Anti-Viral Activity of Indian Plants

B. N. Dhawan

Abstract Plants continue to be a major source for new chemical entities to develop novel therapeutic agents. Large number of plants has been shown to be active in vitro against a variety of human pathogenic viruses or their near congeners. In several cases the active compounds have been isolated and characterized. Very few of them, however, have been investigated in detail in vivo or taken to the clinic. Pure compounds like andrographolide, curcumin and glycyrrhizic acid as well as extracts of *Azadirachta indica* have shown activity against several viruses and should be investigated further for their therapeutic potential. An analysis of available data from several hundred species indicates that antiviral activity is more likely to be found in plants belonging to certain families. It is necessary to screen more plants of these families which are available in India to obtain further leads.

Keywords Antiviral activity · Indian plants · Herpes simplex · Viral hepatitis · Human immunodeficiency virus · Respiratory viruses · Interferon inducers

Introduction

Natural products have been, and continue to be, a major source of new chemical entities (NCE) for development of better therapeutic agents against infective and non-infective disorders. The bio-molecules are more stable, clinically more specific and available from renewable source [1]. Plants of Indian origin have provided several novel leads in the past [2] and are likely to yield more NCE in future also.

The contribution of natural products to anti-viral chemotherapy, however, has been more modest. Several factors have contributed to this scenario. Viral infections like the common cold are self limited and require only symptomatic treatment. Public health measures like vector control have succeeded in controlling vector transmitted infections. Similarly, development of effective vaccines has played a major role in eliminating diseases like small pox, near eradication of poliomyelitis and treatment of rabies. A major reason for limited input from Indian plants has been the non-availability of strict containment facility needed for such work at most institutions in the country. A large number of plants found in India have, therefore been investigated and found active in Japan, South Korea, US, etc. Data on all such plants also has been included in the present review along with analysis of data generated within the country. Plants active in viruses closely related to human virus [e.g. feline Human Immunodeficiency Virus (HIV) or duck hepatitis] have also been included. Maximum plants have been screened against Ranikhet disease (RNA) virus (RDV) and vaccinia (DNA virus) followed by herpes, HIV and hepatitis. The data in following sections has been arranged in the same order.

Most of the studies have used in vitro test systems and crude extracts of various parts of the plants. Pure compounds have been tested in some cases and in vivo procedures have been used in very few cases. In limited number of cases clinical studies also have been done. In several cases the name of the plant or family has been changed now. The name given in the original publication has been retained in the present review to avoid confusion but the names of family have been revised.
Ranikhet Disease and Vaccinia Viruses

CSIR Central Drug Research Institute Lucknow (CDRI) has been the pioneer institute to undertake large scale screening of Indian plants for anti-microbial and other biological activities using about 80 in vitro and in vivo tests. The program has used 50% ethanolic extracts of botanically authenticated plant samples. The extracts have been screened in vitro against one RNA virus (Ranikhet disease virus) and one DNA virus (vaccinia virus). Some samples have also been screened against encephalomyocarditis (EMCV), Japanese Encephalitis B (JE) and Semliki Forest (SFV) viruses. Extracts showing high degree of antiviral activity were fractionated according to a standardized protocol to localize activity in one or more fractions. The results of testing 3,789 samples from 3,482 plants belonging to 233 families have been reported in a series of publications [3–14]. In addition, 967 of these plants were also tested for interferon-like activity against RD and vaccinia viruses [15]. A mid-term review of the work has also been published [16]. Antiviral activity was observed in 242 samples belonging to 96 families. The results have been summarized in Table 1. The plants have been listed under the appropriate families which have been arranged alphabetically. It also indicates plants where activity has been confirmed further in fractions or those exhibiting anticancer activity also.

Some of the active plants have been followed up at CDRI for isolation and characterization of the active constituents. The antiviral activity of (+) odorinol isolated from Aglaia roxburghiana has been reported by Joshi et al. [17]. Subsequently two new triterpinoids also have been isolated and characterized [18]. Lupeol has been identified as the active moiety of hexane fraction of Vicia indica. It was effective against EMCV, RDV and SFV. Lupeol isolated from same fraction was active against RDV only [19]. Furomolligin isolated from Rubia cardifolia was active against EMCV [20].

The interferon like activity of five plants (Acacia auriculiformis, Cassia fistula, Olex polyama, Senecio tenuifolius and Zingiber capitatum) has been investigated further. The classical fractionation failed to localize activity in a particular fraction. The activity could be localized in each case in non-dialyzable fraction. It was destroyed on treating the fraction with trypsin. These results suggest the presence of an interferon-like or interferon inducing substance in the non-dialyzable fraction [15].

CDRI has also tested plants used as hepato-protective agents in traditional systems of Indian medicine for their anti-hepatitis B virus surface antigen (HBsAg) activity in serum of patients or carriers. Promising results were obtained with Phyllanthus amarus [21] and Picrorhiza

### Table 1: Plants showing anti-viral activity in CDRI’s biological screening program

| No. | Family & plant | Part | Activity | References |
|-----|----------------|------|----------|------------|
| 1.  | Adhatoda vasica | Rt   | R        | [3]        |
| 2.  | Barleria cuspidata | Pl   | R, r     | [7, 15]    |
| 3.  | Nilgiriantus ciliatus | Px   | V        | [12]       |
| 4.  | Strobilanthes wightianus | Px | R, r     | [7, 15]    |
| 5.  | Cotinus coggyria | Px   | R        | [3]        |
| 6.  | Pistacia integerrima | Sb   | R        | [3]        |
| 7.  | Rhus parviflora | Px   | V, v, C  | [5, 15]    |
| 8.  | Rhus succedanea | Lf   | R, r     | [3, 15]    |
| 9.  | Rhus succedanea | Px   | R        | [12]       |
| 10. | Miliusa macrocarpa | Px   | R        | [12]       |
| 11. | Pimpinella diversifolia | Pl | R        | [3]        |
| 12. | Ichnarpinus frutescens | Pl    | R        | [3]        |
| 13. | Ilex wightiana | Px   | V        | [12]       |
| 14. | Hedera colchica | Px   | R        | [5]        |
| 15. | Schefflera rostrata | Lf, In | R       | [12]       |
| 16. | Schefflera wallichiana | St | R        | [12]       |
| 17. | Hemidesmus indicus | Pl  | R, r     | [3, 15]    |
| 18. | Polystichum biaristatum | Pla | R       | [12]       |
| 19. | Artemisia parviflora | Pl   | V        | [6]        |
| 20. | Cnicus wallichii | Pl   | R        | [3]        |
| 21. | Conyza visicidula | Pl   | V        | [5]        |
| 22. | Eclipta alba | Pl   | R        | [3]        |
| 23. | Lagascea molis | Pl  | r, V     | [6, 15]    |
| 24. | Laggera pirodanta | Pl   | R        | [5]        |
| 25. | Saussurea obtallata | Fl   | R        | [11]       |
| 26. | Siegesbeckia orientalis | Pl | R, r     | [3, 15]    |
| 27. | Senecio tenuifolius | Pl   | R, r, v, C | [8, 15] |
| 28. | Tagetes erecta | Pl   | R        | [4]        |
| 29. | Tagetes minuta | Pl   | R, r     | [4, 15]    |
| 30. | Vernonnia cinerea | Pl   | R        | [3]        |
| 31. | Vittadinia auralis | Pl   | V        | [4]        |
| 32. | Berberis lyceum | Rt   | R        | [3]        |
| 33. | Alnus nepalensis | Px   | R        | [12]       |
| 34. | Alnus nitida | Sb   | R, V     | [6]        |
Table 1 continued

| No. | Family & plant | Part | Activity | References |
|-----|----------------|------|----------|------------|
| 55. | *Heterophragma adenophyllum* | Px   | V        | [5]        |
| 56. | *Stereospermum suaveolens*  | Rt   | R, r, C  | [3, 15]    |
| 37. | *Bixa orellana*             | Fr   | V        | [12]       |
| 38. | *Salmalia malabarica*       | Fl   | R, r     | [3, 15]    |
| 39. | *Descarainia sophia*        | Pl   | R        | [10]       |
| 40. | *Caesalpinia bondacella*    | Rt   | V        | [3]        |
| 41. | *Cassia auriculata*         | Px   | R, r     | [3, 15]    |
| 42. | *Cassia auriculata*         | Rt   | V, v     | [3, 15]    |
| 43. | *Cassia fistula*            | Pb   | R, V     | [3, 15]    |
| 44. | *Cassia fistula*            | Pb   | R, V     | [3]        |
| 45. | *Cassia tora*               | Pl   | R        | [3]        |
| 46. | *Caesalpinia sepiaria*      | Rt   | R, V     | [4]        |
| 47. | *Hardwickia binata*         | Pl   | R, r, v  | [5, 15]    |
| 48. | *Tamarindus indica*         | Fl   | R        | [3]        |
| 49. | *Capparis multiflora*       | Px   | R        | [12]       |
| 50. | *Capparis longispina*       | Px   | R        | [3]        |
| 51. | *Lonicera leschenaultii*    | Pxa  | R        | [11]       |
| 52. | *Euonymus angulatus*        | Pxa  | R        | [13]       |
| 53. | *Salacia roxburghii*        | Px   | R, r     | [6, 15]    |
| 54. | *Terminalia chebula*        | Fr   | R        | [3]        |
| 55. | *Terminalia chebula*        | Lf   | R        | [11]       |
| 56. | *Terminalia chebula*        | Sw   | R, r     | [11, 15]   |
| 57. | *Terminalia paniculata*     | Pxa  | R, C     | [12]       |
| 58. | *Connarus wightii*          | Px   | R        | [6]        |
| 59. | *Cuscuta reflexa*           | Px   | R, r     | [4, 15]    |
| 60. | *Cucumis callosus*          | Px   | R, V     | [12]       |
| 61. | *Cupressus torulosa*        | Px   | R, r     | [7]        |
| 62. | *Carex obscura*             | Pl   | R        | [10]       |
| 63. | *Cyperus niveus*            | Pl   | R, r     | [3, 15]    |
| 64. | *Cyperus pangorei*          | Pxa  | V        | [12]       |
| 65. | *Dillenia pentagyna*        | Sb   | R        | [14]       |
| 66. | *Shorea robusta*            | Px   | R        | [10]       |

Table 1 continued

| No. | Family & plant | Part | Activity | References |
|-----|----------------|------|----------|------------|
| 67. | *Diospyros chloroxylon* | Px   | R        | [6]        |
| 68. | *Diospyros marmorata*    | Pxa  | R        | [13]       |
| 69. | *Diospyros peregrina*    | Sb   | R, r     | [3, 15]    |
| 70. | *Maba nigrescens*        | Px   | R, r, V, v| [6, 15]    |
| 71. | *Hipppophae salicifolia* | Sb   | R        | [11]       |
| 72. | *Elaeocarpus tectorius*  | Lf   | R, V     | [11]       |
| 73. | *Elaeocarpus glandulosus*| Px   | R, C     | [12]       |
| 74. | *Agapetes odonalocera*    | Tu   | R        | [12]       |
| 75. | *Rhododendron arboreum*  | Pxa  | R        | [14]       |
| 76. | *Aporosa villosula*       | Px   | R        | [13]       |
| 77. | *Baccaurea ramiiflora*    | Fr   | S        | [14]       |
| 78. | *Bridelia retusa*         | Sb   | R, r, C  | [5, 15]    |
| 79. | *Bridelia squamosa*       | Px   | R        | [6]        |
| 80. | *Euphorbia prolifer*      | Pl   | R, C     | [3]        |
| 81. | *Euphorbia royleana*      | St   | R        | [3]        |
| 82. | *Glochidion hohenackerii* | Px   | R        | [3]        |
| 83. | *Glochidion subsessile*   | Px   | R        | [12]       |
| 84. | *Glochidion zeylanicum*   | Px   | R        | [12]       |
| 85. | *Jatropha glandulifera*   | Px   | R, r     | [10, 15]   |
| 86. | *Kerangelia reticulata*   | Px   | R        | [3]        |
| 87. | *Kerangelia tanarius*     | Px   | R, V     | [12]       |
| 88. | *Mallotus resinus*        | Px   | R, V     | [12]       |
| 89. | *Margaritaria indica*     | Px   | V        | [12]       |
| 90. | *Ricinus communis*        | Lf   | V        | [3]        |
| 91. | *Emblica officinalis*     | Fr   | R        | [3]        |
| 92. | *Crotolaria semperflorens*| Px   | R        | [11]       |
| 93. | *Dunbaria ferruginea*     | Pxa  | R        | [12]       |
| 94. | *Indigofera pulchella*    | Rt   | V        | [3]        |
| 95. | *Indigofera cassioides*   | Pxa  | R        | [12]       |
| 96. | *Mundulea sericea*        | Px   | R, r     | [6, 15]    |
| 97. | *Ougeinia oojeinensis*    | Sb   | R        | [3]        |
| 98. | *Phaseolus trilobus*      | Pl   | V        | [5]        |
| 99. | *Sesbania procumbens*     | Px   | R        | [14]       |
| 100.| *Sesbania sesban*         | Px   | R        | [6]        |
| 101.| *Sophora glauca*          | Px   | R        | [7]        |
| 102.| *Urania lagopoides*       | Pl   | R, r     | [4, 15]    |
| 103.| *Wisteria chinensis*      | Px   | R        | [12]       |
| 104.| *Castanea sativa*         | Sb   | R        | [3]        |
| 105.| *Castanopsis indica*      | Sb   | R, r, C  | [7, 15]    |
| 106.| *Fagus sylvatica*         | Px   | r, V     | [5, 15]    |
| 107.| *Lithocarpus dealbatus*   | Sb   | R        | [11]       |
| 108.| *Lithocarpus dealbatus*   | Fr   | R        | [11]       |
| No. | Family & plant Part | Activity | References |
|-----|---------------------|----------|------------|
| 109. | Lithocarpus dealbatus Lf, Tw | R | [11] |
| 110. | Quercus himalayana Px | V | [11] |
| 111. | Quercus lamellosa Sb | R, r, V, v | [3, 15] |
| 112. | Quercus lanceafolia Sb | R, r, V, v | [3, 15] |
| 113. | Quercus pachyphylla Sb | R | [3] |
| 114. | Quercus thomsonii Px* | R | [12] |
| 115. | Gentianaceae | | |
| 116. | Canscora diffusa Pl | R | [4] |
| 117. | Guttiferae | | |
| 118. | Garcinia talbotii Pl | r, V | [5, 15] |
| 119. | Hippocrateaceae | | |
| 120. | Loeseneriella arnottiana Px* | R | [13] |
| 121. | Juglandaceae | | |
| 122. | Juglans regia Lf | V | [6] |
| 123. | Lamiaceae | | |
| 124. | Leonurus sibiricus Pl | V | [5] |
| 125. | Leucas prostrata Pl* | V | [12] |
| 126. | Rabdosia coetsa Px | R | [11] |
| 127. | Teucrium quadrifarium Pl | r, V | [6, 15] |
| 128. | Teucrium royleanum Pl | R | [10] |
| 129. | Juglans regia Lf | V | [6] |
| 130. | Dendrophthoe falcata Pxa | V | [15] |
| 131. | Euphorbiaceae | | |
| 132. | Ficus hirta Px* | R | [14] |
| 133. | Gentianaceae | | |
| 134. | Canscora diffusa Pl | R | [4] |
| 135. | Cinnamomum iners Px | R, r | [6, 15] |
| 136. | Lindera pulcherrima Px | R | [9] |
| 137. | Litsea coriacea Px | R | [13] |
| 138. | Cinnamomum iners Px | R, r | [6, 15] |
| 139. | Amoora wallichi St | R, r, V, v | [3, 15] |
| 140. | Cinnamomum iners Px | R, r, v | [15] |
| 141. | Pomaraea mirabilis Sb | R | [3] |
| 142. | Plantaginaceae | | |
| 143. | Abarema angulata Px | R | [13] |
| 144. | Acacia auriculiformis Px, Sb | r, v | [15] |
| 145. | Acacia catechu St | R | [3] |
| 146. | Acacia radiana Px | R | [11] |
| 147. | Albizzia procera Px | r, V, C | [5, 15] |
| 148. | Mimosa pudica Pl | r, V | [4, 15] |
| 149. | Moraceae | | |
| 150. | Ficus religiosa Sb | R, r | [3, 15] |
| 151. | Moringaceae | | |
| 152. | Myristicaceae | | |
| 153. | Myristicaeae | | |
| 154. | Myrtaceae | | |
| 155. | Myrtaceae | | |
| 156. | Eugenia codyensis Px* | R | [12] |
| 157. | Eugenia mangifolia Px | R | [11] |
| 158. | Eugenia thwaitesii Px* | R | [12] |
| 159. | Syzygium densiflorum Px | R | [11] |
| 160. | Syzygium kurzii Px* | S | [14] |
| 161. | Syzygium occidentalis Px | R | [12] |
| 162. | Syzygium samarangense Px | R, V | [12] |
| 163. | Syzygium tetragonum Px | R | [11] |
| 164. | Ochnaceae | | |
| 165. | Oleaceae | | |
| 166. | Olea polygama Px | r, v | [17] |
| 167. | Nyctanthes arbore-tristis Fr | E | [14] |
| 168. | Ximenia americana Px | R | [6] |
| 169. | Ochnaceae | | |
| 170. | Jasminum officinale Sb | R | [4, 15] |
| 171. | Achyranthes aspera St | R, r, v | [3, 15] |
| 172. | Annonaceae | | |
| 173. | Annona reticulata Sb | R, r, v | [15] |
| 174. | Passiflora mollissima Px | R | [11] |
| 175. | Passiflora mollissima Px | R | [11] |
| 176. | Plumbaginaceae | | |
| 177. | Vogelia indica Pl | R | [4] |
Table 1 continued

| No. | Family & plant | Part | Activity | References |
|-----|----------------|------|----------|------------|
| 176 | Poaceae        |      |          |            |
| 177 | Cynodon dactylon | Px⁵ | V        | [3]        |
| 178 | Hordeum vulgare | Sd   | R, r     | [3, 15]    |
| 179 | Imperata cylindrica | Px   | R, r     | [5, 15]    |
| 180 | Isachne kunthiana | Pl   | R        | [12]       |
| 181 | Saccharum species | Lf   | R        | [11]       |
| 182 | Poaceae        |      |          |            |
| 183 | Hordeum vulgare | Sd   | R, r     | [3, 15]    |
| 184 | Isachne kunthiana | Pl   | R        | [12]       |
| 185 | Imperata cylindrica | Px   | R, r     | [5, 15]    |
| 186 | Isachne kunthiana | Pl   | R        | [12]       |
| 187 | Imperata cylindrica | Px   | R, r     | [5, 15]    |
| 188 | Isachne kunthiana | Pl   | R        | [12]       |
| 189 | Imperata cylindrica | Px   | R, r     | [5, 15]    |
| 190 | Isachne kunthiana | Pl   | R        | [12]       |
| 191 | Imperata cylindrica | Px   | R        | [5, 15]    |
| 192 | Isachne kunthiana | Pl   | R        | [12]       |
| 193 | Imperata cylindrica | Px   | R, r     | [5, 15]    |
| 194 | Isachne kunthiana | Pl   | R        | [12]       |
| 195 | Imperata cylindrica | Px   | R, r     | [5, 15]    |
| 196 | Isachne kunthiana | Pl   | R        | [12]       |
| 197 | Imperata cylindrica | Px   | R, r     | [5, 15]    |
| 198 | Isachne kunthiana | Pl   | R        | [12]       |
| 199 | Imperata cylindrica | Px   | R, r     | [5, 15]    |
| 200 | Isachne kunthiana | Pl   | R        | [12]       |

Table 1 continued

| No. | Family & plant | Part | Activity | References |
|-----|----------------|------|----------|------------|
| 201 |?family & plant|      |          |            |
| 202 |?family & plant|      |          |            |
| 203 |?family & plant|      |          |            |
| 204 |?family & plant|      |          |            |
| 205 |?family & plant|      |          |            |
| 206 |?family & plant|      |          |            |
| 207 |?family & plant|      |          |            |
| 208 |?family & plant|      |          |            |
| 209 |?family & plant|      |          |            |
| 210 |?family & plant|      |          |            |

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Activity against herpes virus has been reported in 49 Indian plants. These have been listed in Table 2. The activity is distributed widely and the plants belong to 34 families. Most of them have been reported active against herpes-1 virus though a few are active against both herpes-1 and 2. In 12 cases the strain used has not been mentioned. Only four publications have reported in vivo activity. Pure isolated compounds have been tested in 26 cases. Two of the compounds glycyrrhizin and lupeol are active against other human viruses also and this has been indicated at appropriate places in this review. Unfortunately none of them appear to have been followed up further. The results have been published in 43 papers and only 9 of them are from Indian laboratories. Table 2 includes only those plants from foreign publications which are found in India.

Human Immunodeficiency Virus

Large number of papers has been published in recent years reporting anti-HIV activity in numerous natural products, partly because of the large screening program of US National Cancer Institute. Activity has been reported only in 38 Indian plants in 32 papers. These have been shown in Table 3 and belong to 28 families. Data on 41 materials has been reported and 24 of them are pure compounds. Most investigators (26) have studied the activity on HIV-1 and in 10 cases the strain has not been mentioned. HIV-2 has been included in two studies only. Two of the reported plants have been found active against feline immunodeficiency virus (FIV), a close congener of HIV. Most of the publications in this case also are from foreign laboratories and there are only seven Indian publications. There have been claims of usefulness of Ayurvedic and Siddha formulations in treatment of AIDS but no reliable clinical data is available either with these formulations or with the plants listed in Table 3. Data with Curcuma longa has not been included in this table because curcumin isolated from this plant and its several semi-synthetic and synthetic analogues have been tested. The data has been included in concluding remarks.

Hepatitis Viruses

Large number of medicinal plants has been used for treatment of hepatic disorders in most traditional system of medicine. The parameters generally followed were clearance of jaundice and return of liver function tests to normalcy. Clearance of viraemia in infective hepatitis, the commonest hepatic disorder, became an important parameter after the demonstration of carrier stage and possible induction of malignancy in such persons. One of the earliest demonstrations of viral clearance was provided by the pioneering studies of Thyagarajan et al. [106] with Phyllanthus amarus. This led to screening of large number of plants for activity against the virus. The availability of the duck model for in vivo studies materially facilitated these studies. Protective effect has been reported with 17 Indian plants belonging to 14 families. These have been listed in Table 4. Most of the plants have been tested against hepatitis B virus by several in vitro procedures. The active compound has been isolated and characterised in nine of these plants.

Several hepatoprotective plants have been tested for anti-hepatitis B virus surface antigen (HBsAg) activity in vitro using serum from patients or asymptomatic carriers harbouring the infection. Neutralizing activity has been reported with extract of Phyllanthus amarus [21]. A purified standardized extract (Picroliv) and a pure compound catalpol isolated from Picrorhiza kurroa were also found active while andrographolide (active constituent of Andrographis paniculata) and silymarin were inactive [22].

Clinical studies have been undertaken with some of the active plants in patients of infective hepatitis. As already reported above [23] efficacy of Picroliv has been demonstrated in Phase III multicentric trials. Beneficial effects have been reported with Phyllanthus amarus and glycyrrhizin also. These and other studies have been reviewed by Handa in a comprehensive publication [114] on hepatoprotective activity of Indian medicinal plants.

Respiratory Viruses

Interest in respiratory virus has increased following the recent epidemics of SARS and H1N1 infection. Activity has
| Plant               | Family          | Product | Strain | References |
|---------------------|-----------------|---------|--------|------------|
| 1. *Adansonia digitata* | Bombaceae       | Ext     | HSV    | [27]       |
| 2. *Aglai odorata*    | Meliaceae       | Ext     | 1<sup>a</sup> | [28]       |
| 3. *Aloe vera*        | Liliaceae       | Ext     | 2      | [29]       |
| 4. *Andrographis paniculata* | Acanthaceae | Diterpenes | 1      | [30]       |
| 5. *Atlantia sp.*    | Rutaceae        | Pyrophorbide | 2      | [31]       |
| 6. *Azadirachta indica* | Meliaceae     | Ext     | 1      | [32]       |
| 7. *Barleria lupulina* | Acanthaceae    | Iridoid glycoside | 1    | [33]       |
| 8. *Bauhinia racemosa* | Caesalpiniaceae | Ext     | HSV    | [34]       |
| 9. *Bauhinia variegata* | Asteraceae     | Ext     | 1,2    | [35]       |
| 10. *Bidens pilosa*  | Asteraceae      | Ext     | 1,2    | [36]       |
| 11. *Cedrus libani*  | Pinaceae        | Ext, oil | 1      | [37]       |
| 12. *Cissus quadrangularis* | Vitaceae     | Ext     | 1,2    | [38]       |
| 13. *Conyza aegyptica* | Asteraceae    | Ext     | HSV    | [27]       |
| 14. *Cyperus rotundus* | Cyperaceae     | Ext     | 1      | [39]       |
| 15. *Euphorbia peplus* | Euphorbiaceae  | Diterpene esters | 2    | [40]       |
| 16. *Glycyrrhiza glabra* | Fabaceae      | Glycyrrhizin | HSV  | [41]       |
| 17. *Heliotropium marifolium* | Boraginaceae | Alkaloid | HSV  | [42]       |
| 18. *Holoptelea integrifolia* | Ulmaceae     | Ext     | HSV    | [43]       |
| 19. *Houttuynia cordata* | Saraiaceae    | Ext     | 1,2    | [36]       |
|                    | Pure compounds | 1       |        |            |
| 20. *Hypericum hookerianum* | Hyperaceae     | Ext     | 1      | [45]       |
| 21. *Hypericum myosorens* | Hyperaceae     | Ext     | 1      | [45]       |
| 22. *Lippia alba*     | Verbenaceae     | Ext     | 1      | [46]       |
| 23. *Melia azaderach* | Meliaceae       | Ext     | 2<sup>a</sup> | [47]       |
|                    | Meliacine       | 1       |        |            |
| 24. *Mentha piperata* | Lamiaceae       | Essential oil | 1,2    | [49]       |
| 25. *Momordia charantia* | Cucurbitaceae | Ext     | 1      | [50]       |
| 26. *Moringa oleifera* | Moringaceae     | Ext     | 1<sup>a</sup> | [28]       |
| 27. *Myrica rubra*    | Myricaceae      | Pure compounds | 2    | [51]       |
| 28. *Neerium indicum* | Apocynaceae     | Ext     | HSV    | [43]       |
| 29. *Pandanus amaryllifolius* | Pandanaceae    | Pandanin | 1    | [52]       |
| 30. *Peganum harmala* | Rutaceae        | Ext     | 1      | [53]       |
| 31. *Phyllanthus emblica* | Euphorbiaceae | Pure compounds | HSV  | [54]       |
| 32. *Phyllanthus urinaria* | Pure compounds | 1,2    |        | [55]       |
| 33. *Pinus massoniana* | Pinaceae        | Ext     | HSV    | [56]       |
| 34. *Plantago major*  | Plantaginaceae  | Ext     | HSV    | [56]       |
| 35. *Portulaca oleracea* | Portulacaceae  | Polysaccharides | 2    | [57]       |
| 36. *Salvia officinalis* | Lamiaceae    | Ext     | 1,2    | [58]       |
| 37. *Santalum album*  | Santalaceae     | Oil     | 1,2    | [59]       |
| 38. *Scinata hatei*   | Liagoneaceae    | Polysaccharides | HSV  | [60]       |
| 39. *Scoparia dulcis* | Scrophulariaceae | Scopadulcic acid | 1    | [61]       |
| 40. *Solanum torvum*  | Solanaceae      | Torvanol A | 1    | [62]       |
|                    | Torvoside H     | 1       |        |            |
| 41. *Sorghum bicolor* | Poaceae         | Peptide | 1      | [63]       |
| 42. *Strobilanthes cusia* | Acanthaceae    | Lupeol  | 1       | [64]       |
| 43. *Swertia chirata* | Gentianaceae    | Ext     | 1      | [65]       |
| 44. *Syzygium aromaticum* | Myrtaceae      | Eugenin  | 1      | [66]       |
| 45. *Syzygium jambos* | Myrtaceae       | Ext     | 1      | [67]       |
been reported in 18 Indian plants belonging to 16 families. Pure compounds isolated from plants have been tested in nine cases. Activity has been reported against five respiratory viruses. Activity against influenza has been observed in seven samples and against H1N1 in four cases. One sample was active against SARS. The data about active plants has been summarized in Table 5.

**Pox Viruses**

Interest in this group of viruses has continued because of continued occurrence of chicken-pox and measles infection. Only 14 plants have been reported active against a variety of pox viruses. These plants belong to 13 families. Glycyrrhizin from *Glycyrrhiza glabra* is the only pure compound reported active. Extract from *Hibiscus sabdariffa* is the only product showing activity against measles. Most of the extracts have been found active against fowl pox. Details of activity have been shown in Table 6.

**Other Viruses**

Activity in several Indian plants has also been reported against a variety of other viruses causing human infection or their close congeners. Table 7 shows such plants belonging to 24 families. In 10 cases pure compounds isolated from plants have been found active. The list includes 12 viruses. The preparations showing activity against chikungunya, Japanese encephalitis and rotavirus are of particular interest due to wide occurrence of these infections in the country and need to be investigated on a priority basis.

**Concluding Remarks**

The broad based biological screening program of CDRI had included tests for several other activities also with the same standardized protocol. An analysis of the results has shown that each particular activity was preferentially observed in certain families. The top 11 families for anti-viral activity and three other major activities have been arranged in rank order in Table 8. It will be observed that rank order is different for different activities even though some families exhibit more than one type of activity. The top 11 families in each case contain 35–45% of the plants for the concerned activity. The 11 families identified for anti-viral activity contain about 41% of the 242 active plants from 96 families. About 27% plants reported active against other viruses and included in Tables 2, 3, 4, 5, 6 and 7 also belong to these 11 families. It should be useful to screen other plants of these families to obtain more active plants. It will be evident from data in Tables 1 and 8 that many plants and families have both anti-viral and anticancer properties. It may be mentioned also that several smaller countries like Egypt [39], Nepal [43], Sudan [54] and Togo [27] have undertaken systematic evaluation of their flora for anti-viral activity following the lead given by CDRI.

It is evident from the data reviewed above that little effort has been made to study the marine flora around the vast Indian coast line for antiviral compounds. Several Indian mangrove plants (*Ceriops decandra*, *Excocaria agallocha* and three species of *Rhizophora* i.e. *lamarckii*, *mucoranata* and *spiculata*) have been reported to exhibit potent anti-HIV activity [142] highlighting the need of further exploration of this valuable resource.

Most of the data reported in this review is from in vitro studies and the leads do not appear to have been followed up. This is partly because of lack of suitable animal models for several infections and partly due to lack of the requirement containment facility in majority of Indian institutions. It is suggested that multi-pronged strategy should be adopted to utilise these leads. There are certain viral infections like Japanese encephalitis, chikungunya or rotavirus which are major national concern. Only few leads are available against them and these need to be followed.
A number of pure compounds have demonstrated activity against several viral infections. These are compounds of varying chemical complexity ranging from simple compounds like curcumin to complicated structures like iridoids glycosides. Adequate attention has not been paid to use them as basic templates to optimise the activity

| Plant                     | Family       | Product        | Strain | References |
|---------------------------|--------------|----------------|--------|------------|
| 1. Acacia nilotica        | Mimosaceae   | Ext            | HIV    | [70]       |
| 2. Acacia tortilis        |              | Ext            | 1      | [71]       |
| 3. Ailanthus allisima     | Simaroubaceae| Ocotillone     | 1      | [72]       |
| 4. Alpinia galanga        | Zingiberaceae| Ext            | 1      | [73]       |
| 5. Anisomeles indica      | Lamiaceae    | Ovatodiolide   | HIV    | [74]       |
| 6. Artemisia carausioli   | Asteraceae   | Coumaryl spermines | 1    | [75]       |
| 7. Camellia japonica     | Theaceae     | Camelliatannin H | 1    | [76]       |
| 8. Cardioperum helicabum  | Sapindaceae  | Ext            | 1,2    | [77]       |
| 9. Chrysanthemum morifolium | Asterae   | Flavonoids     | 1      | [78]       |
| 10. Cinnamomum cassia     | Lauraceae    | Ext            | 1,2    | [77]       |
| 11. Desmos sp.            | Annonaceae   | Flavonoids     | HIV    | [79]       |
| 12. Ficus glomerata       | Moraceae     | Ext            | 1      | [80]       |
| 13. Glycyrrhiza glabra    | Fabaceae     | Glycyrrhizin   | 1      | [41]       |
| 14. Harrisonia perforata  | Simaroubaceae| Ext            | 1      | [80]       |
| 15. Hyssopus officinalis  | Lamiaceae    | Ext            | 1      | [81]       |
| 16. Illicium verum        | Illiciaceae  | Illicinone-A    | HIV    | [82]       |
| 17. Justicia replans      | Acanthaceae  | Ext            | HIV    | [83]       |
| 18. Lippia javanica       | Verbenaceae  | Piperitenone    | 1      | [84]       |
| 19. Mimusops elengi       | Sapotaceae   | Minusopic acid | HIV    | [85]       |
| 20. Momordia charantia    | Cucurbitaceae| Lectin         | 1      | [86]       |
|                           |              |                | Protein MRK 29 | 1      | [87]       |
| 21. Morinda citrifolia    | Rubiaceae    | Ext            | 1      | [88]       |
| 22. Nelumbo nucifera      | Nymphaceae   | Cocalaurine    | HIV    | [89]       |
|                           |              | Nucliferine    | HIV    |            |
| 23. Pedilanthus sp.       | Euphorbiaceae| Pedilotanin    | 1      | [90]       |
| 24. Pericampylus glaucus  | Menispermaceae| Periguauains  | 1      | [91]       |
| 25. Phaseolus vulgaris    | Fabaceae     | Lectin         | 1      | [86]       |
| 26. Polyalthea suberosa   | Annonaceae   | Furans         | HIV    | [92]       |
| 27. Polygonon viscousum   | Polygonaceae | Quercitin      | 1      | [93]       |
| 28. Ricinus communis      | Euphorbiaceae| Lectins        | 1      | [86]       |
| 29. Rhus sinensis         | Anacardiacae | Benzofuranones | 1      | [94]       |
|                           |              | Rhuscholide A  | HIV    | [95]       |
| 30. Sambucus nigra        | Caprifoliaceae| Ext            | HIV(f) | [96]       |
| 31. Schisandra rubriflora | Schisandraceae| Rubrifloxeine | 1      | [97]       |
| 32. Scoparia dulcis       | Scrophulariaceae| Ext      | 1      | [98]       |
| 33. Sida sp.              | Malvaceae    | Ext            | HIV    | [99]       |
| 34. Sophora flavescens    | Fabaceae     | Ext            | 1      | [76]       |
| 35. Terminalia chebula    | Combretaceae | Galloyl glucose | 1    | [100]      |
| 36. Urtica dioica         | Urticaceae   | Ext            | FIV    | [96]       |
| 37. Ximenia americana     | Oleaceae     | Ext            | 1      | [101]      |
| 38. Zingiber officinale   | Zingiberaceae| Ext            | 1      | [73]       |

Ext crude extract in different solvents; HIV strain not specified; 1, 2 HIV I or II strain; FIV feline immunodeficiency virus (has many common features with HIV) [96]
### Table 4  Indian plants active against hepatitis virus in vitro

| Plant Family | Product | Strain | References |
|--------------|---------|--------|------------|
| 1. Agrimonia eupatoria | Rosaceae | Ext B | [102] |
| 2. Alpinea galanga | Zingiberaceae | Ext C | [73] |
| 3. Bupleurum sp | Apiaceae | Saikosaponins B | [103] |
| 4. Glycyrrhiza glabra | Fabaceae | Glycyrrhizin B, C | [41] |
| 5. Hypericum perforatum | Hypericaceae | Hypericin C | [104] |
| 6. Oenanthe javanica | Apiaceae | Phenolics B | [105] |
| 7. Pericampylus glaucus | Menispermaceae | Periglaucines B | [91] |
| 8. Phyllanthus amarus | Euphorbiaceae | Ext B | [21, 106] |
| 9. Phyllanthus urinaria | | Ext B | [107] |
| 10. Picrorhiza kurroa | Scrophulariaceae | Picroliv B | [22] |
| 11. Potentilla anserina | Rosaceae | Triterpine saponins B, E | [108] |
| 12. Ranunculus sceleratus | Ranunculaceae | Apigenins B | [109] |
| 13. Rubia cardifolia | Rubiaceae | Naphthoquinones B | [110] |
| 14. Saussurea lappa | Asteraceae | Ext B | [111] |
| 15. Terminalia chebula | Combretaceae | Ext B | [112] |
| 16. Wrightia tinctoria | Apocynaceae | Ext C | [113] |
| 17. Zingiber officinalis | Zingiberaceae | Ext C | [73] |

*Ext crude extract in different solvents; B, C, E the strain of virus used

### Table 5  Indian plants active in vitro against respiratory viruses

| Plant Family | Product | Virus | References |
|--------------|---------|-------|------------|
| 1. Alpinia officinarum | Zingiberaceae | Diaryl heptanoids | H1N1 | [115] |
| 2. Andrographis paniculata | Acanthaceae | Andrographolide | Influenza | H1N1 | [116] |
| 3. Avicennia marina | Aveccinniaceae | Ext | Newcastle | [117] |
| 4. Barleria prionitis | Acanthaceae | Iridoids | Resp. Syn. | [118] |
| 5. Bergenia ligulata | Saxifragaceae | Ext | Influenza | [43] |
| 6. Caesalpinea sappan | Cesalpineaceae | Sappan chalcones | Influenza | [119] |
| 7. Curcuma longa | Zingiberaceae | Curcumin | Newcastle | [120] |
| 8. Ephedra sinica | Ephedraceae | Catechin | H1N1 | [121] |
| 9. Gardenia sp | Rubiaceae | Ext | Influenza | [122] |
| 10. Glycyrrhiza glabra | Fabaceae | Glycyrrhizin | Influenza | [41] |
| 11. Hottunynia cordata | Piperaceae | Ext | SARS | [123] |
| 12. Neerium indicum | Apocynaceae | Ext | Influenza | [43] |
| 13. Nigelia sativa | Ranunculaceae | Ext | Newcastle | [117] |
| 14. Pandanus amaryllifolius | Pandanaceae | Pandanin | H1N1 | [52] |
| 15. Phyllanthus amarus | Euphorbiaceae | Ext | Newcastle | [120] |
| 16. Punica granatum | Puniaceae | Ext | Influenza | [124] |
| 17. Wickstroemia indica | Thymelaceae | Daphnoretin | Resp. Syn. | [125] |
| 18. Zizyphus spira-christi | Rhamnaceae | Ext | Newcastle | [117] |

*Ext crude extract in different solvents

a Tested in vivo

b Respiratory synticial virus
c Main source of catechin is Acacia catechu [126]
d Tested in vitro and in vivo
in synthetic or semi-synthetic derivatives. Successful use of this strategy has been made in the case of andrographolide [143] and curcumin [136], for example.

Activity has also been reported in certain compounds which have undergone extensive clinical evaluation in non-viral diseases. Their available safety and dosage regimen data would help in initiating clinical evaluation in viral infection where in vitro or in vivo activity data is available. Andrographolide is a potent hepatoprotective agent [114] besides being active against herpes [30], influenza and H1N1 infections [116]. Dehydroandrographolide succinic acid monoester is active against HIV [143]. Another clinically authenticated hepatoprotective agent Picroliv [23] is also active against several viral infections including hepatitis B [24–26]. Curcumin has received the maximum attention after its activity against HIV [143]. Its boron complexes; semi-synthetic reduced curcumin, allyl curcumin and tocopheryl-curcumin and synthetic analogues dicafferoyl methane and rosemarinic acid are highly active against HIV in a variety of in vitro protocols. Curcumin is active against herpes simplex 2 in a mouse model and Human papilloma and Epstein Barr viruses in vitro. These activities have been reviewed recently by Krishnaswamy [136]. Its in vitro activity against Friends leukaemia [25], Newcastle and Poliomyelitis viruses [120] has also been reported. Fiore et al. [41] in a recent review have provided reference for activity of glycyrrhizin and its analogues against herpes, hepatitis (including clinical trial), influenza, respiratory syncytial, SARS and vesicular stomatitis viruses. Other investigators have found it active against Japanese encephalitis [137], poliomyelitis [138], vaccinia and varicella [130]. It perhaps has the widest spectrum of antiviral activity among the natural products so far investigated. Adequate clinical evaluation is necessary to assess its role in treatment of viral disorders.

Azadirachta indica also is a promising plant, even though most of the studies have used its extract. It has a variety of compounds and also has a long history of use in traditional medicine in many countries of the world. The viruses against which the extracts or some of the isolated compounds have shown activity include chikungunya, fowl pox, measles, vaccinia [128], buffalopox [127], Coxsackie [134] and herpes [32]. Detailed studies against some of these viruses, specially herpes and chikungunya are strongly warranted. In conclusion it may be stated that the rich and valuable resource of Indian plants needs to be more extensively exploited to provide new drugs for the treatment of viral disorders.

| Plant Family       | Product     | Virus                   | References |
|--------------------|-------------|-------------------------|------------|
| Acacia nilotica   | Ext         | Fowl pox                | [117]      |
| Aristolochia bracteolate | Ext         | Fowl pox                | [117]      |
| Avicennia marina   | Ext         | Buffalo pox             | [127]      |
| Azadirachta indica | Ext         | buffalo pox Fowl pox    | [128]      |
| Bauhinia variegata | Ext         | Vaccinia                | [35]       |
| Cissus quadrangularis | Ext       | Fowl pox                | [117]      |
| Eugenia jambolana  | Ext         | Buffalo pox             | [129]      |
| Glycyrrhiza glabra | Glycyrrhizin| Vaccinia                | [41]       |
| Hibiscus sabdariffa| Ext         | Measles                 | [131]      |
| Ipomea carnea     | Ext         | Fowl pox                | [117]      |
| Maerua oblongifolia| Ext         | Fowl pox                | [117]      |
| Ocimum sanctum    | Ext         | Vaccinia                | [3]        |
| Prosopis chilensis| Ext         | Fowl pox                | [117]      |
| Trebulus terrestris| Ext        | Fowl pox                | [117]      |
| Trigonella foenum graecum | Ext      | Fowl pox                | [117]      |

Ext: crude extract in different solvents.
Table 7  Indian plants active in vitro against other human viruses

| Plant Family                  | Product | Virus                  | References |
|-------------------------------|---------|------------------------|------------|
| 1. Adansonia digitata         | Ext     | Polio                  | [27]       |
| 2. Aegle marmelos            | Ext     | Coxsackie              | [132]      |
| 3. Alpinia galanga           | Ext     | Cytomegalus            | [73]       |
| 4. Artocarpus integrifolia   | Ext     | Rotavirus              | [133]      |
| 5. Azadirachta indica        | Ext     | Chikungunya            | [128]      |
| 6. Baccaurea ramiflora       | Ext     | Semiliki\(^a\)          | [14]       |
| 7. Bauhinia variegata        | Ext     | Ves Stomatitis\(^b\)   | [35]       |
| 8. Berberis aristata         | Berberine | Friends Leu\(^c\)   | [25]       |
| 9. Camellia sinensis         | Triterpinoids | Epstein Barr | [135]      |
| 10. Conyza aegyptica         | Ext     | Polio                  | [27]       |
| 11. Curcuma longa            | Curcumin | Epstein Barr          | [136]      |
| 12. Glycyrrhiza glabra       | Glycyrrhizin | JE\(^e\)          | [137]      |
| 13. Heliotropium marifolium  | Alkaloids | Coxsackie           | [42]       |
| 14. Hernandia ovigera        | Lignans | Epstein Barr          | [139]      |
| 15. Kalanchoe pinnata        | Bryophyllin A | Epstein Barr | [140]      |
| 16. Lippa alba               | Ext     | Polio                  | [64]       |
| 17. Mallotus philippensis    | Triterpinoids | Epstein Barr | [141]      |
| 18. Momordica charantia      | Ext     | Sindbis                | [50]       |
| 19. Myristica fragrans       | Ext     | Rotavirus              | [134]      |
| 20. Nyctanthes arbor-tristis | Ext     | EMCV\(^f\)              | [14]       |
| 21. Paedaria scandens        | Paederoside | Epstein Barr        | [26]       |
| 22. Phyllanthus amarus       | Ext     | Polio                  | [120]      |
| 23. Picrorrhiza kurroa        | Ext     | Epstein Barr           | [26]       |
| 24. Plumbago zeylanica       | Ext     | Picroliv               | [24]       |
| 25. Scilla hyacinthine       | Ext     | Coxsackie              | [46]       |
| 26. Spondias lutea           | Ext     | Semiliki               | [14]       |
| 27. Syzigium jambos          | Ext     | Ves Stomatitis         | [67]       |
| 28. Turpinea pomifera        | Ext     | JE                     | [14]       |
| 29. Zingiber officinale      | Ext     | Cytomegalus            | [73]       |

Ext crude extract in different solvents

\(^a\) Semiliki Forest virus

\(^b\) Vesicular stomatitis

\(^c\) Friends leukemia

\(^d\) Human papilloma virus

\(^e\) Japanese encephalitis

\(^f\) Encephalomyocarditis virus
**Table 8** Top 11 families for selected pharmacological activities in CDRI plants

| Anti-viral | Anti-cancer | CNS active | Hypoglycemic |
|-----------|-------------|------------|--------------|
| No. of active plants | No. in top 11 families | No. of active plants | |
| 239 | 228 | 639 | 156 |
| 98 | 41.0 | 58 | 44.2 |

% in top 11 families

| Rank order of top 11 families |
|------------------------------|
| Lauraceae | Acanthaceae | Asteraceae | Rubiaceae | Lamiaceae | Convolvulaceae | Rosaceae | Anacardiaceae | Euphorbiaceae | Fabaceae |
| No. 1 | No. 2 | No. 3 | No. 4 | No. 5 | No. 6 | No. 7 | No. 8 | No. 9 | No. 10 |
| 239 | 228 | 197 | 192 | 189 | 186 | 183 | 181 | 175 | 171 |
| 158 | 154 | 153 | 152 | 151 | 150 | 149 | 148 | 147 | 146 |

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