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# A review on phytochemical constituents and pharmacological potential of *Calotropis procera*

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*Calotropis procera* is locally known as *Aak* or *Madar* in Hindi, milk weed in English and belongs to the family Apocynaceae and subfamily Asclepiadoideae. Although a wasteland plant, it is of sacred use as its flowers are offered for worshipping Lord Shiva, a Hindu God. Tribes all over the world use the plant in treatment of various diseases like snake bite, body pain, asthma, epilepsy, cancer, sexual disorders, skin diseases and many more. This plant contains various phytoconstituents such as flavonoids, terpenoids, cardenolides, steroids oxypregnanes etc. Though literature searches reveal many reviews about ethnomedicinal uses, chemical composition and pharmacological activities, no recent papers are available that provide an overview of the therapeutic potential and toxicity of *Calotropis procera*. Hence, the insight of this review is to provide a systemic summary of phytochemistry, pharmacology, toxicology and therapeutic potential of *Calotropis procera* and to highlight the gaps in the knowledge so as to offer inspiration for future research.

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## 1. Introduction

*Calotropis* belongs to the Apocynaceae family, which is commonly known as milkweed or *Aak*. Plants of this genus are known as milkweeds due to the exudation of white and sticky latex from different plant parts. Genus *Calotropis* has two common species viz. *Calotropis procera* (Rakta arka) and *Calotropis gigantea* (Sweata arka), which are described as possessing vital pharmacological properties in Ayurvedic toxicology and therapeutics. Other species are *C. sussuela* and *C. acia*.

*Calotropis procera* (Aiton) W. T. Aiton is an erect, soft wooded, evergreen perennial shrub and commonly known as 'Sodom apple' or 'Madar shrub'. In Bengali, it is known as 'Akanda' and in Hindi as 'Aak'. It manifests its wide utilization in Indian, Arabic and Sudanese traditional medicinal systems for healing global range of diseases.

The Dangas tribe in Gujarat,<sup>1</sup> Singhum tribe in Bihar,<sup>2</sup> tribes of Ghatigaon forest in Gwalior,<sup>3</sup> tribes of Andhra Pradesh<sup>4</sup> have been using this plant in the treatment of various disorders such as ear pain, cough, fever, abdominal pain, dysentery and elephantiasis.

*Calotropis procera* is more toxic than *Calotropis gigantea* and assumed to be even more poisonous than cobra venom. It is interesting that the cobra and other poisonous snakes cannot

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moieties.



even bear its smell; hence snake charmers of Bengal use this plant for controlling or taming cobras.<sup>5</sup>

Earlier reviews<sup>6–16</sup> have discussed on phytochemistry, ethnobotany and pharmacological potential of *Calotropis procera*. Review on *Calotropis* species<sup>17–20</sup> comparing *procera* and *gigantea* have deliberated their therapeutic importance. The present review summarizes the phytochemistry, pharmacology, commercial aspects, traditional medicinal uses, toxicology and recent studies on *Calotropis procera*. The future scope of *Calotropis procera* has also been affirmed with a view to establish its multiple biological activities and mode of action.

## 2. Unique properties of *Calotropis procera*

### 2.1 Toxicity

*C. procera* finds its widespread distribution over many regions of the globe. What makes its phytochemistry interesting is the exudation of milky and toxic latex from all the plant parts. The



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latex is referred to as vegetable mercury as it shows mercury like effects on human body.<sup>21</sup>

Every part of this plant is toxic, but stem (latex) and roots are more poisonous than leaves. The leaves of this plant have three toxic glycosides calotropin, calotoxin and uscharin, whereas its latex contains calotropin, calotoxin and calactin, which are caustic and considered poisonous in nature. Besides this, the concentration of calactin, which is a toxic glycoside, gets increased as defense mechanism on encounter of grasshopper or insect attack and this is the rationale behind the plant not being consumed by cattles or other grazing animals.<sup>22</sup> Other than this, osmotin, a laticifer protein purified from latex also provides protection to plant against phytopathogens.<sup>23</sup> Its milk is irritant, neurotoxic and has anticholinergic activity, which causes toxicity and fatal complications. Madar juice and latex has bitter taste and a burning pain which causes salivation, stomatitis, vomiting, diarrhoea, dilated pupils, titanic convulsion, collapse and death. The fatal period varies from half an hour to eight hours.<sup>24</sup> If latex enters into the eye, it causes kerato-conjunctivitis, corneal edema and dimness of vision without any pain.<sup>25–27</sup> Some cases showed permanent endothelial cell damage, which was evident after three weeks.<sup>5,28</sup> *C. procera* was found toxic at the dose of 100 mg kg<sup>-1</sup> to chick embryo. Its toxicity caused hepatocellular degeneration in liver, brain congestion, dilation of central veins, sinusoids, underdeveloped lung and kidneys.<sup>29</sup> Hence, bearing in mind the toxic effects of certain extracts and glycosides, further studies should be focused to explain toxicity and safe use of *C. procera*.

### 2.2 Ability to survive under extreme climatic conditions

Another interesting aspect of this plant is its ability to tolerate adverse environmental conditions like scarcity of water, arid environment or any kind of harsh climate. To understand this, Akhkh<sup>30</sup> studied the effect of stress caused due to water scarcity and found that photosynthetic machinery remained uninfluenced, infact rate of photosynthesis gets raised at mild water



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Table 1 Ethnomedicinal applications of *C. procera*

| Plant part                | Disease                                     | Preparation/administration  | References                        |    |
|---------------------------|---|---|-----------------------------------|----|
| Root/root bark            | Amoebic dysentery                           | Paste with/without opium taken orally   | 44–46                             |    |
|                           | Cholera                                     | Powder orally taken or paste along with black pepper and ginger juice   | 44                                |    |
|                           | Dysentery                                   | Powder orally taken   | 47                                |    |
|                           | Elephantiasis and hydrocele                 | Paste mixed with fermented rice water applied on the affected area  | 48–50                             |    |
|                           | Epilepsy                                    | Grounded with goat milk and used as nasal drops   | 46                                |    |
|                           | Indigestion                                 | Powder orally taken   | 47                                |    |
|                           | Jaundice                                    | Taken with rice in grounded form  | 51                                |    |
|                           | Neuritis                                    | Orally administered with cow butter   | 46                                |    |
|                           | Rheumatism                                  | Powder taken with milk and sugar  | 48                                |    |
|                           | Snake bite                                  | Powder orally taken. Paste applied on wounds and internally taken with ghee   | 47 and 52                         |    |
|                           | Spider and insect bite                      | Powdered and taken with vinegar   | 48                                |    |
|                           | Syphilis                                    | Root bark powder taken orally   | 46                                |    |
|                           | Latex                                       | Boils   | Applied externally                | 46 |
|                           |   | Black scar on the face  | Applied along with turmeric paste | 44 |
| Ascites                   |   | Applied externally  | 47                                |    |
| Liver and spleen disorder |   | Taken after dilution  | 47                                |    |
| Leprosy                   |   | Applied on the affected area  | 47                                |    |
| Migraine                  |   | Applied on the affected side vein of forehead   | 44                                |    |
| Piles (haemorrhoids)      |   | Applied externally  | 44                                |    |
| Dog/jackal bite           |   | Applied on wound  | 44 and 48                         |    |
| Ring worm                 |   | Applied externally  | 46                                |    |
| Scabies                   |   | Applied externally  | 46                                |    |
| Snake bite                |   | Applied on wounds or taken orally (20–30 drops for adults and 15–20 for infants)                                    | 46                                |    |
|                           |   | Five drops with 50 drops of distilled water injected hypodermally   | 46                                |    |
|                           |   | Applied externally with sesame oil  | 48 and 50                         |    |
|                           |   | Applied on affected tooth   | 48 and 50                         |    |
| Leaf                      | Vertigo                                     | Applied on affected parts   | 53                                |    |
|                           | Cold, cough, asthma and bronchitis          | Warmed along with ghee and bandaged on the chest of infants   | 44                                |    |
|                           | Calculus, liver and spleen disorder         | Powder taken orally   | 48                                |    |
|                           | Ear ache or ear troubles                    | Juice along with fermented boiled rice water used as ear drops  | 50                                |    |
|                           | Eczema and skin eruptions                   | Applied externally along with turmeric and sesame oil   | 48, 50 and 53                     |    |
|                           | Enlargement of abdominal viscera and spleen | Oral administration of powder   | 48 and 51                         |    |
|                           | Gonorrhoea                                  | Decoction used for washing and taken orally   | 51                                |    |
|                           | Inflammatory swellings                      | Covered on affected part after warming  | 51                                |    |
|                           | Joint pain                                  | Powder taken  | 47                                |    |
|                           | Malaria and intermittent fever              | Oral administration of fresh juice  | 46, 49 and 51                     |    |
|                           | Body pain                                   | Paste applied after warming   | 51                                |    |
|                           | Paralysis and sciatica                      | Massaged after preparing decoction with sesame oil  | 47                                |    |
|                           | Snake bite                                  | Oral administration of fresh juice  | 50                                |    |
|                           | Ulcers, wounds, sores                       | Powder orally administered or external application  | 47, 49 and 51                     |    |
| Flowers                   | Health tonic                                | Oral administration of powder   | 47                                |    |
|                           | Cough                                       | Burnt to produce ash, then taken with honey   | 44                                |    |
|                           | Rat bite                                    | Oral administration of powder   | 47 and 49                         |    |
|                           | Dog/jackal bite (rabies)                    | Seven tepals chewed with fine rice on seventh day of biting, continued for seven days decreasing one tepal everyday | 44                                |    |
|                           | Feet pain                                   | Decoction used for fomentation  | 46                                |    |
|                           | Epilepsy                                    | Oral administration of paste with black pepper  | 46                                |    |
|                           | Asthma and bronchitis                       | Fruit taken with jaggery  | 3                                 |    |
| Fruit                     | Liver and spleen disorder                   | Administered along with milk  | 46                                |    |
|                           | Eye disorder                                | Decanted ash water applied on eye lids  | 44                                |    |
|                           | Anemia                                      | Mixed with same quantity of red chilli, mineral salt and taken with milk.   | 46                                |    |
| Whole plant               | Rheumatic pain and hyperacidity             | Paste directly taken  | 44                                |    |
| Young twigs               | Purgative                                   | Juice taken   | 54                                |    |



Table 2 Brief summary of the pharmacological properties

| S. no. | Pharmacological activities                    | Parts/extracts/possible chemical constituents   | References  |
|--------|---|---|-------------|
| 1      | Wound healing potential                       | Latex: aqueous extract  | 67          |
|        |   | Latex   | 68          |
|        |   | Bark: ethanolic extract   | 69          |
|        |   | Leaves: aqueous extract   | 70          |
|        |   | Bark: aqueous extract   | 71          |
| 2      | Anticoccidial activity                        | Dried leaves powder   | 72          |
| 3      | Toxicity activity                             | Leaves: aqueous extract   | 73 and 74   |
|        |   | Leaves and stem bark extracts   | 75          |
|        |   | Leaves and stem: ethanolic extract  | 29          |
|        |   | Leaves: ethanolic extract   | 79          |
| 4      | Biopesticidal/insecticidal activity           | Leaves: extract   | 80 and 81   |
|        |   | Leaves: methanolic extract, latex protein fraction, flavonoids (quercetin-3-O-rutinoside) | 35          |
| 5      | Antimycoplasmal activity                      | Leaves: acetone extract   | 82          |
| 6      | Hepatoprotective activity                     | Root bark: methanolic extract   | 83          |
|        |   | Flowers: hydroethanolic extract   | 84          |
| 7      | Antimicrobial/antibacterial activity          | Roots: chloroform extract   | 85          |
|        |   | Leaves: methanolic extract, flavonoids (quercetin-3-O-rutinoside)                         | 86          |
|        |   | Leaves and latex: ethanol, aqueous, and chloroform extract                                | 87          |
|        |   | Leaves and stem: aqueous, ethanolic, methanolic extract                                   | 88 and 89   |
|        |   | Endophytic fungi of <i>C. procera</i>   | 90          |
|        |   | Seeds: chloroform extract   | 91          |
|        |   | Root: pet. ether, methanolic extract  | 92          |
|        |   | Flowers: ethanolic extract  | 93          |
|        |   | Latex   | 94          |
|        |   | Leaves: methanolic extract  | 95          |
|        |   | Leaves, flower, root bark: ethanolic extract  | 96          |
| 8      | Central nervous system activity               | Leaves and latex: aqueous, ethanolic extract  | 97 and 98   |
|        |   | Leaves: aqueous, methanolic extract   | 99          |
|        |   | Latex: aqueous extract  | 78          |
|        |   | Latex proteins  | 100         |
|        |   | Leaves, flower, fruit, latex  | 101         |
|        |   | Leaves: aqueous, methanolic extract, quercetin and its derivatives                        | 76          |
|        |   | Leaves: aqueous and methanolic extract  | 102         |
| 9      | Antioxidant activity                          | Leaves, flowers and fruits: methanolic extract  | 103         |
|        |   | Bark: ethanolic extract   | 69          |
|        |   | Latex protein   | 104         |
|        |   | Flowers: crude powder, aqueous and methanolic extract                                     | 105         |
| 10     | Antinociceptive activity                      | Latex: fresh, dried aqueous extract   | 106 and 107 |
|        |   |   |             |
| 11     | Antihelmintic activity                        |   | 108 and 109 |
|        |   | Dry latex   | 110         |
|        |   | Stem bark: chloroform and hydro-alcoholic extract   | 77          |
|        |   | Latex: hexane, dichloromethane, ethyl acetate, <i>n</i> -butanol and aqueous extract      | 111         |
|        |   | Latex: pet. ether, acetone, methanol extract  | 112         |
|        |   | Leaves: aqueous extract   | 93          |
|        |   | Flowers: ethanolic extract  | 45          |
|        |   | Bark: Arkamula Tvarka (Ayurvedic preparation)   | 113         |
|        |   | Latex   | 114         |
|        |   | Aqueous bark extract  | 115         |
| 12     | Antifungal activity                           | Leaves: aqueous, methanol, acetone and ethanol extract                                    | 116         |
|        |   | Root bark   | 117         |
|        |   | Latex   | 118         |
| 13     | Antimycotic activity against dermatophytes    | Fresh latex   | 119         |
|        |   | Crude latex and ethanolic extract of leaf   | 120         |
| 14     | Antimycofloral activity (fungi in wheat)      | Leaves: ethanolic extract   | 121         |
|        |   | Leaves: aqueous extract   | 122         |
|        |   | Flower, young bud, mature leaves and stems: ethanolic extract                             | 123         |
|        |   | Flowers: aqueous extract  | 124         |
|        |   | Latex   | 125         |
| 15     | Larvicidal activity                           | Latex   | 125         |
| 16     | Tobacco mosaic virus (TMV) inhibitor activity | Ethanolic extract of roots  | 125         |
|        |   |   |             |
| 17     | Antifertility activity                        |   |             |



Table 2 (Contd.)

| S. no. | Pharmacological activities           | Parts/extracts/possible chemical constituents                       | References |
|--------|--------------------------------------|---|------------|
|        |                                      | Leaves: ethanolic extract   | 79         |
|        |                                      | Roots (calotropin)  | 59         |
|        | Abortifacient activity               | Latex   | 126        |
|        | Antisperm activity                   | Root: chloroform extract  | 127        |
|        | Oestrogenic/antiovarulatory activity | Roots: ethanolic and aqueous extract                                | 128        |
| 18     | Plasma clotting activity             | Protein fraction isolated from fresh latex                          | 129        |
| 19     | Antiplasmodial activity              | Different plant parts: ethyl acetate, ethanolic and acetone extract | 130        |
|        |                                      | Leaves extract  | 131        |
| 20     | Antipyretic activity                 | Dry latex: aqueous extract  | 132        |
|        |                                      | Flowers: ethanolic extract  | 93         |
| 21     | Antiasthmatic activity               | Flowers   | 133        |
| 22     | Anticonvulsant activity              | Root extracts   | 134        |
| 23     | Cytotoxic activity                   | Root (2''-oxovoruscharin)   | 62         |
|        |                                      | Laticifer proteins (LP) recovered from latex                        | 135        |
|        |                                      | Root: methanolic, aqueous, ethyl acetate, hexane extracts           | 136        |
|        |                                      | Plant: methanolic extract   | 137        |
|        |                                      | Stems: uzarigenin   | 138        |
|        |                                      | Root bark: calotropocerosol A                                       | 139        |
|        |                                      | Root: alcoholic, hydro-aqueous and aqueous                          | 140        |
|        |                                      | Leaf: ethanolic extract   | 149        |
| 24     | Analgesic activity                   | Flowers: Ethanolic extract  | 93         |
| 25     | Antihyperglycemic activity           | Leaves: pet ether, methanol and aqueous extracts                    | 141        |
| 26     | Antiarthritis activity               | Latex   | 142        |
|        |                                      | Protein sub fraction of latex                                       | 143        |
| 27     | Antimolluscicidal activity           | Latex: 95% aqueous ethanol (uscharin)                               | 144        |
| 28     | Antitermites activity                | Latex   | 145        |
| 29     | Antimigraine activity                | Dried terminal leaves   | 146        |
| 30     | Anti-ulcer activity                  | Root: chloroform extract  | 147        |
|        |                                      | Plant: 50% ethanolic extract  | 148        |
|        |                                      | Leaf: ethanolic extract   | 149        |
|        |                                      | Stem bark: chloroform and hydroalcoholic extract                    | 110        |
| 31     | Spasmolytic activity                 | Plant: aqueous extract  | 150        |
| 32     | Allelopathic activity                | Leaves: aqueous extract   | 151        |
| 33     | Anti-keloidal activity               | Latex   | 68         |
| 34     | Anti-hyperbilirubinemic activity     | Leaves: aqueous extract   | 70         |
| 35     | Antiapoptotic activity               | Latex   | 152        |

regime (50%) which can be considered as a compensatory mechanism. Further Ramadana *et al.*<sup>31</sup> studied the influence of light and irrigation on cumulation of  $\beta$ -sitosterol in *C. procera*. They hypothesized that  $\beta$ -sitosterol biosynthesis pathway supported the plant to bear drought and light intensity stress.

### 2.3 Commercial prospective

**2.3.1 As biofuel.** *C. procera* is rich in hydrocarbons and contains biologically degradable materials similar to that found in other agricultural crops. Traore<sup>32</sup> conducted fermentation experiments and found that it is a good substrate for biogas synthesis. Barbosa *et al.*<sup>33</sup> found that oil composition of its seeds varies from 19.7 to 24.0% which proves its future potential as biodiesel, specially in those areas where people rely mainly on wood as source of energy production.

**2.3.2 As biopesticide.** Laticifer proteins (LP) from *Calotropis procera* were assayed for insecticidal activity against different crop pests to assess the biological role of latex. Diets

containing 4% latex led to decreased weight gain ( $ED_{50} = 3.07\%$ ) and affected survival ( $LD_{50} = 4.61\%$ ) of third instars of *Ceratitis capitata*.<sup>34</sup> The crude flavonoid fraction (Cf), the latex protein fraction (LP) and the leaf methanolic extract showed significant insecticidal activity.<sup>35</sup> These studies suggest that it can be developed as natural biopesticidal agent.

### 2.4 Industrial prospective

**2.4.1 Cheese making agent.** In West Africa, crude aqueous extract of *C. procera* is used as milk clotting enzyme in traditional method of cheese production.<sup>36</sup> It displayed an optimum activity at a temperature of 75 °C, which is essential for cheese production.<sup>37</sup> Calotropain enzyme found in the plant is more efficient than papain, ficin and bromelin, moreover it can lead to milk coagulation, digestion of meat, casein and gelatin.<sup>38,39</sup> These studies supported its traditional use as cheese making agent.

**2.4.2 As surfactant.** *C. procera* milk latex was used as a surfactant for facile synthesis of  $Eu^{3+}$  activated  $La(OH)_3$  and



Table 3 Summary of cytotoxic studies of *C. procerca*

| <i>C. procerca</i> : plant part/chemical constituent   | Cancer cell lines/model  | Method of analysis/assay   | Mechanism of action/investigation  | Observation  | References |
|--|--|--|--|--|------------|
| Uscharin and its derivatives<br>2'-Oxovoruscharin and its derivatives  | Lung cancer (A549)<br>Two glioblastoma (Hs683, U373) and two colon cancer (HCT-15 and LoVo)                  | MTT colorimetric assay, intraperitoneal (ip) injection-related toxicity  | Na <sup>+</sup> /K <sup>+</sup> -ATPase inhibition activity  | Cardenolides derived from 2'-oxovoruscharin exhibited significant <i>in vitro</i> antitumor activity and high <i>in vivo</i> tolerance                                 | 62         |
| Laticifer proteins (LP) recovered from latex   | HL60 (promyelocytic leukemia), HCT-8 (colon), MDA-MB-435(breast), SF-295(brain)                              | 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide MTT     | LP is a target for DNA topoisomerase I triggering apoptosis in cancer cell lines   | IC <sub>50</sub> values for LP ranged from 0.42 to 1.36 µg mL <sup>-1</sup> to SF-295, MDA-MB-435 respectively   | 135        |
| Root: methanolic, aqueous, ethyl acetate, hexane extracts (1, 5, 10, 25 µg mL <sup>-1</sup> )  | Human Hep 2  | Tetrazolium bromide (MTT), colorimetry                                   | Treatment initiated apoptotic mechanism by blocking the cell cycle at S-phase and thus preventing cells from entering proliferative (G2/M) phase   | Ethyl acetate extract showed strongest cytotoxic effect  | 136        |
| Plant: methanolic extract (0, 5, 10, 20 and 40 µg mL <sup>-1</sup> )   | Human skin melanoma cells (SK-MEL-2)   | Annexin-V FITC flow cytometry method, MTS assay                          | Methanolic extract induced apoptosis as shown by the accumulation of cells in the G2/M phase and the decrease of cell percentage in the G0/G1 phase  | At 40 µg mL <sup>-1</sup> late apoptotic cell percentage was increased up to 80%. <i>C. procerca</i> exerted cytotoxic potential                                       | 137        |
| 5-Hydroxy-3,7-dimethoxyflavone-4-O-β-glucopyranoside; uzarigenin; β-anhydroepidigitoxigenin; 2β,19-epoxy-3β,14β-dihydroxy-19-methoxy-5-α-card-20(22)-enolide; β-anhydroepidigitoxigenin-3β-O-glucopyranoside | HT 29, HepG2 (human cancer cell lines), NIH-3T3 (mouse fibroblast cell line)                                 | CellTiter-Blue® cell viability assay                                     | —  | Uzarigenin showed moderate cytotoxicity  | 138        |
| Calotropoceryl acetate A; calotropoceryl taraxasterol; calotropursenyl acetate B; stigmasterol; (E)-octadec-7-enoic acid   | A549 non-small cell lung cancer (NSCLC), the U373 glioblastoma (GBM) and the PC-3 prostate cancer cell lines | 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay | Growth inhibition action   | Calotropoceryl A exhibited <i>in vitro</i> growth inhibitory activity in all the three cancer cell lines with effects comparable to those of cisplatin and carboplatin | 139        |
| Calotroposide I; calotroposide J; calotroposide K; Calotroposide L; calotroposide M; calotroposide N   | A549 non-small cell lung cancer (NSCLC), U373 glioblastoma (GBM), and PC-3 prostate cancer cell lines        | MTT colorimetric assay   | Calotroposide K and M exhibited subnanomolar growth inhibition activity with IC <sub>50</sub> ranging from 0.5 to 0.7 µM against U373 glioblastoma (GBM) and PC-3 prostate cancer cell lines | <i>C. procerca</i> exhibited cytotoxic potential   | 153        |
| Calotroposide S  | PC-3 prostate cancer, A549 non-small cell lung cancer (NSCLC), and U373 glioblastoma (GBM) cell lines        | MTT colorimetric assay   | Calotroposide S showed potent anti-proliferative activity  | <i>C. procerca</i> exerted anti-proliferative activity   | 154        |
| Latex: hexane, chloroform, ethyl acetate and aqueous extract. Calactin; 15β-hydroxy calactin;  | A549 (lung) and hela (cervix) cancer cell lines using cisplatin as a positive control                        | MTT colorimetric assay   | Growth inhibition action   | Highest cytotoxic activity was displayed by chloroform extract. Amongst isolated compounds,  | 65         |



Table 3 (Contd.)

| Cancer cell lines/chemical constituent   | Cancer cell lines/model | Method of analysis/assay     | Mechanism of action/investigation                             | Observation   | References |
|--|-------------------------|------------------------------|---|---|------------|
| afroside; uscharin; 15 $\beta$ -hydroxy uscharin; calotoxin; 12 $\beta$ -hydroxycoroglaucigenin; afroginin; calactoprocin; procegenin A; procegenin B  |                         |                              |   | calactin displayed highest cytotoxic activity   |            |
| Root: alcoholic, hydro-aqueous and Human oral (KB) and central aqueous extracts(10 $\mu\text{g mL}^{-1}$ , 30 $\mu\text{g}$ nervous system (SNB-78) cancer cell $\text{mL}^{-1}$ , 100 $\mu\text{g mL}^{-1}$ ) |                         | Sulforhodamine-B (SRB) assay | Alcoholic extract showed significant growth inhibition action | <i>C. procera</i> roots exhibited <i>in vitro</i> cytotoxicity against oral and CNS human cancer cell lines | 140        |

La<sub>2</sub>O<sub>3</sub> nanophosphors through green mediated hydrothermal route. The latex reflected good capping potency for controlling the morphology and phase of the nanophosphor.<sup>40</sup> Hence its latex can be a good source of natural surfactant.

**2.4.3 As corrosion inhibitor.** Extract of *C. procera* was studied for its corrosion inhibition action by weight loss, electrochemical, SEM and UV methods, significant corrosion inhibitive effect in sulphuric acid medium on mild steel was observed.<sup>41</sup> Hence, it can be used as green corrosion inhibitor.

**2.4.4 As dehairing agent of leather.** Latex peptidases of *C. procera* when assayed against skin representative substrates, revealed complete dehairing process, while no changes in leather structure were observed. Thus, it can be an appropriate environment friendly dehairing agent as compared to toxic sodium sulphite treatment for tanneries.<sup>42</sup>

### 3. Ethnomedicinal uses

An insight into Ayurveda, Unani and folk uses of different parts of *C. procera* and *C. gigantea* to cure various ailments was compiled by Misra *et al.*<sup>43</sup> Ethnomedicinal uses of plant parts of *C. procera* in curing various diseases have been summarized in Table 1.

### 4. Major milestone of *Calotropis* phytochemistry

Phytochemistry of *Calotropis procera* has always attracted the attention of researchers because despite its toxicity, it employs wide applications in traditional medicinal system till date. Dating back to 1936, Hesse *et al.*<sup>55</sup> identified calotropin as the first compound from this plant. Further Hesse and his coworkers<sup>56,57</sup> isolated heart poisons or cardiac glycosides namely calotropin, calotoxin, calactin, uscharin, voruscharin and uscharidin.<sup>58</sup> Root powder of this plant is used in tribes to induce abortion in women and as an uterotonic since ancient period. Later it was found that it was due to the compound calotropin. Gupta *et al.*<sup>59</sup> administered calotropin to gerbils and rabbits and observed reduction in spermatids count by 65% and 94% respectively.

In 1955, Rajagopalan *et al.*<sup>60</sup> identified chemical constituents of seed *viz.* coroglaucigenin, corotoxigenin and frugoside (cardenolides). Later Bruschiweiler *et al.*<sup>61</sup> identified three additional cardenolides *viz.* uzarigenin, syriogenin and procerosid. A novel cardenolide, 2''-oxovoruscharin was isolated from the root bark by Quaquebeke *et al.*<sup>62</sup> and modified into its semi-synthetic derivative, *i.e.*, UNBS1450. Akhtar and Malik<sup>63</sup> isolated a new cardenolide named proceragenin from the hexane-insoluble fraction of *C. procera*.

A fascinating feature of the plant is its potential to curb Alzheimer's disease (AD), the most predominant root cause of dementia, a neurodegenerative disease. Its dried latex showed attenuation of  $\beta$ -amyloid deposition in mouse brain and cerebral protective activities.<sup>64</sup> Hence, it is imperative to evaluate the mechanism of metabolites, so that it can lead to promising direction to search new scaffolds for AD treatment. In 2015,

Table 4 Summary of *in vivo* studies of wound healing potential of *C. procera*

| Model                   | <i>C. procera</i> extract/dose/duration                                  | Negative control             | Investigation  | Result                                   | References |
|-------------------------|--|------------------------------|--|--|------------|
| Guinea pigs             | 20 mL of 1.0% sterile solution of the latex twice daily for 7 days       | Excision wounds              | Wounds exhibited marked dryness, no visual sign of inflammation  | Significant prohealing property          | 67         |
| Male albino-Wistar rats | Ethanol extract of bark (50 mg per wound)                                | Incision and excision wounds | Extract demonstrated wound healing effect by accelerating wound closure and epithelialization  | Excellent dermal wound healing potential | 69         |
| Wistar rats             | Aqueous extract of <i>C. procera</i> (25 mg and 50 mg kg <sup>-1</sup> ) | Incision and excision wounds | Significant ( $P < 0.05$ ) increase in breaking strength and percentage wound contractions with decreased epithelization period was observed | Significant wound healing property       | 70         |

Mohamed *et al.* isolated three non-glycosidic cardenolides namely calactoprocen, procegenin A and procegenin B from the latex.<sup>65</sup>

A patent claimed that polar extract of *C. procera* showed anti-ulcerative colitis activity in dose-dependent manner in a subject mammal and was found to be more effective than the standard drug Prednisolone.<sup>66</sup>

## 5. Pharmacology

Over the last many years, researchers have carried out numerous pharmacological activities, which are summarized in Table 2.

The details enumerated in the Table 2 is indicative of the fact that the different plant parts demonstrate large number of

Table 5 Summary of *in vivo* anti-inflammatory potential of *C. procera*

| Model                                   | <i>C. procera</i> extract/dose/duration  | Negative control   | Investigation  | Result  | References |
|---|--|--|--|---|------------|
| Male albino rats and albino guinea pigs | 50 mg, 200 mg 500 mg and 1 g kg <sup>-1</sup> dry latex  | Carrageenan-induced oedema test, cotton pellet granuloma and vascular permeability <i>etc.</i> | Dry latex suppressed fluid exudation, due to its influence on vascular permeability and also delayed the onset and intensity of UV induced erythema  | Significant anti-inflammatory potential                       | 108        |
| Male albino rats                        | Dry latex  | Carrageenin and formalin-induced pedal oedema test   | At dose 5 mg per rat, showed 71% inhibition in the case of the carrageenin-induced oedema ( $P < 0.005$ ) and 32% inhibition for the formalin-induced oedema ( $P < 0.05$ ). At higher dose (50 mg per rat), 96% and 98%, for carrageenin- and formalin-induced oedema groups respectively | Potent anti-inflammatory activity                             | 109        |
| Albino rats of either sex               | Stem bark: chloroform and hydro-alcoholic extract  | Carrageenan-induced paw oedema   | Significant reduction in the inflammation at 100, 200 and 400 mg kg <sup>-1</sup> displayed by chloroform extract  | Significant anti-inflammatory potential                       | 110        |
| Male Wistar rats                        | Dry latex: petroleum ether, acetone, methanol and aqueous extracts (50 mg per rat)   | Carrageenan induced paw oedema   | Maximum anti-inflammatory effect (59% and 53% inhibition) by the aqueous and acetone extracts respectively compared to (63%) inhibition exhibited by phenylbutazone  | Latex of <i>C. procera</i> exerted anti-inflammatory property | 111        |
| Male Wistar rats                        | Crude latex: hexane, dichloromethane, ethyl acetate, <i>n</i> -butanol and aqueous fractions (1.0, 5.0 or 10.0 mg kg <sup>-1</sup> and 0.2 mL) | Carrageenan-induced peritonitis  | Dichloromethane, ethyl acetate, and aqueous fractions inhibited carrageenan-induced neutrophil migration in rats at the ratios 67%, 56%, and 72%, respectively   | Latex of <i>C. procera</i> possess anti-inflammatory property | 77         |





Table 6 Summary of larvicidal potential of *C. procera*

| Vector species  | <i>C. procera</i> extract/dose/duration  | Observation  | Result  | References |
|---|--|--|---|------------|
| <i>Culex quinquefasciatus</i> 3 <sup>rd</sup> instar larvae   | Crude latex and ethanolic extract of leaves  | 100% larval mortality at 300 ppm concentration of latex and at 1000 ppm concentration of ethanolic leaf extract. LC <sub>50</sub> values of the latex and ethanolic leaves extract were 57.3 and 388.7 ppm respectively                              | Crude latex exerted stronger larvicidal potential than ethanolic extract  | 119        |
| <i>Musca domestica</i> 3 <sup>rd</sup> instar larvae  | Ethanolic extract of leaves (500 mg L <sup>-1</sup> )  | 100% mortality at 500 ppm. LC <sub>50</sub> value of the extract 282.5 ppm   | Leaves exerted insecticidal potential   | 120        |
| <i>Anopheles arabiensis</i> and <i>Culex quinquefasciatus</i> 2 <sup>nd</sup> , 3 <sup>rd</sup> , 4 <sup>th</sup> instar larvae | Aqueous extract of leaves (1000, 500, 200 ppm)   | LC <sub>50</sub> value 273.53, 366.44, 454.99 ppm for 2 <sup>nd</sup> , 3 <sup>rd</sup> and 4 <sup>th</sup> instar larvae  | Leaves showed oviposition deterrent, larvicidal and adult emergence activity  | 121        |
| <i>Anopheles stephansi</i> 3 <sup>rd</sup> instar larvae  | Ethanolic extracts of different parts <i>viz.</i> flower, young bud, mature leaves and stems (100 to 5000 ppm) | Mature leaves extract exhibited 100% mortality at 2000 ppm after 48 hours of incubation  | Mature leaves showed high larvicidal activity against tested larvae   | 122        |
| <i>Culex</i> species 4 <sup>th</sup> instar   | Aqueous extract of flowers (1%, 2.5% and 5%)/24 h  | At 1% concentration, the mortality rate was 0%, 60% and 100% and at 2.5% concentration, mortality rate was 20%, 80% and 100% at the end of 1, 3 and 4 days of exposure, and at 5% concentration, 100% mortality was recorded at the end of third day | Flowers exhibited remarkable larvicidal properties against the pupae and late 4 <sup>th</sup> instar larvae of <i>Culex</i> sp. | 123        |

Table 7 Summary of *in vivo* and *in vitro* studies of anthelmintic potential of *C. procera*

| Model   | <i>C. procera</i> extract/dose  | Compared with drug | Observation  | Result   | References |
|---|---|--------------------|--|--|------------|
| <i>In vivo</i> : sheep infected with mixed species of nematodes <i>in vitro</i> : <i>Haemonchus contortus</i> | Crude powder (CP), crude aqueous (CAE) and crude methanolic extracts (CME)  | Levamisole         | 88.4%, 77.8% and 20.9% reduction in egg count percent for CAE, CP and CME respectively   | Aqueous extract of <i>C. procera</i> has good anthelmintic potential         | 105        |
| Earthworms  | Aqueous extract of dry latex (5, 10, 50 and 100 mg mL <sup>-1</sup> ) and fresh latex (1.45, 7.25, 29, 72.5 and 145 mg mL <sup>-1</sup> ) | Piperazine         | At 5 to 10 mg mL <sup>-1</sup> concentration paralysis at 90 min, at 100 mg mL <sup>-1</sup> death within 60 min. Fresh latex also showed dose-dependent paralysis | Latex showed wormicidal activity, hence can be used as an anthelmintic agent | 106        |

pharmacological activities. Moreover, maximum number of activities were conducted at extract level, therefore horizons for further research is still bright, wherein the active principle constituents responsible for the activities may be identified. Here some of the very vital biological activities are being discussed in detail.

### 5.1 Cytotoxic potential

Various phytoconstituents and plant extracts were examined for their *in vitro* anticancer potential on various cancer cell lines,

and showed significant cytotoxic activities as summarized in Table 3.

Over past decade, cytotoxic activities of various extracts and chemical constituents of *C. procera* have been carried out. Majority of studies were conducted on various cancer cell line models *in vitro*, except the one conducted using UNBS1450. UNBS1450, a semi-synthesized cardenolide was compared to reference anticancer agents and classic cardenolides in prostate cancer cell line *in vitro* and *in vivo* following s.c. (subcutaneous) and orthotopic prostate cancer cell grafting into mice; it was



Table 8 Summary of *in vitro* studies of antioxidant potential of *C. procera*

| <i>C. procera</i> part            | Extract/dose/duration  | Investigation                 | Result  | References |
|-----------------------------------|--|-------------------------------|---|------------|
| Leaves, fruits, flowers and latex | Methanolic solution of dried extract   | DPPH radical scavenging assay | Leaves exhibited maximum DPPH radical scavenging activity with $IC_{50} = 0.18 \text{ mg mL}^{-1}$ , whereas latex showed minimum activity with $IC_{50} = 0.42 \text{ mg mL}^{-1}$ | 101        |
| Leaves                            | Aqueous and methanolic extract (1, 5, 10, 50, 100 and $500 \mu\text{g mL}^{-1}$ )  | DPPH radical scavenging assay | $IC_{50}$ of the methanol extract was $110.25 \mu\text{g mL}^{-1}$ , the aqueous extract showed mild antioxidant activity   | 102        |
| Leaves                            | $2\text{--}100 \text{ mg mL}^{-1}$ for quercetin in methanol and $20\text{--}100 \text{ mg mL}^{-1}$ for AME and quercetin derivatives with different methoxy substitution | DPPH radical scavenging assay | Varying degrees of antioxidant activity was exerted by quercetin derivatives, but quercetin was found to be most active   | 76         |
| Leaves, flowers and fruits        | Methanolic extracts of the samples of different concentrations (100–1000 ppm)  | DPPH radical scavenging assay | $IC_{50}$ values in leaves, fruits and flowers were 16.08, 16.06 and $10.31 \mu\text{g mL}^{-1}$ respectively, showing strong antioxidant activity of <i>C. procera</i>             | 103        |

Table 9 Summary of *in vitro* schizontocidal activity of *C. procera*

| Model   | <i>C. procera</i> extract/dose   | Investigation   | Result  | References |
|---|--|---|---|------------|
| Chloroquine sensitive strain, MRC 20 and a chloroquine resistant strain, MRC 76 of <i>Plasmodium falciparum</i> | Ethyl acetate, acetone, methanol fractions of flower, bud, root: ( $62\text{--}125 \text{ mg mL}^{-1}$ ) | Percentage inhibition varied from 7.51 to 61.38% between the various fractions against MRC 20 and for MRC 76, percentage inhibition varied from 3.437 to 41.08% between the various fractions | At the lower dose range, the root extracts of <i>C. procera</i> found to be the most effective for both <i>P. falciparum</i> MRC 20 and MRC 76. Hence, <i>C. procera</i> exerted antiplasmodial potential | 130        |

Table 10 Summary of *in vivo* hepatoprotective potential of *C. procera*

| Model                     | <i>C. procera</i> extract/dose   | Negative control              | Investigation  | Result   | References |
|---------------------------|--|-------------------------------|--|--|------------|
| Albino rats of either sex | Methanol extract (MCP) of root and its sub fractions <i>viz.</i> hexane (HCP), ethyl acetate (ECP) and chloroform (CCP) ( $200 \text{ mg kg}^{-1}$ ) | Carbon tetra chloride         | MCP and its sub fractions HCP, ECP displayed hepatoprotective effect by reducing the elevated serum levels of, serum glutamic pyruvic transaminase, alkaline phosphatase and serum glutamic oxaloacetic transaminase, it increased high density lipoprotein. CCP does not show effective results | <i>C. procera</i> exerted hepatoprotective potential   | 83         |
| Wistar rats of either sex | Hydro-ethanolic extract of <i>C. procera</i> flowers ( $200 \text{ mg kg}^{-1}$ and $400 \text{ mg kg}^{-1}$ )                                       | Paracetamol-induced hepatitis | Improvement in the hepatic architecture was observed   | <i>C. procera</i> flowers have hepatoprotective effect | 84         |



found to be more effective than tested reference compounds, such as mitoxantrone, taxol, oxaliplatin, irinotecan and temozolomide and less toxic than cardenolides.<sup>155,156</sup> Mechanism of UNBS1450 was studied and proven to be a potent sodium pump inhibitor as it inhibits NF- $\kappa$ B transactivation and triggers apoptosis by recruitment of pro-apoptotic Bak and Bax protein thereby leading to cell death.<sup>157,158</sup> Carrying out further *in vivo* studies will play a crucial role in ascertaining the safer use of UNBS1450. Therefore, further studies are necessary to obtain the clinically important lead molecules for the development of potent anticancer drugs.

## 5.2 Wound healing potential

*C. procera* has folk medicinal reputation as a wound healing agent. *In vivo* studies proved its wound healing potential as summarized in Table 4.

These data strongly support its ethnomedicinal use in wound healing potential and skin problems. *In vivo* screening showed considerable results in dose-dependent manner when compared to positive controls. A future perspective of studying the side effects and toxicity of the extracts at the dose level can also be unravelled.

## 5.3 Anti-inflammatory potential

Anti-inflammatory potential of extracts from *C. procera* have been summarized in Table 5.

On the basis of studies mentioned in Table 5, it can be concluded that the anti-inflammatory effect of dry latex needs to be further characterized as well as the nature of active principle leads responsible for anti-inflammatory activity remains to be identified.

## 5.4 Larvicidal/insecticidal potential

Aqueous and ethanolic extracts of leaves and other parts of *C. procera* showed significant larvicidal activities against various vector species as summarized in Table 6.

Above studies indicated that aqueous and ethanolic extracts of leaves of *C. procera* possessed phenomenal oviposition deterrent and larvicidal effect, thus it can be developed as environment friendly alternative for the synthetic insecticides for mosquito control.

## 5.5 Anthelmintic potential

*C. procera* is used as an anthelmintic by ruminant farmers as proved by activities summarized in Table 7.

## 5.6 Antioxidant potential

Leaves of *C. procera* displayed highest antiradical activity as evident from activities summarized in Table 8.

Above activities proved that quercetin, aqueous and methanolic extracts of leaves of *C. procera* possessed remarkable antiradical activity. Evaluation of the *in vivo* antioxidant potential would be indispensable, so that it can be used as natural antioxidant ingredients in food and drug industries.

## 5.7 Antiplasmodial potential

Traditional practitioners use *C. procera* as antimalarial agent. Activity summarized in Table 9.

Over past decades, reduction in efficiency of chloroquine has been observed, thus resistivity to antimalarial drugs can be a threat to control malaria. The hunt for analogues with reduced toxicity and improved antimalarial activity still prevails. The possibilities of finding active compounds and correlating with specific dose effective antimalarial activity, from those parts of the plant, which are used separately or together could be further pursued.

## 5.8 Hepatoprotective activity

*In vivo* experimental study proves that *C. procera* has hepatoprotective potential as summarized in Table 10.

## 5.9 Miscellaneous activities

Antiapoptotic activity of latex of *C. procera* was carried out by Sayed *et al.* (2016) on catfishes exposed to (100  $\mu\text{g L}^{-1}$ ) 4-nonylphenol as chemical pollutant. Significant ( $P < 0.05$ ) decrease in apoptotic cells, enzymes (superoxidase dismutase, acetylcholinesterase cortisol *etc.*) and ions validated antiapoptotic activity of the crude latex against the toxicity of 4-nonylphenol.<sup>152</sup> Hence, crude latex exerted antiapoptotic activities against the toxicity of 4-nonylphenol.

Anti-hyperbilirubinemic activity of leaves was evaluated using phenylhydrazine and paracetamol induced Wistar rats. Significant ( $P < 0.05$ ) decrease in concentrations of serum total bilirubin in hyperbilirubinemic rats proved bilirubin lowering activity of aqueous extracts of *C. procera*.<sup>70</sup>

Recent studies indicated that *C. procera* has significantly broader range of beneficial effects as it contains bioactive phytochemicals with therapeutic potential. By far only cytotoxic studies on cancer cell lines have been well established in clinical trials, whereas other activities have been evidenced by basic studies. Most of the studies are limited to *in vitro* studies which lack exploration of molecular mechanism of action. Therefore, mechanism based *in vitro* and *in vivo* studies should be carried out, which can lead to understanding of underlying mechanism related to traditional uses.

## 6. Phytochemistry

*C. procera* contains cardenolides, flavonoids, sterols, oxypregnanes triterpenoids, glycosides and other constituents as elaborated in Table 11.<sup>7</sup> Flavonoid and its glycosides (Fig. 1) are the major compounds isolated from the leaves of *C. procera*. Steroids (Fig. 2) and cardenolides (Fig. 3) are the major secondary metabolites found in the latex. Cardenolides have also been reported from other plant genera of the family Apocynaceae or Asclepiadaceae like *Strophanthus*, *Cerbera*, *Apocynum*, *Nerium*, and *Thevetia*.<sup>159</sup> Traditionally they are employed in curing of congestive heart failure.<sup>160</sup> Cardenolides are C23 steroids with steroid nucleus having a glycoside moiety at C-3 and a lactone moiety at C-17.<sup>6</sup> Cardiac glycosides can be novel antineoplastic agents as cancer cells are more prone to these compounds.<sup>159</sup> Terpenoids (ursane, olenane type and pentacyclic triterpenes *etc.*) (Fig. 4) have been



Table 11 Compounds isolated from *Calotropis procera*

| S. No.                         | Compound name (molecular formula)  | Extract/fraction                                 | Eluent  | Plant part & references  |
|--------------------------------|--|--|---|--|
| <b>Flavonoids</b>              |  |  |   |  |
| 1                              | 5-Hydroxy-3,7-dimethoxyflavone-4'-O-β-glucopyranoside (C <sub>23</sub> H <sub>24</sub> O <sub>11</sub> )   | Ethanol extract                                  | Benzene-chloroform  | Stem <sup>138</sup>  |
| 2                              | Isorhamnetin 3-O-β-D-rutinoside (C <sub>28</sub> H <sub>32</sub> O <sub>16</sub> )   | 85% methanolic extract                           | 10–40% methanol   | Leaves <sup>76,164</sup>   |
| 3                              | Isorhamnetin 3-O-β-D-robinoside (C <sub>28</sub> H <sub>32</sub> O <sub>16</sub> )   | 85% methanolic extract                           | 10–40% methanol   | Leaves <sup>76,164</sup>   |
| 4                              | Isoquercitrin (C <sub>21</sub> H <sub>20</sub> O <sub>12</sub> )   | 85% methanolic extract                           | 70% methanol  | Leaves <sup>76</sup>   |
| 5                              | Quercetagenin-6-methyl ether 3-O-β-D- <sup>4</sup> C <sub>1</sub> -galacturonopyranoside (C <sub>22</sub> H <sub>20</sub> O <sub>14</sub> )  | 85% methanolic extract                           | 40–60% methanol   | Leaves <sup>76</sup>   |
| 6                              | Quercetin (C <sub>15</sub> H <sub>10</sub> O <sub>7</sub> )  | 85% methanolic extract                           | 80% methanol  | Leaves <sup>76</sup>   |
| 7                              | Isorhamnetin (C <sub>16</sub> H <sub>12</sub> O <sub>7</sub> )   | 85% methanolic extract                           | 80% methanol  | Leaves <sup>76</sup>   |
| 8                              | Azaleatin (C <sub>16</sub> H <sub>12</sub> O <sub>7</sub> )  | 85% methanolic extract                           | 80% methanol  | Leaves <sup>76</sup>   |
| 9                              | 3,3'-Dimethoxy quercetin (C <sub>17</sub> H <sub>14</sub> O <sub>7</sub> )   | 85% methanolic extract                           | 50–60% ethyl acetate  | Leaves <sup>76</sup>   |
| 10                             | 3,6,3',4'-Tetramethoxy quercetin (C <sub>18</sub> H <sub>16</sub> O <sub>7</sub> )   | 85% methanolic extract                           | 50–60% ethyl acetate  | Leaves <sup>76</sup>   |
| 11                             | 3,6,7,3',4'-Pentamethoxy quercetin (C <sub>19</sub> H <sub>18</sub> O <sub>7</sub> )   | 85% methanolic extract                           | 60–100% ethyl acetate   | Leaves <sup>76</sup>   |
| 12                             | Kaempferol-3-O-rutinoside (C <sub>27</sub> H <sub>30</sub> O <sub>15</sub> )   | Methanolic extract                               | Ethyl acetate : water : formic acid : glacial acetic acid (100 : 26 : 11 : 11, v/v) | Leaves <sup>86</sup>   |
| 13                             | Quercetin-3-O-rutinoside (C <sub>27</sub> H <sub>30</sub> O <sub>16</sub> )  | Methanolic extract                               | Ethyl acetate : water : formic acid : glacial acetic acid (100 : 26 : 11 : 11, v/v) | Leaves <sup>86</sup>   |
| 14                             | Luteolin (C <sub>15</sub> H <sub>10</sub> O <sub>6</sub> )   | Ethanol–water extract (60 : 40)/butanol fraction | <i>n</i> -Hexane–acetone (70 : 30)  | Stem bark <sup>165</sup>   |
| 15                             | Epicatechin (C <sub>15</sub> H <sub>14</sub> O <sub>6</sub> )  | Ethanol–water extract (60 : 40)/butanol fraction | <i>n</i> -Hexane–acetone (60 : 40)  | Stem bark <sup>165</sup>   |
| 16                             | Kaempferol 3-O-α-L-rhamnopyranosyl-(1 → 6)-β-D-glucopyranoside (C <sub>27</sub> H <sub>30</sub> O <sub>15</sub> )  | Ethanol extract                                  | Water–methanol (1 : 1)  | Fruits <sup>149</sup>  |
| <b>Steroids</b>                |  |  |   |  |
| 17                             | Stigmasterol (C <sub>29</sub> H <sub>48</sub> O)   | Methanolic extract/hexane fraction               | Hexane–ethyl acetate  | Flowers, <sup>166</sup> root bark, <sup>139</sup> latex <sup>167</sup>   |
| 18                             | β-Sitosterol (C <sub>29</sub> H <sub>50</sub> O)   | Ethanol extract/chloroform fraction              | Hexane–ethyl acetate  | Flowers, <sup>166</sup> latex, <sup>167</sup> aerial part <sup>168</sup> |
| 19                             | Daucosterol or β-sitosterol glucoside (C <sub>35</sub> H <sub>60</sub> O <sub>6</sub> )  | Ethanol extract/chloroform fraction              | 10% aq. methanol and hexane   | Latex, aerial part, <sup>168</sup> roots <sup>169</sup>                  |
| 20                             | Benzoyllineolone (C <sub>28</sub> H <sub>36</sub> O <sub>6</sub> )   | Ether extract/chloroform fraction                | Benzene–chloroform  | Root bark <sup>170</sup>   |
| 21                             | Benzoylisolineolone (C <sub>28</sub> H <sub>36</sub> O <sub>6</sub> )  | Ether extract/chloroform fraction                | Benzene–chloroform  | Root bark <sup>170</sup>   |
| 22                             | Lineolone (C <sub>21</sub> H <sub>32</sub> O <sub>5</sub> )  | Ether extract                                    | —   | Root bark <sup>170</sup>   |
| 23                             | Isolineolone (C <sub>21</sub> H <sub>32</sub> O <sub>5</sub> )   | Ether extract                                    | —   | Root bark <sup>170</sup>   |
| 24                             | Cyclosadol (C <sub>31</sub> H <sub>52</sub> O)   | Methanolic extract                               | —   | Flowers <sup>166</sup>   |
| 25                             | β-Sitost-4-en-3-one (C <sub>29</sub> H <sub>48</sub> O)  | Methanolic extract                               | <i>n</i> -Hexane–ethyl acetate (95 : 5)   | Flowers <sup>166</sup>   |
| <b>Steroids : cardenolides</b> |  |  |   |  |
| 26                             | Calactin (C <sub>29</sub> H <sub>40</sub> O <sub>9</sub> )   | Ethanol extract/chloroform fraction              | 10% aq. methanol and hexane   | Roots, <sup>62</sup> latex, <sup>65</sup> aerial part <sup>168</sup>     |
| 27                             | 15β-Hydroxycalactin (C <sub>29</sub> H <sub>40</sub> O <sub>10</sub> )   | Ethanol extract/chloroform fraction              | —   | Latex <sup>65</sup>  |
| 28                             | Calactoprocine or 14β,15β-dihydroxy-19-oxo-2α,3β-[(2 <i>S</i> ,3 <i>S</i> :4 <i>R</i> ,6 <i>R</i> )-tetrahydro-3-hydroxy-4-methoxy-6-methyl-2 <i>H</i> -pyran-2,3-diyl]bis(oxy)-5α-card-20(22)-enolide (3'β-methoxy-15β-hydroxy calactin) (C <sub>30</sub> H <sub>42</sub> O <sub>10</sub> ) | Ethanol extract/chloroform fraction              | —   | Latex <sup>65</sup>  |
| 29                             | Afroside (C <sub>29</sub> H <sub>42</sub> O <sub>9</sub> )   | Ethanol extract/chloroform fraction              | —   | Latex <sup>65</sup>  |
| 30                             | Calotoxin (C <sub>29</sub> H <sub>40</sub> O <sub>10</sub> )   | Ethanol extract/chloroform fraction              | —   | Aerial part, <sup>168</sup> latex <sup>65</sup>                          |
| 31                             | Calotropin (C <sub>29</sub> H <sub>40</sub> O <sub>9</sub> )   | Ethanol extract/chloroform fraction              | —   | Root bark, <sup>62</sup> latex and aerial part <sup>168</sup>            |
| 32                             | 12β-Hydroxycoroglaucigenin (C <sub>23</sub> H <sub>34</sub> O <sub>6</sub> )   | Ethanol extract/chloroform fraction              | —   | Latex <sup>65</sup>  |



Table 11 (Contd.)

| S. No.                     | Compound name (molecular formula)  | Extract/fraction  | Eluent                               | Plant part & references  |
|----------------------------|--|---|--------------------------------------|--|
| 33                         | Procegenin A or 3 $\alpha$ ,12 $\beta$ ,14 $\beta$ -trihydroxy-19-hydroxymethyl-5 $\alpha$ -card-20(22)-enolide or 3- <i>epi</i> ,12 $\beta$ -hydroxycoroglaucigenin (C <sub>23</sub> H <sub>34</sub> O <sub>6</sub> ) | Ethanollic extract/<br>chloroform fraction                    | —                                    | Latex <sup>65</sup>  |
| 34                         | Procegenin B or 3 $\alpha$ ,12 $\beta$ ,14 $\beta$ -trihydroxy-19-oxo-5 $\alpha$ -card-20 (22)-enolide or 12 $\beta$ -hydroxy carpogenin (C <sub>23</sub> H <sub>32</sub> O <sub>6</sub> )                             | Ethanollic extract/<br>chloroform fraction                    | —                                    | Latex <sup>65</sup>  |
| 35                         | Afrogenin (C <sub>23</sub> H <sub>34</sub> O <sub>6</sub> )  | Ethanollic extract/<br>chloroform fraction                    | —                                    | Latex <sup>65</sup>  |
| 36                         | Desglucouzarin (C <sub>29</sub> H <sub>44</sub> O <sub>9</sub> )   | Ethanollic extract/<br>chloroform : ethyl acetate fraction    | Chloroform–methanol (9 : 1)          | Stem <sup>171</sup>  |
| 37                         | Frugoside (C <sub>29</sub> H <sub>44</sub> O <sub>9</sub> )  | Ethanollic extract/<br>chloroform : ethyl acetate fraction    | Chloroform–methanol (9 : 1)          | Seeds, <sup>60</sup><br>stem, <sup>171</sup> root<br>bark <sup>172</sup> |
| 38                         | Uzarigenin (C <sub>23</sub> H <sub>34</sub> O <sub>4</sub> )   | Ethanollic extract/<br>chloroform : ethyl acetate fraction    | Chloroform–methanol (9.5 : 0.5)      | Latex <sup>61</sup><br>Stem <sup>168,171,173</sup>                       |
| 39                         | Uzarigenone (C <sub>23</sub> H <sub>32</sub> O <sub>4</sub> )  | Ethanollic extract/<br>benzene                                | Chloroform–methanol (9.5 : 0.5)      | Stem <sup>171</sup>  |
| 40                         | $\beta$ -Anhydroepidigitoxigenin-3 $\beta$ -O-glucopyranoside (C <sub>29</sub> H <sub>42</sub> O <sub>8</sub> )  | Ethanollic extract/<br>benzene : chloroform                   | Chloroform–methanol (9 : 1)          | Stem <sup>138</sup>  |
| 41                         | $\beta$ -Anhydroepidigitoxigenin or 3 $\beta$ -hydroxy-5 $\alpha$ -carda-14(15),20(22)-dienolide (C <sub>23</sub> H <sub>32</sub> O <sub>3</sub> )   | Ethanollic extract →<br>benzene : chloroform                  | Chloroform–methanol (9 : 2)          | Stem <sup>138</sup>  |
| 42                         | Calotropagenin (C <sub>23</sub> H <sub>32</sub> O <sub>6</sub> )   | Chloroform extract  | Hexane–diethyl ether (9 : 11)        | Aerial part <sup>174</sup>   |
| 43                         | Ischarin (C <sub>31</sub> H <sub>41</sub> NO <sub>8</sub> S)   | Ethanollic extract  | Chloroform                           | Aerial part <sup>168</sup>   |
| 44                         | Ischaridin (C <sub>29</sub> H <sub>42</sub> O <sub>8</sub> )   | Ethanollic extract/10%<br>aq. methanol and hexane<br>fraction | Chloroform–methanol (98 : 2)         | Aerial part <sup>168</sup>   |
| 45                         | 2''-Oxovoruscharin (C <sub>31</sub> H <sub>41</sub> NO <sub>9</sub> S)   | Methanolic extract  | Dichloromethane–methanol<br>(98 : 2) | Root bark <sup>62</sup>  |
| 46                         | Proceraside A (C <sub>31</sub> H <sub>44</sub> O <sub>10</sub> )   | Methanolic extract/ethyl<br>acetate fraction                  | Chloroform–methanol                  | Root bark <sup>172</sup>   |
| 47                         | Syriogenin (C <sub>23</sub> H <sub>34</sub> O <sub>5</sub> )   | Methanolic extract  | Water–methanol                       | Latex <sup>61</sup>  |
| 48                         | Proceroside (C <sub>29</sub> H <sub>40</sub> O <sub>10</sub> )   | Methanolic extract  | Water–methanol                       | Latex <sup>61</sup>  |
| 49                         | Uscharidin (C <sub>29</sub> H <sub>38</sub> O <sub>9</sub> )   | Ethanollic extract  | —                                    | Aerial part <sup>56</sup>  |
| 50                         | Voruscharin (C <sub>31</sub> H <sub>43</sub> NO <sub>8</sub> S)  | Methanolic extract  | Acetone–methanol (8 : 2)             | Roots <sup>62</sup>  |
| 51                         | Coroglaucigenin (C <sub>23</sub> H <sub>34</sub> O <sub>5</sub> )  | Chloroform extract  | —                                    | Seeds <sup>60</sup>  |
| 52                         | Corotoxigenin (C <sub>23</sub> H <sub>32</sub> O <sub>5</sub> )  | Ether extract   | —                                    | Seeds <sup>60</sup>  |
| 53                         | 3-[ $\beta$ -(4-O- $\beta$ -D-Glucopyranosyl- $\beta$ -D-6-desoxyalloypyranosyl)oxy] uzarigenin (C <sub>35</sub> H <sub>54</sub> O <sub>13</sub> )   | 70% ethanollic extract/<br>benzene : chloroform               | Chloroform–methanol (9 : 1.5)        | Stem <sup>173</sup>  |
| 54                         | Uzarin or 3-[ $\beta$ -(2-O- $\beta$ -D-glucopyranosyl- $\beta$ -D-glucopyranosyl)oxy] uzarigenin (C <sub>35</sub> H <sub>54</sub> O <sub>14</sub> )   | 70% ethanollic extract/<br>benzene : chloroform               | Chloroform–methanol (9 : 2)          | Stem <sup>173</sup>  |
| 55                         | 15 $\beta$ -Hydroxyuscharin (C <sub>31</sub> H <sub>41</sub> NO <sub>9</sub> S)  | Ethanollic extract  | Chloroform                           | Latex <sup>65</sup>  |
| 56                         | Uscharin (C <sub>31</sub> H <sub>41</sub> NO <sub>8</sub> S)   | Methanolic extract  | Chloroform–methanol (70 : 30)        | Aerial part, <sup>168</sup><br>latex <sup>65,168</sup>                   |
| 57                         | Proceragenin or 7 $\beta$ ,14 $\beta$ -dihydroxy-5 $\alpha$ -card-20(22)-enolide (C <sub>23</sub> H <sub>34</sub> O <sub>4</sub> )   | Methanolic extract/<br>chloroform fraction                    | Hexane–chloroform (1 : 9)            | Aerial part <sup>63</sup>  |
| 58                         | 2 $\beta$ ,19-Epoxy-3 $\beta$ ,14 $\beta$ -dihydroxy-19-methoxy-5 $\alpha$ -card-20(22)-enolide (C <sub>24</sub> H <sub>34</sub> O <sub>6</sub> )  | Ethanollic extract/<br>benzene : chloroform<br>fraction       | Chloroform–methanol (9 : 2)          | Stem <sup>138</sup>  |
| 59                         | Procesterol or (24S)-24-ethyl-stigmast-4-en-6 $\alpha$ -ol-3-one (C <sub>29</sub> H <sub>48</sub> O <sub>2</sub> )   | Ethanollic extract/<br>chloroform fraction                    | Hexane–chloroform (3 : 2)            | Fresh and<br>undried<br>flowers <sup>176</sup>                           |
| <b>Terpenes/terpenoids</b> |  |   |                                      |  |
| 60                         | $\alpha$ -Amyrin (C <sub>30</sub> H <sub>50</sub> O)   | Methanolic extract/<br>hexane : ethyl acetate<br>gradients    | Dichloromethane–methanol<br>(1 : 1)  | Flowers <sup>176</sup>   |
| 61                         | $\beta$ -Amyrin (C <sub>30</sub> H <sub>50</sub> O)  | Methanolic extract/<br>hexane : ethyl acetate<br>gradients    | Dichloromethane–methanol<br>(1 : 1)  | Flowers <sup>176</sup>   |
| 62                         | $\alpha$ -Amyrin acetate (C <sub>32</sub> H <sub>52</sub> O <sub>2</sub> )   | Methanolic extract  | Pet. ether–chloroform (1 : 9)        | Roots <sup>169</sup>   |
| 63                         |  | Methanolic extract  | Pet. ether–chloroform (1 : 1)        | Roots <sup>177</sup>   |



Table 11 (Contd.)

| S. No.                             | Compound name (molecular formula)   | Extract/fraction                        | Eluent                                | Plant part & references                                     |
|------------------------------------|---|---|---------------------------------------|---|
| 64                                 | Procerursenyl acetate or urs-18 $\alpha$ -H-12,20(30)-diene-3 $\beta$ -yl acetate (C <sub>32</sub> H <sub>50</sub> O <sub>2</sub> )<br>Calotropenyl acetate or urs-19(29)-3 $\beta$ -yl acetate (C <sub>32</sub> H <sub>52</sub> O <sub>2</sub> )   | Chloroform extract                      | Benzene–hexane (60 : 40)              | Flower, <sup>175</sup> latex and aerial part <sup>168</sup> |
| 65                                 | Calotropoleanyl ester or olean-13(18)-en-3 $\beta$ -yl acetate (C <sub>32</sub> H <sub>52</sub> O <sub>2</sub> )  | Ethanol extract                         | Pet. ether                            | Root bark <sup>178</sup>                                    |
| 66                                 | Calatropocero A or urs-5,12,20(30)-trien-18 $\alpha$ H-3 $\beta$ -ol (C <sub>30</sub> H <sub>46</sub> O)  | Methanolic extract                      | <i>n</i> -Hexane–ethyl acetate        | Root bark <sup>139</sup>                                    |
| 67                                 | Calatropoceryl acetate A or urs-5,12,20(30)-trien-18 $\alpha$ H-3 $\beta$ -yl acetate (C <sub>32</sub> H <sub>48</sub> O <sub>2</sub> )   | Methanolic extract                      | <i>n</i> -Hexane–ethyl acetate        | Root bark <sup>139</sup>                                    |
| 68                                 | Calatropocero A or urs-5,12,20(30)-trien-18 $\alpha$ H-3-one (C <sub>30</sub> H <sub>44</sub> O)  | Methanolic extract                      | <i>n</i> -Hexane–ethyl acetate        | Root bark <sup>139</sup>                                    |
| 69                                 | Calatropoceryl acetate B or urs-5,12,20-trien-18 $\alpha$ H-3 $\beta$ -yl acetate (C <sub>32</sub> H <sub>48</sub> O <sub>2</sub> )   | Methanolic extract                      | <i>n</i> -Hexane–ethyl acetate        | Root bark <sup>139</sup>                                    |
| 70                                 | Calatropursenyl acetate B or urs-12,19(29)-diene-3 $\beta$ -yl acetate (C <sub>32</sub> H <sub>50</sub> O <sub>2</sub> )  | Methanolic extract                      | <i>n</i> -Hexane–ethyl acetate        | Root bark <sup>139,180</sup>                                |
| 71                                 | Pseudo-taraxasterol acetate (C <sub>32</sub> H <sub>52</sub> O <sub>2</sub> )   | Methanolic extract                      | <i>n</i> -Hexane–ethyl acetate        | Root bark <sup>139</sup>                                    |
| 72                                 | Taraxasterol (C <sub>30</sub> H <sub>50</sub> O)  | Methanolic extract                      | <i>n</i> -Hexane–ethyl acetate        | Root bark <sup>139</sup>                                    |
| 73                                 | Proceroleanol A or olean-13(18)-en-9 $\alpha$ -ol (C <sub>30</sub> H <sub>50</sub> O)   | Ethanol extract                         | Benzene–chloroform                    | Root bark <sup>178</sup>                                    |
| 74                                 | Proceroleanol B or olean-5,13(18)-dien-3 $\alpha$ -ol (C <sub>30</sub> H <sub>48</sub> O)   | Ethanol extract                         | Benzene–chloroform (1 : 1)            | Root bark <sup>178</sup>                                    |
| 75                                 | Cycloart-23-ene-3 $\beta$ ,25-diol (C <sub>30</sub> H <sub>50</sub> O <sub>2</sub> )  | Ethyl acetate extract                   | Hexane–ethyl acetate (2 : 1)          | Flowers <sup>166</sup>                                      |
| 76                                 | Lupeol (C <sub>30</sub> H <sub>50</sub> O)  | Ethanol extract                         | —                                     | Latex <sup>179</sup>  |
| 77                                 | 3- <i>epi</i> -Moretenol (C <sub>30</sub> H <sub>50</sub> O)  | Ethanol extract                         | —                                     | Latex <sup>179</sup>  |
| 78                                 | Multiflorenol (C <sub>30</sub> H <sub>50</sub> O)   | Pet. ether fraction                     | Chloroform–ethyl acetate (3 : 2)      | Flowers, <sup>166</sup> latex <sup>167</sup>                |
| 79                                 | Urs-19(29)-en-3 $\beta$ -ol (C <sub>30</sub> H <sub>50</sub> O)   | Acetone fraction                        | Pet. ether–acetone (8 : 2)            | Latex <sup>167</sup>  |
| 80                                 | Calotropenyl acetate or urs-19(29)-en-3-yl acetate (C <sub>32</sub> H <sub>52</sub> O <sub>2</sub> )  | Pet. ether fraction                     | Chloroform–ethyl acetate (3 : 5)      | Latex <sup>167</sup>  |
| 81                                 | 3 $\beta$ ,27-Dihydroxy-urs-18-en-13,28-olide (C <sub>30</sub> H <sub>46</sub> O <sub>4</sub> )   | Ethyl acetate fraction                  | Benzene–ethyl acetate (8 : 2)         | Latex <sup>167</sup>  |
| 82                                 | Calatropfriedelenyl acetate or friedelin-1-ene-3 $\beta$ -yl acetate (C <sub>32</sub> H <sub>52</sub> O <sub>2</sub> )  | Ethanol extract                         | —                                     | Root bark <sup>180</sup>                                    |
| 83                                 | Calotropterpenyl ester or 6,10,14-trimethylpentadec-6-enyl-2',4',8',12',16'-pentamethyl nonadecane ester (C <sub>42</sub> H <sub>82</sub> O <sub>2</sub> )  | Ethanol extract                         | —                                     | Root bark <sup>180</sup>                                    |
| 84                                 | Phytol iso-octyl ether or 3,7,11,15-tetramethyl hexadecanyl-6'-methyl hept-5'-enyl ether (C <sub>28</sub> H <sub>56</sub> O)  | Methanolic extract                      | Pet. ether–chloroform (1 : 3)         | Roots <sup>181</sup>  |
| 85                                 | Dihydrophytol tetraglucoside or 3,7,11,15-tetramethylhexadecanoyl- $\beta$ -D-glucopyranosyl-(2 $\rightarrow$ 1)- $\beta$ -D-glucopyranosyl-(2 $\rightarrow$ 1)- $\beta$ -D-glucopyranosyl (2 $\rightarrow$ 1)- $\beta$ -D-glucopyranosyl (2 $\rightarrow$ 1)- $\beta$ -D-glucopyranoside (C <sub>44</sub> H <sub>80</sub> O <sub>22</sub> )  | Methanolic extract                      | Chloroform–methanol (3 : 2)           | Roots <sup>181</sup>  |
| 86                                 | Procerasesterpenoyl triglucoside or 2,6,10,14,18-pentamethylnonadecanoyl- $\beta$ -D-glucopyranosyl-(2 $\rightarrow$ 1)- $\beta$ -D-glucopyranosyl-(2 $\rightarrow$ 1)- $\beta$ -D-glucopyranoside (C <sub>42</sub> H <sub>78</sub> O <sub>17</sub> )   | Methanolic extract                      | Chloroform–methanol (3 : 1)           | Roots <sup>181</sup>  |
| 87                                 | Oleanolic acid (C <sub>30</sub> H <sub>48</sub> O <sub>3</sub> )  | Chloroform extract/<br>butanol fraction | Benzene–ethyl acetate (10 : 1–1 : 10) | Stem bark <sup>165</sup>                                    |
| 88                                 | Lupeol-3-O-acetate (C <sub>32</sub> H <sub>52</sub> O <sub>2</sub> )  | Ethanol extract                         | Chloroform–methanol (9.3 : 0.7)       | Leaves <sup>149</sup>                                       |
| 89                                 | Proceraursenolide or 18- $\alpha$ H-urs-12-en-3,25-olide (C <sub>30</sub> H <sub>46</sub> O <sub>2</sub> )  | Ethanol extract                         | Pet. ether–chloroform (1 : 3)         | Roots <sup>183</sup>  |
| <b>Oxypregnane oligoglycosides</b> |   |   |                                       |   |
| 90                                 | Calatroposide H or 12-O-benzoylisolineolon-3-O- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-oleandropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-oleandropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl (C <sub>63</sub> H <sub>96</sub> O <sub>21</sub> )   | Methanolic extract/<br>butanol fraction | Chloroform–methanol (85 : 15)         | Root bark <sup>153</sup>                                    |
| 91                                 | Calatroposide I or 12-O-benzoylisolineolon-3-O- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-oleandropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-oleandropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-oleandropyranosyl (C <sub>63</sub> H <sub>96</sub> O <sub>21</sub> )   | Methanolic extract/<br>butanol fraction | Chloroform–methanol (85 : 15)         | Root bark <sup>153</sup>                                    |
| 92                                 | Calatroposide J or 12-O-benzoylisolineolon-3-O- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-oleandropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-oleandropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)-(6-O-acetyl)- $\beta$ -D-glucopyranoside (C <sub>71</sub> H <sub>108</sub> O <sub>27</sub> ) | Methanolic extract/<br>butanol fraction | Chloroform–methanol (85 : 15)         | Root bark <sup>153</sup>                                    |
| 93                                 | Calatroposide K or 12-O-benzoylisolineolon-3-O- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-   | Methanolic extract/<br>butanol fraction | Chloroform–methanol (85 : 15)         | Root bark <sup>153</sup>                                    |



Table 11 (Contd.)

| S. No.                                  | Compound name (molecular formula)  | Extract/fraction                               | Eluent                          | Plant part & references  |
|---|--|--|---------------------------------|--------------------------|
| 94                                      | oleandropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-cymaropyranosyl-(1 → 4)-β-D-glucopyranoside (C <sub>69</sub> H <sub>106</sub> O <sub>26</sub> )<br>Calotroposide L or 12-O-benzoylisolineolon-3-O-β-D-cymaropyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 4)-β-D-cymaropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-oleandropyranoside (C <sub>68</sub> H <sub>104</sub> O <sub>28</sub> ) | Methanolic extract/ <i>n</i> -butanol fraction | Chloroform-methanol (85 : 15)   | Root bark <sup>153</sup> |
| 95                                      | Calotroposide M or 12-O-benzoylisolineolon-3-O-β-D-cymaropyranosyl-(1 → 4)-β-D-cymaropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-oleandropyranoside-(1 → 4)-(6-O-acetyl)-β-D-glucopyranoside (C <sub>78</sub> H <sub>120</sub> O <sub>30</sub> )   | Methanolic extract/ <i>n</i> -butanol fraction | Chloroform-methanol (85 : 15)   | Root bark <sup>153</sup> |
| 96                                      | Calotroposide N or 12-O-benzoylisolineolon-3-O-β-D-cymaropyranosyl-(1 → 4)-β-D-cymaropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-glucopyranoside-(1 → 4)-β-D-gluopyranoside (C <sub>75</sub> H <sub>116</sub> O <sub>31</sub> )  | Methanolic extract/ <i>n</i> -butanol fraction | Chloroform-methanol (85 : 15)   | Root bark <sup>153</sup> |
| 97                                      | Calotroposide S or 12-benzoylisolineolon-3-O-β-D-cymaropyranosyl-(1 → 4)-β-D-cymaropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-cymaropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-oleandropyranosyl-(1 → 4)-β-D-oleandropyranoside (C <sub>84</sub> H <sub>132</sub> O <sub>30</sub> )  | Methanolic extract/ <i>n</i> -butanol fraction | Chloroform-methanol (85 : 15)   | Root bark <sup>154</sup> |
| <b>Aliphatic and phenolic glycoside</b> |  |  |                                 |                          |
| 98                                      | Methyl resorciny triglycoside or <i>O</i> -methyl resorciny-β-D-glucuronopyranosyl (2 → 1)-β-D-glucopyranosyl-(2 → 1)-β-D-glucopyranoside (C <sub>25</sub> H <sub>36</sub> O <sub>18</sub> ) (phenolic glycoside)  | Methanolic extract                             | Chloroform-methanol (3 : 2)     | Roots <sup>169</sup>     |
| 99                                      | Butanediol diglucuronoside or ( <i>n</i> -butan-1,4-diol-1,4-β-D-diglucuronopyranoside) (C <sub>16</sub> H <sub>26</sub> O <sub>14</sub> ) (aliphatic glycoside)   | Methanolic extract                             | Chloroform-methanol (4 : 1)     | Roots <sup>169</sup>     |
| 100                                     | ( <i>E</i> )-3-(4-Methoxyphenyl-2-O-β-D- <sup>4</sup> C <sub>1</sub> -glucopyranoside)-methyl propenoate (C <sub>17</sub> H <sub>22</sub> O <sub>9</sub> )   | 85% methanolic extract                         | 40–60% aqueous methanol         | Leaves <sup>76</sup>     |
| 101                                     | Methyl 4-O-β-D-glucopyranosyl ferulate (C <sub>17</sub> H <sub>22</sub> O <sub>9</sub> )   | Ethanol extract                                | Water-methanol (1 : 1)          | Flowers <sup>149</sup>   |
| <b>Lignan glycoside</b>                 |  |  |                                 |                          |
| 102                                     | 7'-Methoxy-3'- <i>O</i> -demethyl-tanegool-9-O-β-D-glucopyranoside (C <sub>26</sub> H <sub>34</sub> O <sub>12</sub> )  | Ethanol extract                                | Water-methanol (6 : 4)          | Flowers <sup>149</sup>   |
| 103                                     | Pinoresinol-4- <i>O</i> -glucoside (C <sub>26</sub> H <sub>32</sub> O <sub>11</sub> )  | Ethanol extract                                | Water-methanol (1 : 1)          | Flowers <sup>149</sup>   |
| 104                                     | Syringaresinol-4- <i>O</i> -glucoside (C <sub>28</sub> H <sub>36</sub> O <sub>13</sub> )   | Ethanol extract                                | Water-methanol (1 : 1)          | Fruits <sup>149</sup>    |
| <b>Terpene glycoside</b>                |  |  |                                 |                          |
| 105                                     | Labdan-18-ol-β-D-galactofuranoside (C <sub>26</sub> H <sub>48</sub> O <sub>6</sub> )   | Methanolic extract                             | Chloroform-methanol (9 : 1)     | Roots <sup>182</sup>     |
| 106                                     | Proceralabdanoside/labdan-3β-ol-11,15-olide-18,20-dioic acid-3β-D-galactofuranoside (C <sub>26</sub> H <sub>40</sub> O <sub>12</sub> )   | Methanolic extract                             | Chloroform-methanol (9 : 1)     | Roots <sup>182</sup>     |
| <b>Caffeic acid derivatives</b>         |  |  |                                 |                          |
| 107                                     | Methyl caffeate (C <sub>10</sub> H <sub>10</sub> O <sub>4</sub> )  | 85% methanolic extract                         | 30–50% aqueous methanol         | Leaves <sup>76</sup>     |
| 108                                     | Caffeic acid (C <sub>9</sub> H <sub>8</sub> O <sub>4</sub> )   | 85% methanolic extract                         | 30–50% aqueous methanol         | Leaves <sup>76</sup>     |
| 109                                     | Rosmarinic acid (C <sub>18</sub> H <sub>16</sub> O <sub>8</sub> )  | Ethanol extract                                | Chloroform-methanol (8.5 : 1.5) | Flowers <sup>149</sup>   |
| 110                                     | Methyl rosmarinate (C <sub>19</sub> H <sub>18</sub> O <sub>8</sub> )   | Ethanol extract                                | Chloroform-methanol (8.5 : 1.5) | Flowers <sup>149</sup>   |
| <b>Others</b>                           |  |  |                                 |                          |
| 111                                     | 2-Propenyl-2Z-hydroxyethyl carbonate   | —  | —                               | Leaves <sup>186</sup>    |
| 112                                     | Glyceryl mono-oleoyl-2-phosphate (C <sub>21</sub> H <sub>41</sub> O <sub>7</sub> P)  | Methanolic extract                             | Pet. ether-chloroform (1 : 3)   | Roots <sup>177</sup>     |
| 113                                     | Methyl behenate (C <sub>23</sub> H <sub>46</sub> O <sub>2</sub> )  | Methanolic extract                             | Chloroform-methanol (99 : 1)    | Roots <sup>177</sup>     |
| 114                                     | <i>N</i> -Dotriacont-6-ene (C <sub>32</sub> H <sub>64</sub> )  | Methanolic extract                             | Pet. ether-chloroform (3 : 1)   | Roots <sup>177</sup>     |
| 115                                     | Methyl myristate (C <sub>15</sub> H <sub>30</sub> O <sub>2</sub> )   | Methanolic extract                             | Chloroform                      | Roots <sup>177</sup>     |
| 116                                     | Glyceryl-1,2-dicapriate-3-phosphate (C <sub>23</sub> H <sub>45</sub> O <sub>8</sub> P)   | Methanolic extract                             | Chloroform-methanol (97 : 3)    | Roots <sup>177</sup>     |
| 117                                     | ( <i>E</i> )-Octadec-7-enoic acid (C <sub>18</sub> H <sub>34</sub> O <sub>2</sub> )  | Methanolic extract/ <i>n</i> -hexane fraction  | <i>n</i> -Hexane-ethyl acetate  | Root bark <sup>139</sup> |
| 118                                     | Proceranol or <i>n</i> -triacontan-10β-ol (C <sub>30</sub> H <sub>62</sub> O)  | Methanolic extract                             | Chloroform-methanol (99 : 1)    | Roots <sup>177</sup>     |
| 119                                     | Methyl ferulate  | Methanolic extract                             | Chloroform-methanol (8.5 : 1.5) | Flowers <sup>149</sup>   |
| 120                                     | 1,2-Dihexadecanoyl-3-phosphatyl glycerol (C <sub>35</sub> H <sub>69</sub> O <sub>8</sub> P)  | Methanolic extract                             | Chloroform-methanol (99 : 1)    | Roots <sup>181</sup>     |
| 121                                     |  | Methanolic extract                             | Pet. ether-chloroform (1 : 3)   | Roots <sup>183</sup>     |



Table 11 (Contd.)

| S. No. | Compound name (molecular formula)  | Extract/fraction   | Eluent                        | Plant part & references    |
|--------|--|--------------------|-------------------------------|----------------------------|
|        | <i>n</i> -Tetradecanyl palmitoleate/ <i>n</i> -tetradecanyl <i>n</i> -hexadec-9-enoate (C <sub>30</sub> H <sub>58</sub> O <sub>2</sub> ) |                    |                               |                            |
| 122    | Tricapryl glyceride (C <sub>33</sub> H <sub>62</sub> O <sub>6</sub> )  | Methanolic extract | Pet. ether                    | Roots <sup>183</sup>       |
| 123    | Oleodipalmityl glyceride (C <sub>53</sub> H <sub>100</sub> O <sub>6</sub> )  | Methanolic extract | Pet. ether–chloroform (9 : 1) | Roots <sup>183</sup>       |
| 124    | Tribehenyl glyceride (C <sub>69</sub> H <sub>134</sub> O <sub>6</sub> )  | Methanolic extract | Pet. ether–chloroform (1 : 1) | Roots <sup>183</sup>       |
| 125    | Capryl glucoside/ <i>n</i> -decanoyl-β-D-glucopyranoside (C <sub>16</sub> H <sub>31</sub> O <sub>7</sub> )                               | Methanolic extract | Chloroform–methanol (49 : 1)  | Roots <sup>182</sup>       |
| 126    | Palmityl glucoside/ <i>n</i> -hexacosanoyl-β-D-glucopyranoside (C <sub>22</sub> H <sub>43</sub> O <sub>6</sub> )                         | Methanolic extract | Chloroform–methanol (19 : 1)  | Roots <sup>182</sup>       |
| 127    | Stearyl glucoside/ <i>n</i> -octadecanoyl-β-D-glucopyranoside (C <sub>24</sub> H <sub>47</sub> O <sub>7</sub> )                          | Methanolic extract | Chloroform–methanol (93 : 7)  | Roots <sup>182</sup>       |
| 128    | <i>n</i> -Heptanoate/heptylate (C <sub>8</sub> H <sub>16</sub> O <sub>2</sub> )  | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 129    | <i>n</i> -Octanoate/caprylate (C <sub>9</sub> H <sub>18</sub> O <sub>2</sub> )   | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 130    | <i>n</i> -Nonanoate (C <sub>10</sub> H <sub>20</sub> O <sub>2</sub> )  | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 131    | <i>n</i> -Tridecanoate/tridecylate (C <sub>14</sub> H <sub>28</sub> O <sub>2</sub> )   | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 132    | <i>n</i> -Pentadecanoate/pantadecylate (C <sub>16</sub> H <sub>32</sub> O <sub>2</sub> )   | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 133    | <i>n</i> -Hexadecanoate/palmitate (C <sub>16</sub> H <sub>34</sub> O <sub>2</sub> )  | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 134    | <i>n</i> -Heptadecanoate/margarate (C <sub>18</sub> H <sub>36</sub> O <sub>2</sub> )   | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 135    | Methyl nonanotetracnoate (C <sub>10</sub> H <sub>12</sub> O <sub>2</sub> )   | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 136    | <i>n</i> -Decenoic acid (C <sub>10</sub> H <sub>18</sub> O <sub>2</sub> )  | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 137    | 9-Decenoate (C <sub>11</sub> H <sub>20</sub> O <sub>2</sub> )  | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 138    | Undecadienoate (C <sub>12</sub> H <sub>20</sub> O <sub>2</sub> )   | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 139    | 9-Dodecenoate (C <sub>13</sub> H <sub>24</sub> O <sub>2</sub> )  | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 140    | Tridecatrienoate (C <sub>14</sub> H <sub>22</sub> O <sub>2</sub> )   | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 141    | 2,4,5-Tetradecatrienoate (C <sub>15</sub> H <sub>24</sub> O <sub>2</sub> )   | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 142    | Hiragonate (C <sub>17</sub> H <sub>28</sub> O <sub>2</sub> )   | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 143    | Heptadecadienoate (C <sub>18</sub> H <sub>22</sub> O <sub>2</sub> )  | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 144    | Heptadecenoate (C <sub>18</sub> H <sub>38</sub> O <sub>2</sub> )   | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 145    | 9-Eicosenoate/gadoleate (C <sub>21</sub> H <sub>40</sub> O <sub>2</sub> )  | Ethanol extract    | Hexane–chloroform             | Aerial part <sup>162</sup> |
| 146    | Gallic acid (C <sub>7</sub> H <sub>6</sub> O <sub>5</sub> )  | Ethanol extract    | HPLC analysis                 | Aerial part <sup>184</sup> |
| 147    | Ferulic acid (C <sub>10</sub> H <sub>10</sub> O <sub>4</sub> )   | Ethanol extract    | HPLC analysis                 | Aerial part <sup>184</sup> |
| 148    | <i>p</i> -Coumaric acid (C <sub>9</sub> H <sub>8</sub> O <sub>3</sub> )  | Ethanol extract    | HPLC analysis                 | Aerial part <sup>184</sup> |
| 149    | Vanillic acid (C <sub>8</sub> H <sub>8</sub> O <sub>4</sub> )  | Ethanol extract    | HPLC analysis                 | Aerial part <sup>184</sup> |
| 150    | Rutin (C <sub>27</sub> H <sub>30</sub> O <sub>16</sub> )   | Ethanol extract    | HPLC analysis                 | Aerial part <sup>184</sup> |
| 151    | 4-Hydroxy-4-methylpentan-2-one (C <sub>6</sub> H <sub>12</sub> O <sub>2</sub> )  | Acetone extract    | GC-MS analysis                | Latex <sup>161</sup>       |
| 152    | 2,3,4-Trimethylhexane (C <sub>9</sub> H <sub>20</sub> )  | Acetone extract    | GC-MS analysis                | Latex <sup>161</sup>       |
| 153    | Decane (C <sub>10</sub> H <sub>22</sub> )  | Acetone extract    | GC-MS analysis                | Latex <sup>161</sup>       |
| 154    | <i>n</i> -Pentadecane (C <sub>15</sub> H <sub>32</sub> )   | Acetone extract    | GC-MS analysis                | Latex <sup>161</sup>       |
| 155    | 2,6-Dimethyl tetra-1,5-decaene (C <sub>16</sub> H <sub>28</sub> )  | Acetone extract    | GC-MS analysis                | Latex <sup>161</sup>       |
| 156    | <i>n</i> -Eicosane (C <sub>20</sub> H <sub>42</sub> )  | Acetone extract    | GC-MS analysis                | Latex <sup>161</sup>       |
| 157    | 3,7,11-Trimethyl-2,6,10,12-pentadecatrien-1-ol (C <sub>18</sub> H <sub>30</sub> O)   | Acetone extract    | GC-MS analysis                | Latex <sup>161</sup>       |
| 158    | 2,6,10,15,19,23-Hexamethyl-2,6,10,14,18,22-tetracosahexaene (C <sub>30</sub> H <sub>50</sub> )   | Acetone extract    | GC-MS analysis                | Latex <sup>161</sup>       |
| 159    | 1,3,5-Tri-isopropylbenzene (C <sub>15</sub> H <sub>24</sub> )  | Acetone extract    | GC-MS analysis                | Latex <sup>161</sup>       |
| 160    | 6,10,14-Trimethyl-pentadecanone-2 (C <sub>18</sub> H <sub>36</sub> O)  | Hexane extract     | GC-MS analysis                | Leaves <sup>185</sup>      |
| 161    | 9-Octadecenoic acid ( <i>Z</i> )-(C <sub>18</sub> H <sub>34</sub> O)   | Hexane extract     | GC-MS analysis                | Leaves <sup>185</sup>      |
| 162    | (6 <i>Z</i> ,9 <i>Z</i> )-Pentadecadien-1-ol (C <sub>15</sub> H <sub>28</sub> O)   | Hexane extract     | GC-MS analysis                | Leaves <sup>185</sup>      |
| 163    | Farnesol isomer (C <sub>15</sub> H <sub>26</sub> O)  | Hexane extract     | GC-MS analysis                | Leaves <sup>185</sup>      |
| 164    | Tetratetracontane (C <sub>44</sub> H <sub>90</sub> )   | Hexane extract     | GC-MS analysis                | Leaves <sup>185</sup>      |
| 165    | Ergost-5-en-3-ol (C <sub>28</sub> H <sub>48</sub> O)   | Hexane extract     | GC-MS analysis                | Leaves <sup>185</sup>      |

isolated from flowers, root bark and latex. Oxypregnane glycosides (Fig. 5) have recently been reported from root bark of this plant.<sup>153,154</sup> They have steroidal skeleton containing a 2-deoxy sugar moiety. These oxypregnanes have benzoyl moiety at C-12 and a straight 5–7 units sugar chain connected to C-3 of the aglycone.<sup>6</sup> Some glycosides (Fig. 6), lignan glycosides (Fig. 7), terpeny glycosides (Fig. 8) and caffeic acid derivatives (Fig. 9) have also been isolated from this plant.

A number of hydrocarbons, saturated and unsaturated fatty acids were also identified from *C. procera* extract by GC-MS.<sup>161,162</sup> Similarly fatty acid ester, phthalate derivatives, and pentacyclic triterpenes were identified from chloroform extract of roots of *Calotropis procera*.<sup>163</sup>

Apart from the compounds mentioned in Table 11, terpenoids named α-calotropol and β-calotropol have been isolated from ethanolic extract of latex.<sup>179</sup> A cardenolide named 19-





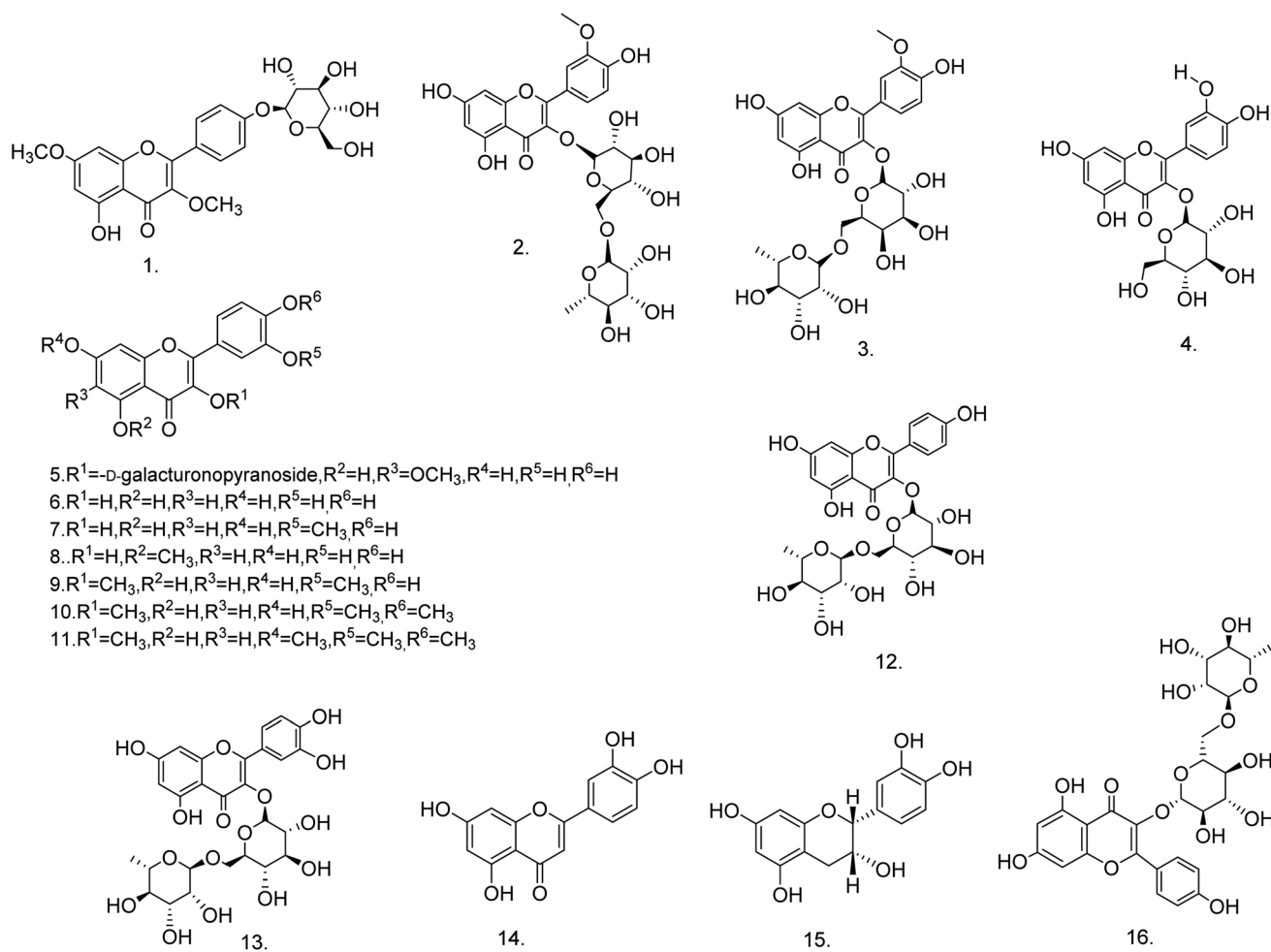


Fig. 1 Chemical structures of flavonoids.

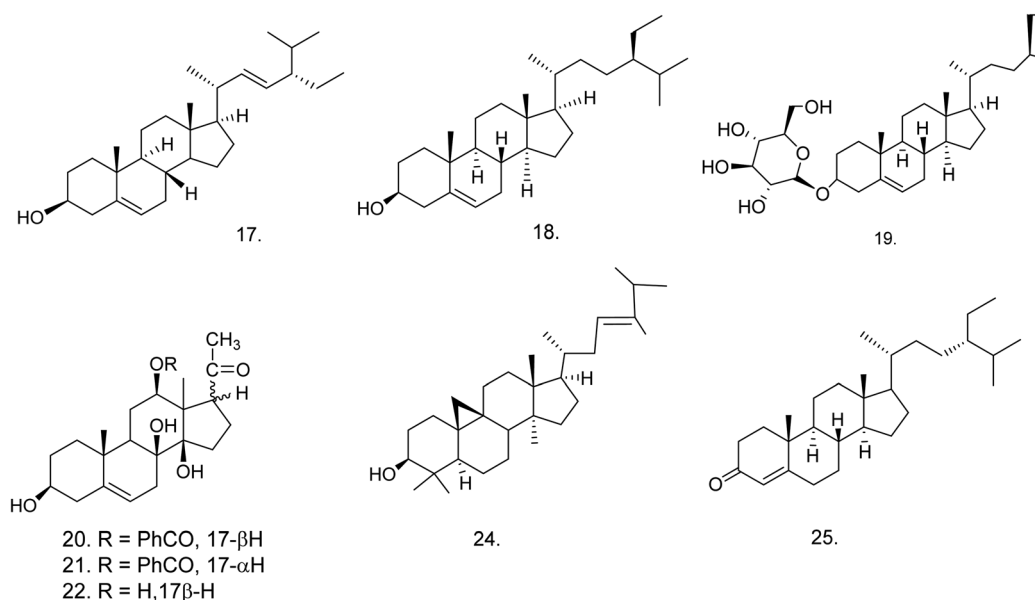


Fig. 2 Chemical structures of steroids.



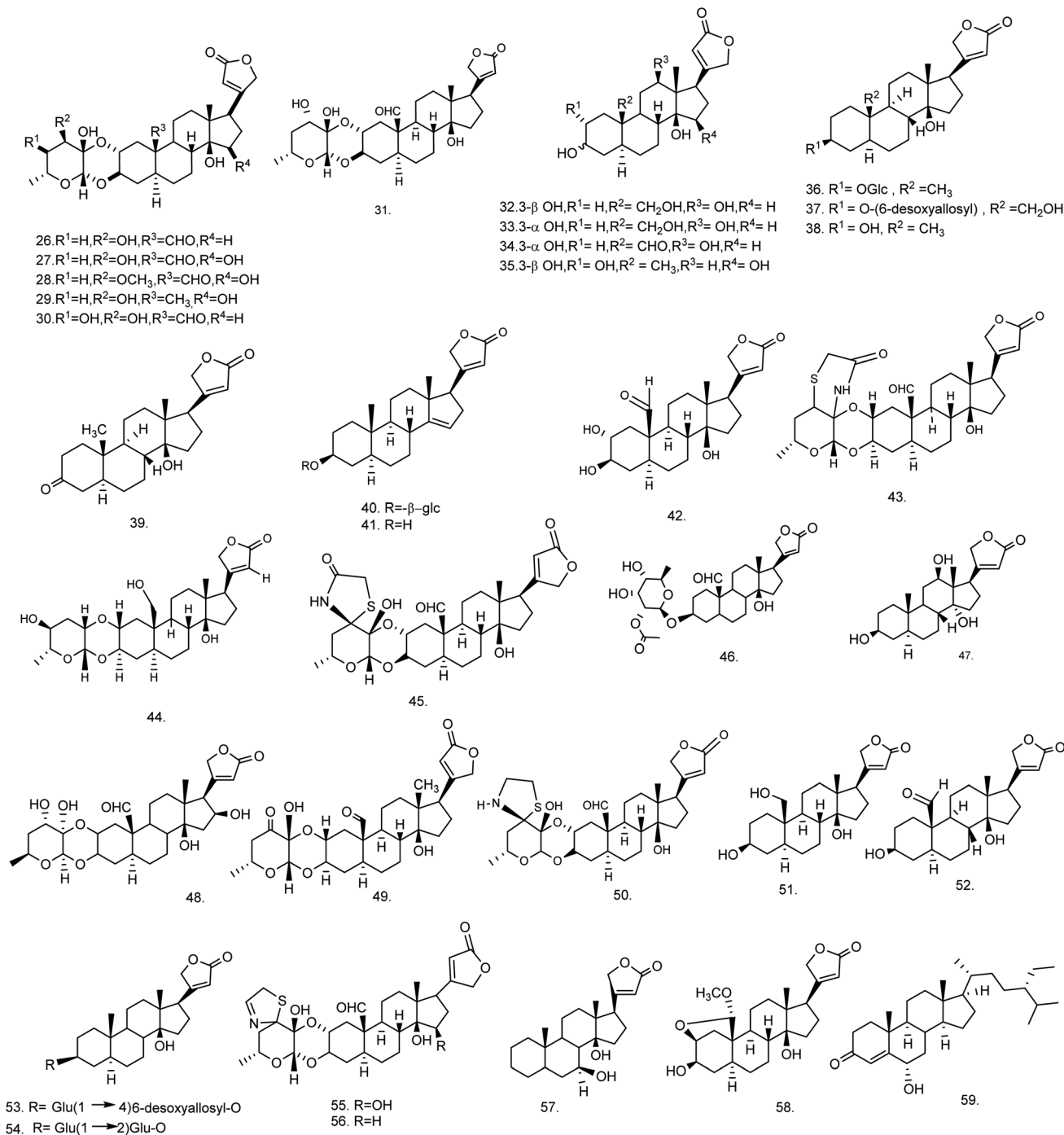


Fig. 3 Chemical structures of cardenolides.

dihydrocalotropagenin and flavonoid named 3'-O-methyl-quercetin-3-O-rutinoside have also been reported from ethanolic extract of aerial parts.<sup>168</sup>

## 7. Conclusion, discussion and future perspectives

In the present review, the research progress in phytochemistry and pharmacology of *C. procera* have been summarized. There

have been acquisitions in the research; still some gaps came across our studies which are as follows:

(1) Folks and tribes have been using *C. procera* since ancient times; still investigations can be carried out on inception time of traditional uses of *C. procera*.

(2) Secondary metabolites of plant vary according to several factors like region, environment, quality of soil, age of plant *etc.* Moreover, latex and root bark seem to be exhaustively investigated for phytoconstituents, not much research on flowers, pods and seeds for phytoconstituents have been conducted.



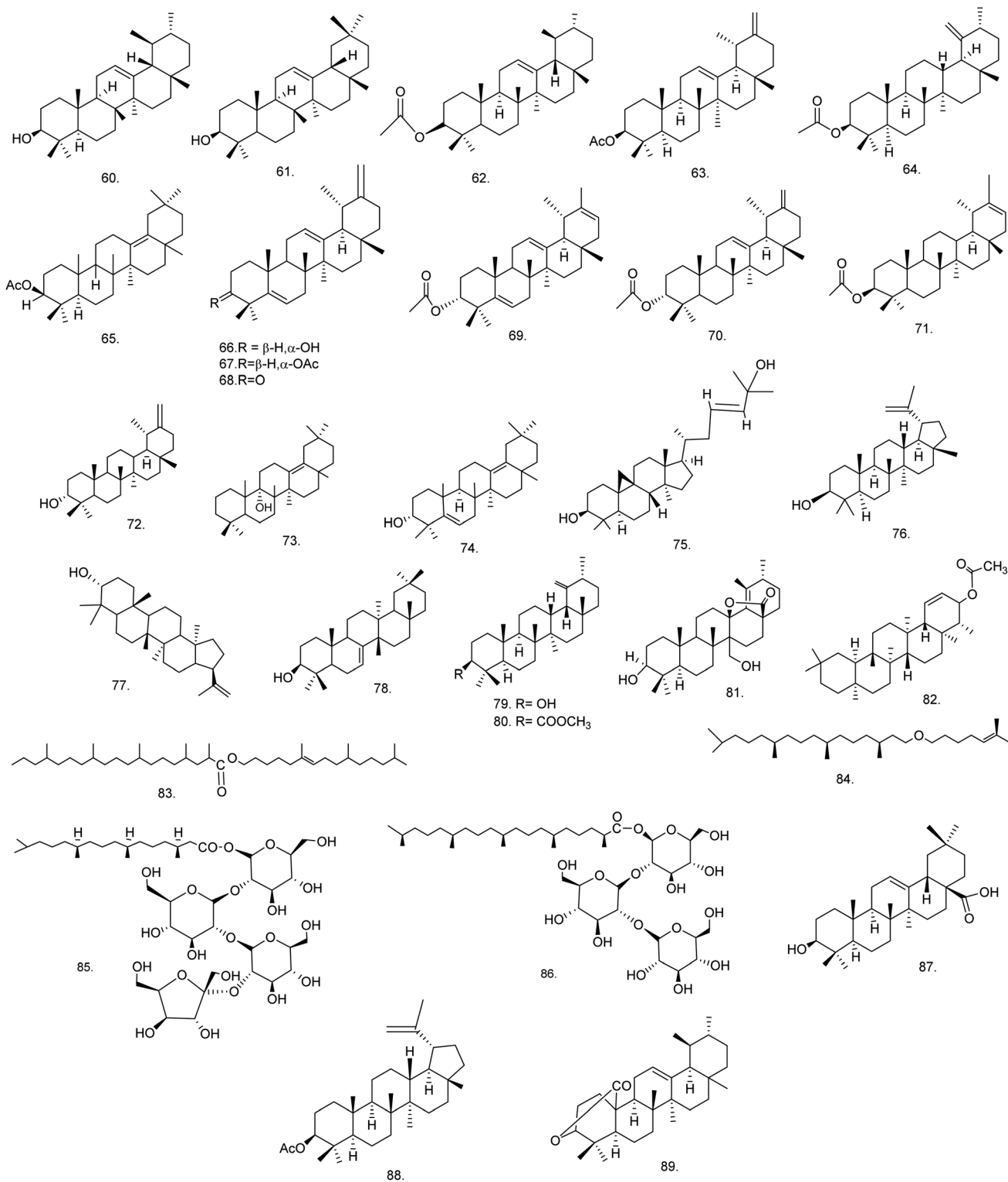


Fig. 4 Chemical structures of terpenoids.

Further exploring these parts can lead to discovery of new phytoconstituents of interest.

(3) The plant can be employed commercially as scientific studies have proved its use as cheese making agent, dehairing of leather, natural surfactant, biopesticide and corrosion inhibitor.

(4) Numerous activities on validation of its cytotoxic and anti-inflammatory potential have been conducted. A few have been carried out on its antimigraine, antiplasmodial and anti-convulsant effects. Carrying out further scientific studies in these fields can provide medical science with effective and promising new drugs.



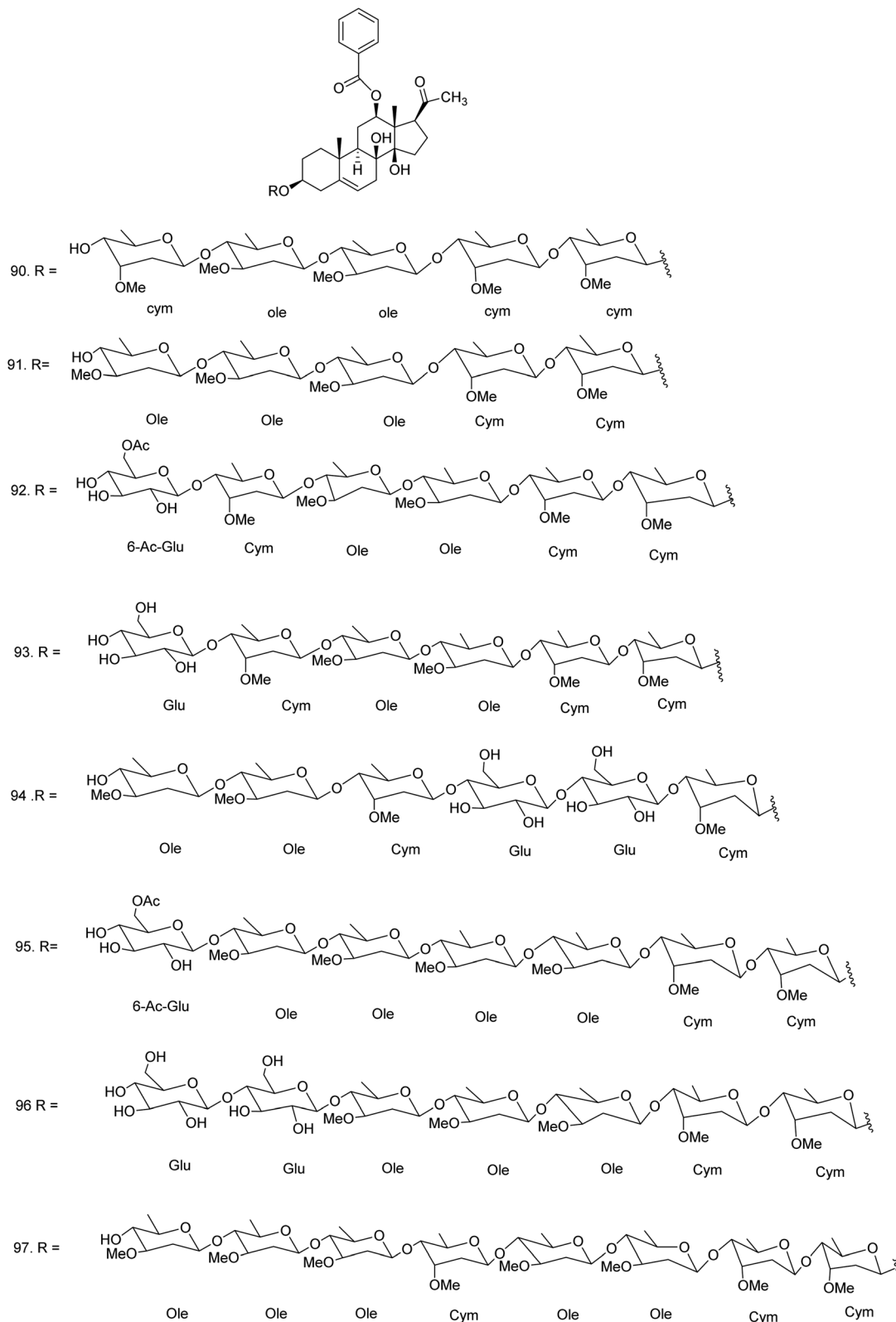


Fig. 5 Chemical structures of oxypregnanes.

(5) Most of the cytotoxic activities conducted are *in vitro* except the one conducted on UNS1450; a semi-synthesized cardenolide. Further studies should be carried out to examine its *in vivo* potential.

(6) Right route and right dose can convert a dreadful toxicant into an outstanding drug whereas even a drug in lack of proper dosage and route can become a fatal poison. Folk practitioners have been employing *C. procerca* as antifertility and uterotonic



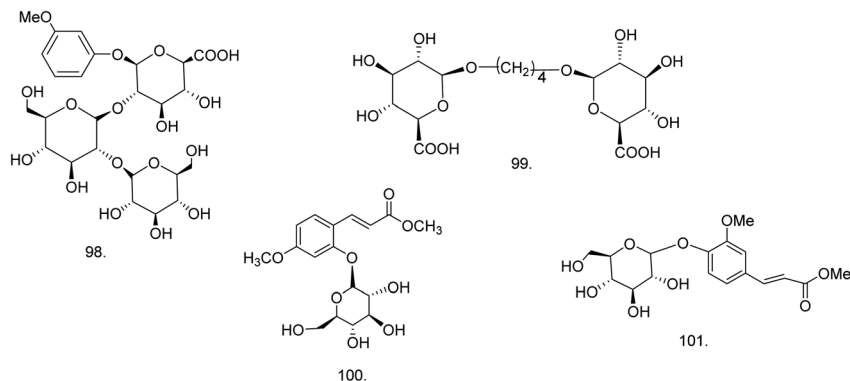


Fig. 6 Chemical structures of glycosides.

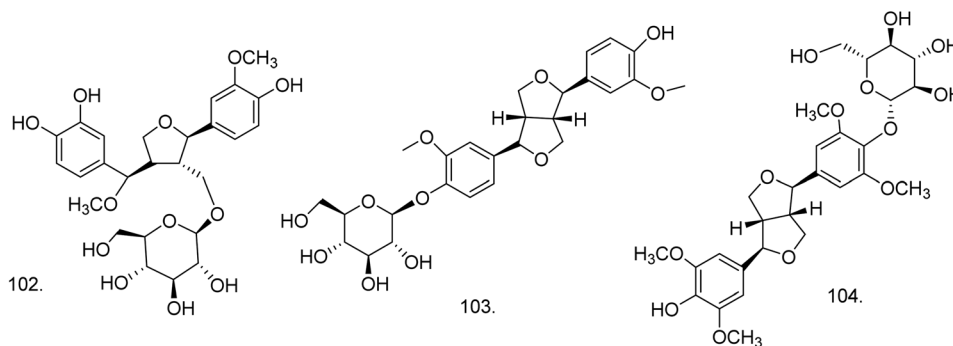


Fig. 7 Chemical structures of lignan glycosides.



Fig. 8 Chemical structures of terpene glycosides.

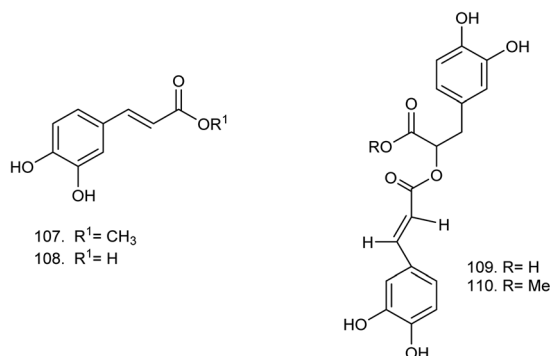


Fig. 9 Chemical structures of caffeic acid derivatives.

agent. Further studies using positive controls, study of toxicity and side effects can lead to discovery of effective and natural contraceptive drugs.

(7) Active principles behind many of the activities are unknown, except the one known for cytotoxic, antibacterial, antifertility, antimolluscicidal and insecticidal activity. More research can be carried out to know the active principles so that potent drugs can be made.

(8) Replicable and environment benign sources of energy are the need of hour, *Calotropis procera* being rich source of various hydrocarbons, thus can prove to be a promising biofuel agent.

Overall, the pharmacology, toxicology, traditional uses, use of secondary metabolites, clinical trials and quality control has been reviewed in this paper. However, there seems to be a good correspondence between pharmacological activities and traditional uses. Further research in this field is essential to determine the active principles and the underlying mechanisms.

## Author contributions

Barkha Darra Wadhvani: literature collection, evaluation and draft manuscript preparation. Deepak Mali and Pooja Vyas: literature collection: pharmacological activity and analyses of chemicals constituents of *C. procera*. Rashmy Nair: reviewing and editing. Poonam Khandelwal: concept development; idea generation; manuscript preparation; reviewing and editing.

## Conflicts of interest

The authors confirm that this article content has no conflict of interest.



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