Damnacanthol -15-O-β-D-primeveroside  
\[ \text{M. citrifolia} \]  
\[
\begin{array}{c}
\text{O} \\
\text{OMe} \\
\text{CH}_2\text{O}\text{Glc(6\epsilon-1)Xyl} \\
\text{OH} \\
\text{O} \\
\end{array}
\]

61  Digiferruginol (=1-Hydroxy-2-hydroxymethyl anthraquinone )  
\[ \text{M. parvifolia} \]  
\[
\begin{array}{c}
\text{O} \\
\text{OH} \\
\text{CH}_2\text{OH} \\
\text{O} \\
\text{O} \\
\end{array}
\]

\[ \text{M. citrifolia} \]  
\[
\begin{array}{c}
\text{O} \\
\text{OMe} \\
\text{CH}_2\text{O}\text{Glc(6\epsilon-1)Glc} \\
\text{O} \\
\text{O} \\
\end{array}
\]

63  Digiferruginol -15-O-β-primeveroside  
\[ \text{M. citrifolia} \]  
\[
\begin{array}{c}
\text{O} \\
\text{OMe} \\
\text{CH}_2\text{O}\text{Glc(6\epsilon-1)Xyl} \\
\text{O} \\
\text{O} \\
\end{array}
\]
64 1-Methyl-3-hydroxy anthraquinone  \( M. \) citrifolia  \[39\]

\[
\text{O} \quad \text{OH} \\
\text{O} \\
\text{O}
\]

65 1,3-Dihydroxyanthraquinone  \( M. \) umbellata  \[41\]
(\( = \) xanthopurpurin)

\[
\text{O} \quad \text{OH} \\
\text{O} \\
\text{O}
\]

66 1-Methoxy-3-hydroxy anthraquinone  \( M. \) citrifolia  \[39\]

\[
\text{O} \quad \text{OMe} \\
\text{O} \\
\text{O}
\]

67 1,3- Dimethoxyanthraquinone  \( M. \) citrifolia  \[56\]

\[
\text{O} \quad \text{OMe} \\
\text{O} \\
\text{O}
\]

68 Munjistin
(\( = \) 2-Carboxy-1,3-dihydroxyanthraquinone)  \( M. \) umbellata  \[41\]

\[
\text{O} \quad \text{OH} \quad \text{COOH} \\
\text{O} \\
\text{O}
\]
69 Morindaparvin A  
(=1,2-Methylenedioxy anthraquinone)  

\[ \text{M. parvifolia} \quad [49] \]

70 Anthragallol -2,3-dimethyl ether  

\[ \text{M. citrifolia} \quad [53] \]

71 Lucidin  
(= 1,3-Dihydroxy-2-hydroxy methylanthraquinone)  

\[ \text{M. citrifolia} \quad [50] \]  
\[ \text{M. umbellata} \quad [41] \]

72 Lucidin -3-methyl ether  

\[ \text{M. citrifolia} \quad [42] \]

73 Lucidin -\( \omega \)-methyl ether  

\[ \text{M. elliptica} \quad [45] \]  
\[ \text{M. officinalis} \quad [21] \]  
\[ \text{M. parvifolia} \quad [43] \]
Review on Different *Morinda* Species

74 Lucidin-\(\omega\)-butyl ether \(M.\) angustifolia [51]

\[
\begin{array}{c}
\text{O} \\
\text{OH} \text{CH}_2\text{OBu} \\
\text{O} \\
\end{array}
\]

75 Ibericin (= lucidin-\(\omega\)-ethyl ether) \(M.\) citrifolia [39], \(M.\) parvifolia [43], \(M.\) angustifolia [51]

\[
\begin{array}{c}
\text{O} \\
\text{OH} \text{CH}_2\text{OEt} \\
\text{O} \\
\end{array}
\]

76 Lucidin-1,3,\(\omega\)-trimethyl ether \(M.\) citrifolia [39]

\[
\begin{array}{c}
\text{O} \\
\text{OMe} \text{CH}_2\text{OMe} \\
\text{OMe} \\
\end{array}
\]

77 Lucidin-3-\(O\)-\(\beta\)-D- primeveroside \(M.\) citrifolia [54], \(M.\) citrifolia [50], \(M.\) coreia [19], \(M.\) angustifolia [51]

\[
\begin{array}{c}
\text{O} \\
\text{OH} \text{CH}_2\text{OH} \\
\text{O} \\
\text{OMe} \text{Glc(6\(\rightarrow\)1)Xyl} \\
\end{array}
\]

78 1,2-Dihydroxy-3-methyl anthraquinone \(M.\) officinalis [46]

\[
\begin{array}{c}
\text{O} \\
\text{OH} \text{OH} \\
\text{O} \\
\end{array}
\]

79 2-Hydroxymethyl-3-hydroxy anthraquinone \(M.\) officinalis [46]

\[
\begin{array}{c}
\text{O} \\
\text{CH}_2\text{OH} \\
\text{O} \\
\end{array}
\]
80  1,3-Dihydroxy-2-methoxyanthraquinone  
    (= anthragallol 2-methyl ether) 
    \[ M.\ citrifolia \]  
    [17,47]  

81  2-Hydroxy-3-hydroxymethylantraquinone  
    \[ M.\ citrifolia \]  
    [42]  

82  1-Hydroxy -2,3-dimethylantraquinone  
    \[ M.\ officinalis \]  
    [21]  

83  1-Hydroxy -3-hydroxymethylantraquinone  
    \[ M.\ officinalis \]  
    [21]  

84  1-Methoxy -2-primeverosyloxy methyl- 
    anthraquinone -3-olate  
    \[ M.\ citrifolia \]  
    [55]
<table>
<thead>
<tr>
<th>Page</th>
<th>Compound Description</th>
<th>Species</th>
<th>Reference(s)</th>
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<tbody>
<tr>
<td>85</td>
<td>1-Hydroxy-2-primeverosyloxy methylanthraquinone-3-olate</td>
<td><em>M. citrifolia</em></td>
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<td><img src="image1.png" alt="Chemical Structure" /></td>
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<td>86</td>
<td>Soranjidiol (=1,6-Dihydroxy-2-methylanthraquinone)</td>
<td><em>M. citrifolia</em></td>
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<tr>
<td></td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td><em>M. elliptica</em></td>
<td>[45]</td>
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<tr>
<td></td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td><em>M. lucida</em></td>
<td>[40]</td>
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<tr>
<td>87</td>
<td>1-Hydroxy-6-hydroxymethylanthraquinone</td>
<td><em>M. parvifolia</em></td>
<td>[43]</td>
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<tr>
<td></td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>(=Morindaparvin B)(= 1,5-Dihydroxy-2-hydroxymethylanthraquinone)</td>
<td><em>M. parvifolia</em></td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89</td>
<td>5,15-Di-O-methylmorindol</td>
<td><em>M. citrifolia</em></td>
<td>[17,26]</td>
</tr>
<tr>
<td></td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Natural Products Chemistry** 288
90  1,5,15-Tri-O-methylmorindol  \[M. citrifolia\] [17]  
\[M. citrifolia\] [27]  
\[M. citrifolia\] [25]  

91  Morindone (=1,5,6-Trihydroxy-2-methylanthraquinone)  \[M. citrifolia\] [53]  
\[M. citrifolia\] [52]  
\[M. citrifolia\] [50]  
\[M. elliptica\] [45]  
\[M. umbellata\] [57]  

92  Morindone -5-methyl ether  \[M. citrifolia\] [39]  
\[M. elliptica\] [45]  
\[M. citrifolia\] [47]  

93  Morindone 6-methylether  \[M. citrifolia\] [58]  

94  Morindone -6-O-gentiobioside  \[M. tinctoria\] [59,60]
Review on Different *Morinda* Species

95  3-Hydroxymorindone  

![Chemical structure of 3-Hydroxymorindone](image)

*M. citrifolia* [50]

96  Morindone -6-*O*-β-D-primeveroside  

![Chemical structure of Morindone -6-*O*-β-D-primeveroside](image)

*M. citrifolia* [54]  
*M. citrifolia* [50]  
*M. lucida* [61]  
*M. persicaefolia* [62]  
*M. tinctoria* var. tomentosa [63]

97  3-Hydroxymorindone -6-*O*-β-D-primeveroside  

![Chemical structure of 3-Hydroxymorindone -6-*O*-β-D-primeveroside](image)

*M. citrifolia* [50]

98  5,6-Dihydroxylucidin  

![Chemical structure of 5,6-Dihydroxylucidin](image)

*M. citrifolia* [50]

99  5,6-Dihydroxylucidin -3-*O*-β-D-primeveroside  

![Chemical structure of 5,6-Dihydroxylucidin -3-*O*-β-D-primeveroside](image)

*M. citrifolia* [50]
100  7-Hydroxy-8-methoxy -2-methylantraquinone  \( M. \text{citrifolia} \) [64]

101  1,4-Dihydroxy-2-methoxy -7- methylantraquinone  \( M. \text{citrifolia} \) [65]

102  2-Methyl-3,5,6-trihydroxy anthraquinone  \( M. \text{citrifolia} \) [50]

103  1,3,6-Trihydroxy-2- methylantraquinone  \( M. \text{citrifolia} \) [42]

104  1,3,8-Trihydroxy-2-methoxyanthraquinone  \( M. \text{officinalis} \) [46]
THESIS, PART-IV  
Review on Different *Morinda* Species

105  Anthragallol-1,3-dimethyl ether  
*M. citrifolia*  [26]

106  6-Hydroxyanthragallol 1,3-dimethyl ether  
*M. citrifolia*  [26]

107  2-Methoxy-1,3,6-trihydroxyanthraquinone  
*M. citrifolia*  [47]

108  1,6-Dihydroxy-5,15-dimethoxy anthraquinone  
*M. citrifolia*  [17,47,66]

109  8-Hydroxy-5-*O*-methyl- morindol  
*M. citrifolia*  [47]

110  1,8-Dihydroxy-2-hydroxymethyl-5-methoxyanthraquinone  
*M. citrifolia*  [47]
111 1,5,7-Trihydroxy-6-methoxy-6-methoxymethyl anthraquinone  
\[\text{M. citrifolia} \quad [66]\]

112 1,8-Dihydroxy-2-methyl-3,7-dimethoxyanthraquinone  
\[\text{M. angustifolia} \quad [51]\]

113 1,8-Dihydroxy-3-methyl-6-methoxyanthraquinone (=Physcion)  
\[\text{M. citrifolia} \quad [67] \\
\text{M. officinalis} \quad [46]\]

114 Physcion-8-\(O\) [\(\alpha\)-L-arabinopyranosyl (1→3)] \(\beta\)-D-galactopyranosyl (1→6) \(\beta\)-D-galactopyranoside  
\[\text{M. citrifolia} \quad [67]\]
115 2-Methyl-3,5,6-trihydroxyanthraquinone-6-O-β-D-primeveroside  
\( \text{M. citrifolia} \) [50]

![Diagram of 2-Methyl-3,5,6-trihydroxyanthraquinone-6-O-β-D-primeveroside]

116 6,8-Dimethoxy-3-methyl-anthraquinone-1-O-β-rhamnosyl-(1→4) β-D-glucopyranoside  
\( \text{M. citrifolia} \) [68]

![Diagram of 6,8-Dimethoxy-3-methyl-anthraquinone-1-O-β-rhamnosyl-(1→4) β-D-glucopyranoside]

117 1-Hydroxy-5,6-dimethoxy-2-methyl-7-primeverosyloxy anthraquinone  
\( \text{M. citrifolia} \) [55]

![Diagram of 1-Hydroxy-5,6-dimethoxy-2-methyl-7-primeverosyloxy anthraquinone]

118 Oruwal (= 9,10-Dimethoxy anthracene-2-aldehyde)  
\( \text{M. lucida} \) [40]

![Diagram of Oruwal (= 9,10-Dimethoxy anthracene-2-aldehyde)]

119 Oruwalol (= 5 or 8-Hydroxy-9,10-dimethoxyanthracene-2-aldehyde)  
\( \text{M. lucida} \) [40]

![Diagram of Oruwalol (= 5 or 8-Hydroxy-9,10-dimethoxyanthracene-2-aldehyde)]

R or R' = OH
Review on Different *Morinda* Species

120 Morindicione (=9-Hydroxy-2-methoxy-4-methyl-3,10-anthracenedione)  
*M. citrifolia*  [44]

[C] **Flavonoids**

121 Apigenin 7-*O*-glucopyranoside  
*M. morindoides*  [69]

122 Apigenin-5,7-dimethyl-4′-*O*-β-galactopyranoside  
*M. citrifolia*  [70]

123 Acacetin-7-*O*-β-D-glucopyranoside  
*M. citrifolia*  [70]

124 Luteolin  
*M. citrifolia*  [66]
Luteolin-7-O-β-D-glucopyranoside  
M. morindoides  [69]

Chrysoeriol-7-O-neohesperidoside  
M. morindoides  [69]

Kaempferol  
M. citrifolia  [71]

Kaempferol -3-O-rhamnoside  
M. morindoides  [69]

Nicotifloroside  
(M. citrifolia  [23]  
M. citrifolia  [23,28]  
M. morindoides  [47,69]  
M. tinctoria  [73])
130 Kaempferol 3-\( \text{O-}\beta \text{-D-glucopyranosyl} \ (1 \rightarrow 2) -\)
[\( \alpha \text{-L-rhamnopyranosyl} \)-(1\( \rightarrow \)6) \( \beta \text{-D-galactopyranoside} \)]

\[
\begin{align*}
&\text{HO} \quad \text{O}\nonumber \\
&\text{HO} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{HO} \quad \text{O}\nonumber \\
\end{align*}
\quad \text{Gal(2\( \rightarrow \)1)Glc}
\quad (1 \rightarrow 6)
\quad \text{Rha}

131 Quercetin

\[
\begin{align*}
&\text{HO} \quad \text{O}\nonumber \\
&\text{HO} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
&\text{OH} \quad \text{O}\nonumber \\
\end{align*}
\quad \text{OH}
\]

132 Quercetin-3-\( \text{O-}\beta \text{-D-glucopyranoside} \)

133 Quercetin-3-\( \text{O-}\text{rhamnoside} \)
134 Rutin (= Quercetin-3-O-rutinoside) 

\[
\text{OH} \quad \text{OH} \\
\text{OH} \quad \text{O} \\
\text{Glc(6\rightarrow1)Rha}
\]

*M. citrifolia* [28], *M. citrifolia* [15,17,25], *M. morindoides* [69], *M. tinctoria* [73]

135 Quercetin-3-0-β-D-glucopyranosyl(1→2)-[α-L-rhamnopyranosyl-(1→6)] β-D-galactopyranoside 

\[
\text{OH} \quad \text{OH} \\
\text{OH} \quad \text{O} \\
\text{Gal(2\rightarrow1)Glc(1\rightarrow6)Rha}
\]

*M. citrifolia* [28]

136 Quercetin 7,4'-dimethyl ether 

\[
\text{MeO} \\
\text{OH} \\
\text{OH} \\
\text{OMe}
\]

*M. morindoides* [69]

137 Narcissoside 

\[
\text{OH} \quad \text{OH} \\
\text{OH} \quad \text{O} \\
\text{Glc(6\rightarrow1)Rha}
\]

*M. citrifolia* [23]
[D] **Hemiterpenoids**

138 3-Methylbuten-1-ol  
\[\text{M. citrifolia} \quad [74]\]

139 1-O-(3'-Methylbut-3'-enyl)-\(\beta\)-D-glycopyranoside  
\[\text{M. citrifolia} \quad [16,17,22]\]

140 Nonioside A  
1-O-(3'-Methylbut-3'-enyl)-6-O-\(\beta\)-D-glycopyranosyl-\(\beta\)-D-glycopyranoside  
\[\text{M. citrifolia} \quad [17,22,75]\]

141 Nonioside K  
\[\text{M. citrifolia} \quad [22]\]

142 Nonioside L  
\[\text{M. citrifolia} \quad [22]\]

143 Nonioside M  
\[\text{M. citrifolia} \quad [22]\]

[E] **Fatty Acids and Their Saccharide Esters**

144 Caproic acid (= n-Hexanoic acid)  
\[\text{M. citrifolia} \quad [14,74]\]
145  Caprylic acid  (= n-Octanoic acid)  \[ M. citrifolia \] [14,74]

146  Methyl octanoate  \[ M. citrifolia \] [74]

147  \[ n-Decanoic\ acid \]  \[ M. citrifolia \] [74]

148  Palmitic acid  \[ M. citrifolia \] [76]

149  Hexacosanoic acid  \[ M. lucida \] [40]

150  \[ 1-\ Monopalmitin \]  \[ M. citrifolia \] [47]

151  Linoleic acid  \[ M. citrifolia \] [77]

152  Ricinoleic acid  \[ M. citrifolia \] [78]
153 13- Hydroxy-9,11,15-octadecatrienoic acid  
\( M. \text{ citrifolia} \)  [27]

154 Nonioside B  
\( M. \text{ citrifolia} \)  [15,17,22]

155 Nonioside C  
\( M. \text{ citrifolia} \)  [17,22,75]

156 Nonioside D  
\( M. \text{ citrifolia} \)  [17,22,75]

157 Nonioside E  
\( M. \text{ citrifolia} \)  [17,22]

158 Nonioside F  
\( M. \text{ citrifolia} \)  [79]

159 Nonioside G  
\( M. \text{ citrifolia} \)  [79]
Review on Different \textit{Morinda} Species

160 Nonioside H \hspace{1cm} \textit{M. citrifolia} [79]

\begin{center}
\begin{tikzpicture}
\node at (0,0) [anchor=center] {\includegraphics[width=0.2\textwidth]{nonioside_h.png}};
\end{tikzpicture}
\end{center}

161 Nonioside I \hspace{1cm} \textit{M. citrifolia} [17,22]

\begin{center}
\begin{tikzpicture}
\node at (0,0) [anchor=center] {\includegraphics[width=0.2\textwidth]{nonioside_i.png}};
\end{tikzpicture}
\end{center}

162 Nonioside J \hspace{1cm} \textit{M. citrifolia} [17,22]

\begin{center}
\begin{tikzpicture}
\node at (0,0) [anchor=center] {\includegraphics[width=0.2\textwidth]{nonioside_j.png}};
\end{tikzpicture}
\end{center}

163 Nonioside N \hspace{1cm} \textit{M. citrifolia} [22]

\begin{center}
\begin{tikzpicture}
\node at (0,0) [anchor=center] {\includegraphics[width=0.2\textwidth]{nonioside_n.png}};
\end{tikzpicture}
\end{center}

164 Nonioside O \hspace{1cm} \textit{M. citrifolia} [22]

\begin{center}
\begin{tikzpicture}
\node at (0,0) [anchor=center] {\includegraphics[width=0.2\textwidth]{nonioside_o.png}};
\end{tikzpicture}
\end{center}

165 \( (4R, 5S)-5\)-Hydroxyhexan-4-olide \hspace{1cm} \textit{M. officinalis} [21]

\begin{center}
\begin{tikzpicture}
\node at (0,0) [anchor=center] {\includegraphics[width=0.2\textwidth]{hydroxyhexan_4_olide.png}};
\end{tikzpicture}
\end{center}

[F] \textbf{Aliphatic Dicarboxylic Acids and Their Esters}

166 Succinic acid \hspace{1cm} \textit{M. citrifolia} [80]

\begin{center}
\begin{tikzpicture}
\node at (0,0) [anchor=center] {\includegraphics[width=0.2\textwidth]{succinic_acid.png}};
\end{tikzpicture}
\end{center}
167 1- n-Butyl-4-methyl-2-hydroxysuccinate \( M. \) citrifolia [16]

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{O} & \quad \text{O-nBu}
\end{align*}
\]

168 1- n-Butyl-4-methyl-3-hydroxysuccinate \( M. \) citrifolia [16]

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{O} & \quad \text{O-nBu}
\end{align*}
\]

169 1-n-Butyl-4-(5'-formyl-2'-furyl)-methylsuccinate \( M. \) citrifolia [16]

\[
\begin{align*}
\text{OHC} & \quad \text{O} \\
\text{O} & \quad \text{O-nBu}
\end{align*}
\]

170 4- Ethyl-2-hydroxysuccinate \( M. \) citrifolia [25]

\[
\begin{align*}
\text{EtO} & \quad \text{OH} \\
\text{O} & \quad \text{O}
\end{align*}
\]

171 Malic acid \( M. \) citrifolia [81]

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{O} & \quad \text{OH}
\end{align*}
\]

172 Malonic acid \( M. \) citrifolia [81]

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{O} & \quad \text{OH}
\end{align*}
\]

173 Fumaric acid \( M. \) citrifolia [81]

\[
\begin{align*}
\text{HOOC} & \quad \text{COOH}
\end{align*}
\]
**Lignans**

174 Decumbic acid

M. *citrifolia*  [39]

175 Americanol A

M. *citrifolia*  [82]

176 Americanin A

M. *citrifolia*  [23,25,66,82]

177 Americanoic acid A

M. *citrifolia*  [82]

178 Americanin D

M. *citrifolia*  [25,66]

179 Morindolin

M. *citrifolia*  [82]
Review on Different *Morinda* Species

180 Balonophonin  

181 (-) Pinoresinol  

182 (-) 3,3'-Bisdemethyl pinoresinol  

183 (-) 3,4,3',4'-Tetrahydroxy-9,7'-epoxylignano-7β,9'-lactone  

184 (+) 3,4,3',4'-Tetrahydroxy 9,7'-α-epoxylignano - 7α,9'-lactone  

185 Americanin
<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Name</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>186</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(7′E), (7R,8S)-3,4,9-Trihydroxy-4′,7-epoxy-8,3′-oxyneolignan-7′-en-8′-oic acid</td>
<td><em>M. citrifolia</em> [83]</td>
</tr>
<tr>
<td>187</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>Isoamericanoic acid A</td>
<td><em>M. citrifolia</em> [66]</td>
</tr>
<tr>
<td>188</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>(7R,8R)-3-Methoxy-1′-carboxy-4′,7-epoxy-8,3′-oxyneolignan-4,9-diol</td>
<td><em>M. citrifolia</em> [83]</td>
</tr>
<tr>
<td>189</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>(7R,8R)-3,4,9-Trihydroxy-4′,7-epoxy-8,3′-oxyneolignan-1′-al</td>
<td><em>M. citrifolia</em> [83]</td>
</tr>
<tr>
<td>190</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>(+) 3,3′-Bisdemethyltanegool</td>
<td><em>M. citrifolia</em> [71]</td>
</tr>
</tbody>
</table>
Review on Different *Morinda* Species

191 Trans-(3E)-3 (3,4-Dihydroxy benzylidene)-5-(3,4-dihydroxyphenyl)-4-(hydroxymethyl) dihydrofuran-2(3H)-one

\[
\text{HO} \quad \text{O} \quad \text{O} \\
\text{O} \quad \text{H} \\
\text{HO}
\]

*M. citrifolia* [83]

192 Isoprincepin

\[
\text{HO} \quad \text{O} \\
\text{O} \quad \text{H} \\
\text{HO}
\]

*M. citrifolia* [82]

[G] **Coumarins**

193 Scopoletin

\[
\text{MeO} \quad 8 \quad 5 \quad 8 \\
\text{HO} \quad 7 \quad 2 \quad 3
\]

*M. citrifolia* [16,25,47, 56,71]  
*M. officinalis* [46,74]

194 Isoscopoletin

\[
\text{HO} \\
\text{MeO}
\]

*M. citrifolia* [71,72]

195 Aesculetin

\[
\text{HO} \\
\text{HO}
\]

*M. citrifolia* [72]

196 Pteryxin

\[
\text{OAc}
\]

*M. citrifolia* [27]
197 Peucedanocoumarin III  

![Peucedanocoumarin III](image)

**M. citrifolia** [27]

[H] Phenolics

198 $p$ - Cresol  

![p-Cresol](image)

**M. citrifolia** [66]

199 $p$- Hydroxybenzaldehyde  

![p-Hydroxybenzaldehyde](image)

**M. citrifolia** [66]

200 $p$ - Hydroxybenzoic acid  

![p-Hydroxybenzoic acid](image)

**M. citrifolia** [66]

201 2,5-Dihydroxy-4-methoxy - benzaldehyde  

![2,5-Dihydroxy-4-methoxy - benzaldehyde](image)

**M. citrifolia** [66]

202 Vanillin  

![Vanillin](image)

**M. citrifolia** [66,71]

203 4-Hydroxy-3-methoxy cinnamaldehyde  

![4-Hydroxy-3-methoxy cinnamaldehyde](image)

**M. citrifolia** [47,66]
204  $\beta$-Hydroxypropiovanillone

$\text{HO-} \begin{array}{c} \text{CO-CH}_2\text{-CH}_2\text{-OH} \\ \text{MeO} \end{array}$

$M. \text{citrifolia}$ [47]

205  Morintrifolin A

$M. \text{citrifolia}$ [42]

206  Morintrifolin B

$M. \text{citrifolia}$ [42]

207  Nonin A

$M. \text{citrifolia}$ [39]

208  Nonin B

$M. \text{citrifolia}$ [39]

209  Nonin C

$M. \text{citrifolia}$ [39]
<table>
<thead>
<tr>
<th>Number</th>
<th>Compound Description</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>210</td>
<td>3,4,5-Trimethoxyphenyl-1-O-β-apiofuranosyl(1'→6')-β-glucopyranoside</td>
<td><em>M. coreia</em></td>
<td>[19]</td>
</tr>
<tr>
<td>211</td>
<td>Morinaphthalenone</td>
<td><em>M. citrifolia</em></td>
<td>[56]</td>
</tr>
<tr>
<td>112</td>
<td>Morinthone (= 4-Methoxy-3-heptadecylxanthone)</td>
<td><em>M. citrifolia</em></td>
<td>[44]</td>
</tr>
<tr>
<td>[I]</td>
<td><strong>Triterpenoids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>213</td>
<td>Ursolic acid</td>
<td><em>M. citrifolia</em></td>
<td>[84]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. lucida</em></td>
<td>[85]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. citrifolia</em></td>
<td>[25]</td>
</tr>
<tr>
<td>214</td>
<td>19α-Hydroxyursolic acid</td>
<td><em>M. citrifolia</em></td>
<td>[31]</td>
</tr>
</tbody>
</table>
215 Rotungenic acid  
*M. officinalis*  

![Rotungenic acid](image)

216 Barbinervic acid  
*M. citrifolia*  

![Barbinervic acid](image)

217 3-O-Acetylpomolic acid  
*M. citrifolia*  

![3-O-Acetylpomolic acid](image)

218 Clethric acid  
*M. citrifolia*  

![Clethric acid](image)
Oleanolic acid  
\[
\text{H} \quad \text{O} \quad \text{C} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{C} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\
\]

\(M. \text{citrifolia}\) \[27\]
\(M. \text{lucida}\) \[85\]

Hederagenin  
\[
\text{H} \quad \text{O} \quad \text{C} \quad \text{O} \quad \text{H} \quad \text{H} \\
\text{C} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\
\]

\(M. \text{citrifolia}\) \[27\]

Cycloartenol  
\[
\text{H} \quad \text{O} \\
\text{H} \quad \text{H} \quad \text{H} \\
\text{C} \quad \text{O} \\
\text{H} \quad \text{H} \\
\]

\(M. \text{citrifolia}\) \[86\]

\[J\] Steroids

\(\beta\)-Sitosterol  
\[
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\]

\(M. \text{citrifolia}\) \[47\]
\(M. \text{citrifolia}\) \[84,86\]
\(M. \text{officinalis}\) \[21,43\]
\(M. \text{officinalis}\) \[21\]
Pharmacological activities

Several pharmacological activities of crude extracts of different parts of *Morinda* species or on the isolated phytochemicals from the active fractions of these extracts have been reported. Most of these pharmacological activities are highlighted.

a) Anxiolytic and neuroprotective activity

The *n*-BuOH and H₂O soluble phases of MeOH extract of noni fruits showed 78 and 81% binding inhibition of [³H]-muscimol to the GABAₐ (gamma- amino butyric acid A) receptor at a concentration of 100 μg/ml with *IC₅₀* of 27.2 and 17.1 μg/ml, respectively. HPLC fingerprint of the MeOH extract revealed the presence of scopoletin (193), rutin (134) and quercetin (131) as major chemical constituents. Possibly these chemicals bind to the GABAₐ receptors and serve as agonists and induce anxiolytic and sedative effects [87].
The EtOAc extract of *M. citrifolia* fruits (EMC) (200, 400 mg/kg, p.o) exhibited neuroprotective effect on β-amyloid (25-35) peptide-induced cognitive dysfunction in mice by increasing the short-term and long-term memory (p< 0.05). The study on the effect of neurotransmitter enzymes indicated that at the higher dose (400 mg/kg) of EMC, a significant reduction in acetyl cholinesterase (p< 0.05) and monoamine oxidase A (p< 0.01) levels and increase in serotonin and dopamine levels (p< 0.01) was noticed. Moreover, the antioxidant enzymes such as superoxide dismutase, glutathione reductase, glutathione peroxidase were decreased significantly in the β - amyloid peptide injected group, whose levels were restored significantly (p< 0.01) by administration of EMC (400 mg/kg) [88].

b) *Anti-arteriosclerotic activity*

The MeOH extract of *M. citrifolia* fruits and its EtOAc soluble phase showed 88 and 96 % inhibition, respectively on copper induced LDL oxidation in TBARS assay model. Among the isolated chemicals from EtOAc soluble phase, six lignans showed inhibition in a dose-dependent manner. Among them, four compounds, 3,3'-bisdemethylpinoresinol (182), americanol A (175), morindolin (179), and isoprincepin (192) exhibited stronger inhibitory activity with IC$_{50}$ values of 1.057, 2.447, 2.020, and 1.362 μM, respectively, which were very similar to that of known oxidant, BHT (IC$_{50}$, 2.382 μM). The enhanced activity of these lignans was due to their number of phenolic hydroxyl groups. These observations suggest that noni fruits extract or its active compounds may be useful in prevention of life style related diseases such as diabetes, hypertension and cardiopathy and cerebral apoplexy caused by arteriosclerosis [82].

c) *Antibacterial, antifungal and antiviral activities*

Iridoids, aucubin (5) and L-asperuloside (3) and anthraquinone, alizarin (52) and other anthraquinones isolated from noni roots showed antibacterial activities against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli, Salmonella typhosa* and *Shigella paradys*. Possibly these
chemicals in noni roots are responsible for treatment of microorganism related skin infections and other diseases [24].

1,8-Dihydroxy-2-methyl-3,7-dimethoxy anthraquinone (112) from \textit{M. angustifolia} showed antimicrobial activity against \textit{Bacillus subtilis}, \textit{E.coli}, \textit{Micrococcus luteus}, \textit{Sarcina lutea}, \textit{Candida albicans} and \textit{Saccharomyces sake} [51].

An iridoid rich \textit{n}-BuOH soluble fraction of MeOH extract of noni (\textit{M. citrifolia}) fruits containing deacetyl asperulosidic acid (2) and asperulosidic acid (1) as major constituents in a ratio of 3.55 : 1, exhibited antimicrobial activity against \textit{Candida albicans}, \textit{E.coli} and \textit{S.aureus}. Of the three tested organisms, \textit{C. albicans} was most sensitive, at 0.82 mg of iridoids/ml, the cell growth was arrested. At the same concentration, most of \textit{E.coli} growth was suppressed, but complete cessation of growth was observed at concentration of 1.41 mg of iridoids/ml, while \textit{S.aureus} was less sensitive, a more linear response was found throughout the tested concentration of iridoid mixture [89].

The EtOH extract from \textit{M. citrifolia} leaves and its hexane fraction exhibited antitubercular activity against \textit{Micobacterium tuberculosis} H37Rv strain in radio respirometric assay with 89 and 95% inhibition, respectively. Among the isolated lipid constituents from hexane fraction only cycloartenol (221) showed significant inhibition with MIC of >64 \(\mu\)g/ml, respectively [86].

Damnacanthal (57) isolated from noni roots suppressed the cytopatic effect of HIV infected MT – 4, without inhibiting cell growth [90].

d) \textit{Anti-complementary activity}

Gaertnerside (26), acetylgaertnerside (27) and gaertneric acid (33), isolated from \textit{M. morindoides} leaves inhibited the activation of the classical pathway of the complement system with IC\(_{50}\) of 58 ± 6, 71 ± 6 and 69± 24 \(\mu\)M, respectively, compared to positive control, dextrane sulphate (IC\(_{50}\) ; 0.19± 0.05 nM ). These iridoids might be useful for treatment of rheumatic pains [32].

e) \textit{Antidiabetic and hypoglycemic activities}
The administration of the combined aqueous fruits extracts of *M. citrifolia* and *Coccinia indica* at a dose of 300 mg/kg/d, *p.o.* to alloxan induced diabetic rats for a period of 30 days, reverted the blood glucose level to normal level and significantly increased the plasma insulin level. This hypoglycemic effect was possibly due to lowering of gluconeogenic process by increasing the glucose transports and its uptake in peripheral tissues. The increase in plasma insulin was due to stimulation of the function of β-cells of islets of langerhans [91].

*n*-BuOH soluble phase of the MeOH extract of *M. citrifolia* roots showed significant reduction of blood sugar levels in streptozotocin (STZ) induced diabetic mice in a dose-dependent manner. The maximum response was obtained at 5 h after oral administration at a dose of 1.0 g/kg, which decreased for doses over 3.0 g/kg. Two iridoids and three anthraquinone glycosides were isolated from this bioactive *n*-BuOH soluble phase. Among these isolated phytochemicals, only two anthraquinone glycosides, damnacanthol-3-*O-β*-D-primeveroside (59) and lucidin-3-*O-β*-D-primeveroside (77) showed significant hypoglycemic effect in STZ-induced diabetic mice after a single administration of each compound (100 mg/kg, *p.o.*). These findings indicated that anthraquinones having no substituents on one aromatic ring seem to play key role in hypoglycemic effect [54].

The MeOH extract of *M. lucida* leaves showed significant hypoglycaemic effect in normal rats in a dose-dependent manner. Within 4 h after oral administration of the extract (400 mg/kg) lowered the plasma glucose level to 42.5±0.4 mg/100 ml, compared to control, 67.4±1.2 mg/100 ml. In streptozotocin treated hyperglycaemic rats the extract produced a significant (P< 0.05) antidiabetic effect from day 3 after oral administration (400 mg/kg) having plasma glucose level of 248.7±5.3 mg/100 ml, which was compared to glibenclamide (10 mg/kg) treated animals with a plasma glucose level of 251.5±5.8 mg/100 ml [92].

The oral administration of H2O and MeOH extracts (240 mg/kg/d, *p.o.*) of *M. lucida* stem-bark for 7 days showed significant antidiabetic effect in alloxan-induced hyperglycemic rats by reducing blood sugar level by 73.5 and 39.0%, respectively [93].

Episesamin 2,6-dicatechol (182), liroresinol B (224), liroresinol B dimethyl ether (225) and ursolic acid (213) isolated from *Morinda citrifolia*...
showed antidiabetic effect by showing inhibitory effects on PTP1B (Protein tyrosine phosphatase 1B) enzyme with IC$_{50}$ values of 21.86, 15.01, 16.82 and 4.12 µM, respectively. Furthermore, these compounds showed strong stimulating effects on 2NBDG uptake in 3T3-L1 adipocyte cells [83].

f) **Anthelmintic activity**

An ethanol extract of tender noni (M. citrifolia) leaves induced paralysis and death of human parasitic nematode, *Ascaris lumbricoides* [94].

g) **Anti-inflammatory, anti-nociceptive and analgesic activities**

Noni fruit juice at a dose of 10, 200 mg/kg, *p.o.* showed anti-inflammatory activity in carrageenan induced paw edema in rats. These doses were also effective in reducing the bradykinin-induced oedema in rat paw [95].

Monotropein 15 (20, 30 mg/kg/d, *p.o.*) isolated from *M. officinalis* roots exhibited antinociceptive activity by reducing significantly stretching episodes and prolonged action time in mice in acetic acid-induced writhing and hot plate assays. At the same doses, it also exhibited anti-inflammatory activity by reducing carrageenan-induced acute paw edema in rats [96].

Monotropein (15) also exhibited anti-inflammatory effect by inhibiting the expressions of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (cox-2), TNF-α and interleukin-1ß (IL-1ß) mRNA in LPS-induced RAW 264.7 macrophages. In dextran sulfate sodium (DSS)-induced colitis model in mice, it reduced disease activity index (DAI), myeloperoxidase (MPO) activity and inflammation related protein expressions by suppressing NF-κB activation in colon mucosa [97].

The CHCl$_3$ soluble phase (3 g/kg, *p.o.*) of MeOH extract of noni roots showed anti-nociceptive and anti-inflammatory activities by reducing pain related behavior observed in formalin test and histamine-induced paw edema in mice. Anthraquinone, damnacanthal (57) isolated from the CHCl$_3$ soluble phase showed both these activities at the doses of 10-100 mg/kg, *p.o.*[98]

Three Lignans 3,3′-bisdemethylpinoresinol (182), (+)3,3′-bisdemethyltanegool (190), and (+)-3,3′,4′-tetrahydroxy-9,7α-epoxylignano-7α,9′-lactone(184) and quercetin (131) isolated from *M. citrifolia* fruits showed strong anti-inflammatory effects by inhibiting 15- and 5- lipooxyxygenases
activities with $IC_{50}$ values of <1.0 and 0.79 to 9.2 μM, respectively. Quercetin showed also inhibition against COX-2 enzyme with $IC_{50}$ of 28.6 μM [71].

Saccharide fatty acid esters, noniosides B (154), C (155), D (156) and J (162) exhibited potent anti-inflammatory activity against TPA – induced inflammation (1 μg/ear) in mice with $ID_{50}$ values of 0.46 – 0.79 mg/ear. Their inhibitory activity was higher than that of quercetin ($ID_{50}$, 1.6 mg/ear) but less than that of indomethacin ($ID_{50}$, 0.30 mg/ear) [17].

Tahitian noni fruits juice (TNJ) exhibited antigout activity by inhibiting xanthine oxidase (XO) activity in a concentration-dependent manner. At the concentration of 1, 5 and 10 mg/ml, TNJ inhibited XO by 11, 113 and 148 %, respectively with an $IC_{50}$ of 3.8 mg compared with an $IC_{50}$ value of 2.4 μM for allopurinol. The MeOH extract of TNJ at the concentration of 0.1 mg/ml inhibited XO by 64% [99].

The aqueous extract of M. citrifolia roots did not exhibit any toxic effects but showed a significant dose-related central analgesic activity in the writhing and hot plate tests. This analgesic effect of the extract was confirmed by the antagonistic action of naloxone. This extract at higher doses also decreased behavioral parameters such as induced sleeping time and light/darkness time suggesting sedative properties [100].

h) **Antioxidant activity**

Neolignan, americanin A (176) and flavonol glycoside, narcissoside (137) isolated from M. citrifolia fruits showed potent antioxidant property in peroxy nitrite (ONOO −) assay with $IC_{50}$ value of 3.3 and 3.8 μM, respectively. The positive control, penicillamine had an $IC_{50}$ of 3.3 μM in the same assay. Americanin A (176) also showed moderate antioxidant activity in DPPH assay with an $IC_{50}$ value of 16.9 μM [23]

Iridoid glucoside, citrifolinin B (19) and flavonol glycosides, quercetin-3-$O$-$β$-D-glucopyranoside (132), quercetin-3-$O$-$α$-L-rhamnopyranosyl(1→6)-$β$-D-glucopyranoside (rutin) (134), quercetin-3-$O$-$β$-D-glucopyranosyl(1→2)[$α$-L-rhamnopyranosyl(1→6)]-$β$-D-galactopyranoside (135), kaempferol-3-$O$-$α$-L-rhamnopyranosyl(1→6)-$β$-D-glucopyranoside (nicotifloroside)(129) and
kaempferol-13-O-β-D-glucopyranosyl(1→2)-[α-L-rhamnopyranosyl(1→6)]-β-D-galactopyranoside (128) isolated from *M. citrifolia* leaves exhibited DPPH radical scavenging activity of 7.7, 85.5, 79.9, 81.3, 4.5 and 28.6 %, respectively at the concentration of 30 µM. The stronger antioxidant property of quercetin glycosides was due to presence of two ortho-hydroxyl groups in B ring of flavonol nucleus, which enhanced the stability of the radicals [28].

Anthraquinones, nordamnacanthal (58) and morindone (91) isolated from cell culture of *M. elliptica* showed stronger antioxidant activity in ferric thiocyanate assay than that of common antioxidant, α-tocopherol [101].

In DPPH assay only morindone exhibited significant radical scavenging activity with *IC*$_{50}$ of 40.6 µg/ml [101]

i) **Antiosteoporotic activity**
Rubiadin-1-methyl ether (56) and 2-hydroxy-1-methoxyanthraquinone (48), isolated from *M. officinalis* roots promoted osteoblast proliferation, while 1,2-dihydroxy-3-methylantraquinone (78) and 1,3,8-trihydroxy-2-methoxyanthraquinone (104) increased osteoblast ALP (alkaline phosphatase) activity. Physcion (113), rubiadin1-methylether (56), 2-hydroxy-1-methoxyanthraquinone (48), 1,2-dihydroxy-3-methyl anthraquinone (78), 1,3,8-trihydroxy-2-methoxyanthraquinone (104), 2-hydroxymethyl-3-hydroxyanthraquinone (79), 2-methoxyanthraquinone (49) and scopeletin (193) isolated from *M. officinalis* roots exhibited antiosteoporotic activity by inhibiting osteoclast TRAP (tartrate resistant acid phosphatase) activity and bone resorption at a concentration of 10$^{-6}$ M/l [46].

j) **Anti-protozoal activity**
Among the isolated iridoids from *M. morindoides* leaves, iridoids, 3″-methoxygaertneroside (28), gaertneroside (26), 6′-O-acetyl-3″-methoxygaertneroside (29) and 6′-O-acetylgaeartneroside (27) exhibited significant *in vitro* antimalarial activity against malaria parasite, *Plasmodium falciparum* with *IC*$_{50}$ of 0.04, 0.1, 0.8 and 4.1 µM, respectively. All these tested iridoids had little cytotoxicity (4.3–13.4 %) against human KB-3-1 cells. Hence either crude extract containing these iridoids or their mixture could be a potential antimalarial drug [33].
The EtOH, CH₂Cl₂ and petroleum ether extracts of *M. lucida* leaves exhibited *in vitro* antiplasmodial activity against a chloroquine-sensitive *Plasmodium falciparum* strain with IC₅₀ values of 5.7±1.3, 5.2±0.8 and 3.9±0.3 ml/ml, respectively. *In-vivo* an oral dose of 200 mg/kg, they produced about 62.5, 67.5 and 72.2 % reduction of parasitemia in mice infected with *Plasmodium berghei berghei*. Ursolic acid (213) and oleanolic acid (219) isolated from the petroleum ether extract of *M. lucida* leaves exhibited *in vitro* antiplasmodial activity against chloroquine sensitive *Plasmodium falciparum* strain with IC₅₀ value of 3.1±1.3 and 15.2±3.4 µg/ml, respectively. *In vivo*, at a daily dose of 200 mg/kg they produced 97.7 and 37.4 % chemosuppression, respectively in mice infected with *Plasmodium berghei* [85].

The 50% MeOH extract of *M. lucida* leaves significantly suppressed the level of parasitemia against *Trypanosoma brucei* infection in mice dose dependently with maximum effect at 1000 mg/kg, o.p. The best trypanocidal activity was found when the extract was treated simultaneously with trypanosome inoculation [102].

k) *Anti-thrombotic activity*

*M. citrifolia* fruit juice (5 and 10%) mixed with heparin showed anti-thrombotic effect on jugular vein thrombosis induced by FeCl₃ in SD rats. This antithrombotic effect is due to activation of activated partial thromboplastin time (a PTT) without inducing thrombocytopenia [103].

l) *Cytotoxic activity*

The MeOH extract of *M. citrifolia* fruits at a concentration of 0.1mg/ml exhibited cytotoxicity against MCF-7 (breast cancer) and LAN-5 (neuroblastoma) cells with 29 and 36% inhibition of cell proliferation, respectively. Whereas, at the same concentration had little toxicity to vero, BHK (baby hamster kidney) and Hep2 cells[104].

Noni juice at a concentration of 5% (v/v) strongly inhibited the initiation of new vessel sprouts from an angiogenic model of human placental vein explants. At the concentration of 10%, vessel degeneration and the apoptosis was observed within a few days of its application. This concentration was also effective in
inhibiting capillary initiation in explants and led to degeneration of vessels and disappearance of capillary sprouting [105].

A polysaccharide rich substance obtained as a ppt by addition of EtOH on noni fruit juice exhibited antitumor potential against the immunomodulator sensitive sarcoma 180 tumor system in allogenic mice with a cure rate of 25–45% and this activity was completely abolished by concomitant administration of specific inhibitors of macrophages, T and NK cells. This ppt also showed synergistic effect when combined with chemotherapeutic drugs namely cisplatin, adriamycin, mitomycin C, bleomycin, etoposide, 5-fluorouracil, vincristine or camptothecin [106].

Damnacanthal (57) isolated from the CHCl₃ extract of M. citrifolia roots inhibited tumor growth in k-ras transformed NRK cells but had no effect on the morphology of RSV- transformed NRK cells. It may be noted that the ras cells are the precursors of various human cancers including lung, colon, pancreas and leukaemia [107].

Pretreatment of human fibroblast UV-T-1 cells with damnacanthal (10.0 μg/ml) prior to ultraviolet irradiation stimulated the UV-induced apoptosis. Immunoblot analysis results indicated that pretreatment of damnacanthal increased phosphorylation of both extracellular signal regulated kinases (ERKs) and stress-activated protein kinases (SAPK/JNK). This concurrent increase of both phosphorylated ERKs and SAPK might be related to the stimulating effect on apoptosis [108].

Nonioside C (155) and asperulosidic acid (1) isolated from Hawaiian noni fruits exhibited antitumorigenic effect by suppressing TPA-or EGF (epidermal growth factor) induced cell transformation and associated AP-1 activation in mouse epidermal JB6 cell line. TPA- or EGF-induced phosphorylation of c-Jun, but not extra cellular signal regulated kinases (ERKs) or p38 kinases and hence c-Jun-N-terminal kinases(JNK) have critical role to induce AP -1 activity and subsequent cell transformation in JB6 cells [109].

Four anthraquinones, 1,2-dihydroxyanthraquinone (52) 1,3-dihydroxy-2-methylantraquinone (55), 2-hydroxyl 3-hydroxymethylantraquinone (81) and 1,3,6-trihydroxy-2-methylantraquinone (103) isolated from M. citrifolia roots
exhibited cytotoxicity against Hepa 1c17 cells by inducing significant quinone reductase (QR) activity with concentration required to double QR activity of 12.0, 8.1, 0.94 and 0.56 μM, respectively [42].

Anthraquinone, 1,5,15-tri-O-methylmorindol (90) and noniosides B,C and J isolated from *M. citrifolia* fruits exhibited moderate antitumorigenic activity against EBV-EA activation induced by TPA with IC$_{50}$ values of 386-578 M ratio/32 pM TPA [17].

Noni fruit juice (5% and 10% v/v) had preventive effect at the initiation stage of 7,12-dimethylbenz(a)-anthracene (DMBA)-induced mammary tumorigenesis in female SD rats by reducing the levels of DMBA-DNA adducts to about 30% in heart, 41% in lung, 42% in liver and 80% in kidney. The noni juice also showed this antitumor effect in male C57BL-6 mice [110].

Six anthraquinones, nordamnacanthal (58), alizarin-1-methylether (54), rubiadin (55) soranjidiol (86), lucidin-ω-methylether (73) and morindone (91) isolated from *M. elliptica* cell culture exhibited potent antitumor promoting activity at the concentration of 2 μg/ml when assayed against Epstein Barr Virus activated Raji cells. Among them, the activity of nordamnacanthal was more significant, at the concentration of 0.4 μg/ml showed 75% inhibition rate, which was stronger than that of reference compounds, genistein and quercetin [101].

1,5,15-Trimethylmorindol (90) isolated from *M. citrifolia* leaves at the concentration of 25 μg/ml did not show significant cytotoxicity on Jurkat cell, but when combined with TRAIL (0.5-1.5 μg/mL), it showed cytotoxicity with IC$_{50}$ of 14.5-15.0 μg/ml. It may be noted that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) selectively induces apoptosis of a wide variety of cancer and transformed cells without damaging most normal cells [27].

Citrifolinin A (31) isolated from *M. citrifolia* leaves displayed significant suppressing activity on UVB-induced AP-1 with IC$_{50}$ of 69.6 μM. The property of the iridoid may be useful for treatment of UV-irradiated skin cancer [34].

Another iridoid, citrifolinoside A (25) isolated from the leaves of the same plant also suppressed UVB-induced AP-1 activity with IC$_{50}$ of 29.0 μM [36]

Quinone derivatives, nonins B (208) and C (209) and anthraquinones, 2-formylanthraquinone (43), 1-hydroxy-2-methylantraquinone (47), damnacanthal
(57) and tectoquinone (42) isolated from noni roots showed significant cytotoxicity against H1299 and HCT116 cancer cells with \( IC_{50} \) values in the range of 4.3-32.8 \( \mu \)g/ml. Among them, 2-formylantraquinone exhibited highest inhibitory activity on H1299 and HT116 cells growth with \( IC_{50} \) value of 4.9±1.2 and 5.9±1.5 \( \mu \)g/mL, respectively [39].

2-Methoxy-1,3,6-trihydroxyanthraquinone (107) isolated from \( M. \) citrifolia fruits exhibited potent Quinone Reductase inducing activity against Hepa IcIc 7 murin hepatoma cells in MTT assay model. It was about 40 times more potent (CD is 0.009 \( \mu \)M/mL) than the positive control, L-sulforaphane (CD, 0.34 \( \mu \)M/ml). Moreover, this compound showed no discernible cytotoxicity at the highest dose tested [47].

Anthraquinones, morindaparvin B (88), lucidin-\( \omega \)-methylether (73), digiferruginol (61) and 2-hydroxymethylanthraquinone (46) isolated from \( M. \) parvifolia root and rhizome showed significant in vitro cytotoxicity against KB cells with \( ED_{50} \) of 4.0,0.62,0.09 and 2.6 \( \mu \)g/ml, respectively. 2-Hydroxymethylanthraquinone also showed significant activity (T/C = 150%) against in vivo growth of P-388 lymphocytic leukemia in mice at a dose of 10mg/kg/d [43].

Damnacanthal (57) and nordamnacanthal (58) isolated from \( M. \) elliptica roots exhibited in vitro cytotoxic effect against HL-60 cells with \( IC_{50} \) value of 4.0 and 20 \( \mu \)g/ml, respectively in MTT assay [111].

An oligosaccharide mixture extracted from \( M. \) officinalis fruits inhibited corticosterone (10 \( \mu \)M for 5d) induced apoptosis in PC 12 cells [112].

m) Hypolipidemic activity

Administration of noni seed oil in both normolipidemic and hyperlipidemic induced mice resulted reduction of total cholesterol and triglycerides levels in both models. Hypolipidemic effect was higher in hyperlipidemic-induced mice [113].

n) Immunomodulatory activity

The administration of a polysaccharide rich substance (obtained by precipitation of fresh noni fruit juice with 95% ethanol) (0.8 – 1.6 mg/mouse) significantly enhanced the duration of survival of inbred C57 BL/6 mice inoculated with Lewis
lung carcinoma (LLC) (2-4×10⁵ cells/mouse). The precipitate did not exert significantly cytotoxic effect in an adapted culture of LLC cells (LLC1), but indirectly exerted significant cytotoxic effect against LLC1 cells by eliciting the tumoricidal activity of peritoneal exudate cells (PEC). Concomitant treatment of immunosuppressive agent, 2-chloroadenosine or cyclosporine diminished this immunomodulatory activity [114].

o) **Liver protective activity**

Administration (p.o) of noni fruit juice 10% v/v in CCl₄-induced acute liver injured SD female rats resulted hepatoprotective effect by reducing the elevated levels of serum alanine amino-transferase and aspartate amino transferase compared to the placebo group [115].

p) **Melanogenesis inhibitory activity**

Three iridoids asperulosidic acid (1), scandoside methyl ester (6), 9-epi-6α-methoxygeniposidic acid (8), hemiterpene glycosides, noniosides K (141), L (142) and M (143) and saccharide fatty acid ester, nonioside O (164) isolated from noni fruits exhibited significant melanogenesis inhibitory effect with 34-49% reduction of melanin content in the B16 melanoma cells induced by α-MSH at 100 μM. All these compounds showed almost no toxicity to the cells at this concentration (100 μM). These compounds may be useful as depigmentation agent for skin whitening in the cosmetic industry [22].

q) **Tyrosine kinase inhibitory activity**

Damnacanthal (57) isolated from M. citrifolia roots was found to be potent and selective inhibitor of p56⁹ck tyrosine kinase with IC₅₀ value of 17nM. This property of damnacanthal may be useful for treatment of T-cell leukemia, lymphomas and autoimmune disease such as rheumatoid arthritis [116].

This activity of damnacanthal was due to release of intracellular Ca²⁺ stores and promoting Ca²⁺ entry in human dermal fibroblast [117].

r) **Wound-healing activity**

The study on the mechanism of in vivo wound healing process using fresh noni leaves juice on the PDGF and A₂₅ receptors indicated that in mice leaves juice at the concentration of 1 mg/ml displayed 166% binding inhibition of the ligand binding of the agonist [¹²⁵I] PDGF-BB to the PDGF receptors, while at the same
concentration, it had only 7% inhibition of the ligand binding to the A$_{2\text{A}}$ receptors. Whereas ethanol extract of noni leaves (NLEE) and its hexane (HF) and methanol fractions (MF) showed significant affinity to A$_{2\text{A}}$ receptors, concentration-dependently, with $IC_{50}$ values of 34.1, 42.9 and 86.7 µg/ml, respectively. These results suggest that noni leaf juice significantly accelerated wound healing in mice via its ligand binding to the PDGF and A$_{2\text{A}}$ receptors [118].

Administration of aqueous extract of *M. citrifolia* leaves (200 mg/kg) enhanced *wound healing* process by increasing wound contraction rate, tensile strength, granuloma breaking strength, collagen content and hydroxyproline content and decreasing epithelialisation period and blood melondialdehyde levels in rats in incision and excision wound models [119].

s) *Wrinkle inhibitory activity*

1,4-Dihydroxy-2-methoxy-7-methylantraquinone (101) isolated from *M. citrifolia* fruits exhibited significant wrinkle inhibitory activity by increasing elaboration of procollagen type 1C terminal peptide and glycosaminoglycans and reducing expression of the collagenase matrix metalloproteinase-1 dose-dependently in human dermal fibroblasts [65].
Section 2: A brief review of naturally occurring coumarins reported in the last five years

Coumarins are large class of phenolic substances and are made of fused benzene and α-pyrene rings. Structurally they are known as 2H-1-benzopyran-2-one (226). More than 1300 coumarins have been identified from plants, bacteria and fungi [120]. They are distributed over nearly 30 different plant families, of which a few important ones are Rubiaceae, Umbelliferae, Clusiaceae, Guttiferae, Oleaceae, Nyctaginaceae and Apiaceae.

Natural coumarins are broadly classified into seven types based on the chemical structures. Simple coumarins (226), furano coumarins (227), dihydrofurano coumarins (228), pyrano coumarins (229), aryl coumarins (230), bis coumarins (231) and prenylated coumarins (232) [121].

The therapeutic potential of natural coumarins depends upon the pattern of substitution. To highlight the substitution pattern of naturally occurring coumarins
a list of new naturally occurring coumarins reported during the last six years (2009-2014) is provided in Table 4.2.

**Table 4.2.** List of new naturally occurring coumarins reported during 2009-2014.

<table>
<thead>
<tr>
<th>Str. No.</th>
<th>Name and Structure</th>
<th>Source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>[A]</td>
<td>Simple coumarins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>223</td>
<td>8-Hydroxy-7-methoxy-6 (2R-hydroxy-3-methylbut-3-enox) 2H-1-benzopyran-2-one</td>
<td><em>Cedrelopsis rakotozafyi</em> (Rutaceae)</td>
<td>[122]</td>
</tr>
<tr>
<td>234</td>
<td>5-Hydroxy isomeranzin</td>
<td><em>Citrus grandis</em> (Rutaceae)</td>
<td>[123]</td>
</tr>
<tr>
<td>235</td>
<td>Isocopoletin 6-(6-O-β-apiofuranosyl-β-glucopyranoside)</td>
<td><em>Morus alba</em> (Moraceae)</td>
<td>[124]</td>
</tr>
<tr>
<td>236</td>
<td>Diosfeboside A</td>
<td><em>Diospyros crassiflora</em> (Ebenaceae)</td>
<td>[125]</td>
</tr>
</tbody>
</table>
237 Diosfeboside B

\[
\text{Diospyros crassiflora (Ebenaceae)} \quad [125]
\]

238 8 \((3-(2,4-\text{Benzenediol})-\text{propionic acid methyl ester})-\text{coumarin 7-}\beta-D-\text{glucoside}\)

\[
\text{Edgeworthia chrysantha (Thymelaceae)} \quad [126]
\]

239 Daphnecin

\[
\text{Daphne mucronata (Thymelaceae)} \quad [127]
\]

240 Eleutheroside B_2

\[
\text{Acanthopanax senticosus} \quad [128]
\]

241 Aesculetin 6-O-(6\text{'-galloyl})-\beta-D-galactopyranoside

\[
\text{Euphorbia soongarica (Euphorbiaceae)} \quad [129]
\]
THESIS, PART-IV

Review on New Natural Coumarins

242 Fraxetin-8-O-(6′-O-galloyl)-β-D-galactopyranoside

\[
\text{Euphorbia soongarica}
\]
(Euphorbiaceae)

243 4,6-Dihydroxy-7-formyl-3-methylcoumarin

\[
Pestalotiopsis vesicolor
\]
(Endophytic fungi)

244 Nitensoside A

\[
\text{Chimonanthus nitens}
\]
(Calycanthaceae)

245 Nitensoside B

\[
\text{Chimonanthus nitens}
\]
(Calycanthaceae)

246 3-Chloro-7-methoxy-4-methylchromen-2-one

\[
\text{Ficus krishnae}
\]

247 6-Hydroxy-7-methoxy-4-methylcoumarin

\[
\text{Ammi majus}
\]
(Apiaceae)

248 6-Hydroxy-7-methoxycoumarin

\[
\text{Ammi majus}
\]
(Apiaceae)

249 7-O-β-D-Glucopyranosyl-8-methoxycoumarin

\[
\text{Rhododendron lepidotum}
\]
(Ericaceae)
250. 7-Hydroxy-8- O-β-D-Glucopyranosyl coumarin

\[ \text{Rhododendron lepidotum} \] (Ericaceae)

251. Hydramicromelin D

\[ \text{Micromelum integerrimum} \] (Rutaceae)

252. 7-Hydroxy-4,8-dimethoxy-3,5-dimethyl coumarin

\[ \text{Sideritis pullulans} \] (Lamiaceae)

253. (+) Hopeyhopin

\[ \text{Citrus hystrix} \] (Rutaceae)

[B] Furano coumarins

254. Claucoumarin A

\[ \text{Clausena lansium} \] (Rutaceae)

255. Claucoumarin B

\[ \text{Clausena lansium} \] (Rutaceae)
256  Claucoumarin C  \(\text{Clausena lansium}\) (Rutaceae) [138]

257  Claucoumarin D  \(\text{Clausena lansium}\) (Rutaceae) [138]

258  5-Methoxychalepensin  \(\text{Dorstemia foetida}\) [139]

259  5-(2,3-Epoxy-3-methylbutoxy) chalepensin  \(\text{Dorstemia foetida}\) [139]

260  5-Methoxy-3-(3-methyl-2,3-dihydroxybutyl)-psoralen diacetate  \(\text{Dorstemia foetida}\) [139]

261  Psoroheraclin  \(\text{Heracleum pastinacifolium}\) (Apiaceae) [140]
[C] Dihydrofurocoumarins

262 \(3'\)-Isobutyryl-3'\)-hydroxymarmesin

\[\text{Opopanax hispidus} \quad [141]\]

(Umbelliferae)

[D] Pyrano coumarins

263 Hystrixarin

\[\text{Citrus hystrix} \quad [137]\]

(Rutaceae)

264 Glabranin

\[\text{Melicope glabra} \quad [142]\]

(Rutaceae)

265 \(\alpha\)-Hydroxytormentolide A

\[\text{Calophyllum apetalum} \quad [143]\]

(Guttiferae)

266 Anticarin B

\[\text{Antiaris toxicaria} \quad [144]\]

(Moraceae)
Prenylated Coumarins

267 Pedilanthocoumarin A

Pedilanthus tithymaloides
(Euphorbiaceae)

268 6-(4-Acetoxy-3-methyl-2-butenyl) 7-hydroxycoumarin

Aegle marmelos
(Rutaceae)

269 6-(2-Hydroxy-3-hydroxymethyl-3-butenyl)-7-hydroxycoumarin

Aegle marmelos
(Rutaceae)

270 Hoseimarin

Calophyllum hosei (Gultiferae)

271 7-Demethyl murralonginol isovalerate

Micromelum minutum
(Rutaceae)
272 Muralonginol  
\[ \text{Micromelum minutum} \]  
(Rutaceae)

273 Anticarin A  
\[ \text{Antiaris toxicaria} \]  
(Moraceae)

274 Mammeasin A  
\[ \text{Mammca siamensis} \]  
(Calophyllaceae)

275 Angepubebisin  
\[ \text{Angelica pubescens} \]  
(Umbelliferae)

276 Hydroxyosthole epoxide  
\[ \text{Cnidium monnieri} \]  

Mammeasin B

Mammca siamensis
(Calophyllaceae)

Geranyloxy coumarins

7-Geranyloxy-5-methoxycoumarin
Toddalia asiatica
(Rutaceae)

8-Geranyloxy-5,7-dimethoxycoumarin
Toddalia asiatica
(Rutaceae)

7 [(E) 3',7'-Dimethyl-6'-oxo-2'7'-octadienyl]-oxy coumarin
Zanthoxylum schinifolium
(Rutaceae)

Minutin A
Micromelum minutum
(Rutaceae)

Minutin B
Micromelum minutum
(Rutaceae)
283 5'-Methoxy auraptene

\[ \text{Zanthoxylum avicennae (Rutaceae)} \]

284 6,5'-Dimethoxyauraptene

\[ \text{Zanthoxylum avicennae (Rutaceae)} \]

285 5'-Methoxy collinin

\[ \text{Zanthoxylum avicennae (Rutaceae)} \]

286 7-((2'E,5'E)-7'-Methoxy-3'7'-dimethylocta-2'5'-dienyloxy) coumarin

\[ \text{Zanthoxylum avicennae (Rutaceae)} \]

287 6-Methoxy-((2'E,5'E)-7'-Methoxy-3'7'-dimethylocta-2'5'-dienyloxy) coumarin

\[ \text{Zanthoxylum avicennae (Rutaceae)} \]

288 (2'S,7'S)-O-2-Methylbutanoylecolumbianetin

\[ \text{Corydalis heterocarpa} \]

289 (2'S)-Columbianetin-3'-sulfate

\[ \text{Corydalis heterocarpa} \]
290  Integerrimelin  

```
     HO
    1'  2'' 3''
   /   /   /
  /    3'  H_n
 /      /
O      O
1''     4''
```

*Integerrimelin*  
*Micromelum integerrimum*  
(Rutaceae)  
[135]

291  Diversin  

```

```

*Diversin*  
*Ferula diversivittata*  
(Umbelliferae)  
[157]

292  Altissima coumarin G  

```

```

*Altissima coumarin G*  
*Ailanthus altissima*  
(Simaroubaceae)  
[158]

293  Pedilanthocoumarin B  

```

```

*Pedilanthocoumarin B*  
*Pedilanthus tithymaloides*  
(Euphorbiaceae)  
[145]
Pedilanthocoumarin C  
*Pedilanthus tithymaloides*  
(Euphorbiaceae)  

Cajunus lactone  
*Cajanus cajan*  
(Luguminaceae)  

7,4′-Dihydroxy-6,8-dimethoxy-4-phenylcoumarin  
*Calophyllum polyanthum*  
(Guttiferae)  

7-Hydroxy-6,8,4′-trimethoxy-4-phenylcoumarin  
*Calophyllum polyanthum*  
(Guttiferae)
298 2’-Hydroxy-5’-(7”-methoxy coumarin-6”-yl)-4’-methoxyphenyl propanoic acid

Hypericum riparium (Guttiferae)

[H] Bis coumarins
299 7,7’-Dihydroxy-6,6’-biscoumarin

Hypericum riparium (Guttiferae)

300 7,7’-Dihydroxy-8,8’-biscoumarin

Hypericum riparium (Guttiferae)

301 7-Methoxy-6,7’-dicoumarinyl ether

Hypericum riparium (Guttiferae)

[I] Miscellaneous coumarins
302 3 [[(3-Hydroxy-4-ethylpropanpicatephenyl) oxy]-6-methoxy-7-hydroxycoumarin

Daphne pedunculata (Thymelaceae)

303 Ferulone C

Ferula persica (Apiaceae)
304 Paniculacin

305 Goniothaline A

306 Goniothaline B

307 Flemicoumarin A

308 Loranthin

Murraya paniculata
(Rutaceae)

Goniothalamus australis

Goniothalamus australis

Flemingia philippinensis
(Leguminosae)

Plicosepalus acacia
(Loranthaceae)
Pharmacological activities

Coumarins exhibited different pharmacological activities. Some important of these activities are highlighted.

a) Anti-inflammatory activity

6-Hydroxy-7-methoxy-4-methyl coumarin (247) and 6-hydroxy-7-methoxy coumarin (248) isolated from Ammi majus aerial parts showed anti-inflammatory activity in carrageenan induced rat paw edema model with 37.81% and 36.80% inhibition of paw edema at the dose of 0.01 mg/100 g bw, which was comparable to that of positive control indomethacin (60.50% inhibition at 0.01 mg/100 g bw) [133].

Geranylated coumarins, mammeasins A (274) and B (277) isolated from Mammea siamensis flowers exhibited strong anti-inflammatory activity by inhibition of nitric oxide (No) production in LPS-activated RAW 264.7 cells with
IC₅₀ values of 1.8 and 6.4 μM, respectively [149]. Isoscopoletin 6-[(6-O-β-apiofuranosyl-β-glucopyranoside) (235) isolated from the stems of Morus alba showed anti-inflammatory activity by inhibiting NO production in lipopolysaccharide (LPS)-induced B7-2 microglial cells with IC₅₀ of 80.0 μM [124].

b) Cytotoxic activity

7-[(E)-3',7'-Dimethyl-6'-oxo-2',7'-octadienyl]-oxy coumarin (280) isolated from the leaves of Zanthoxylum schinifolium showed potent cytotoxic effect against Jurkat T cells in MTT assay with IC₅₀ value of 8.10 μM. Auraptene used as positive control showed IC₅₀ value of 55.36 μM [153].

Muralonginol (309) isolated from the fruits of Micromelum minutum exhibited cytotoxicity against cholangiocarcinoma (KKU-100), KB, NC1-H187 and breast cancer MCF-7 cells with IC₅₀ value of 10.0, 17.8, 27.1 and 8.2 μg/ml, respectively [148].

Preynlated coumarin, diversin (291) isolated from Ferula diversivittata roots exhibited strong cytotoxic effect in in vitro Epstein-Barr-virus early antigen (EBr-EA) assay with IC₅₀ value of 7.7 nM. It also exhibited cytotoxicity in in vivo mouse skin papillomas formation in 7,12-dimethylbenz[a]anthracene (DMBA)-12-O-tetradecanoyl phorbol-13-acetate (TPA) induced mouse skin carcinogenesis assay [157].

(2'S)-Columbianetin-3'-sulfate (289) isolated from Corydalis heterocarpa whole plants showed potent anti-proliferative activity against AGS, HT-1080 and MCF-7 cancer cells with IC₅₀ of 42.7, 35.2 and 50.8 μM, respectively. The study of mechanism of apoptosis indicated that the compound produced inhibitory effect against the cancer cells by induction of apoptosis through activation of Bax, p53 and p21 expressions [156].

Toddaculin (310) isolated from Toddalia asiatica stem bark showed potent anti-leukemic activity against U-937 leukemic cells with IC₅₀ and CC₅₀ values of 51.38 and 138.90 μM, respectively. The study of the expression of apoptosis revealed that at 250 μM, it induced apoptosis by decreasing phosphorylation levels of EKR and AKt, but at 50μM, it induced apoptosis by reducing NBT and...
expression of differentiation markers CD88 and CD11b but no change of p-AKT and p-ERK levels [168].

c) **Antioxidant activity**

Flavanocoumarin, loranthin (308) isolated from *Plicosepalus acacia* whole plant exhibited antioxidant activity in DPPH assay with 38.4% inhibition of free radical [167].

Glabranin (264), umbelliferone (311) and scopoletin (312) isolated from *Melicope glabra* bark showed significant DPPH free radical scavenging activity with IC$_{50}$ of 240.20, 810.02 and 413.19 µg/mL, respectively [142].

d) **Antileishmanial activity**

Monoterpene coumarins, minutins A (281) and B (282) isolated from *Micromelum minutum* leaves exhibited leishmanicidal activity against *Leishmania major* with IC$_{50}$ values of 26.2 and 20.2 µM, respectively [154].

e) **Antibacterial activity**

Cajanuslactone (295) isolated from pigeon pea (*Cajanus cajan*) leaves showed potent antibacterial activity against *Staphylococcus aureus* (ATCC6538) with MIC and MBC values of 0.031 and 0.125 mg/mL, respectively [159]. 5,6,7-Trimethoxy coumarin (313) and scopoletin (312) isolated from *Chimonanthus nitens* showed moderate antibacterial activity against *Micrococcus luteus* [131].

f) **Neuroprotective activity**

Claucomarain D (257) isolated from *Clausena lansium* stems exhibited neuroprotective effect on PC-12 cells induced by serum deprivation, Ap$_{25-35}$ and sodium nitroprusside with cell survival rate of 67.3 and 80.2%, respectively at 10µM concentration [138].

g) **Cell protective activity**

4-Aryl coumarins, 7,4'-dihydroxy-6,8-dimethoxy-4-phenylcoumarin (296) and 7-hydroxy-6,8,4'-trimethoxy-4-phenylcoumarin (297) isolated from the seeds of *Calophyllum polyanthum* exhibited cell protective activity against H$_2$O$_2$-induced human umbilical vein endothelial cell (HUVEC) damage with cell survival rate of 102% at the tested concentration of 1X10$^{-5}$ mol/L [160].
Section 3: A brief history, taxonomical description and classification of Morinda citrifolia

_Morinda citrifolia_ L. (Rubiaceae), known as “Noni”, is widely distributed in India, tropical Asia, and the Pacific Islands. Almost all parts of this plant including fruits, flowers, leaves, bark, stem and roots have been used as food, medicine and fabric dyes for more than 2000 years by the Polynesian people [169]. The plant has displayed a wide range of pharmacological properties including antibacterial, antifungal, antiviral, antitumor, anthelmintic, analgesic, hypotensive, anti-inflammatory and immuno-enhancing activities [170]. More than 150 phytochemicals have been identified from this plant, including anthraquinones, flavonoids, iridoids, lignans and triterpenoids as predominant groups [47].

Taxonomically, _M. citrifolia_ is climbing shrubs with opposite leaves, axillary inflorescence, hemispheric calyx tube, funnel shaped corolla tube, 4-5 lobes, valvate in bud. The fruits have many 4 sided pyramidal sections each with 4 cartilaginous or bony pyrenes, pyrenes often with an empty ventral cavity; seeds ovoid (Plate 4.1) [171].

Taxonomically, the plant was classified as per Bentham and Hooker system [172,173]:

- **Phylum**: Magnoliophyta
- **Class**: Dicotyledons
- **Order**: Rubiales
- **Family**: Rubiaceae
- **Genus**: Morinda
- **Species**: Morinda citrifolia
Plate 4.1. Photographs of *Morinda citrifolia*
Section 4: Isolation, Structure elucidation and pro-protein convertase enzyme inhibitory activity of scopoletin

Isolation:
Scopoletin (312) was isolated from the CH$_2$Cl$_2$ soluble extract of methanolic extract of Morinda citrifolia ripe fruits by silica gel column chromatography in yellow needle like crystals, mp 208-210°C. It was homogeneous in TLC in different solvent systems [silica gel G, R$_f$ 0.45 in Pet-EtOAc = 2:1]

Structure elucidation:

a) Molecular formula
The molecular formula of the compound was assigned as C$_{10}$H$_8$O$_4$ from its quasi-molecular ions at m/z 193.0504 [M+H]$^+$ (Calcd for C$_{10}$H$_8$O$_4$: 193.0501) in HR-FAB-MS and analysis of $^{13}$C-DEPT NMR data.

b) The IR spectrum
The IR spectrum of the compound in KBr (Fig. 4.1) showed absorption bands for hydroxyl (3341 cm$^{-1}$), lactone carbonyl (1708 cm$^{-1}$) and aromatic 1618, 1607 and 1568 cm$^{-1}$) functions.

c) The $^1$H-NMR spectrum
The 600 MHz $^1$H-NMR spectrum of the compound (Fig. 4.2) (Table 4.3) in DMSO-d$_6$ showed the signals of a paired of ortho-coupled olefinic protons [$^\delta$H 6.21 and 7.91 (each 1H, d, J=9.6 Hz)], two aromatic protons [$^\delta$H 6.78 and 7.22 (each 1H, s)], one aromatic methoxyl [$^\delta$H 3.81 (3H, s)] and one phenolic hydroxyl proton [$^\delta$H 10.31 (1H, s)], suggesting its 6,7-dioxygenated coumarin structure [174]. In NOE experiment, the irradiation of aromatic proton signal at $^\delta$H 6.78 resulted the enhancement of methoxyl signal ($^\delta$H 7.91). It suggested the location of methoxyl group at C-6 position (Fig. 4.3).

d) The $^{13}$C-NMR spectrum
The 150 MHz $^{13}$C-NMR spectrum of the compound (Fig. 4.4) (Table 4.3) in DMSO-d$_6$ recorded 10 carbon signals which on DEPT experiment showed for 1 methyl, 4 methine and 5 quaternary carbons. The chemical shift values of carbons could be assigned well by considering its coumarin structure [175].
Table 4.3. $^1$H- and $^{13}$C-NMR spectral data$^a$ for compound 312 (in DMSO-$d_6$, δ, ppm)

<table>
<thead>
<tr>
<th>H/C Position</th>
<th>$\delta_H$</th>
<th>$\delta_C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-</td>
<td>160.7 (C)</td>
</tr>
<tr>
<td>3</td>
<td>6.21 d (9.6)</td>
<td>111.7 (CH)</td>
</tr>
<tr>
<td>4</td>
<td>7.91 d (9.6)</td>
<td>144.5 (CH)</td>
</tr>
<tr>
<td>5</td>
<td>6.78 s</td>
<td>102.8 (CH)</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>145.2 (C)</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>151.1 (C)</td>
</tr>
<tr>
<td>8</td>
<td>7.22 s</td>
<td>109.6 (CH)</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>149.5 (C)</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>110.5 (C)</td>
</tr>
<tr>
<td>6-OMe</td>
<td>3.81 s</td>
<td>56.0 (CH$_3$)</td>
</tr>
<tr>
<td>7-OH</td>
<td>10.31 s</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$600 MHz for $^1$H- and 150 MHz for $^{13}$C-NMR; Assignments based on HSQC, HMBC and DEPT experiments.

e) The FAB-MS
The FAB-MS of the compound (Fig. 4.5) showed mass ions at $m/z$ 193 [M+H]$^+$, 164 [M-28]$^+$, 136 and 107. The genesis of these mass ions could be rationalized by considering its coumarin structure having a methoxyl and a hydroxyl group in the aromatic ring (Scheme 4.1) [176].

f) Conclusion
The spectral data of the compound were very similar to those reported for scopoletin [175]. Therefore, the structure of the compound was elucidated as scopoletin or 7-hydroxy-6-methoxycoumarin (312) (Fig. 4.3). It is a known natural product.
Scheme 4.1. FAB mass fragmentation of scopoletin (312).

Fig. 4.3. Structure of scopoletin and its selected NOE interactions.
Fig. 4.1. IR spectrum of scopoletin (312) in KBr.
Fig. 4.2. 1H-NMR spectrum of scopoletin (312) in DMSO-$_d_6$. 
Fig. 4.2a. $^1$H-NMR spectrum (expanded) of scopoletin (312) in DMSO-$d_6$
Fig. 4.4. $^{13}$C-NMR spectrum of scopoletin (312) in DMSO-$d_6$. 
Fig. 4.4a. $^{13}$C-DEPT NMR spectra of secoptolin (312) in DMSO-$d_6$. 
Isolation and Structure Elucidation

Fig. 4.5. FAB-MS of secopeptin (312).
Pro-protein Convertase Enzymes inhibitory activity of scopoletin

Pro-protein Convertase (PCs) also known as PCSKs are the members of Ca\(^{2+}\)-dependent serin endoproteases that are responsible for the conversion of inactive precursor proteins into functionally active forms by the cleavage of endopeptide bonds at the selected sites. Among them, furin enzyme is the key member and is involved in the growth of cancer, viral and bacterial infections in our body by conversion of inactive protein molecules of bacterial and viral cells into active forms. Hence, discovery of potent antifurin drugs might be useful to combat such diseases. Earlier works in this area revealed that 4-hydroxy coumarin (314) and its two derivatives (compounds 315 and 316) have been shown to inhibit PCSK activity [177]. This fact prompted us to evaluate the anti-furin activity of scopoletin (named MCD-1) using the substrate BOC-RVRR-MCA (where BOC = tert-butyloxy carbonyl, MCA = 4-methylcoumarin 7-amide, R = arginine and V = valine) in fluorimetric assay. Our results indicated that scopoletin (312) strongly inhibited the activity of furin with a measured inhibition constant Ki value of \(~7\ \mu\text{M}\), determined by both stop time and progress (on line) curve using Cornish-Bowden plot with three different substrate concentration (Fig. 4.6) [178,179].

![Fig. 4.6 Cornish-Bowden plot showing inhibition of furin activity by MCD-1 (scopoletin) as measured with three different concentrations of substrate Boc-RVRR-MCA.](image-url)
The graph suggested both competitive and reversible nature of inhibition. Scopoletin displayed IC$_{50}$ values of furin inhibition that depend on the concentration of the substrate used. All the IC$_{50}$ values were determined by using sigmoidal graph plotting the fluorescence release/hour considered as the velocity of reaction against the logarithm of concentration of the inhibitor (scopoletin) as shown in Fig. 4.7 using the measured IC$_{50}$ values for various substrate concentration and Cheng-Prusoff equation (Ki = IC$_{50}$/([S]/Km), where IC$_{50}$ = half maximal inhibitory concentration, Km = Michaelis-Menten constant, S = substrate concentration, Ki = inhibition constant) for true competitive inhibition.

![Fig. 4.7](image)

**Fig. 4.7.** Determination of IC$_{50}$ values for inhibition of furin activity by MCD-1 (scopoletin) using three different concentrations of substrate Boc-RVRR-MCA.

We calculated the Ki value as ~4.8 μM, which was found to be in good agreement with the measured value of 7.5 μM (Table 4.4) [180].
Table 4.4. Comparison of $K_i$ values for inhibition of furin activity by Scopoletin (312) using Boc-RVRR-MCA as substrate as determined by Cornish-Bowden plot and calculated from measured IC$_{50}$ values and $K_m$ of furin

<table>
<thead>
<tr>
<th>Substrate concentration (µM)</th>
<th>IC$_{50}$ value (µM)</th>
<th>$K_m$ value of furin (µM)</th>
<th>Calculated $K_i$ value (µM) Based on Chang-Prusoff Equation</th>
<th>Average $K_i$ (µM) from Cornish Bowden Plot</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>4.2</td>
<td>15.5</td>
<td>1.6</td>
<td>4.8</td>
</tr>
<tr>
<td>40</td>
<td>6.6</td>
<td>3.7</td>
<td></td>
<td>7.5</td>
</tr>
<tr>
<td>20</td>
<td>11</td>
<td>9.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Michaelis-Menten constant $K_m$ of furin used in the above equation was determined by Michaelis-Menten graph (Fig. 4.8).

Fig. 4.8. Progress curve assay showing inhibition of furin activity by MCD-1 (scopoletin) using Boc-RVRR-MCA as substrate (50 mM) concentration. (B) Michaelis-Menten curve showing the release of fluorescence upon cleavage by furin of various concentrations of fluorogenic substrate Boc-RVRRMCA.
We also evaluated the activity of MCD-1 against other PCSK enzymes and found that IC$_{50}$ values were above 100 μM (Table 4.5).

**Table 4.5.** Measured IC$_{50}$ values for inhibition of various PCSK enzymes by scopoletin

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>ENZYME</th>
<th>SUBSTRATE USED</th>
<th>IC$_{50}$ VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopoletin</td>
<td>Furin (PCSK3)</td>
<td>Boc-RVRR-MCA</td>
<td>5 μM (60 μM substrate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 μM (40 μM substrate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 μM (20 μM substrate)</td>
</tr>
<tr>
<td>PCSK4</td>
<td></td>
<td>pEERTKR-MCA</td>
<td>&gt;100 μM</td>
</tr>
<tr>
<td>PCSK7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SKI-1 (PCSK8)</td>
<td></td>
<td>Q-SKI$_{132-142}$</td>
<td></td>
</tr>
</tbody>
</table>

Overall our results indicated that scopoletin or MCD-1 (312) could be a potent furin inhibitor and might be a useful candidate for treatment of cancer, and bacterial and viral infections.

![Chemical structures](image-url)
Section 5: Isolation and structure elucidation of quercetin-3-O-rutinoside (135)

Isolation:
Quercetin-3-O-rutinoside (135) was isolated from the butanol soluble fraction extract of methanolic extract of Morinda citrifolia leaves by successive column chromatography through Diaion HP-20 and silica gel in yellow amorphous solid. It was homogeneous in TLC in different solvent systems [Silica gel G, Rf: .05 in CHCl3-MeOH = 5:1]

Structure elucidation:

a) The molecular formula
The molecular formula of the compound was determined as C27H30O16 from its quasi-molecular mass ions at m/z 611.1610 [M+H]+ (Calcd for C27H30O16: 611.1612) and m/z 633.1430 [M+Na]+ (Calcd for C27H30O16.Na: 633.1432) in HR-ESI-MS and analysis of 13C-/DEPT NMR data.

b) The UV spectrum
The UV-Vis spectrum of the compound in MeOH (Fig. 4.9) showed absorption maxima at λmax 260, 300 sh and 358 nm, characteristic of flavonols [18].

c) The IR spectrum
The IR spectrum of the compound in KBr (Fig. 4.10) showed the bands for hydroxyl (3360 cm⁻¹), α,β-unsaturated carbonyl (1650 cm⁻¹) and glycosidic (1260 cm⁻¹) functions.

d) The 1H-NMR spectrum
The 600 MHz 1H-NMR spectrum of the compound in DMSO-d6 (Fig. 4.11) (Table 4.6) showed signals for two meta-coupled aromatic protons [δH 6.19 and 6.38 (each 1H, d, J=1.8 Hz)], three aromatic protons as an ABX spin system [δH 7.54 (1H, d, J=1.8 Hz), 7.52 (1H, dd, J=8.4 and 1.8 Hz) and 6.83 (1H, d, J=8.4 Hz)] and two anomic sugar protons [δH 5.34 (1H, d, J=7.2 Hz) and 4.38 (1H, brs) suggesting its quercetin glycoside like structure having two sugar units [182]. The presence of methyl signal [δH 0.98 (3H, d, J=6.6 Hz)] indicated that one of the sugar moieties was a rhamnose unit.
THESIS, PART-IV  
Isolation and Structure Elucidation

e) The $^{13}$C-NMR spectrum

The 150 MHz $^{13}$C-NMR spectrum of the compound in DMSO-$d_6$ (Fig. 4.12) (Table 4.6) recorded 27 carbon signals, which on DEPT experiments revealed for 1 methyl, 1 methylene, 15 methine and 10 quaternary carbons. The five aromatic methine carbon signals at $\delta_C$ 93.7, 98.8, 115.3, 116.3 and 121.7 coupled with four quaternary carbon signals at $\delta_C$ 133.3, 161.2, 164.2 and 177.4 suggested its quercetin like skeletal structure [183]. Two anomeric carbon signals at $\delta_C$ 100.8 and 101.2 along with eight methine carbon signals in the range $\delta_C$ 68.3-76.5, one methylene carbon and one methyl carbon signals at $\delta_C$ 67.1 and 17.8, respectively suggested the presence of a rutinosyl moiety in the compound [183].

f) The ESI-TOF-MS

The ESI-MS of the compound (Fig. 4.13) showed mass ions at $m/z$ 633 [M+Na]$^+$, 611 [M+H]$^+$, 301, 465[MH-147+H]$^+$ and 301 supporting the quercetinrutinoside structure.

g) Conclusion

The spectral data of the compound were very similar to those reported for quercetin-3-O-rutinosid (= rutin) [183,184]. On the basis of these evidences, the structure of the compound was assigned as quercetin-3-O-rutinoside or rutin (135) (Fig. 4.14). It is a known natural product.

![Fig. 4.14. Structure of quercetin 3-O-rutinoside (135)](image-url)
Table 4.6. \(^1\)H- and \(^{13}\)C-NMR spectral data\(^a\) for compound 135 (in DMSO-\(d_6\), \(\delta\), ppm)

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<thead>
<tr>
<th>H/C Position</th>
<th>(\delta_H)</th>
<th>(\delta_C)</th>
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<tr>
<td>2</td>
<td>-</td>
<td>156.7 (C)</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>133.3 (C)</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>177.4 (C)</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>161.2 (C)</td>
</tr>
<tr>
<td>6</td>
<td>6.19 d (1.8)</td>
<td>98.8 (CH)</td>
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<tr>
<td>7</td>
<td>-</td>
<td>164.2 (C)</td>
</tr>
<tr>
<td>8</td>
<td>6.38 d (1.8)</td>
<td>93.7 (CH)</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>156.5 (C)</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>103.9 (C)</td>
</tr>
<tr>
<td>1'</td>
<td>-</td>
<td>121.7 (C)</td>
</tr>
<tr>
<td>2'</td>
<td>7.54 d (1.8)</td>
<td>115.3 (CH)</td>
</tr>
<tr>
<td>3'</td>
<td>-</td>
<td>144.8 (C)</td>
</tr>
<tr>
<td>4'</td>
<td>-</td>
<td>148.5 (C)</td>
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<tr>
<td>5'</td>
<td>6.83 d (8.4)</td>
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<td>6'</td>
<td>7.52 dd (1.8, 8.4)</td>
<td>121.7 (CH)</td>
</tr>
<tr>
<td>1''</td>
<td>5.34 d (7.2)</td>
<td>101.2 (CH)</td>
</tr>
<tr>
<td>2''</td>
<td>-</td>
<td>74.1 (CH)</td>
</tr>
<tr>
<td>3''</td>
<td>3.05 – 3.71</td>
<td>76.5 (CH)</td>
</tr>
<tr>
<td>4''</td>
<td>-</td>
<td>70.6 (CH)</td>
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<td>76.0 (CH)</td>
</tr>
<tr>
<td>6''</td>
<td>5.10 br d (14.4)</td>
<td>67.1 (CH(_2))</td>
</tr>
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</tr>
<tr>
<td>2'''</td>
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<td>70.4 (CH)</td>
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<tr>
<td>3'''</td>
<td>-</td>
<td>70.1 (CH)</td>
</tr>
<tr>
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<td>6'''</td>
<td>0.98 d (6.6)</td>
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<td>5-OH</td>
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<td>7-OH</td>
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<td>3'-OH</td>
<td>9.21 br s</td>
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\(^a\)600 MHz for \(^1\)H- and 150 MHz for \(^{13}\)C-NMR
**Fig. 4.9.** UV spectrum of quercetin-3-\textit{O}-rutinoside (135) in MeOH.
Fig. 4.10. IR spectrum of quercetin 3-O-rutinoside (135) in KBr.
Fig. 4.11. $^1$H-NMR spectrum of Quercetin-3-O-rutinoside (135) in DMSO-d6.
Fig. 4.11a. $^1$H-NMR spectrum (expanded) of Quercetin-3-O-rutinoside (135) in DMSO-$d_6$. 

IICB
Fig. 4.11b. 1H-NMR spectrum (expanded) of Quercetin-3-O-rhamnoside (385) in DMSO-d6.
Fig. 4.12: 13C-NMR spectrum of Quercetin-3-C-glucoside (135) in DMSO-d6.
Fig. 4.12a. $^{13}$C-NMR spectrum (expanded) of quercetin-3-O-rutinoside (135) in DMSO-$d_6$. 
Fig. 4.12b. $^1$C-DEPT NMR spectra of quercetin-3-O-rutinoside (135) in DMSO-$d_6$. 

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Fig. 4.13. ESI-MS of ruhn (135).

THESIS, PART-IV

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Natural Products Chemistry
References


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