Traditional uses and pharmacological properties of *Clerodendrum* phytochemicals

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1. Introduction

*Clerodendrum* is a genus of flowering plants in the family Lamiaceae and widely distributed throughout the whole world. Up to now, many species of this genus have been described in various indigenous systems of medicine and are used in preparation of folklore medicines for the treatment of various life-threatening diseases, and more than eleven species of the *Clerodendrum* genus have been very well studied for their chemical constituents and biological activities, and 283 compounds, including monoterpenes, sesquiterpenoids, triterpenoids, flavonoids and flavonoid glycosides, phenylethanoid glycosides, steroids and steroid glycosides, cyclohexylethanoids, anthraquinones, cyanogenic glycosides, and others have been isolated and identified. Pharmacological studies have shown that these compounds and extracts from the *Clerodendrum* genus have extensive activities, such as anti-inflammatory and anti-nociceptive, anti-oxidant, anti-hypertensive, anticancer, antimicrobial, anti-diarrheal, hepatoprotective, hypoglycemic and hypolipidemic, memory enhancing and neuroprotective, and other activities. In this review, we attempt to highlight over phytochemical progress and list the phytoconstituents isolated from the genus *Clerodendrum* reported so far. The biological activities of this genus are also covered.

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Japan, Thailand, and Africa.\textsuperscript{5–9} The traditional or ethnomedical claims of the species have also been evaluated. The biological activities of these species described in ancient literature have been reported to be associated with the chemical constituents present in the species.

A variety of constituents have been isolated and characterized from this genus, including: monoterpenes and its derivatives,\textsuperscript{10} sesquiterpene,\textsuperscript{5} diterpenoids,\textsuperscript{12,13} triterpenoids,\textsuperscript{14,15} flavonoid and flavonoid glycosides,\textsuperscript{16} phenyllethanoid glycosides,\textsuperscript{17,18} steroids and steroidal glycosides,\textsuperscript{19} cyclohexylethanoids,\textsuperscript{20} anthraquinones,\textsuperscript{21} cyanogenic glycosides,\textsuperscript{22} and others. Some of these constituents have been evaluated with a number of biological properties, mainly including anti-inflammatory and anti-nociceptive, anti-oxidant, anti-hypertensive, anticancer, antimicrobial, anti-diarrheal, hepatoprotective, hypoglycemic and hypolipidemic, memory enhancing and neuroprotective, and other activities.

In this review, we will summarize all identified chemical constituents and biological activities from the genus Clerodendrum over the past few decades. It will provide a basis for the development of therapeutic agents and utilization of these plants in forthcoming studies.

2. Phytochemistry

To the best of our knowledge, over 280 chemical constituents have been isolated and identified from different species of the genus Clerodendrum. These compounds could be divided into: \textbf{27} monoterpenes and its derivatives, \textbf{3} sesquiterpenes, \textbf{58} diterpenoids, \textbf{31} triterpenoids, \textbf{43} flavonoid and flavonoid glycosides, \textbf{40} phenylethanoid glycosides, \textbf{43} steroids and steroidal glycosides, \textbf{13} cyclohexylethanoids, \textbf{4} anthraquinones, \textbf{2} cyanogenic glycosides, \textbf{19} and others (Table 1). With respect to isolated phytochemicals of the genus, aerial parts, roots and leaves were the most common targets of investigation for bioactive principles and most of these compounds were reported from \textit{C. serratum}, \textit{C. inerme}, \textit{C. bungei}, \textit{Clerodendrum incisum}, \textit{C. infortunatum}, and \textit{C. trichotomum}. Diterpenoids, flavonoids, phenylethanoid glycosides, and steroids are abundant and major bioactive principles of this genus.

2.1. Monoterpene and its derivatives

Monoterpenes are a class of terpenes that consist of two isoprene units and have the molecular formula C\textsubscript{10}H\textsubscript{16}. Monoterpenes may be linear (acyclic) or contain rings. Most monoterpenes are fragrant and the main composition of essential oil. \textbf{Twenty-seven} monoterpenes and derivatives (1–27) were isolated from the roots, leaves, aerial parts of \textit{C. serratum}, \textit{C. inerme}, \textit{C. chinense}, \textit{C. trichotomum}, \textit{Clerodendrum ugandense}, and \textit{C. chinense}.

2.2. Sesquiterpenes

Sesquiterpenes are bitter substances and a class of terpenes that consist of three isoprene units and have the molecular formula C\textsubscript{15}H\textsubscript{24}. They often contain \textalpha{}-, \beta{}-unsaturated-\gamma{}-lactone as a major structural feature. In recent studies, sesquiterpenes have been associated with anti-tumor, cytotoxic, and anti-microbial activities. But, only \textbf{three} sesquiterpenes (28–30) were obtained from the aerial parts and roots of \textit{C. inerme} and \textit{C. bungei}, respectively.

2.3. Diterpenoids

To date, \textbf{fifty-eight} diterpene compounds (31–88) have been isolated and identified from this genus, and all of them are labdane diterpenoids. These compounds can be sorted to five types based

| No. | Phytochemicals | Plant parts | Source |
|-----|----------------|-------------|--------|
| 1   | Serratulin A   | Aerial parts| \textit{C. serratum} |
| 2   | Serratoside A  | Aerial parts| \textit{C. serratum} |
| 3   | Serratoside B  | Aerial parts| \textit{C. serratum} |
| 4   | 7-O-\textalpha{}-coumaroylxyloglucoside | Aerial parts | \textit{C. serratum} |
| 5   | Monomelittoside | Aerial parts| \textit{C. inerme} |
| 6   | Melitotside     | Aerial parts| \textit{C. inerme} |
| 7   | Sammangoaside C | Aerial parts| \textit{C. inerme} |
| 8   | Inerminosides A | Leaves      | \textit{C. inerme} |
| 9   | Inerminosides C | Leaves      | \textit{C. inerme} |
| 10  | Inerminosides D | Leaves      | \textit{C. inerme} |
| 11  | Inerminoside C  | Aerial parts| \textit{C. inerme} |
| 12  | Inerminoside A  | Aerial parts| \textit{C. inerme} |
| 13  | Inerminoside A hexacetate | Aerial parts | \textit{C. inerme} |
| 14  | Inerminoside B  | Aerial parts| \textit{C. inerme} |
| 15  | Inerminoside B heptacetate | Aerial parts| \textit{C. inerme} |
| 16  | 8-O-galactosylheulephroside | Roots | \textit{C. inerme} |
| 17  | 2′,8-O-difoliamethylephroside | Roots | \textit{C. inerme} |
| 18  | Euphroside      | Roots      | \textit{C. inerme} |
| 19  | Plantarenoside  | Roots      | \textit{C. inerme} |
| 20  | Aucubin         | Whole plants| \textit{C. thomsonae} |
| 21  | 8-O-acetylharpagide | Whole plants| \textit{C. thomsonae} |
| 22  | Harpagide       | Whole plants| \textit{C. thomsonae} |
| 23  | Ajugoside       | Leaves   | \textit{C. thomsonae} |
| 24  | 8-O-acetylmioporoside | Whole plants| \textit{C. thomsonae} |
| 25  | Reptoside       | Whole plants| \textit{C. trichotomum} |
| 26  | Ugandoside      | Whole plants| \textit{C. trichotomum} |
| 27  | 5-\beta{}-glucopyranosyl-harpagide | Aerial parts| \textit{C. chinense} |

| No. | Phytochemicals | Plant parts | Source |
|-----|----------------|-------------|--------|
| 28  | Sammangoaside A | Aerial parts| \textit{C. inerme} |
| 29  | Sammangoaside B | Aerial parts| \textit{C. bungei} |
| 30  | 2-[(2S,5R)-5-\{1E\}-4-hydroxy-4-methylhexa-1,5-dien-1-yl\}]-propan-2-yl\beta{}-o-glucopyranoside | Aerial parts| \textit{C. trichotomum} |

| No. | Phytochemicals | Plant parts | Source |
|-----|----------------|-------------|--------|
| 31  | Mandarone A    | Stems      | \textit{C. mandarinorum} |
| 32  | Mandarone B    | Stems      | \textit{C. mandarinorum} |
| 33  | Mandarone C    | Stems      | \textit{C. mandarinorum} |
| 34  | Clerodendron A | Whole plants| \textit{C. philippinum} |
| 35  | Bungone A      | Stems      | \textit{C. bungei} |
| 36  | Bungone B      | Stems      | \textit{C. bungei} |
| 37  | Inermine A     | Leaves     | \textit{C. inerme} |
| 38  | Inermine B     | Leaves     | \textit{C. inerme} |
| 39  | 14,15-dihydro-15\beta{}-methoxy-3-epierycypiton | Leaves | \textit{C. inerme} |
| 40  | 14,15-dihydro-15\beta{}-methoxy-3-epierycypiton | Leaves | \textit{C. inerme} |
| 41  | Clerodermic acid | Whole plants| \textit{C. inerme} |
| 42  | Cleroerinmorn | Whole plants| \textit{C. inerme} |
| 43  | 3-epierycypiton | Whole plants| \textit{C. inerme} |
| 44  | Clerodin       | Whole plants| \textit{C. inerme} |
| 45  | Uncinateone    | Stems      | \textit{C. trichotomum} |
| 46  | 2-acetoxyclerodendrin B | Whole plants| \textit{C. trichotomum} |
| 47  | Clerodendrin A  | Whole plants| \textit{C. trichotomum} |
| 48  | Clerodendrin B  | Whole plants| \textit{C. trichotomum} |
| 49  | Clerodendrin C  | Whole plants| \textit{C. trichotomum} |
| 50  | Clerodendrin D  | Whole plants| \textit{C. trichotomum} |
| 51  | Clerodendrin E  | Whole plants| \textit{C. trichotomum} |
| 52  | Clerodendrin F  | Whole plants| \textit{C. trichotomum} |
| 53  | Clerodendrin G  | Whole plants| \textit{C. trichotomum} |
| 54  | Clerodendrin H  | Whole plants| \textit{C. trichotomum} |

(continued on next page)
| No. | Phytochemicals | Plant parts        | Source                      | Ref. |
|-----|----------------|--------------------|-----------------------------|------|
| 55  | Trichotomone    | Roots              | C. trichotomum             | 43   |
| 56  | Sugiol          | Stems              | C. trichotomum             | 39   |
| 57  | Teuvinenone A   | Stems              | C. trichotomum             | 39   |
| 58  | Teuvinenone B   | Stems              | C. trichotomum             | 39   |
| 59  | Teuvinenone F   | Stems              | C. trichotomum             | 40   |
| 60  | Teuvinenone H   | Stems              | C. trichotomum             | 41   |
| 61  | Cyrtophyllone B | Stems              | C. trichotomum             | 39   |
| 62  | Bungnate A      | Roots              | C. bungei                  | 40   |
| 63  | Bungnate B      | Roots              | C. bungei                  | 40   |
| 64  | 15-dehydro-17-  | Roots              | C. bungei                  | 40   |
|     | hydroxycytrophi-|                    |                             |      |
|     | llone A         |                    |                             |      |
| 66  | 12,16-epoxy-11,14,17-trihydroxy-6-methoxy-17(15→16)-abeo-abiet-5,8,11,13-tetraene-7-one | Roots | C. bungei | 40 |
| 67  | Cyrtophyllone A | Roots              | C. bungei                  | 40   |
| 68  | Villiscin       | Roots              | C. bungei                  | 40   |
| 69  | 19-hydroxyteuvinencine F | Roots | C. bungei | 40 |
| 70  | Mandaron E      | Roots              | C. bungei                  | 40   |
| 71  | 12,16-epoxy-11,14-dihydroxy-6-methoxy-17(15→16)-abeo-abiet-5,8,11,13-tetraene-3,7-diene | Roots | C. trichotomum | 41 |
| 72  | 12-O-β-D-glucopyranosyl-3,11,16-trihydroxyabiet-8,11,13-triene | Roots | C. bungei | 40 |
| 73  | 6-methoxyvilsolin C | Roots | C. trichotomum | 41 |
| 74  | 18-hydroxy-6- methoxyvilsolin C | Roots | C. trichotomum | 41 |
| 75  | (10R,16S)-12,16-epoxy-11,14-dihydroxy-6-methoxy-17(15→16)-abeo-abiet-5,8,11,13-tetraene-7-one | Roots | C. trichotomum | 41 |
| 76  | (10R,16S)-12,16-epoxy-11,14-dihydroxy-18-oxo-17(15→16),18(4→3)-diabeno-abiet-3,5,8,11,13-pentaene-7-one | Roots | C. trichotomum | 41 |
| 77  | (10R,16S)-12,16-epoxy-11,14,17-trihydroxy-17(15→16),18(4→3)-diabeno-abiet-3,5,8,11,13-pentaene-2,7-diene | Roots | C. trichotomum | 41 |
| 78  | (35,48,10S)-12,16-diepoxy-11,14-dihydroxy-17(15→16),18(4→3)-diabeno-abiet-5,8,11,13-tetraene-7-one | Roots | C. trichotomum | 41 |
| 79  | (12R,16S)-11,14- dihydroxy-6-methoxy-17(15→16)-abeo-abiet-5,8,11,13,15-pentaene-3,7-diene | Roots | C. trichotomum | 41 |
| 80  | Formidol        | Roots              | C. trichotomum             | 41   |
| 81  | Teuvinenone E   | Roots              | C. trichotomum             | 41   |
| 82  | 12,16-epoxy-17(15→16),18(4→3)-diabeno-abiet-3,5,8,12,15-pentaene-7,11,14-triene | Roots | C. trichotomum | 41 |
| 83  | 3β-(β-D-glucopyranosyl)-isopimara-7,15-diene-11x,12x-diol | Roots | C. bungei | 44 |
| 84  | 16-O-β-D-glucopyranosyl-3β-20-epoxy-3- hydroxyabiet-8,11,13-triene | Roots | C. bungei | 44 |
| 85  | Coleon U        | Whole plants       | C. canescens               | 45   |
| 86  | Coleon U-12-methyl ether | Whole plants | C. canescens | 45 |
### Table 1 (continued)

| No. | Phytochemicals | Plant parts | Source | Ref. |
|-----|----------------|-------------|--------|------|
| 147 | Cynaroside | Aerial parts | C. inerme | 48 |
| 148 | 2,4'-trihydroxy-6'-methylchalcone | Aerial parts | C. inerme | 13 |
| 149 | Cirsimaritin | Aerial parts | C. mandarinorum | 71 |
| 150 | Cirsimaritin-4'-glucoside | Aerial parts | C. mandarinorum | 71 |
| 151 | Quercetin-3'-methyl | Aerial parts | C. mandarinorum | 71 |
| 152 | Pectolinarigenin | Roots | C. indicum | 49 |
| 153 | 5-hydroxy-6,7,4'-trimethoxyflavone | Aerial parts | C. inerme | 53 |
| 154 | 5,7,4'-trihydroxy-flavone | Leaves | C. trichotomum | 72 |
| 155 | 5,7,4'-trihydroxy-3'-methylmethoxyflavone | Whole plants | C. serratum | 56 |
| 156 | 3,2,3'-trihydroxy-4'-methoxycalcone | Seeds | C. phlomidis | 74 |
| 157 | 3,2'-di-hydroxy-4,5'-dimethoxychalcone | Seeds | C. phlomidis | 74 |
| 158 | 5-hydroxy-7',7-methoxyflavonone | Seeds | C. phlomidis | 74 |
| 159 | 5-hydroxy-7'-methoxyflavonone | Seeds | C. phlomidis | 74 |
| 160 | Kaempferol-3-O-a-L-rhamnopyranoside | Seeds | C. phlomidis | 74 |
| 161 | Hispidulin-7-O-glucopyranoside | Aerial parts | C. infortunatum | 63 |
| 162 | Naringin-4'-O-a-L-rhamnopyranoside | Flowers | C. phlomidis | 66 |

### Phenylethanoid glycosides

| No. | Phytochemicals | Plant parts | Source | Ref. |
|-----|----------------|-------------|--------|------|
| 163 | Decaffeoylverbascoside | Aerial parts | C. inerme | 75 |
| 164 | Dangrodense B | Roots | C. bungei | 40 |
| 165 | Dangrodense E | Aerial parts | C. bungei | 25 |
| 166 | Verbascoside | Roots | C. villosum | 49 |
| 167 | Isoverbacoside | Roots | C. inerme | 75 |
| 168 | Campeoside I | Aerial parts | C. bungei | 76 |
| 169 | Cistanoside E | Aerial parts | C. inerme | 75 |
| 170 | Purpureasis B | Aerial parts | C. inerme | 75 |
| 171 | 2-phenylethyl-3-O-(6-demethoxy-3,4-dihydroxyphenyl)-b-D-glucopyranoside | Roots | C. bungei | 32 |
| 172 | Campeoside II | Aerial parts | C. bungei | 76 |
| 173 | Martynoside | Whole plants | C. japonicum | 55 |
| 174 | Jionoside D | Aerial parts | C. trichotomum | 75 |
| 175 | Clerodendronoside | Aerial parts | C. bungei | 76 |
| 176 | Cistanoside C | Aerial parts | C. bungei | 76 |
| 177 | Jionoside C | Aerial parts | C. bungei | 76 |
| 178 | Leucoceptoside A | Roots | C. bungei | 40 |
| 179 | Cistanoside D | Aerial parts | C. bungei | 76 |
| 180 | Cistanoside F | Aerial parts | C. bungei | 76 |
| 181 | Bunegine A | Aerial parts | C. bungei | 78 |
| 182 | Monoaetymartynoside | Whole plants | C. japonicum | 55 |
| 183 | Clerodendoa A | Whole plants | C. japonicum | 55 |
| 184 | 3,4'-di-hydroxyphenylethanol | Whole plants | C. indicum | 25 |
| 185 | Isomartynoside | Roots | C. bungei | 40 |
| 186 | Serratunoside A | Aerial parts | C. serratum | 79 |
| 187 | Bunginoside A | Roots | C. bungei | 40 |
| 188 | 3'-O-di-O-acetylmartynoside | Roots | C. bungei | 40 |
| 189 | Acetylmartynoside A | Roots | C. bungei | 40 |
| 190 | Acetylmartynoside B | Roots | C. bungei | 40 |
| 191 | 3'-O-acetylmartynoside | Roots | C. bungei | 40 |
| 192 | 2'-O-acetylmartynoside | Roots | C. bungei | 40 |
| 193 | Martynoside | Roots | C. bungei | 40 |
| 194 | Trichotoside | Roots | C. bungei | 40 |
| 200 | Markhaminoside F | Aerial parts | C. inerme | 75 |
| 201 | Benzylicglycoside | Aerial parts | C. inerme | 75 |
| 202 | Myricoside | Aerial parts | C. serratum | 79 |

### Steroids and steroidal glycosides

| No. | Phytochemicals | Plant parts | Source | Ref. |
|-----|----------------|-------------|--------|------|
| 203 | Stigmasterol | Roots | C. indicum | 49 |
| 204 | 2-methylsterol | Leaves | C. trichotomum | 47 |
| 205 | Stigmasterol-3-O-β-D-glucopyranoside | Whole plants | C. serratum | 73 |
| 206 | Serratin | Whole plants | C. serratum | 80 |
| 207 | Clerosterol | Roots | C. indicum | 49 |
| 208 | Bungesterol | Whole plants | C. bungei | 51 |
| 209 | 4αβ-methyl-24β,4αβ-stigmasterol| Aerial parts | C. inerme | 36 |
| 210 | 4αβ,24,24-trimethyl-5β-cholest-7,25-dien-3β-ol | Whole plants | C. inerme | 62 |
| 211 | 4αβ-methyl-5β-cholest-7,25-dien-3β-ol | Whole plants | C. inerme | 62 |
| 212 | Gramsterol | Whole plants | C. inerme | 62 |
| 213 | 4αβ-methyl-24α,4β-stigmasterol| Whole plants | C. inerme | 62 |
| 214 | Obtussifolol | Whole plants | C. inerme | 62 |
| 215 | 24,24-dimethyl-5β-cholest-7,25-dien-3β-ol | Whole plants | C. inerme | 62 |
| 216 | 22,23-dihydrotigmasterol | Whole plants | C. japonicum | 55 |
| 217 | 25,26-dehydrotigmasterol | Whole plants | C. inerme | 55 |
| 218 | 22-dehydrochlorosterol β-D-(6-O-margaroyl)-glucopyranoside | Leaves | C. trichotomum | 82 |
| 219 | Sitosterol | Leaves | C. trichotomum | 47 |
| 220 | Stigmasterol | Aerial parts | C. inerme | 48 |
| 221 | 24β,25-dihydroxycholest-5,22E,25-trien-3β-ol | Whole plants | C. fragrans | 83 |
| 222 | 24αβ,25-dihydroxycholest-5,22E,25-trien-3β-ol | Whole plants | C. fragrans | 83 |
| 223 | Colebrin A | Aerial parts | C. colebrookianum | 84 |
| 224 | Colebrin B | Aerial parts | C. colebrookianum | 84 |
| 225 | Colebrin C | Aerial parts | C. colebrookianum | 84 |
| 226 | Colebrin D | Aerial parts | C. colebrookianum | 84 |
| 227 | Colebrin E | Aerial parts | C. colebrookianum | 84 |
| 228 | Dehydroprop-o-ferasterol | Aerial parts | C. splendens | 25 |
| 229 | Campesterol | Stems | C. phlomidis | 85 |
| 230 | Cholestanol | Stems | C. phlomidis | 85 |
| 231 | (22E)-stigmasta-4,22,25-trien-3-one | Roots | C. indicum | 49 |
| 232 | Stigmasta-4,22,25-trien-3-one | Roots | C. indicum | 49 |
| 233 | Stigmasta-4,22,25-trien-3-one | Roots | C. indicum | 49 |
| 234 | 22-dehydrocholersterol | Roots | C. indicum | 49 |

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on the pentacyclic ring on C12: a furan ring, dihydrofuran ring, lactone ring, aβ-undersaturated lactone ring, and tetrahydrofuran ring. Many of these chemical compounds have shown remarkable bioactivities in vivo or in vitro study.

2.4. Triterpenoids

So far, a total of thirty-one triterpenoids (89–119), including 3-O-acetylatedolic acid (89), 3-O-acetylatedolic acid (90), glu- tinol (91), friedelin (92), taraxerol (93), clerodene (94), α-amyrin (95), glocidine (96), glocidionol (97), globichiol (98), lupeol (99), α-amyrin 3-undecanolate (100), lupeol acetate (101), lupeol 3-palmitate (102), melastemic acid (103), β-amyrin acetate (104), betulinic acid (105), magnifoli (106), glutinone (107), etc. have been purified and characterized from the whole plants, roots, leaves, or aerial parts of C. inerme, C. trichotomum, C. indicum, C. bungei, Clerodendrum canescens, Clerodendrum villasum, Clerodendrum wildii, Clerodendrum japonicum, C. serratum, Clerodendrum philippinum, or Clerodendrum glabrum.

2.5. Flavonoid and flavonoid glycosides

Flavonoids, important secondary metabolites, are widespread throughout the plant kingdom. Flavonoids and their derivatives are the main bioactive components of this genus, and receiving extreme attention. Up to now, forty-three flavonoid and flavonoid glycosides (120–162), including astragalin (123), apigenin (124), and tricin (125), hesperidin (126), hesperidin-glucuronide (127), eupafolin (128), scutellarein (130), pectolinigr genin (131), 7-hydroxylavone (132), 7-hydroxyflavanone 7-O-glucoside (133), luteolin (134), chalcone glycoside (135), etc. have been isolated and identified from the roots, leaves, aerial parts of different Clerodendrum species.

2.6. Phenylethanoid glycosides

Phenylethanoid glycosides are another kind of characteristic compounds of the Clerodendrum species with antioxidant activity. To date, forty phenylethanoid glycosides (163–202) have been obtained from this genus and the structure contains three parts: sugar chain, phenylacyl, and coffee-acyl or ferulic-acyl. The sugar chain is often composed of glucose, rhamnose, xylose or arabinose. The phenylacyl is connected with the C4 or C6 of glucose. The coffee-acyl or ferulic-acyl is often connected with the C4 or C6 of glucose.
Total forty-three steroids and steroid glycosides (203–245) have been obtained and identified from Clerodendrum species, mainly from C. trichotomum, Clerodendrum colebrookianum, and C. bungei.

2.8. Cyclohexylethanoids

A series of cyclohexylethanoids (246–258), including two new compounds 1-hydroxy-1-(8-palmitoyloxethyl) cyclohexaneone (246) and 5-O-butyl clerodin D (247), together with four known ones, rengyolone (248), clerodin C (249), clerodin B (250), rengyol (251), were isolated from the leaves of C. trichotomum, and the others (252–258) were obtained and identified from the aerial parts and roots of C. bungei.

2.9. Anthraquinones

Only four anthraquinones (259–262), aloe-emodin (259), emodin (260), chrysophanol (261) and 2,5-dimethoxybenzoquinone (262), have been isolated and identified from the stem of C. trichotomum and C. serratum.

2.10. Cyanogenic glycosides

Two cyanogenic glycosides (263–264), including (R)-lucumin (263) and (R)-prunasin (264) have been obtained and identified from the leaves of C. grayi.

2.11. Others

A range of other compounds (265–283) were isolated and identified from the aerial parts, stems, leaves and roots of C. inerme, C. trichotomum, C. serratum, C. bungei, C. phlomidis, and Clerodendrum kiangsiense.

3. Pharmacological properties

Wide clinical uses of traditional Chinese medicine of the genus Clerodendrum have inspired researchers to investigate its pharmacological properties and to validate the uses of different species as therapeutic remedy. More and more studies showed that extracts or active compounds isolated from Clerodendrum species exhibited a wide range of pharmacological activities (Table 2).

3.1. Anti-inflammatory and anti-nociceptive activities

Many studies have provided data on anti-inflammatory effects of C. phlomidis, C. petasites, Clerodendrum laevifolium, C. inerme, C. bungei, and C. serratum extracts of aerial parts, roots, leaves and stems. Of these, lots of studies have provided data on anti-inflammatory effects of C. serratum (Bharangi) extracts of aerial parts, roots and stems. An aqueous extract of roots reported significant anti-inflammatory effects at high dose (180 mg/kg, p.o.) in granuloma pouch model in rats. Roots in low dose (90 mg/kg, p.o.) and stems in high dose (180 mg/kg, p.o.) showed significant preventive effects in comparison with dexamethasone (a standard anti-inflammatory agent). Thus, it can be postulated that roots are more effective than stems and it would be useful as antiallergic and anti-inflammatory drug for disease like asthma. 50, 56 The methanolic extract of the aerial parts of C. serratum was demonstrated dual inhibitory effects on arachidonic acid metabolism or an inhibitor of phospholipase A2 when studied in ethyl phenylpropionate-induced ear edema and in carrageenan and arachidonic acid induced hind paw edema in rats, and the extract exerted an inhibitory activity on the acute phase of inflammation due to an inhibition of synthesis and inflammatory mediators release through cyclooxygenase and lipooxygenase pathways. 57 In contrast, the alcoholic root extract of C. serratum showed a potent antiinflammatory effect by reducing paw edema (acute) and cotton-pellet granuloma (chronic) in inflammation models. 58 Apigenin-7-glucoside isolated from C. serratum roots has been demonstrated for anti-inflammatory effects in rats. 59 The hydro-alcoholic extract (50, 200 and 500 mg/kg dose) of Bharangyadi preparation showed inhibition of carrageenan induced inflammation due to the inhibition of the enzyme cyclooxygenase and subsequent inhibition of prostaglandin synthesis which rationalizes traditional use of this plant in bronchial asthma and related inflammatory conditions. 60 This anti-inflammatory effect of C. serratum might be observed due to flavonoids and saponins, but other active substances might also be responsible leading to synergistic effects. Prakash et al reported that the monomer compound 3-hydroxy, 2-methoxy-sodium butanoate (HMSB, at doses of 25, 50, 100 mg/kg, i.g.) isolated from the leaves of C. phlomidis displayed anti-inflammatory and anti-arthritic effects on carrageenan-induced inflammation and Freund complete adjuvant (FCA)-induced arthritic rat models. The results showed that HMSB could significantly reduce the paw edema response, decrease lysosomal enzymes, protein-bound carbohydrates, and acute phase protein levels. In addition, HMSB could significantly down-regulate pro-inflammatory cytokines TNF-IL-1 and IL-6 protein levels and mRNA expression in the joints with a dose-dependent manner. 61 These results indicated that the HMSB possess considerable potency in anti-inflammatory action and has a prominent anti-arthritic effect. Panthong et al evaluated the anti-inflammatory and antipyretic activities of the methanol extract (at doses of 1.0, 2.0, 4.0 mg/ear, i.g.) from C. petasites. The results proved that the extract possessed moderate inhibitory activity on acute phase of inflammation in a dose-related manner on ethyl phenylpropiolate-induced ear edema (ED50 = 2.34 mg/ear) as well as carrageenan-induced paw edema (ED50 = 420.41 mg/kg) in rats, and also reduced the alkaline phosphatase activity in serum. Moreover, the extract exhibited an excellent antipyretic effect in yeast-induced hyperthermic rats. 62 The anti-inflammatory and antipyretic effects of the methanol extract may be caused by the inhibition of the prostaglandin synthesis. The ethanol extract from the leaves of C. laevifolium exhibited the greatest anti-inflammatory activity against lipooxygenase with the IC50 of 14.12 μg/ml in vitro study. 63 In addition, the methanolic extract from the aerial parts of C. inerme exhibited anti-inflammatory activity at doses of 50, 100 and 200 mg/kg in formalin induced hind paw edema animals. 63 The anti-inflammatory activity of petroleum ether, chloroform, ethyl acetate, alcohol, and aqueous extracts of fresh leaves from Clerodendrum paniculatum Linn was evaluated by in vitro (human red blood cell membrane stabilization method) and in vivo methods (0.1 ml of 1% w/v carrageenan-induced rat paw edema model). Petroleum ether and chloroform extracts which showed, best in vitro anti-inflammatory activity also showed a dose dependent (200 and 400 mg/kg) significant reduction in paw edema when compared to the control (indomethacin, 10 mg/kg). 64 Srissok et al found that two flavones, hispidulin (126) and acacetin (146) isolated from the ethyl acetate (EA) extracts from the leaves of C. inerme exhibit the most potent inhibitory activity on nitric oxide (NO) production in RAW 264.7 macrophage stimulated with lipopolysaccharide (LPS). Furthermore, IC50 values of hispidulin and acacetin were 43.7 ± 4.0 and 43.5 ± 6.4 μM, respectively. Hispidulin also inhibited prosta glandin E2 (PGE2) production as well as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 expressions via the blockade of nuclear factor kappa B (NF-κB) DNA binding activity and the c-Jun NH2-terminal protein kinase (JNK) way. 65
### Pharmacological activities

| Pharmacological activities                          | Extract/Compound                  | Types      | Testing subjects                                      | Dose           | Effects                                                                 | Ref.  |
|----------------------------------------------------|-----------------------------------|------------|-------------------------------------------------------|----------------|------------------------------------------------------------------------|-------|
| Anti-inflammatory and anti-nociceptive activity     | 3-Hydroxy, 2-methoxy-sodium       | In vivo    | Carrageenan-induced inflammation and freund complete adjoint (FCA)-induced arthritic rat models | 25, 50, 100 mg/kg, i.g. | Reduced the paw edema response, decrease lysosomal enzymes, protein-bound carbohydrates, and acute phase protein levels | 90    |
|                                                    | Methanol extract from C. petasites | In vivo    | Ethyl phenylpropionate-induced ear edema and carrageenan-induced paw edema in rats | 1, 2, 4 mg/ear, i.g. | Inhibited prostaglandin synthesis                                      | 91    |
|                                                    | Ethanol extract from C. laevifolium | in vitro  | lipoxynase                                             | 10–1000 µg/ml | Displayed the greatest inhibition capacity with the IC50 value of 14.12 µg/ml | 92    |
|                                                    | Methanolic extract from C. inerme | In vivo    | Formalin induced hind paw edema animals                | 50, 100, 200 mg/kg, i.g. | Inhibited main inflammatory mediators Showed 57.15% protection and 48.98% protection of HRBC in hypotonic solution, respectively | 93    |
| Petroleum ether and chloroform extracts from C. paniculatum | In vitro | Human red blood cell membrane stabilization method | 1000 µg/ml |                                                      | 93    |
| Petroleum ether and chloroform extracts from C. paniculatum | In vivo | Carrageenan-induced rat paw edema model | 200 400 mg/kg, i.g. | Inhibited of the cyclooxygenase leading to inhibition of prostaglandin synthesis | 93    |
| Hipsidulin                                         | In vitro                          | RAW 264.7 macrophage stimulated with LPS | 12.5, 25, 50, 100, and 200 µM |                                                      | 94    |
| Methanolic extract from C. serratum                | In vivo                            | Carrageenan and arachidonic acid induced hind paw edema in rats | 50, 100, 200 mg/kg, i.g. | Inhibition of synthesis and inflammatory mediators release prolonged the latency reaction, suppressed the prostaglandin production | 97    |
| n-Butyl extract from C. bungei                    | In vivo                            | acetic acid-induced writhing model | 1.0 g/kg, i.p. |                                                      | 102   |
| Aqueous extracts from C. bungei                    | In vivo                            | DNF-induced hypersensitivity | 10 and 20 g/kg, i.p. | Restrained the phlogistic infiltration, improved the ear edema, reduced the writhes of abdominal cavity and the ear edema | 103   |
| Methanolic extract of C. indicum                   | In vivo                            | Carrageenan and arachidonic acid induced hind paw edema in rats | 200 and 400 mg/kg, i.g. |                                                      | 104   |
| Aqueous extract from C. inerme                     | In vivo                            | Milk-induced hyperpyrexia in rabbits | 100 and 200 mg/kg, p.o. | Raising the pain threshold at different time of observation | 105   |
| Anti-oxidant activity                              | Ethanol extract from C. infortunatum | In vitro  | DPPH-radicals                                         | 250 µg/ml | Raising the pain threshold at different time of observation | 106   |
|                                                    | Phenolic extracts from C. volubile | In vitro  | DPPH-radicals, OH radicals                             | 0–100 µg/ml | Inhibited DPPH free radicals and OH radicals                                                      | 107   |
|                                                    | Monoacletylarninioside             | In vitro  | DPPH-radicals                                         | 25 µmol/l | Inhibited DPPH                                                      | 108   |
|                                                    | 3',4'-O-acetyltarninioside         | In vitro  | DPPH-radicals                                         | 37 µmol/l | Inhibited DPPH                                                      | 108   |
|                                                    | Acteoside                          | In vitro  | DPPH-radicals                                         | 60 µmol/l | Inhibited DPPH                                                      | 108   |
|                                                    | Methanolic extract from C. inerme  | In vitro  | DPPH-radicals                                         | 100 µg/ml | Inhibited DPPH                                                      | 53    |
|                                                    | 5-Hydroxy-6,7,4'-trimethoxyflavone | In vitro  | DPPH-radicals                                         | 20 µM | Inhibited DPPH                                                      | 53    |
|                                                    | Ethanallic extract from C. volubile | In vitro  | DPPH-radicals, FRAP, hydrogen peroxide radical DPPH-radicals, FRAP, hydrogen peroxide radical | 50–250 µg/ml | Inhibited DPPH, FRAP, hydrogen peroxide radical | 109   |
|                                                    | Methanolic extract from C. serratum | In vitro  | DPPH-radicals, AR f-2-pyrrolidinone radicals, AR f-2-pyrrolidinone radicals | 0.125–1.0 mg/ml | Inhibited DPPH                                                      | 110   |
|                                                    | Methanolic extract from C. serratum | In vitro  | DPPH-radicals                                         | 200–1000 µg/ml | Inhibited DPPH                                                      | 111   |
|                                                    | Phenolic extracts from C. volubile | In vitro, in vivo | DPPH-radicals, lipid peroxidation assay DPPH-radicals, lipid peroxidation assay | 0–312.60 µg/ml | Reduced the MDA content | 107   |
|                                                    | Methanolic extract from C. umbellatum | In vivo  | Schistosoma mansoni-infected mice                      | 100, 200, and 400 mg/kg, i.g. | Decreased MDA level, increase CAT activity and GSH level | 113   |
|                                                    | Methanolic extracts from C. siphananthus | In vitro  | Thioyanate method, DPPH-radicals                       | 0–120 mg/ml | Scavenging lipid peroxide (IC50 = 8 mg/ml) and DPPH radicals (IC50 = 7 mg/ml) | 114   |
| Anti-cancer activity                               | In vivo                            | Carrageenan-induced inflammation and freund complete adjoint (FCA)-induced arthritic rat models | 25, 50, 100 mg/kg, i.g. | Reduced the number of writhes with 62.57%, inhibited the acetic acid-induced writhing test with 70.76%, respectively | 115,116 |
Table 2 (continued)

| Pharmacological activities | Extract/Compound | Types | Testing subjects | Dose | Effects | Ref. |
|----------------------------|------------------|-------|------------------|------|---------|-----|
| Anti-obesity activity      | Methanolic extract from C. serratum | In vitro | DMBA-induced skin tumorigenesis in male mice, DLA cell model | 300, 600 and 900 mg/kg, i.g., 100 and 200 mg/kg | Curtailed tumor development, Reduced skin papilloma incidence and multiplicity, Exhibited cytotoxicity | 117 |
|                           | Methanolic extract from C. serratum | In vitro | HL-60, SMMC-7721, IA-549, MCF-7 cell lines | 1.8–5.0 μM | | 89 |
|                           | Cryptopyallonol, fortinu E, 12-methoxy-6,11,14,16-tetrahydroxy-17(15→16)-abeno-5,8,11,13-abietatetraen-3,7-dione | In vitro | BGC-823, Huh-7, KB, KE-97, and Jurkat | 0.83–50.99 μM | Exhibited cytotoxicity | 41 |
|                           | Compounds 45, 70, 76, 81, and 82 | In vitro | HepG2 | 0.025–250 μg/ml | Inhibited HepG2 cells proliferation | 119 |
|                           | Total flavonoids from C. Bungei | In vitro | A549, Jurkat, BGC-823 and 293T WT | 7.51–19.38 μM | Exhibited cytotoxicity | 43 |
|                           | Compounds 240 and 243 | In vitro | Hela cell | 28.92–35.67 μg/ml | Exhibited moderate cytotoxicity | 82 |
| Anti-bacterial activity    | Methanolic extract from C. siphonanthus | In vitro | Klebsiella pneumoniae, Proteus mirabilis, Salmonella typhi, Staphylococcus aureus, Escherichia coli, and Bacillus subtilis | 5 μg/disc | The inhibition zones were 30, 16, 12, 11.5 and 10 mm, respectively | 114 |
|                           | n-Butyl extract from C. bungei | In vitro | Staphylococcus aureus and Micrococcus pyogenes | 50 μg/ml | The MIC values were 50 mg/ml and 25 mg/ml, respectively | 120 |
|                           | Aqueous extract from C. bungei | In vitro | Rhizoctonia cerealis, Fusarium graminearum, Rhizoctonia solani, and Sclerotinia verticillarum | 50–400 μg/ml | Displayed the strong antibacterial action on Fusarium graminearum, and the MIC values 10 mg/ml | 121 |
| Anti-fungal activity       | Ethyl acetate extract from C. inerme | In vitro | Alternaria, Lasiodiplodia, Pestalotiopsis, Nigrospora, Diaporthe, and Phomopsis | 50 μg/disc | Inhibited the growth of most fungi | 122 |
|                           | Ethyl acetate and chloroform extracts from C. infortunatum | In vitro | B. megaterium, S. typhi, K. pneumoniae and to fungi against A. niger and C. albicans | 1–512 μg/ml | Inhibited B. subtilis, K. pneumonia, S. aureus and E. coli growth | 123 |
| Anti-plasmodial activity   | Ethyl acetate, methanol and aqueous extracts from C. rotundifolium | In vitro | NF54 chloroquine sensitive and FCR3 chloroquine-resistant strains of Plasmodium falciparum | 5 μg/ml | Inhibited the growth of NF54 and FCR3 strains of Plasmodium falciparum | 124 |
| Insecticidal activity      | Aqueous extract from C. chinense | In vitro | A. subpictus, A. albopictus, and C. tritaeniorhynchus | 647.05–6877.28 μg/ml | Reduced populations of vector mosquitoes without detrimental effects on predation rates of non-target aquatic organisms, such as D. indicus, A. bouvieri and G. affinis | 125 |
| Anti-hypertensive activity | Aqueous extract from C. colebrookianum | In vivo, in vitro | Fructose-induced hypertension model in rats and in isolated frog heart. | 50–100 mg/ml | | 126 |
|                           | Compounds 64, 166, 178, 196 | In vitro | ACE and α-glucosidase inhibitory activity assay | 0.1–0.7 mM | Inhibited ACE and α-glucosidase. | 123 |
| Anti-obesity activity      | Methanolic extract from C. phlomidis | In vivo | High fat diet induced obesity in female mice | 200–400 mg/kg, i.g. | Decreased food consumption, body weight, adiposity index, pancreatic lipase activity, adiposity diameter, glucose, insulin, SGOT, SGPT, TG, TC and LDL-c levels | 40 |
|                           | Aqueous extract from C. glandulosum | In vivo | High fat diet induced obesity in C57BL/6J mice | 0–200 μg/ml | Decreased adipogenesis, TG accumulation, leptin release and GJPH activity | 130 |
| Anti-diarrheal activity    | Methanolic extract and chloroform fraction from the C. indicum | In vitro | Castor oil-induced diarrhea testing | 400 mg/kg | Inhibited defecation | 104 |
|                           | Methanolic extract from C. phlomidis | In vivo | Castor oil induced diarrhea and PGE2 induced enterpooling in rats | 600–800 mg/kg, p.o. | Exhibited significant inhibitory activity | 131 |

(continued on next page)
Narayanan et al (1999) studied anti-nociceptive effects of an alcoholic extract of C. serratum roots (50, 100 and 200 mg/kg) in acetic acid induced writhing (200 mg/kg) and hot plate method (100 and 200 mg/kg). A reduction in the number of abdominal constrictions in acetic acid induced writhing in mice indicated the anti-nociceptive effect of C. serratum which has further been supported by the findings of hot plate method where a significant increase in area under curve was observed. However, the response was much less when compared to morphine and exact mechanism remains to be investigated in detail. The authors have also indicated significant antipyretic activity of alcoholic extract (100 and 200 mg/kg) of C. serratum roots in rabbit model through a dose dependent reduction in pyrexia after administration of C. serratum. The ethanolic extract of C. serratum leaves has been found to produce considerable centrally acting analgesic activity in tail flick test at 250 mg/kg dose and peripherally acting analgesic activity in acetic acid induced writhing test at 500 mg/kg dose which was found comparable with diclofenac sodium. Blockade of capillary permeability or release of endogenous substances like prostaglandins might be a postulated mechanism. In another study, the author has established a potent analgesic effect of methanolic extract of the aerial parts of C. serratum when injected subcutaneously into the right dorsal hind paw of the mice via an inhibition of peripherally and centrally mediated nociception in early as well as in late phase.

The n-butyl extract (at dose of 1.0 g/kg, i.p.) from the roots of the C. bungei displayed a significant anti-nociceptive effect in an acetic acid-induced writhing model, prolonged the latency reaction in the hot-plate test in 15, 30, 60 and 90 min in mice. Moreover, the extracts administered in combination with naloxone significantly prolonged the latency reaction, and indicating that naloxone did not revert the action of the extract effect. Also, the extracts notably suppressed the production of prostaglandin (PG) in a dose-dependent manner. The extracts from the roots of C. bungei significantly restrained the phlogistic infiltration, improved the ear edema and reduced the writhes of abdominal cavity and the ear edema induced by 2,4-dinitro-1-fluorobenzene (DNFB)-induced hypersensitivity. The methanolic extract of C. indicum at doses of 200 and 400 mg/kg showed a significant (P < 0.001) and dose-dependent reduction in the number of writhes with 62.57% and 70.76% of inhibition in the acetic acid-induced writhing test, respectively. Thirumal et al reported that the aqueous extract obtained from C. inerme leaves (at doses of 100 and 200 mg/kg, p.o.) displayed significant analgesic effect by raising the pain threshold at different time of observation (0–120 min).

The combination of antiinflammatory, anti-nociceptive and antipyretic effects of the Clerodendrum genus indicated a prospect of intervention with prostaglandin synthesis, as prostaglandins have been established as a common mediator in all these responses. However, this possibility remains to be investigated.

Table 2 (continued)

| Pharmacological activities | Extract/Compound | Types | Testing subjects | Dose | Effects | Ref. |
|---------------------------|------------------|-------|------------------|------|---------|-----|
| Hepatoprotective activity | Ethanol extract of C. inerme | In vivo | CCl4-induced liver damage in rats | 200 mg/kg, i.g. | Decreased the serum ALT, AST, ALP, TGL, TC, and increased the GSH level | 132 |
|                          | Alcoholic extract from C. serratum | In vivo | CCl4-induced wistar rats | 20 mg/kg, i.g. | Reduced the level of serum bilirubin and liver function marker enzymes | 133 |
|                          | Alcoholic and aqueous extract from C. serratum | In vivo | CCl4-induced liver damage in rats | 200 mg/kg, i.g. | Restored AST, ALT, and ALP level | 134 |
|                          | Methanolic extract from C. umbellatum | In vivo | Schistosoma mansoni-infected mice | 100, 200 and 400 mg/kg, i.g. | Reduced ALT activity and increase total protein level | 113 |
|                          | Aqueous extract from C. copitatum | In vivo | High fat diet fed rats | 100, 400 and 800 mg/kg, i.g. | Reduced the mean fasting plasma glucose concentration, TC, VLDL-c and LDL-c | 136 |
|                          | Aqueous extract from C. glandulosum | In vivo | High fat diet fed rats | 200, 400 and 800 mg/kg, i.g. | Suppressed the HMG CoA reductase and cholesterol ester synthase activity, increased the plasma lecithin cholesterol acyl transferase and lipoprotein lipase levels | 137 |
| Memory enhancing effects | Methanolic extract from C. infortunatum | In vivo | Rectangular maze and Y maze (interoceptive behavioral models) | 100 and 200 mg/kg, i.g. | Inhibited depolarization-evoked glutamate release and cytosolic free Ca\(^{2+}\) in concentration in the hippocampal nerve terminals, inhibited glutamate release | 138 |
| Neuroprotective effects | Compound 46 | In vivo | Rat hippocampal nerve terminals (synaptosomes) | 10 and 50 mg/kg, i.p. | Exhibited significantly tracheal smooth muscle relaxant activity | 69 |
| Other activities | Ethanol extract from C. petasites | In vitro | Isolated guinea-pig | 2.25–9 mg/ml | Reduced spontaneous activity, decreased exploratory behavioral profiles | 9 |
|                          | Methanolic extract from C phlomidis | In vivo | Phenobarbitone sodium-induced sleeping time | 200, 400 and 600 mg/kg, i.g. | Reduced ALT activity and increase total protein level | 139 |
|                          | Ethanol extract from C. inerme | In vivo | Spontaneous locomotor activity or performance in the rotarod test | 100 mg/kg, i.p. | Reduced methamphetamine-induced hyperlocomotion in mice | 62 |
thoroughly. Advanced studies can be undertaken in the direction of purification of the chemical constituents of the leaves and investigation of the biochemical pathways for the development of a potent analgesic agent with a low toxicity and better therapeutic index.

3.2. Antioxidant activity

Gouthamchandra et al have demonstrated the antioxidant activity of the ethanol extract of leaves of C. infortunatum with the highest scavenging activity in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay (IC50 values 250 μg/ml). Moreover, the ethanol extract at 250 μg/ml concentration displayed significantly scavenging activity in hydroxyl, superoxide anion, and nitric oxide radical in vitro, and the scavenging ratio were 68.58%, 62.06%, and 52.65%, respectively.106 Adeyegha et al reported that the phenolic (free and bound) extracts from the leaves of Clerodendrum voluble scavenging DPPH free radicals and OH radicals in a concentration dependent manner. Interestingly, the IC50 values revealed that the free soluble phenolic extract (IC50 = 83.18 μg/ml and 924.90 μg/ml) have a significantly higher scavenging ability against DPPH free radicals and OH radicals than the bound phenolic extract (IC50 = 133.40 μg/ml and 1224.0 μg/ml), respectively.107 Three phenylethanoid glycosides mono-acetylmartinoside (182), 3’4’-O-acetylmartynoside (188) and acetoside (199) isolated from the roots of Clerodendrum lindleyi exhibited significant antioxidant activity in DPPH assay, and the radical scavenging rate were 25, 37, 60 μmol/L, respectively.108 The methanolic extract and 5-hydroxy-6,7,4'-trimethoxyflavone (153) isolated from the aerial parts of C. inerme showed notably scavenging activity with maximum inhibition of 61.84% for the methanolic extract (100 μg/ml) and 371.9% for 5-hydroxy-6,7,4'-trimethoxyflavone (20 μm), respectively, using DPPH assay.53

Bhujbal et al have demonstrated in-vitro antioxidant effects of ethanolic root extract of C. serratum (50–250 μg/ml) at various concentrations in the DPPH radical scavenging assay (IC50 value 175 μg/ml); FRAP (ferric reducing antioxidant power) assay and hydrogen peroxide radical scavenging assay (IC50 value 85 μg/ml) and suggested the role of polyphenols and flavonoids for the observed antioxidant effects in the extract.109 The antioxidant potential of methanolic extract of leaves of C. serratum was found more potent (EC50 value 0.51 μg/ml) due to higher polyphenolic content than other extracts (petroleum ether, chloroform and water) when evaluated in trolox equivalent antioxidant capacity (TEAC) in DPPH and 2,20-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) assays.110 Antioxidant potential of methanolic extract (200–1000 μg/ml) from the leaves of C. serratum was further supported by additional reports on DPPH assay, reducing power assay and total antioxidant activity assay.111

Feng et al reported that the flavonoid compound from C. bungei exhibited strong scavenging capability on nitrite, superoxide anion free radicals and hydroxyl free radicals, and also showed stronger antioxidant effect on pork fat than vitamin C.112 Also, the phenolic extracts (free and bound) from the C. voluble leaf were able to significantly reduce the MDA content in a dose dependent manner (0–312.60 μg/ml). The free soluble phenolic extract (192.30–779.90%) had a significantly higher concentration dependent inhibition of MDA compared with that of the bound phenolic extract (192.30–91.30%).107 Jatsa et al reported that the methanolic extract (at doses of 100, 200, and 400 mg/kg, i.g.) of Clerodendrum umbellatum significantly decrease malondialdehyde (MDA) level, increase catalase (CAT) activity and glutathione level.113 The methanolic extracts of leaves of Clerodendrum siphoneanthus displayed extremely effective in scavenging lipid peroxide (IC50 = 8 mg/ml) and DPPH radicals (IC50 = 7 mg/ml).114

3.3. Anticancer activity

Chinchali et al reported that administration of methanolic extract of C. serratum leaves significantly reduced tumor development in 7,12-dimethylbenz[a]anthracene (DMBA) induced skin carcinogenicity in testis, liver and kidney of mice.115,116 The researchers have further demonstrated that flavonoids and phenolics can effectively reduce the incidence and multiplicity of skin papilloma, many investigators have confirmed anti-cancer property of C. serratum by various in vivo and in-vitro studies.117,118 The methanolic extract of roots of C. serratum exhibited notably in vivo anticancer activity using DLA cell model at the dose 100 and 200 mg/kg body weight.117 Xu et al reported that diterpenoids cryptopaponin (281), fortunin E (282), 12-methoxy-6,11,14,16-tetrahydroxy-17(15→16)-abero-5,8,11,13-abietatetraen-3,7-dione (283) isolated from the hydroalcoholic extract of the herb of C. kiangsiense exhibited significant cytotoxicity against human myeloid leukemia (HL-60), hepatocellular carcinoma (SMMC-7721), lung cancer (A-549) and breast cancer (MCF-7) cell lines, and the range of IC50 values was 1.8–5.0 μM.109 The results suggested that these compounds might have promising potential to be anticancer agents.

Compounds 45, 70, 76, 78, 81 and 82 isolated and identified from the roots of C. trichotomum displayed remarkable in vitro cytotoxicity activity against five human cancer cell lines (BGC-823, Huh-7, KB, KE-97, and Jurkat) by using the CellTiter Glo™ Luminescent cell viability assay method with the IC50 values ranging from 0.83 to 50.99 μM. Among of them, teuvincenone E (81) exhibited the most potent activity against these five cell lines with the IC50 values of 3.95, 5.37, 1.18, 1.27, and 0.83 μM, respectively.41 The total flavonoids isolated from the C. Bungei significantly inhibited the human hepatoma HepG2 cells proliferation at concentrations of 0.025, 0.25, 2.5, 25, 250 μg/ml in vitro, and the inhibition ratios were 5.5%, 12.73%, 14.84%, 62.44%, and 76.81%, respectively.119 A dimeric diterpene trichotomone (55) isolated from the roots of the C. trichotomum exhibited strong in vitro cytotoxicities against several human cancer cell lines (A549, Jurkat, BGC-823 and 293T WT) with IC50 values ranged from 7.51 to 19.38 μM.115 Two steroids, (20R,22E,24R)-3β-hydroxy-stigmasta-5,22,25-trien-7-one (240), and (20R,22E,24R)-stigmasta-5,22,25-trien-3β,7β-diol (243) isolated from the leaves of C. trichotomum exhibited moderate cytotoxicity against Hela cell with IC50 values at 35.67 and 28.92 μg/ml, respectively.120

3.4. Antimicrobial activity

3.4.1. Antibacterial activity

Arokiyaraj et al reported that the methanolic extract of leaves of C. siphoneanthus exhibited significant antibacterial effect against Klebsiella pneumoniae, Proteus mirabilis, Salmonella typhi, Staphylococcus aureus, Escherichia coli, and Bacillus subtilis, and the inhibition zones were 30, 16, 16, 12, 11.5 and 10 mm, respectively.114 Liu et al reported that the n-butyl extract from the roots of C. bungei displayed prominent antibacterial effect against Staphylococcus aureus and Micrococcus pyogenes, and the minimal inhibitory concentration (MIC) values were 50 mg/ml and 25 mg/ml, respectively.120 Moreover, the aqueous extracts from the roots of C. bungei have notably antibacterial action on Rhizoctonia cerealis, Fusarium graminearum, Rhizoctonia solani, and Sclerotinia turram, especially the aqueous extract exhibited strongest antibacterial action on Fusarium graminearum, and the MIC value is 10 mg/ml.121 The methanolic extract, and chloroform fraction of C. indicum showed a moderate activity against the tested microorganisms in terms of both zones of inhibition (ranged from 9 to 13 mm, 10 to 13 mm and 10 to 13 mm, respectively, at a concentration of 400 μg/disc) and spectrum of activity.104
3.4.2. Antifungal activity

Gong et al firstly found that the crude ethyl acetate extract of endophytes from the stems of C. inerme exhibit broad in vitro antifungal activity against a number of fungal pathogens, including Alternaria, Lasiodiplodia, Pestalotiopsis, Nigrospora, Diaporthe, and Phomopsis, and inhibit the growth of most fungi. The ethyl acetate and chloroform extracts of root, leaf, and stem of the C. infortunatum showed significant inhibitory activity over the bacteria and fungus comparable to the standard drug tetracycline. The maximum average diameter zone of inhibition was recorded to bacterial strains such as Bacillus megaterium, S. typhi, K. pneumoniae and to fungi against Anisops niger and Clerodendrum albicans. The MIC values of ethyl acetate and chloroform root extract were determined as 64 μg/ml to B. subtilis and K. pneumoniae; 8 μg/ml to S. aureus and E. coli for both ethyl acetate and chloroform root extracts but only S. typhi and S. -ß-haemolytics for chloroform extract.123

3.4.3. Antiplasmodial activity

Adia et al revealed that the ethyl acetate, methanol and aqueous extracts from the leaves of Clerodendrum rotundifolium exhibit significantly in vitro antiplasmodial activity against the chloroquine-sensitive and chloroquine resistant Plasmodium falciparum strains with the IC50 < 5 μg/ml for the first time.124

3.4.4. Insecticidal activity

Lots of pharmacological tests and clinical observations have shown that different extract and/ or compound prescriptions derived from C. chinense have significant insecticidal effects against diseases and organisms including schistosomiasis and trichomoniiasis. Govindarajan et al reported that C. chinense-fabricated silver nanoparticles (Ag NPs) display higher toxicity against Anisops subpectis, Anisops albopictus, and Clerodendrum tritaeniorhynchus with the LC50 values of 10.23, 11.10, and 12.38 μg/ml, respectively. Also, C. chinense-fabricated Ag NPs were found safer to non-target organisms Diplonychus indicus, Anisops bouvieri and Gambusia affinis, with respectively LC50 values ranging from 647.05 to 6877.28 μg/ml.125 These results indicated that C. chinense-fabricated Ag NPs are a promising and eco-friendly tool against larval populations of mosquito vectors of medical and veterinary importance, with negligible toxicity against non-target aquatic organisms.

3.5. Antihypertensive activity

Lokesh et al evaluated the anti-hypertensive potential of the aqueous extract, and its aqueous, n-butanol, ethyl-acetate and chloroform fractions of C. colebrookianum leaves using fructose-induced hypertension model in rats and isolated frog heart. The results showed that the each fraction display negative inotropic and chronotropic effect on isolated frog heart and significant reduction in systolic blood pressure and heart rate in hypertensive rats. Moreover, each fraction at 100 mg/ml showed calcium antagonism in rat ileum and at 50 mg/ml and 75 mg/ml doses exhibited Rhokinase (ROCK-II) and phosphodiesterase-5 (PDE-5) inhibition, respectively.126 The anti-hypertensive activity of C. colebrookianum may mediate mainly by cholinergic action and following ROCK-II and PDE-5 inhibition. Liu et al demonstrated that four compounds 15-dehydrocyrtophyllone A (64), verbascoside (166), leucosceptoside A (178), and isoacteoside (196), isolated from dried roots of C. bungei showed inhibitory effects against angiotensin converting enzyme (ACE) and α-glucosidase. Among of them, 5-dehydrocyrtophyllone A exhibited an inhibitory effect against ACE with an IC50 value of 42.7 μM, while the three phenylethanoid glycosides, verbascoside, leucosceptoside A, and isoacteoside, exhibited stronger inhibitory effects against α-glucosidase, with IC50 values of 0.5 mM, 0.7 mM, and 0.1 mM, respectively.104

3.6. Anti-diabetic activity

Bachhawat et al reported that the methanolic extract (100 mg/ml) of C. serratum roots was evaluated for alpha-glucosidase inhibitory activity using enzyme assay. The extract was not found significantly effective (32.3% inhibition rate with IC50 value 265 μg/ml) and may require higher dose to produce the effect.127

3.7. Anti-obesity activity

Obesity, initially thought as a problem of the developed world, has now become a worldwide malady because of increasing prevalence in the developing countries as well as developed countries.128 The impact of methanolic extract of C. phlomidis on weight reduction in feeding high fat diet induced obesity in female mice had been investigated. The studies showed that the methanolic extract of C. phlomidis at 200 and 400 mg/kg significantly decrease food consumption, body weight, adiposity index, pancreatic lipase activity, adiposity diameter, glucose, insulin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), triglycerides (TG), total cholesterol (TC) and low-density lipoprotein (LDL-c) levels induced by feeding high fat diet induced obesity in female mice, and the LD50 value was found to be more than 2000 mg/kg.129 Jadeja et al reported that the aqueous extract from the leaves of Clerodendron glandulosum exhibited significant anti-adipogenic effect by decreasing adipogenesis, TG accumulation, leptin release and glyceroldehyde-3-phosphate dehydrogenase (G3PDH) activity along with higher glicerol release without significantly altering viability of 3T3L1 pre-adipocytes in vitro.130 This study was a profound scrutiny of C. glandulosum extract and its role in preventing adipocyte differentiation and visceral adiposity by down regulation of PPARY-2 related genes and leptin expression. This study validates the traditional therapeutic claim of use of CG extract in controlling obesity.

3.8. Anti-diarrheal activity

Pal et al reported that the methanolic extract and chloroform fraction from the C. indicum at a dose of 400 mg/kg produced 21.74% and 26.96% inhibition of defecation in castor oil-induced diarrhea testing, respectively, which were found to be comparable to that of standard drug loperamide (37.39% inhibition at 50 mg/kg) with regard to the severity of diarrhea. The methanolic extract (at doses of 600 and 800 mg/kg, p.o.) from the leaves of the C. phlomidis showed significant inhibitory activity against castor oil induced diarrhea and PGE2 induced enteropooling in rats. Also, the extract also showed a significant reduction in gastrointestinal motility in charcoal meal test in rats. Anti-diarrheal activity of the plant supported its traditional use in diarrhea by the people of Australia and India.

3.9. Hepatoprotective activity

Gopal et al reported that the ethanol extract of C. inerme leaves exhibit hepatoprotective activity on CCl4-induced (0.5 ml/kg, i.p.) liver damage in rats at a dose of 200 mg/kg. The extract significantly decreases the serum enzyme alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), triglycerides (TGL), total cholesterol (TC), and significantly increased the glutathione level. Udya et al reported that administration of an alcoholic extract from the roots of C. serratum (20 mg/kg) for two
weeks significantly reduced the level of serum bilirubin and liver function marker enzymes in carbon tetrachloride (CCl4) induced wistar rats indicating its potential as a hepatoprotective agent possibly due to the radical scavenging activity of the flavonoids present in the drug.\textsuperscript{113}

Also, Agrawal et al found that the alcoholic (200 mg/kg, p.o.) and aqueous extract (200 mg/kg, p.o.) from the leaves of \textit{C. serratum} possess significant hepatoprotective effects by restoring the normal level of AST, ALT, and ALP with significant reduction in liver weight.\textsuperscript{113} Reports on the biomarker ursoic acid, isolated from alcoholic root extract suggested restorative effects on the levels of AST, ALT and ALP towards respective normal value, to stabilize the plasma membranes as well as to repair hepatic tissue damage caused by CCl4. Ursolic acid was found to normalize the disturbed antioxidant status by maintaining the levels of glutathione and by inhibiting the production of malondialdehyde or may be due to the inhibition of toxicant activation and the enhancement of body defense system.\textsuperscript{99}

The ethanol extract of the polyherbal composition from the roots of \textit{C. serratum} showed significant protection against acetaminophen-induced hepatotoxicity in rats, and the function may be through DPPH free radical scavenging activity.\textsuperscript{115} The methanolic extract (at doses of 100, 200 and 400 mg/kg, i.g.) of \textit{C. umbellatum} significantly reduced ALT activity and increase total protein level.\textsuperscript{113} These findings provided scientific evidence to the ethnomedical reports of \textit{C. serratum} in treating acute jaundice; however investigations are still required to fully explicate the exact mechanisms behind the protection.\textsuperscript{113}

\subsection*{3.10. Hypoglycemic and hypolipidemic activities}

\textit{Adeneye} et al reported that the fresh leaves aqueous extract of \textit{Clerodendrum capitatum} possess obvious hypoglycemic and hypolipidemic activities, the extracts (at doses of 100, 400 and 800 mg/ kg, i.g.) could significantly reduce the mean fasting plasma glucose concentration in a dose-dependent lowering effects. Furthermore, the extracts also could notably decrease the total cholesterol, VLDL-c and LDL-c with a dose-related, but significant elevate the triacylglycerides and HDL-c with a dose-related in plasma.\textsuperscript{116} Jadeja et al reported that the aqueous extract (200, 400 and 800 mg/kg, i.g.) of \textit{C. glandulosum} leaves significantly prevented increment in plasma and tissue lipid profiles in high fat diet (HFD) rats, suppressed activity levels of HMG CoA reductase (Hepatic) and cholesterol ester synthase (Hepatic and intestinal), and increased the activity levels of plasma lecithin cholesterol acyl transferase and lipoprotein lipase (plasma, hepatic and adipose), and increased excretion of triglycerides, cholesterol and bile acids through faeces.\textsuperscript{117}

\subsection*{3.11. Memory enhancing effects}

\textit{Gupta} et al reported that the methanolic extract of \textit{C. infortunatum} leaves exhibited promising memory enhancing effects at dose of 200 mg/kg (i.g.), and the effects was closely approximated the results for the standard drug Brahim, the higher dose evoking pronounced alteration behavior and better learning assessments.\textsuperscript{118} The presence of steroids, terpenoids, fats and flavonoids were confirmed in this extract by TLC. The extract is likely to develop a promising nootropic to prevent dementia senilis disease.

\subsection*{3.12. Neuroprotective effects}

One flavonoid acacetin (146) isolated from the \textit{C. inerme} was investigated for neuroprotective activity. It was observed that acacetin inhibited depolarization-evoked glutamate release and cytosolic free Ca\textsuperscript{2+} concentration in the hippocampal nerve terminals. Moreover, acacetin (at doses of 10 and 50 mg/kg, i.p.) inhibited glutamate release from hippocampal synaptosomes by attenuating voltage-dependent Ca\textsuperscript{2+} entry and effectively prevents kainic acid (KA)-induced in vivo excitotoxicity.\textsuperscript{69}

\subsection*{3.13. Other activities}

Hazeckamp et al found that the ethanolic extract of \textit{C. petasites} leaves exhibited a dose-dependently tracheal smooth muscle relaxant activity on isolated guinea-pig at concentrations from 2.25 to 9 mg/ml, and the active principle was isolated and identified as the flavonoid hispidulin.\textsuperscript{5} The results indicated that hispidulin may be beneficial in the treatment of asthma related diseases. In additional, the methanolic extract (at doses of 200,400 and 600 mg/kg, i.g.) of \textit{C. phlomidis} leaves was found to cause significant reduction in spontaneous activity, and decreases in exploratory behavioral profiles by the Y-maze and head dip test. Also, the extract exhibit significantly reduction in muscle relaxant activity by rotarod, 30° inclined screen and traction tests, as well as significantly potentiated the phenobarbitone sodium-induced sleeping time.\textsuperscript{10} Huang et al demonstrated for the very first time that hispidulin isolated from the dichloromethane and the n-hexane fractions of ethanol extract of \textit{C. inerme} significantly reduced methamphetamine-induced hyperlocomotion (MH) in mice at dose of 100 mg/kg (i.p.) that did not affect their spontaneous locomotor activity or performance in the rotarod test, a measure for motor coordination.\textsuperscript{62} This study suggested that hispidulin may be a good therapeutical potential in hyper-dopaminergic disorders.

\section*{4. Conclusions}

In present review, more than 300 chemical constituents have been isolated and identified from the genus of \textit{Clerodendrum}, and pharmacological studies indicated that the crude extracts and some special monomer compounds of the genus \textit{Clerodendrum} exert various biological activities, such as anti-inflammatory and anti-noiceptive, antioxidant, anticancer, antimicrobial, anti-hypertensive, anti-obesity, anti-diarrheal, hepatoprotective, memory enhancing, and neuroprotective activities. Terpenes, including monoterpene and its derivatives, sesquiterpene, diterpenoids, triterpenoids, as the major characteristic constituents with significant biological activities, have great potential to be developed into new drugs, especially for anti-inflammatory, antioxidant, anticancer, and antimicrobial agents. In addition, important activities, such as anti-hypertensive, anti-obesity, and hepatoprotective activities indicated that \textit{Clerodendrum} genus can be a promising source of biologically active compounds for these diseases.

The genus \textit{Clerodendrum} has gained a wide acceptance for its pharmacological activities against various ailments. Although above 400 species of the genus \textit{Clerodendrum} were distributed all over the world, only a few of them have been investigated and studied so far. From this review, it can be concluded that phytochemical and pharmacology investigations were mainly focused on \textit{C. serratum}, \textit{C. bungei}, \textit{C. inerme}, \textit{C. trichotomum}, \textit{Clerodendrum chinense}, \textit{C. colebrookianum}, \textit{C. phlomidis}, \textit{C. petasites}, \textit{C. grayi}, and \textit{C. indicum}. For some species, such as \textit{C. grayi} was only studied phytochemically, no biological activity was reported up till now. Many other species are totally unknown phytochemically and biologically. Following these species may be of a great importance in discovering new bio-active compounds. On the other hand, few reports have been published concerning the toxic effects of isolated components, and quantitative informations of the genus \textit{Clerodendrum} were also relatively sparse.
All in all, the omnibearing study on this genus Clerodendrum should be performed as soon as possible, which will provide reliable theory evidence for better exploit and utilize the resources of the species in this genus.

Conflict of interest statement

The authors declare no conflict of interest.

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