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Mini Review

Trigonelline: A Versatile Bioactive Alkaloid of Medicinal Plants. A Mini-Review

Suyun Li[1], Tianhe Fang[2], Fuquan Liu[3], Bin Wang[3] and Qiancheng Mao[1*]

[1]*Sun Yat-sen University, College of Agriculture and Biotechnology, Shengzhen 518107, China*

[2]*Shandong University of Traditional Chinese Medicine, Jinan 250355, China*

[3]*Community Health Service Center, Gaozhuang Sub-district, Laiwu District, Jinan 271100, China*

***Corresponding author:** Qiancheng Mao, Sun Yat-sen University, College of Agriculture and Biotechnology, Shengzhen 518107, China

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Abstract

Trigonelline (N-methylnicotinic acid) is a pyridine alkaloid widely distributed in medicinal and dietary plants such as fenugreek (Trigonella foenum-graecum), coffee (Coffea spp.), and wax gourd (Benincasa hispida). Accumulating evidence demonstrates that trigonelline exerts multiple pharmacological activities, including antidiabetic, neuroprotective, and antioxidant effects, together with a favorable safety profile, making it a promising candidate for functional foods and pharmaceutical development. However, the large natural variation in trigonelline content across germplasm resources hampers the stable supply of high-quality plant materials. Recent metabolite-based genome-wide association studies (mGWAS) in medicinal plants have begun to dissect the genetic architecture underlying bioactive metabolite accumulation. Here, we summarize the pharmacological potential of trigonelline and highlight how mGWAS-guided strategies can accelerate the genetic improvement of trigonelline-enriched medicinal crops, with emphasis on ongoing efforts in wax gourd.

Keywords: Trigonelline; Medicinal plants; Metabolite-based genome-wide association study (mGWAS); Molecular breeding; Metabolomics; Bioactive alkaloid

Introduction

Trigonelline (TRG, N-methylnicotinic acid, C7H7NO2) is a pyridine alkaloid first isolated from fenugreek seeds in 1885 [1]. It is widely distributed in medicinal and dietary plants, occurring at 1-3% of dry weight in green coffee beans and at substantial levels in pumpkin and wax gourd [2,3]. Beyond its classical roles in planta as a hormone modulating the cell cycle and nodulation and as an osmoprotectant [4], TRG has attracted growing biomedical interest. A substantial body of evidence supports its multi-targeted antidiabetic, neuroprotective, and antioxidant activities with a remarkable safety profile, positioning TRG as a promising lead for nutraceuticals and pharmaceuticals against metabolic and age-related disorders [2,3]. Nevertheless, TRG content varies markedly among genotypes, tissues, and developmental stages, and the genetic determinants of its accumulation remain largely unknown in most medicinal crops, constraining the breeding of stable, high-TRG varieties. Recent advances in metabolomics and genomics, particularly metabolite-based genome-wide association studies (mGWAS), now provide a powerful framework to bridge this gap [5-7]. This mini-review summarizes the pharmacological potential of TRG and highlights how mGWAS-driven strategies can accelerate the genetic dissection and molecular breeding of TRG-enriched medicinal plants.

Occurrence, Biosynthesis and Pharmacological Potential of Trigonelline

TRG is synthesized from nicotinic acid (vitamin B3) through N-methylation catalyzed by S-adenosyl-L-methionine-dependent nicotinate N-methyltransferases, an extension of the conserved pyridine nucleotide cycle in plants [4,8]. In coffee, TRG accumulates

during fruit development and can be demethylated back to nicotinic acid during roasting, thereby contributing to dietary vitamin B3 intake [8]. The conservation of this pathway offers a tractable entry point for the metabolic engineering of TRG content. Pharmacologically, TRG exerts antidiabetic effects through multiple mechanisms, including inhibition of alpha-glucosidase and DPP-4, modulation of PPARgamma signaling, protection of pancreatic beta-cells, and improvement of insulin sensitivity [2,3]. Its neuroprotective activities involve inhibition of Abeta aggregation, upregulation of neurotrophic factors such as NGF and BDNF, and suppression of neuroinflammation via TLR4/NF-kappaB pathways [3]. TRG also enhances antioxidant defenses (SOD, CAT, GSH) while reducing oxidative damage markers such as MDA and NO [2,3]. Importantly, no acute oral toxicity was observed up to 5000 mg/kg in mice, and epidemiological evidence links higher serum TRG levels with lower HbA1c over a five-year follow-up, supporting its translational potential [2]. These findings underpin the growing demand for standardized, high-TRG plant materials for functional food and pharmaceutical applications.

mGWAS: From Metabolite Variation to Causal Genes in Medicinal Plants

Bioactive metabolite accumulation is a complex quantitative trait controlled by multiple loci and strongly modulated by the environment. mGWAS integrates high-throughput metabolomics with genome-wide polymorphism data, enabling the genetic dissection of metabolite accumulation at population scale [6,9]. Widely targeted metabolomics based on LC-MS/MS now allows simultaneous profiling of hundreds to thousands of metabolites across large germplasm collections [10], while mixed linear models accounting for population structure and kinship ensure statistical robustness [9]. Landmark mGWAS studies in medicinal plants illustrate the power of this approach. In wolfberry (Lycium), metabolomic profiling of 307 re-sequenced accessions identified 563 annotated metabolites, and mGWAS mapped significant SNP-metabolite associations for 340 metabolites, leading to the functional validation of genes controlling flavonoids (LbUGT, LbCHS, LbMYB), betaine (LbSSADH), and spermidine (LbBEAT) [5]. Importantly, the derived KASP markers enable marker-assisted selection (MAS) for quality traits, demonstrating the direct breeding utility of mGWAS outputs [5]. More recently, an mGWAS in Andrographis paniculata dissected the genetic basis of andrographolide accumulation and pinpointed a bifunctional regulatory gene (ApNB-ARC25) whose role was validated by virus-induced gene silencing [7]. These studies confirm that mGWAS can translate natural metabolic variation into actionable gene targets and molecular markers across diverse medicinal species.

Perspectives: Toward Trigonelline-Enriched Varieties

Applying the mGWAS framework to TRG holds great promise. In our laboratory, we are conducting an mGWAS in wax gourd, a major cucurbit vegetable for which a chromosome-level genome is available [11], to dissect the genetic architecture of TRG accumulation. The strategy comprises:

a. Widely targeted metabolomic profiling of TRG and related pyridine alkaloids across a diverse natural population;

b. Population-scale re-sequencing and genome-wide association analysis;

c. Prioritization and functional validation of candidate genes, particularly nicotinate N-methyltransferase family members and their transcriptional regulators; and

d. Translation of elite alleles into KASP markers for MAS, together with exploration of CRISPR-based enhancement of key biosynthetic genes [5,7,12].

Integrating transcriptomic and genomic data will further resolve the regulatory network controlling TRG content. Meanwhile, clinical validation of efficacy, safety, and bioavailability remains essential to translate high-TRG germplasm into evidence-based nutraceutical products [2,3].

Conclusion

Trigonelline is a safe, multi-targeted bioactive alkaloid with substantial potential for functional food and pharmaceutical applications. The combination of metabolomics, genomics, and genetics—exemplified by mGWAS—now offers a realistic roadmap from natural metabolite variation to causal genes and molecular markers. Continued efforts, including our ongoing mGWAS in wax gourd, are expected to accelerate the development of trigonelline-enriched medicinal crops, meeting the growing demand for high-quality natural bioactive products.

Conflict of Interest

The author declares no conflict of interest.

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