The Potential and Outgoing Trends in Traditional, Phytochemical, and Ethnopharmacological Activity of *Gentiana olivieri*: A Comprehensive Review

**Keywords:** Potential and Outgoing Trends, Traditional, Phytochemical, and Ethnopharmacological Activity, *Gentiana olivieri*

**ABSTRACT**

Gentiana, a cosmopolitan and important genus of the Gentianaceae family, comprises 400 species distributed among the world. Based on the studies of Iranian traditional medicine texts, there are some promising bioactivities for this genus that are unknown in modern medicine and some of them are still the basis of new remedies. Whole plant of *Gentiana olivieri* Griseb. holds a rich source of secondary metabolites including alkaloids, bitter secoiridoid glycosides, triterpenes, fats, flavone-c-glycosides (isoorientin). The alkaloids (gentianine, gentianidine) have been culpable for their manifold pharmacological activities such as antibacterial, antifungal, hypotensive and the flavone-c-glycosides (isoorientin) have been responsible for the anti-inflammatory, anti-nociceptive, gastroprotective, hepatoprotective, antidiabetic effect. In this review, an attempt has been made to enlightened morphology, phytochemistry, ethnobotanical and reported pharmacological activities in the last six years for exploring the interminable medicinal potential of *Gentiana olivieri*. 
INTRODUCTION

Indian Ayurveda along with the Siddha, Jammu, Tibetan, Traditional Chinese, and Unani systems of medicine are an essential source of health and livelihood for millions of Asian people. Ayurvedic medicine is broadly practiced particularly in Bangladesh, India, Nepal, Pakistan, and Sri Lanka[1]. Gentianaceae is an ethnobotanically important family used extensively in Unani, Ayurvedic and Chinese traditional medicine systems. Famous Unani formulations (Tiryaq Samania, Tiryaq Arbaa) employed the use of plants from this precious family [2]. The angiosperms family Gentianaceae is comprised of 87 genera and 1615–1688 species and has been celestially accepted in all subsequent considerable classifications. It is a family that appears great adaption in habit, morphology, anatomy, geographical distribution. The plants of the family are annual and perennial herbs or shrubs [3]. Plants belonging to genus Gentiana are very well-known for their ethnomedicinal and phytopharmacological action. People living in the mountains of Pakistan use Gentiana in many ways such as medicines, timber wood, firewood, food, fodder etc. Gentiana is comprised of intensely bitter glycosides[5] which have been responsible for its immense therapeutic potential. Recently interest in this potent medicinal plant has been revived and various significant phytoconstituents like olivierosides, oliveramine, gentianine, isoorientin, gentianamine etc. have been studied for drug development and discovery. [6-7]

Gentiana olivieri Griseb. (Afat), belonging to the Gentianaceae family [8] is widely used as a bitter tonic, stomachic, appetizer, antipyretic, anticonvulsant, antidiabetic, antihypothalamic, antinociceptive, anti-inflammatory, antiulcerogenic, sedative, antioxidant, antidepressant, and antianemic [9]. The plant is known to possess several bitter secoiridoids glycosides, flavonoids (isoorientin and its derivatives), alkaloids, xanthones, triterpenoid acids, and fats [10]. Recently, among the species of the Gentianaceae family, G. olivieri has been a focus of interest due to the identification of phytochemicals such as amarogentin and sweroside as new potential drugs [9-12].

Vernacular Names [13]

Unani: Gul-e-ghafis, English: Gentian, Hindi: Asbarg, Pakistan: Bangera, Turkey: Afat

Taxonomic Classification [14-15]

Kingdom : Plantae
Division : Magnoliophyta
Class : Magnoliopsida
Subclass : Asteridae
Order : Gentianales
Family : Gentianaceae
Genus : Gentiana
Species : Olivieri

Plant Description

Gentiana olivieri Griseb. perennial herbaceous plant 10–40 cm tall grows at an altitude of 350–2300 meters. Linear- elliptic to elliptic-lanceolate, narrowed leaf with acuminate apex and distinct veins. The perennial stem is erect, slender and glabrous. Flowers (3–5) are arranged in terminal corymbose cymes inflorescences. Pedicel is 3 to 5 cm, calyx tube (4–8 mm) is obconic; lobes are triangular, unequal. Corolla is blue colored with obconic lobes having entire margin. Stamens are inserted just below middle of corolla tube; filaments are 6–8 mm; long with linear anthers. Capsules type seeds (0.8–1 mm) are brown, ellipsoid with thick reticulate seed coat [16–17].

Habitat

Gentiana olivieri Griseb. is abundantly found in Temperate and Tropical Asia including regions of Western Asia, Middle Asia, Indian subcontinent, Afghanistan, Pakistan, Iran, Iraq, Syria, Turkey, Armenia. The plant is also found in the temperate region of Gulf countries and some temperate regions of China[18].

Traditional Uses

Gentiana olivieri is used in traditional medicine in Unani and Ayurveda system of medicines
in arthritis, anti-inflammatory, antidepressant, antiulcerogenic, gastro-protectant and sudorific\cite{15,19}. It has been employed as a hepatoprotective, aphrodisiac plant in Turkey\cite{20–21}. In the Uzbekistan Republic, it has been used as ailment of common cold, indigestion, diarrhea, stomachache\cite{22}. Decoction of root is used for urinary tract infections in Pakistan\cite{23}, Kabdeen a famous unani antiviral formulation involves use of extract of Gul-e-ghafis i.e. Gentiana olivieri griseb\cite{24}.

Based on the Iranian traditional medicine texts Gentian's species have different therapeutic properties which are related to the root of the plant. Treatment of urinary retention, menstrual, liver and spleen dysfunctions and detoxifying of animal poisons are the main and common properties among the texts \cite{25-27}.

**Phytochemistry of Gentiana olivieri Griseb.**

*Gentiana olivieri* Griseb. contain major class of secondary metabolites are alkaloids, glycosides, flavonoids, triterpenoids, fats etc. From the ethanolic extract of whole plant of *Gentiana olivieri* Griseb. two alkaloids gentianine and gentianidine have been isolated using silica gel column chromatography eluting with chloroform:hexane (20:1)\cite{28} and different saturated pentadecanoic, hexadecanoic, heptadecanoic, octadecanoic, nonadecanoic along with a unsaturated fatty acid hepta-decatrienoic acid have also been isolated when eluted with hexane:ether (1:3). Methanolic extract also provides three new bitter secoiridoid glycosides, olivierosides A, B and C together with known compounds, gentiopicroside, swero-side, 6'-O-β-D-glucosylgentiopicroside, swertiapunimarin, eustomoside, eustomorusside and septemfidoside\cite{29}. The flowers of *Gentiana olivieri* Griseb. also afforded oleanolic and ursolic acids\cite{19}. The ethyl acetate fraction of ethanolic extract of *Gentiana olivieri* Griseb. when subjected to silica gel column chromatography gave flavone-c-glyco- sides (C-glycosylflavone) – Isoorientin\cite{30-31}. Aerial parts of *Gentiana olivieri* Griseb. provides alkaloids – gentiana- mine, gentianidine, gentianine, gentioflavin, oliverine, olvieridine, gentiotibetine, olvieramine. The structures have been established on the basis of chemical evidence and spectroscopic methods\cite{32–35}.

A new depside, olivieridepside, and a new secoiridoid, olvierigenin were isolated from the aerial parts of *Gentiana olivieri* Griseb. along with four known compounds, gentiopicroside, olivierosides A and B and isoorientin. The structures of the isolates were determined by
extensive 1D and 2D NMR spectroscopy and HR-MS analysis. This is the first report on the occurrence of a depside structure in the genus Gentiana. Moreover, a rare type of non-glycosidic secoiridoid (2) lacking an oxygenated group at C-1 is also being reported for the first time from this genus [36].

**Reported Activity**

Various extracts of *Gentiana olivieri* Griseb. were evaluated for screening *in-vitro/ in-vivo* pharmacological models. Isoorientin isolated from the ethyl acetate fraction of ethanolic extract exhibited significant hypoglycemic, antihyperlipidemic[30] hepatoprotective[31], anti-inflammatory, anti-nociceptive, gastroprotective effects[37]. Furthermore, Gentianine (alkaloid) isolated from ethanolic extract of the whole plant of *Gentiana olivieri* Griseb. showed significant antibacterial, antifungal activity[38] along with hypotensive effects [38–39]. Activities reported in past six years are given below.

**Appetizing Effect**

A case-control study was performed in which the plant’s root extract was used to prepare hydroalcoholic product (2.5%) and its appetizing effect was evaluated in children. Fifty children with anorexia were randomly divided into two groups to receive either the hydroalcoholic extract of the *Gentiana olivieri* or a placebo at the dose of 2.5 mg/kg/day for two months. Variables such as weight, height, waist, consumed calories, and hunger VAS score, liver enzymes fluctuations and some blood biochemistry tests were also monitored. The average age of cases and controls was 56.12 and 56.64 months, respectively. Before treatment, the mean weight in both case and control groups was 13.130±1.56 kg and 13.010±1.27 kg, respectively that changed to 14.275 ± 1.69 kg and 12.962± 1.16 kg after a month and 14.550±1.54 kg and 12.814±1.22 kg, respectively two months after the intervention. Significant effects were seen on received calories and VAS score. The product was found to have a significant effect on weight, food intake and VAS score compared with placebo [40].

The roots of *Gentiana olivieri* (Gentianaceae), an Iranian indigenous plant, were studied to standardize and prepare an appetite-stimulating drug. The bitterness value of the aqueous extract of the plant was evaluated for its efficacy as an appetite-stimulant. It was found to be very bitter, with a bitterness value of 33,183.5, which is comparable to the value reported for...
the internationally well-known bitter plant, Gentiana lutea L. To standardize *G. Olivieri* to prepare an appetite-enhancing drug, separation of the bitter compound gentiopicroside from the plant *G. lutea* was carried out by using Prep TLC. The extracted pure compound was identified by the FTIR method, gas chromatography, mass spectrometry, and HPLC, and then used as a standard for later quantitative research. The *G. Olivieri* extract was standardized based on the amount of gentiopicroside as an effective component. To formulate appetite-stimulating medicine, the extraction of the plant was conducted according to the methods mentioned in the British Pharmacopoeia. Then, a hydroalcoholic solution of the plant extract was formulated. The microbiological control of the plant extract and herbal medicine were investigated. The results showed no microbial growth within 30 days. The amount of gentiopicroside obtained from the hydroethanolic extract of the *G. Olivieri* was 586.6 ppm. Furthermore, the bitterness value of the plant exceeded the amount mentioned in the pharmacopeia for the hydroethanolic extract of *G. lutea*. Therefore, it can be implied that the effect of this natural medicine will be to increase appetite [41].

**Antidepressant Activity**

The antidepressant effect of *G. Olivieri* ethanol extract (GOEE) in a chronic mild stress-induced rat model, which was used to mimic a depressive state in humans, and to compare the effect with that of imipramine. Male Sprague-Dawley rats were randomly divided into six groups: control, stress, treated with imipramine (positive control), and treated with GOEE at three different (200, 500, 1000 mg/kg) doses groups. The rats in all groups, except the control group, were exposed to chronic mild stress. At the end of the 3-week experimental period, biochemical and behavioral parameters were examined. The results showed that treatment with GOEE or imipramine significantly improved rats’ sucrose consumption which was diminished by chronic mild stress, restored serum levels of corticosterone and proinflammatory cytokines (interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α)), prevented the increase of liver index of rats. Moreover, in the hippocampus tissue, decreased serotonin and noradrenaline levels were significantly increased by treatment with GOEE or imipramine, and antioxidant parameters (thiobarbituric acid reactive substances (TBARS), superoxide dismutase (SOD), and glutathione (GSH)) were significantly improved by treatment with GOEE though not with imipramine. The data demonstrate that *G. Olivieri* may exert its antidepressant activity by improving monoaminergic system disorders, and by favorably affecting the antioxidant, inflammatory and endocrine mechanisms [42].
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