Future Natural Products
doi:10.34172/fnp.377 2025;11(1): 1-3 https://fnp.skums.ac.ir

Editorial

Toxicological Concerns Regarding Bilhar (*Ferula aucheri*, Formerly *Dorema aucheri*): Limitations of Current Evidence and the Need for Standardized Studies

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Cite this article as: Zarei MH, Jamshidi-Kia F, Lorigooini Z. Toxicological concerns regarding bilhar (*Ferula aucheri*, formerly *Dorema aucheri*): limitations of current evidence and the need for standardized studies. Future Nat Prod 2025;11(1): 1-3. doi:10.34172/fnp.377

Received: August 23, 2026, **Revised:** August 31, 2026, **Accepted:** August 31, 2026, **ePublished:** October 20, 2026

Growing interest in medicinal plants and natural products has led to increased scientific attention toward endemic and traditionally consumed species such as bilhar [*Ferula aucheri* (Boiss.) Piwczyński, Spalik, M. Panahi, & Puchałka; synonym *Dorema aucheri* Boiss.; Apiaceae], commonly known as Bilhar in Iran (1,2). Considering that most pharmacological and toxicological publications have used the name *Dorema aucheri*, this name is retained below when referring to earlier studies. This plant, which is consumed in some regions of Iran as both a food source and a medicinal herb, has been reported to possess potentially beneficial biological properties, including antioxidant, antimicrobial, metabolic, and wound-healing activities, probably related to its diverse bioactive constituents (3-6). Nevertheless, the traditional use of a medicinal plant does not necessarily imply proven safety, and a careful evaluation of its potential health risks remains essential.

A review of the currently available literature indicates that, Although the available toxicological studies of *D. aucheri* are limited and methodologically heterogeneous, several have reported findings that warrant further safety evaluation. The strongest in vivo hepatotoxicity signal comes from an animal study in which intraperitoneal administration of a hydroalcoholic extract of *D. aucheri* resulted in hepatic tissue injury, elevated liver enzyme levels, and histopathological signs, including cholestasis and hepatocellular necrosis (7). However, given that this study used an intraperitoneal route rather than oral administration, its direct relevance to traditional dietary or medicinal consumption remains uncertain. Moreover, findings from closely related taxa, such as *D. ammoniacum*/*F. ammoniacum*, demonstrate possible hepatic and renal effects after exposure to plant oleo-gum-resin preparations (8). Nonetheless, these data should be interpreted only as indirect genus-level evidence; they should not be extrapolated directly to *D. aucheri*.

Likewise, direct in vitro evidence suggests that some *D. aucheri* preparations may have concentration-dependent and extract-dependent safety concerns. Hydroalcoholic and aqueous extracts of *D. aucheri* produced genotoxic effects in HepG2 cells in a comet assay at higher concentrations, particularly at or above 500 µg/mL (9). Based on other cytotoxicity data, the biological effects of *D. aucheri* are fraction-dependent (3). These findings are important as early safety signals, although in vitro cytotoxicity or genotoxicity cannot by itself define the risk associated with oral human consumption because bioavailability, metabolism, exposure duration, and achievable tissue concentrations may substantially differ in vivo.

Several experimental studies have reported changes in antioxidant markers, vitamins, hematological indices, and reproductive hormones after exposure to *D. aucheri* extracts (10-13), and these changes should be described cautiously. For example, oral administration has been associated with time-dependent and dose-dependent alterations in antioxidant indices rather than a uniform reduction in antioxidant capacity (11). Therefore, such biomarker changes should be interpreted as evidence of biological activity and possible systemic effects, not as definitive proof of toxicity. Similarly, hormonal and hematological findings require confirmation in standardized toxicological designs with adequate dose-response evaluation, gender-specific analysis, and histopathological correlation.

The mechanisms underlying these effects remain unclear. Although phenolic, terpenoid, coumarin-like, and sesquiterpene constituents have been reported in *D. aucheri* and related taxa (6,14,15), the specific compounds responsible for possible toxic effects have not been identified so far. Moreover, available cytotoxicity findings appear to

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be fraction-dependent, suggesting that lipophilic or non-phenolic constituents may also contribute to these effects. Accordingly, broadly attributing toxicity to phenolic or coumarin-like compounds would be premature without phytochemically standardized and mechanistic studies.

A major limitation of the current evidence was the mismatch between experimental exposure routes and traditional use. At least one key hepatotoxicity study employed intraperitoneal administration (7), whereas traditional exposure is predominantly oral. This discrepancy may substantially affect absorption, first-pass metabolism, systemic exposure, and toxicological outcomes. Conversely, some oral animal and human studies exist, primarily designed to investigate pharmacological or biomarker outcomes rather than to establish a complete toxicological profile (6,11).

To the best of our knowledge, no good laboratory practice (GLP)-compliant or Organization for Economic Co-operation and Development (OECD) Test Guideline 407-compliant repeated-dose 28-day oral toxicity study has yet been published for this species. A properly designed OECD 407 study would require repeated oral administration for 28 days with systematic evaluation of clinical observations, body weight, food and water intake, hematology, clinical biochemistry, gross necropsy, organ weights, and histopathology (16). For sub-chronic assessment, OECD Test Guideline 408 would be more appropriate because it evaluates repeated oral exposure over 90 days (17). Accordingly, toxicological parameters, such as the no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL), have not been reliably established for *D. aucheri*.

Additionally, human evidence is insufficient for safety conclusions. A double-blind placebo-controlled clinical trial reported metabolic and oxidative effects after 45 days of oral *D. aucheri* extract administration in patients with type 2 diabetes (6). However, such short-term interventional data, although valuable, do not replace systematic safety monitoring, dose-escalation assessment, long-term follow-up, or post-consumption surveillance. Likewise, the absence of published human case reports should not be interpreted as definitive evidence of safety, since traditional consumers are rarely subjected to systematic clinical monitoring and many potential adverse effects may remain undocumented or underreported.

Given the traditional use of *D. aucheri*/*F. aucheri* in some regions of Iran and the concurrent lack of standardized toxicological data, comprehensive safety investigations are warranted for this species. Hence, future studies should use botanically authenticated plant material, chemically characterized and standardized extracts, and clinically relevant oral routes of administration. Further, priority should be given to acute and repeated-dose oral toxicity studies, OECD 407 and OECD 408-compliant designs, reproductive and developmental toxicity assessments, in vivo genotoxicity testing, mechanistic toxicology, and observational studies among habitual consumers.

Overall, the available evidence suggests that, despite its potential biological benefits, *D. aucheri*/*F. aucheri* may also pose dose-dependent, extract-dependent, concentration-dependent, and route-dependent toxicological risks. However, the current evidence is insufficient to define its long-term oral safety or to quantify human risk. Until comprehensive, standardized, and reproducible toxicological studies are conducted, the widespread or long-term use of this plant should be approached with scientific caution.

Conclusion

The current body of evidence regarding the toxicological safety of *D. aucheri*/*F. aucheri* remains fragmented, methodologically heterogeneous, and insufficient for definitive risk characterization. Although signals of hepatotoxicity, genotoxicity, and systemic biomarker alterations have been reported, these findings are compromised by critical limitations, including non-oral administration routes, the lack of phytochemically standardized extracts, absence of dose-response characterization, and the use of study designs not primarily intended for safety evaluation. Consequently, fundamental toxicological parameters such as NOAEL and LOAEL remain undefined, and no GLP-compliant or OECD-compliant repeated-dose oral toxicity studies have been reported for this species.

Given the plant's traditional consumption in Iran and its documented biological activity, the absence of rigorous safety data should not be equated with evidence of safety. Future investigations must prioritize standardized, guideline-compliant oral toxicological assessments using authenticated and chemically characterized plant material, along with mechanistic studies and post-market surveillance among habitual consumers. Until such evidence becomes available, the widespread or prolonged use of bilhar should be undertaken with scientific caution. Finally, health authorities should consider interim risk communication measures for populations with regular dietary or medicinal exposure.

Artificial Intelligence Disclosure

Artificial intelligence tools were used solely for grammar and language editing of this manuscript.

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Competing Interests

The corresponding author of this article serves as the journal's Editor-in-Chief. Nevertheless, this manuscript was reviewed and published in accordance with the journal's standard procedures for all submissions, ensuring no deviation from established editorial practices.

Ethical Approval

None.

Funding

This study received no financial support.

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