Phytochemistry and pharmacology of *Curculigo orchioides* Gaertn: A review

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**ABSTRACT**
*Curculigo orchioides* Gaertn. is a rare rasayana herb (family Amaryllidaceae) popularly known as “Kali Musli”. Traditionally used in Ayurvedic medicine as an aphrodisiac and adaptogen, the plant is native to India. There is evidence that the plant contains mucilage, phenolic glycosides, saponins, and aliphatic compounds. This folk medicine can treat a wide range of ailments, including impotency, aphrodisiacs, tonics, jaundice, and skin conditions. There are also many scientists who have investigated its antioxidant, anticancer, and hepatoprotective properties. *Curculigo* was isolated for its chlorophenolic glucosides, curculigine, phenolic glycosides, orcinosides, and polysaccharides. As an herbal medicine, *Curculigo’s* quality can be controlled through new analyzing methods. Furthermore, *Curculigo* has been investigated for its pharmacological activity against diabetes, bacteria, inflammation, osteoporosis, oxidative stress, cancer, and neurodegeneration. Scientific methods were gradually developed for the application of herbal medicine. A more comprehensive pharmacological study of the genus *Curculigo* is needed to determine its medicinal value. An updated and comprehensive review of the medicinal plant *C. orchioides* Gaertn is presented here describing traditional uses, phytochemistry, pharmacology, and toxicology, and understanding its future research and development prospects.

**INTRODUCTION**
The traditional Indian medical system is called Ayurveda. There is a long history of disease management in Ayurvedic practice dating back about 3000 years (Hankey, 2001). The Ayurvedic healing process relies heavily on plant-based preparations (Sastri, 2002). In Ayurvedic medicine, approximately 90% of the preparations are derived from plants (Kumar et al., 2017). There are many Asia’s subtropical regions, including China and India, where *Curculigo orchioides* grows as a perennial herb of the Amaryllidaceae family (Bafna and Mishra, 2005; Jiao et al., 2009; Wang et al., 2012). *Curculigo orchioides* Gaertn, of the Amaryllidaceae family has different names such as Golden Eye Grass, Talamuli, Kalimusli, Nilappani, and Nilapanaiin English, Sanskrit, Hindi, Malayalam, and in Tamil, respectively (Joy et al., 2004).

Originally native to India, *C. orchioides* occur everywhere, especially in rocky areas, especially at sea level and up to 2,300 m above the sea level (Mehta and Nama, 2014). Tonic medicine has been used for centuries with the rhizome of *C. orchioides* by the Chinese since the Tang Dynasty for the maintenance of health, energy, and nourishment of renal and hepatic systems. The root of *C. orchioides* was commonly used in the treatment of impotence, limb limping, lumbar and knee joint arthritis, and diarrheal water (Chauhan et al., 2010). Jaundice, asthma, urinary and skin diseases, and bladder and kidney infections were treated with *C. orchioides* in the Ayurvedic System of Medicines (Khare, 2007).

A variety of secondary metabolites are found in the genus *Curculigo* plants. Ten species: their chemistry and pharmacology have been studied to date. These species include
Curculigo capitulata, Curculigo sinensis, Curculigo crassifolia, C. orchioides, Curculigo breviscapa, Curculigo gracilis, Curculigo recurvata, Curculigo glabrescens, Curculigo pilosa, and Curculigo latifolia. The main compounds found in Curculigo species include phenols, phenolic glucosides, terpenoids, and norlignans (Nie et al., 2013). Curculigo plants are increasingly studied phytochemically due to their traditional uses. This genus of plants contains more than 110 compounds, among which are as follows: phenolic glycosides and phenols (Chang and Lee, 1998; Xu and Xu, 1992; Zuo et al., 2010), lignan glycosides and lignans (Li, 1559; Li et al., 2005a, 2005b; Wang et al., 2008; Zhu et al., 2010), triterpenoid glycosides and triterpenes (Xu et al., 1992; Yokosuka et al., 2010; Zuo et al., 2012), eudesmanes, flavones (Tiwari and Mishra, 1976), alkaloids (Li et al., 2005a, 2005b), and other constituents. In China, C. orchioides is considered as a supplemental health product in the form of tea bags and alcoholic beverage (Liu et al., 2022). Curculigo orchioides is reported to have the effects of dissipating carbuncle, strengthening muscles and bones, dispelling cold and dampness, tonifying kidney yang, benefiting essence and blood, immunoregulation, hepatoprotective and neuroprotective activities (Fang et al., 2020). These plants are most likely characterized by norlignans, phenol glucosides, and triterpenoids as their major constituents. Bio-active compounds and extracts of Curculigo plants exhibited a variety of activities including antidiabetic, immunostimulatory, anti-oxidant, radical scavenging, mast cell stabilization, sweet-tasting and taste-modifying, estrogenic and sexual behaviour-modifying, anti-inflammatory, antihistaminic, antidepressant, antitumor, anti-asthmatic, anti-osteoporotic, neuroprotective, nephroprotective, antiarthritic, vasoconstrictor, anti-microbial, hepatoprotective, antistress activity, and adaptive activity (Table 1) (Wang et al., 2021). By using C. orchioides embryos for the green fabrication of gold nanoparticles, an environmentally friendly method for maintaining medicinal plants and preventing them from being overutilized was conducted (Thamilchelvan et al., 2023).

PHOTOCHEMISTRY

Curculigo plants have yielded about 111 secondary metabolites, 3 proteins, and 2 polysaccharides so far. A number of compounds are isolated from extracts of Curculigo species which includes phenolic glycosides, phenols, lignan glycosides, lignans, triterpenoid glycosides, triterpenes, polysaccharides such as COPb-1 and COPF-1, flavones, aliphatic compounds, alkaloids, eudesmanes, and bioactive proteins such as neoculin, curculigine E–G, orcinol glucoside (OG) B, benzyl-O-β-D-glucopyranoside, 3-hydroxy-5-methylphenol-1-O-(β-D-glucopyranosyl-(1-6)-β-D-glucopyranoside), glycosyric acid, 3-hydrox-5-methyl-phenol-1-O-(β-apiosyl-(1-6)-β-glucopyranoside), and OG were isolated from C. orchioides rhizomes (Wang et al., 2013, 2014) (Fig. 1). Four other known phenolic compounds, including orcinose I and J, have been proclaimed to be new heterocyclic phenolic derivatives, including 3-(4-hydroxy-3-methoxyphenyl) propane-1,2-diol, 3-(4-hydroxy-3,5-dimeth-oxyphenyl) propane-1,2-diol, piperoside, 4-ally-2, and 6-dimethoxy phenol glucoside (Chen et al., 2017).

Curculigorhizomes powdered and dried were used to isolate 3,5-Dihydroxy-4-methoxybenzoic acid and p-Hydroxycinnamic acid (Nie et al., 2020). Curculigo orchioides contains natural and rare chlorinated compounds called cuculligines. It was discovered that the rhizome of C. orchioides contains three chlorophenolic glucosides, B, C, and curculigine D (Cao et al., 2009; Xu et al., 1987; Xu and Xu, 1992). The C. orchioides rhizomes were collected for the purpose of obtaining 11 chlorophenolic glucosides, including curculigine E–G, I, and K–O (Wang et al., 2013, 2014, 2018). The C. orchioides rhizomes contain two new chlorophenolic glucosides named ascurculigine P and Q (Deng et al., 2021). Terpenoids are second metabolites produced by Curculigo species. There is evidence that C. orchioides produces cycloartane-type triterpenid ketone in its rhizomes (Jiao et al., 2013) (3S,5R,6S,7E,9R)-megatigma-7-ene-3,5,6,9-tetrol, actinidioin,oside, (6S,9R)-roseoside, (−)-angelicoidenol-2-O-β-D-glucopyranoside, (−)-angelicoidenol-2-O-β-apifuranosyl-(1→6)-β-D-glucopyranosidetetilipropyrene(7R,9S,10R)-3-methyl-5-(4-hydroxy-5-hydroxymethyltetrahydrofuryl)-6-hydroxypryan-2-one are six terpenoid compounds of C. orchioides (Zhang et al., 2019a, 2019b). Rhizomes of C. orchioides contain eight cyclodipeptides, such as cyclo-(L-Ala-L-Tyr), cyclo- (Gly-D-Val), cyclo-(LeuAla), cyclo-(Val-Ala), cyclo-(L-Ser-L-Phe), cyclo-(LeuThr), cyclo-(S-Pro-R-Leu), and cyclo- (Leu-Ser), which are previously known (Chen et al., 2017). The aqueous leaf extract of the plant was observed to contain different alkaloids and phenolic compound from the post preliminary phytochemical analysis using Fourier-transform infrared spectrophotometer (Umar et al., 2021). The presence of alkaloids, phenols, and saponins could be a plausible explanation for the observed toxic effects of C. orchioides’ AL extract in organismal-level toxicity in Drosophila (Kushalan et al., 2022a, 2022b).

PHARMACOLOGICAL ACTIVITY

Immunomodulatory activity

Adaptation to hypoxia and high temperatures is improved by C. orchioides ethanol extract. Extracts from C. orchioides have been found to be sedative, anticonvulsant, and androgen-like. In mice, immunological activity increased as well
Table 1. Effect of *C. orchioides* in many metabolic ailments.

<table>
<thead>
<tr>
<th>Species</th>
<th>Plant part</th>
<th>Extract</th>
<th>Experimental model</th>
<th>Dose</th>
<th>Effects</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Hydroalcoholic extract</td>
<td>STZ-nicotinamide induced diabetic nephropathy</td>
<td>600 mg/kg</td>
<td>Anti-diabetic activity</td>
<td>Zhang et al., 2017</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td>STZ-nicotinamide induced diabetic nephropathy</td>
<td>600 mg/kg</td>
<td>Anti-diabetic activity</td>
<td>Zhang et al., 2017</td>
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<tr>
<td><em>C. latifolia</em></td>
<td>Rhizome</td>
<td>Aqueous extract</td>
<td>HFD + STZ-induced diabetic rats</td>
<td>5 g/day</td>
<td>Anti-diabetic activity</td>
<td>Karigidi and Olaiya, 2020</td>
</tr>
<tr>
<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td>3T3-L1</td>
<td>10 and 100 g/ml</td>
<td>Anti-diabetic activity</td>
<td>Gulati et al., 2015</td>
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<tr>
<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Methanol extract</td>
<td>HFD + STZ-induced diabetic rats</td>
<td>600 mg/kg</td>
<td>Antihypertensive activity</td>
<td>Joshi et al., 2012</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td>Hela cells</td>
<td>10, 20–80 mg/ml</td>
<td>Anticancer activity</td>
<td>Xia et al., 2016</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethyl acetate extract</td>
<td>MCRF-7 cells</td>
<td>80 µg/ml</td>
<td>Anticancer activity</td>
<td>Selvaraj and Agastian, 2017</td>
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<td><em>C. orchioides</em></td>
<td>Whole plant</td>
<td>Aqueous extract</td>
<td>HFD + STZ-induced diabetic rats</td>
<td>40 mg/kg</td>
<td>Anticancer activity</td>
<td>Xia et al., 2016</td>
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<tr>
<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td>HFD + STZ-induced diabetic rats</td>
<td>0.5, 1.0, and 2.0 g/kg</td>
<td>Anticancer activity</td>
<td>Cao et al., 2008</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanolic extract</td>
<td>Radical scavenger for DPPH</td>
<td>25, 50–200 µg/ml</td>
<td>Antioxidant activity</td>
<td>Bagna and Mishra, 2005</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanolic extract</td>
<td>Visitation by peroxidation of lipids</td>
<td>25, 50–125 µg/ml</td>
<td>Antioxidant activity</td>
<td>Bagna and Mishra, 2005</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>hydro-alcoholic extracts</td>
<td>Scavenging DPPH radical</td>
<td>43.57 ± 4.21 mg/ml</td>
<td>Antioxidant activity</td>
<td>Tacchini et al., 2015</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td>Cyclophosphamide-induced oxidative stress</td>
<td>25 mg/kg</td>
<td>Antioxidant activity</td>
<td>Murali and Kuttan, 2015</td>
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<td><em>C. pilosa</em></td>
<td>Rhizome</td>
<td>Aqueous extract</td>
<td>Rat penile homogenate</td>
<td>0.95 mg/ml</td>
<td>Antioxidant activity</td>
<td>Adedefgha et al., 2018</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Methanolic extracts</td>
<td>An assay to measure ferric reducing antioxidant power</td>
<td>0.16–500.70 mmol/l</td>
<td>Antioxidant activity</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td><em>S. pyogenes</em></td>
<td>49 µg/ml</td>
<td>Antibacterial activity</td>
<td>Marasini et al., 2015</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Rhizome oil</td>
<td>Microorganisms that cause human pathogens and phytopathogens</td>
<td>2 mg/l/ml</td>
<td>Antibacterial activity</td>
<td>Jaiswa et al., 1984</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Curculigoside</td>
<td>Fibroblasts from the foreskin of humans</td>
<td>30 mg/ml</td>
<td>Antibacterial activity</td>
<td>Li et al., 2011</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Chloroform extract</td>
<td><em>S. typhimurium, P. aeruginosa</em></td>
<td>2 mg/ml</td>
<td>Antibacterial activity</td>
<td>Nagesh and Shanthamma, 2009</td>
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<td><em>C. pilosa</em></td>
<td>Rhizome</td>
<td>Ethanol crude extract and the neutral metabolite</td>
<td><em>Streptococcus faecalis, P. aeruginosa, E. coli, S. aureus</em></td>
<td>100 mg/ml</td>
<td>Antibacterial activity</td>
<td>Nwokonkwo, 2014</td>
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<tr>
<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td>Mast cells isolated from mouse peritoneum</td>
<td>400 mg/kg</td>
<td>Antiasthmatic activity</td>
<td>Venkatesh et al., 2009</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td>Induction of catalepsy in Swiss mice by haloperidol</td>
<td>250, 375 mg/kg</td>
<td>Antiasthmatic activity</td>
<td>Pandit et al., 2008</td>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td>Anaphylaxis due to passive paws in Wistar rats</td>
<td>350 mg/kg</td>
<td>Antiasthmatic activity</td>
<td>Pandit et al., 2008</td>
</tr>
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<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>OG</td>
<td>Depressive rats induced by CUMS</td>
<td>1.5, 3, 6 mg/kg</td>
<td>Neuroprotective effect</td>
<td>Pandit et al., 2008</td>
</tr>
<tr>
<td><em>C. orchioides</em></td>
<td>Rhizome</td>
<td>Curculigoside</td>
<td>Exposure to N-methyl-d-aspartate (NMDA) leads to the loss of neurons in cortex</td>
<td>1, 10, and 100 µmol/ml</td>
<td>Neuroprotective effect</td>
<td>Ge et al., 2014</td>
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</table>
Curculigo orchioides phenolic glucosides increased haemagglutination titer and delayed type hypersensitivity (DTH) response (Lakshmi et al., 2003). Although polysaccharides stimulate splenocyte proliferation, they do not affect thymocyte proliferation. Using ConA-induced splenocyte proliferation as a model, polysaccharides demonstrated an inhibitory effect on thymocyte and spleenocyte proliferation in vitro. Mice with immunosuppression had larger thymuses and spleens as a result of these effects (Zhou et al., 1996).

It has been suggested that the methanolic extract of C. orchioides (MECO) Gaertn’s could be used to prevent the cytotoxic effects of drugs. When the extract was administered to normal mice or cyclophosphamide-induced immunosuppressed mice, humoral antibodies, DTH, and leukocytes increased depending upon the dose (Bafna and Mishra, 2006). One of the contents of C. orchioides rhizomes, Curculigo saponin, acycloartane-type triterpene saponin, enhanced the number of lymphocytes of the spleen remarkably in mice without affecting antibody production (Lacaille-Dubois and Wagner, 1996). Polysaccharides resulted in increased spleen and thymus indexes in normal mice, along with increased hemolytic index and thicker plantar tissue in serum; Mice immune function is enhanced by polysaccharides, according to these results (Ji, 2011).

Antioxidant activity

DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) and nitric oxide radicals are scavenged effectively by methanol extracts of C. orchioides rhizomes, but lipid peroxidation is moderately effective (Bafna and Mishra, 2005). In addition to DPPH testing, ferric reducing ability of plasma testing as well as 2,2’-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) testing has also been performed on C. orchioides to confirm its antioxidant activity (Surveswaran et al., 2007). DPPH, reducing power, and phosphomolybdenum assays were used to assess C. orchioides’ antioxidant potential ethanolic extract of C. orchioides root demonstrated significant anti-free radical activity, reducing power, and antioxidant properties compared with a reference standard, gallic acid (Table 1) (Ratnam et al., 2013). Methanolic extract of elevated rhizomes treated hepatotoxic rats showed increased levels of antioxidant enzymes such as glutathione transferase (Venukumar and Latha, 2002). Methanolic root extract showed DPPH radical scavenging activity (Kushalan et al., 2022a, 2022b). A major component of C. orchioides’ antioxidant activity is phenolic compounds (Wu et al., 2005).

Anti-inflammatory activity

Curculigoside A which is the vital component of C. orchioides, reduced paw swelling and arthritis index in mice

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>C. orchioides</td>
<td>Rhizome</td>
<td>Curculigoside</td>
<td>Mice</td>
<td>10, 20, 40 mg/kg</td>
<td>Neuroprotective effect</td>
<td>Tian et al., 2012</td>
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<tr>
<td>C. orchioides</td>
<td>Rhizome</td>
<td>Curculigoside</td>
<td>Neuronal cell stimulation by NMDA</td>
<td>1 and 10 µM</td>
<td>Neuroprotective effect</td>
<td>Ge et al., 2014</td>
</tr>
<tr>
<td>C. orchioides</td>
<td>Rhizome</td>
<td>Curculigoside</td>
<td>osteoblasts</td>
<td>25–100 µg/ml</td>
<td>Anti-osteoporosis</td>
<td>Wang et al., 2016</td>
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<tr>
<td>C. orchioides</td>
<td>Rhizome</td>
<td>Curculigoside</td>
<td>Iron-overload mice model</td>
<td>100 mg/kg</td>
<td>Anti-osteoporosis</td>
<td>Zhu et al., 2015a, 2015b</td>
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<tr>
<td>C. orchioides</td>
<td>Rhizome</td>
<td>Methanolic extract</td>
<td>A rat model of liver injury induced by carbon tetrachloride (CCI₄)</td>
<td>70 mg/kg</td>
<td>Hepatoprotective activity</td>
<td>Zhang et al., 2019a, 2019b</td>
</tr>
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<td>C. orchioides</td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td>Ovariectomized young albino rats</td>
<td>300, 600 and 1,200 mg/kg</td>
<td>Sexual behaviour and estrogenic activity</td>
<td>Venukumar and Latha, 2002</td>
</tr>
<tr>
<td>C. orchioides</td>
<td>Rhizome</td>
<td>Ethanol extract</td>
<td>Druckery rats</td>
<td>100 mg/kg</td>
<td>Sexual behaviour and estrogenic activity</td>
<td>Vijayanarayana et al., 2007</td>
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<tr>
<td>C. orchioides</td>
<td>Rhizome</td>
<td>Methanol extract</td>
<td>BALB/c mice</td>
<td>25 mg/ml</td>
<td>Immunostimulatory effect</td>
<td>Chauhan et al., 2007</td>
</tr>
<tr>
<td>C. orchioides</td>
<td>Rhizome</td>
<td>Methanol extract</td>
<td>BALB/c mice</td>
<td>100 µg/ml</td>
<td>Immunostimulatory effect</td>
<td>Lacshmi et al., 2003</td>
</tr>
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<td>C. orchioides</td>
<td>Rhizome</td>
<td>Methanol extract</td>
<td>Cyclophosphamide-induced immunosuppressed mice</td>
<td>100, 200, 400 and 800 mg/kg</td>
<td>Immunostimulatory effect</td>
<td>Bafna and Mishra, 2006</td>
</tr>
</tbody>
</table>

Figure 1. Chief active constituents of C. orchioides.
significantly and decreased serum IL-1β, TNF-α, IL-6, and PGE2 levels, decreased malondialdehyde (MDA) and increased serum superoxide dismutase activity very effectively downregulated NF-kB/NLRP3 pathways in Freund’s complete adjuvant-induced rats with adjuvant arthritis (Ding et al., 2016). Type II collagen-induced arthritis rat showed arthritis scores and paw swelling inhibition, serum pro-inflammatory factor levels of IL-10, TNF-α, IL-17A, IL-6, IL-12, and IL-1β reduced, the expression of JAK3, STAT3, and JAK1 down-regulated and NF-κB p65 and IκBup-regulated because of the active compound curculigoside A (Tan et al., 2019). Carrageen-induced paw edema in rats was significantly reduced by C. orchoides rhizome gel formulation (Dode et al., 2009).

Mice peritoneal mast cells were significantly inhibited from degranulating by an extract of C. orchoides rhizome in ethanol and mice exposed to 48/80-induced systemic anaphylaxis. Anti-inflammatory properties of C. orchoides are attributed to their inhibitory effects on mast cell degranulation and mast cell-derived immediate-type allergic reactions (Venkatesh et al., 2009).

**Estrogenic activity**

Total glucosides from C. orchoides were found to increase the thymus, uterus, and spleen indices, testosterone levels, and estrogen levels, and decrease luteinizing hormone levels in perimenopause model mice (Cao et al., 2016; Xiao et al., 2017). Curculigo orchoides also alleviate streptozotocin-induced hyperglycaemia in male rats, improving sexual dysfunction as well. The effects of the treatment were observed in male sexual behaviour, penile erection index, seminal fructose content, and sperm counting the test samples (Thakur et al., 2012). It increases steroid synthesis and restores sexual function by enhancing the spermatogenesis process. It could also facilitate hormone absorption into the gonads if C. orchoides was administered (Chauhan et al., 2007).

**Anti-osteoporosis activity**

The rhizomes of C. orchoides are asserted to strengthen bones and tendons (Cao et al., 2008). The proliferation of bone marrow stromal cells was enhanced by 100 mM curculigoside, osteogenic genes were enhanced, and osteoprotegerin secretion was increased (Shen et al., 2013). A study indicates that curculigoside A chemical compound inhibits the inflammatory cytokines TNF-α, IL-1α, IL-6, and COX-2 production by rat calvarial osteoblasts induced with dexamethasone and regulates osteoblast COX-2 expression, proliferation, and differentiation (Zhu et al., 2015a, 2015b).

The chlorophenolic glucosides (Curculigine M, Curculigine N, and Curculigine O) isolated from the dried rhizomes of C. orchoides Gaertn showed moderate effect on osteoblast proliferation against MC3T3-E1 cell line by using MTT assays (Wang et al., 2018). A novel homogeneous heteropolysaccharide, COP70-3, was isolated and purified from the crude polysaccharide (CO70) isolated from the rhizomes of C. orchoides (0.94 and 1.87 nM) significantly improved the osteogenic mineralization rate and has favorable anti-osteoporosis activity in vitro (Wang et al., 2018). Curculigoside was able to alleviate bone loss induced by oxidative stress resulting from iron overload, suggesting its potential use for the treatment of primary osteoporosis and bone loss in iron-overload–related diseases (Zhang et al., 2019a, 2019b). The major bioactive component of found in the plant’s rhizomes, curculigoside, a phenolic glycoside, exhibits neuroprotective and anti-osteoporotic properties (Zhu et al., 2021). COP50-4, a crude polysaccharide (COS50) from C. orchoides shows great potential for the treatment of osteoporosis (Yu et al., 2022).

**Antidepressant activity**

The immobility time of the forced swimming test, osmotic fragility test, and tail suspension test was significantly reduced by curculigoside treatment. In the hippocampus of chronic mild stress rats, serotonin, dopamine, and norepinephrine levels significantly increased along with brain-derived neurotrophic factor (BDNF) protein expression following the treatment. There is evidence that curculigoside can treat depression in this way (Wang et al., 2016).

**Neuroprotective activity**

Acetylcholinesterase was effectively inhibited by the extracts of C. orchoides rhizomes, suggesting their potential use in the treatment of Alzheimer’s disease (Pratap and Shantaram, 2019). Curculigoside remarkably reduced NMDA-induced loss of neuron cells, apoptosis, necrosis, excitotoxicity, and reactive oxygen species (ROS) production in cultured cortical neurons. The inhibitory properties of curculigoside in cultured cortical neurons may cause the production of intracellular ROS to be reduced and apoptosis may be inhibited. When neurons are exposed to NMDA-induced neuronal excitotoxicity, curculigoside prevents them from dying and reduces their apoptosis and necrosis (Tian et al., 2012).

Spectrophotometry and autobiography were used to evaluate the anti-acetylcholinesterase activity of C. orchoides extracts in vitro. The anti-acetylcholinesterase role of rhizome extract methanol in the treatment of Alzheimer’s disease appears to be explained by its inhibition of the acetylcholinesterase enzyme (Pratap, 2020). Using curculigoside A, rats with Alzheimer’s can be effectively treated because it inhibits apoptosis in hippocampal neurons and reduces cellular damage (Li et al., 2019). In vitro, curculigoside A modulated VCAM-1/Egr-3/CREB/VEGF signalling in cerebroendothelial cells, providing stroke and brain injury therapies by neurovascular repair (Zhu et al., 2015).

It was demonstrated that OG decreased over activity of the hypothalamic-pituitary–adrenal axis and reduced depressive behavior in chronic unpredictable mild stress rats by up-regulating BDNF expression and phosphorylating ERK1/2 (Ge et al., 2014). Mice showed reduced anxiety-like behaviors after administration of OG, but no sedation was seen (Wang et al., 2016).

**Hepatoprotective activity**

Aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, and gamma-glutamyl transpeptidases were reduced in rats exposed to carbon tetrachloride. Food consumption and weight gain were increased by MECO rhizomes. In addition to lowering liver and serum protein levels, serum lipids, cholesterol, and phospholipids were normalized. These studies showed that C. orchoides rhizome has hepatoprotective properties (Venukumar and Latha, 2002).

**Nephroprotective activity**

Treatment of cyclophosphamide-induced hepatotoxicity and intestinal toxicities with C. orchoides does not compromise cyclophosphamide’s chemotherapeutic efficacy. When
administered along with cyclophosphamide, the whole plant extract of *C. orchioides* significantly decreased serum creatinine levels and blood urea nitrogen levels. Induced urotoxicity and nephrotoxicity by cyclophosphamide are alleviated by *C. orchioides* (Murali and Kuttan, 2016)

**Antidiabetic activity**

Alloxan-induced diabetic rats and glucose-loaded diabetic rats were shown to be antihyperglycemic with aqueous and ethanol extracts (Chauhan et al., 2007). Using streptozotocin–nicotinamide-induced diabetic nephropathy rats, extracts of *C. Orchoides* using ethanol and hydroalcohol reduced hyperglycemia-induced lipid changes, oxidative stress, and renal dysfunction (urea, creatinine, and andalbumin) (Singla and Singh, 2020). Curculigo orchioides was shown to inhibit adipogenesis and enhance glucose uptake in 3T3-L1 adipocytes in an ethanolic extract in a cell-based assay (Gulati et al., 2015).

**Anti-microbial activity**

As well as being antimicrobial against *Bacillus anthracis* and *Bacillus subtilis*, oil of *C. orchioides* rhizomes inhibited *Fusarium solani, Salmonella newport, Staphylococcus aureus, Salmonella pullorum,* and *Aspergillus flavus, Fusarium moniliforme,* and *Cladosporium* species (Jaiswa et al., 1984). The *C. orchioides* extract prepared by steam distillation process showed antibacterial activity significantly against several Gram-positive bacteria (*Staphylococcus epidermidis* and *S. aureus*) and Gram-negative bacteria (*Salmonella typhimurium, Pseudomonas aeruginosa,* and *Escherichia coli*). Antiseptic properties make the extract ideal for preventing bacterial infections (Nagesh and Shanthamma, 2009).

With a minimum inhibitory concentration value of 49 g/ml, *C. orchioides* alcohol extract inhibited methicillin-resistant *P. aeruginosa,* whereas Gram-negative bacteria were not affected (Marasini et al., 2015). *Curculigo orchioides* leaf extracts contain phytochemical-loaded silver nanoparticles which are effective against *S. aureus* and *P. aeruginosa,* but less effective against *Klebsiella pneumonia* and *E. coli* (Perumal et al., 2017).

**Anti-asthmatic activity**

Goat tracheal chains and guinea pig ileum are relaxed by *C. orchioides* ethanol extract. *Curculigo orchioides* ethanol extract significantly reduced bronchoconstriction and passive paw anaphylaxis in guinea pigs, rats, and mice with haloperidol-induced catalepsy, suggesting an antiasthmatic effect (Pandit et al., 2008).

**Anti-stress activity**

In forced swimming and tail suspension tests, *Curculigo orchioides* ethanol extract at 200 mg/kg reduced immobility times. It increased mobility in actophotometer-based tests. Ethanolic extract of *C. orchioides*’ rhizomes increased resistance to heat [50 and 70 infrared (IR) units] in IR testing and rotarod testing. It provides strong evidence that ethanolic extracts have antistress activity (Chauhan et al., 2021).

**Anti-cancer activity**

Aqueous fresh root extract and methanolic dried root extract showed significant cytotoxicity activity on the human lung adenocarcinoma NCI-H-522 cancer cell line. The cytotoxicity may be attributed to the alkaloids and phenols present in it (Aloysius et al., 2020). A new chlorophenolic glucosides curculigines P, isolated from the dried rhizomes of *C. orchioides* showed the most potent inhibitory effect on 5α-reductase activity by a HaCaT-based bioassay and, hence, may be useful in benign prostatic hyperplasia (Deng et al., 2021).

Ethyl acetate fractions of *C. orchioides* Gaertn down regulated the levels of antiapoptotic Bel-2 expression and upregulated the expression of apoptotic proteins caspase-3 and caspase-8 through an intrinsic ROS-mediated mitochondrial dysfunction pathway (Hejazi et al., 2018). The plant extract when administered in combination with cyclophosphamide enhanced the anticancer properties of cyclophosphamide and ameliorated its toxic side effects (Murali and Kuttan, 2015). Silver nanoparticles using *C. orchioides* rhizome extracts showed efficacy against human breast cancer cell line (MDA-MB-231) after 48 hours of incubation (Kayalvizhi et al., 2016). Polysaccharides from *C. orchioides* showed a significant anti-tumor effect on cervical cancer in vivo and in vitro by enhancement of immune function and induction of apoptosis (Xia et al., 2016).

**Anti-gout activity**

Two heterocyclic phenolic derivatives, orcinosides I and J, displayed xanthine oxidase inhibitory activities with IC₅₀ values 0.25 and 0.62 mM, respectively. Hence, they may have anti-gout effect (Chen et al., 2017).

**Anti-hypertensive activity**

MECO root possesses antihypertensive activity by inhibiting angiotensin-converting enzyme in deoxycorticosterone acetate salt-induced hypertensive rats (Joshi et al., 2012).

**Anti-malarial activity**

Silver nanoparticles using *C. orchioides* rhizome extracts showed the highest mortality rate against the malarial vectors such as *Anopheles subpictus* and *Culex quinquefasciatus* (Kayalvizhi et al., 2016).

**CONCLUSION**

This review aims to summarize the existing phytochemistry and pharmacological activities of plant *C. orchioides* which is a perennial herb, belonging to the family Amaryllidaceae. The content gives a brief proof of the traditional uses of this plant. The plant is reported to show immuno-modulatory, anti-oxidant, hepatoprotective, neuroprotective nephrprotective, anti-inflammatory, anti-gout, anti-arthritis, anti-cancer, anti-microbial, anti-bacterial, anti-malarial, anti-diabetic, anti-stress, and antihypertensive activities. These effects may be attributed to the anti-oxidant principles present in them. Many authors and researchers reported the phytochemical, pharmacological, and toxicological results which may provide suitable data for further scientific research.

**AUTHORS’ CONTRIBUTIONS**

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit
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