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Review Article

Trigonelline and Cardiovascular Health: A Narrative Review of Mechanisms, Preclinical Evidence, and Translational Considerations

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ABSTRACT

Trigonelline is a pyridine alkaloid abundant in fenugreek and coffee that has attracted growing interest for its potential cardiometabolic relevance. This narrative review summarizes mechanistic pathways and available evidence linking trigonelline to vascular and cardiac outcomes and highlights key translational gaps. A literature search was conducted in PubMed, Scopus, and Web of Science using combinations of the terms "trigonelline," "cardiovascular disease," and "natural alkaloid," prioritizing English-language in vitro, animal, and human studies focused on vascular function, cardiometabolic risk, and atherosclerotic mechanisms. Preclinical evidence suggests that trigonelline may improve endothelial function, including nitric oxide-related signaling, attenuate oxidative stress and inflammatory pathways, modulate glucose and lipid metabolism, and reduce gut microbiota-linked Trimethylamine N-Oxide (TMAO) generation, mechanisms plausibly relevant to atherosclerosis and hypertension. In contrast, human evidence remains limited and heterogeneous, with few controlled trials and unclear dose-response relationships. Safety data are more robust for trigonelline exposure through dietary sources such as coffee than for long-term isolated supplementation. Overall, trigonelline represents a promising bioactive compound, but clinical translation will require well-designed randomized trials, standardized dosing strategies, detailed pharmacokinetic characterization, and rigorous long-term safety evaluation.

Keywords: Antioxidant, Cardiovascular disease, Natural Alkaloid, Trigonelline.

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INTRODUCTION

With annual estimation of 17.3 million deaths worldwide, cardiovascular diseases are the leading cause of death. Numbers are projected to rise to approximately 23.6 million by the year 2030 (Farraj *et al.*, 2024). A cross-sectional study conducted in Malaysia in 2022 discovered that more than 50% of young adults had a moderate to high risk of cardiovascular disorders (Azzani *et al.*, 2024). Cardiovascular diseases include disorders of the heart and blood vessels, driven by multiple risk factors, such as dyslipidemia, hypertension, diabetes, chronic inflammation, smoking, and others (Konstantinidis *et al.*, 2023). Despite advances in healthcare, there is a need for unique preventive strategies to address this issue. Diet and natural products have gained interest, as evidenced by growing research on coffee and fenugreek seeds-main dietary sources of Trigonelline (TRG) and its positive effects on the cardiovascular system. Derived from the methylation of Vitamin B3, TRG (N-methyl nicotinic acid), a bioactive alkaloid, may contribute to the protective effects of coffee and fenugreek seeds (Nguyen *et al.*, 2024). Here, we synthesize mechanistic and translational evidence on trigonelline's vascular and cardiac relevance, highlight limitations in current human data, and propose priorities for future clinical research. This review aims to evaluate TRG's effects on the cardiovascular system, covering pharmacological aspects (pharmacodynamics and pharmacokinetics), therapeutic uses, and limitations.

METHODOLOGY

This narrative literature review compiled data from PubMed, Scopus, Web of Science and Google Scholar databases published between 2018-2025 using the key words: "Cardiovascular Disease", "Trigonelline" and "Natural Alkaloid". Data was extracted and thematically analyzed for cardioprotective outcomes only from peer-reviewed English-Language articles with inclusion of preclinical outcomes.

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Overview of Cardiovascular Diseases

Cardiovascular disease is a collective term for diseases of the circulatory system encapsulating pathologies of the blood vessels and those that are directly involving the heart. Involving genetic predisposition, lifestyle choices, and environmental factors, its general etiology is multifactorial. Lifestyle factors (e.g., unhealthy diet, physical inactivity, tobacco, alcohol), and metabolic conditions (e.g., hypertension, diabetes, dyslipidemias contribute to endothelial injury and plaque formation, the key causative mechanism of vasculopathies and cardiomyopathies (Konstantinidis *et al*., 2023). Vasculopathies involve degenerative, metabolic, or inflammatory changes to blood vessels. The major causes include:

- Hemostasis and thrombosis because of platelet aggregation and fibrin deposition leading to formation of a thrombus or embolus ultimately causing hypertension or obstruction.
- Inflammation and angiogenesis - occurring in response to injury infection or lipid peroxidation.
- Oxidative and nitrative stress enhancing degeneration of blood vessel endothelium (Thiriet, 2019) (Tables 1 and 2).

Globally, 1/3rd of deaths are related to the cardiovascular system [Thiriet, 2019]. In a nutshell, oxidative stress, inflammation, and dysregulated lipid metabolism are the core pathological events of cardiovascular diseases. Therefore, utilizing the antioxidant and anti-inflammatory approach would be an attractive preventive strategy.

TRIGONELLINE

Properties

TRG / (IUPAC:1-methylpyridin-1-ium-3-carboxylate, $C_7H_7NO_2$) / N-methyl nicotinic acid, first isolated as a hydroalcoholic extract of Fenugreek plant (Trigonella foenum-graecum), is a polar lipophobic pyridine alkaloid (Nguyen *et al*., 2024; Oktaviono *et al*., 2023; Garg *et al*., 2016; Konstantinidis *et al*., 2023). TRG is abundant in green coffee beans (where it makes up 1-3% of its dry mass) and in fenugreek seeds (Nguyen *et al*., 2024). TRG compound is solid and crystallizable with a low common logarithm of octanol-water partition coefficient (log K_{ow} value of -2.53) indicating it is highly hydrophilic (Konstantinidis *et al*., 2023). TRG is not considered heat stable-(Thermolabile), being partially decomposed to volatile pyridines and non-volatile N-methylpyridinium and nicotinic acid (Farraj *et al*., 2024). Therefore, it is worth noting that roasting coffee beans during the brewing process can affect TRG levels (Nguyen *et al*., 2024).

Metabolism

In plants, it is biosynthesized by the methylation of nicotinic acid (Vitamin B3). This reaction involves the methyl-donor S-adenosyl-L-methionine and is catalyzed by trigonelline synthase (N-methyltransferase) enzyme (Konstantinidis *et al*., 2023). On the other hand, metabolism of TRG in humans remains mostly unknown, though 'potential methylation and oxidation products were detected in plasma and urine'(Konstantinidis *et al*., 2023).

Functions

This compound serves as a dietary ingredient, a metabolic product in humans, and a hormone in plants used for regulating plant growth. In the context of cardiovascular diseases, some of the key molecular targets of TRG include [e.g., Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ), Flavin-containing Monooxygenase 3 (FMO3), Malonaldehyde (MDA), Nuclear Factor-kappa B (NF-κB), intracellular antioxidants, apoptotic genes, etc.], which are linked to various pharmacological effects (Nguyen *et al*., 2024; Widjaja, 2025; Jing *et al*., 2022; Oktaviono *et al*., 2023).

Safety Margins

In addition, TRG has a wide safety margin as it displayed no acute toxicity up to 5000 mg/kg according to high-dose oral studies. Providing significant TRG via long-term coffee consumption has a great safety profile (Nguyen *et al*., 2024).

MECHANISMS OF ACTION OF TRG IN CARDIOVASCULAR DISEASES

Targeting Trimethylamine-N-Oxide (TMAO) formation

Trimethylamine (TMA) is formed as a product of the catabolism of choline/carnitine by the gut microbiome. This is further oxidized in the liver by FMO3-dependent oxidation, forming TMAO (Nguyen *et al*., 2024). High TMAO levels are linked to elevated atherothrombotic risk, promoting atherosclerotic plaque formation. Research suggests that TRG interferes with microbial choline metabolism, decreasing TMA production, which in turn decreases TMAO (Anwar *et al*., 2018), as well as obstructing FMO3 enzyme, which reduces TMA conversion to TMAO (Anwar *et al*., 2018; Jing *et al*., 2022). According to animal studies, dependent reduction in circulating TMAO and improved lipid profiles were observed in choline-fed mice upon treatment with TRG (Anwar *et al*., 2018). This results in a lowered TMAO-driven vascular inflammation. Nevertheless, there is still limited direct evidence that isolated TRG lowers TMAO and is currently at the hypothesis level (Jing *et al*., 2022).

Lipid metabolism

PPARs are inducers of peroxisome proliferation. PPAR-α, majorly expressed in the cardiovascular system, skeletal muscle, and liver,

promotes the gene expression involved in the uptake of fatty acids, and lipolysis (β-oxidation). It also exhibits anti-inflammatory action (Zhang *et al.*, 2024). This essentially leads to decreased Triacylglyceride (TAG) and Very-Low Density Lipoproteins (VLDL) synthesis. PPAR-β ultimately facilitates lipolysis as well by activating Carnitine Palmitoyl Transferase enzyme. PPAR-γ on the contrary, upregulated genes involved in the synthesis of fatty acids, and increases glucose utilization which in turn, reduces the glucose-fatty acid cycle (Zhang *et al.*, 2024).

TRG aids in modulating the transcription factors for lipid regulation. For instance, research suggested that TRG from coffee led to the upregulation of PPAR-α and downregulation of PPAR-γ (Zhang *et al.*, 2024). Consequently, β-oxidation of fatty acid is promoted rather than lipogenesis, which decreases TAG and VLDL levels. TRG has been reported to improve serum lipid profiles in animal models of high cholesterol diets via PPAR-mediated hypolipidemic effect (Anwar *et al.*, 2018; Zhang *et al.*, 2024). In rodent cardiometabolic models, hypothesis-generating data support improved serum lipid profile upon TRG consumption (Nguyen *et al.*, 2024). This results in decreased risk of atherosclerosis.

Antioxidant activity

The role of TRG within the paradigm of antioxidant response involves either upregulating intracellular antioxidant enzymes Superoxide Dismutase, Catalase, Glutathione Peroxidase (SOD, CAT, GPx), which hunt down free radicals, decreasing lipid peroxidation (MDA), or Nuclear Factor E2-Related Factor 2 (Nrf2) signaling, to correct the redox balance (Nguyen *et al.*, 2024; Sekhar *et al.*, 2024). Based on research, TRG pretreatment had corrected serum cardiac enzyme markers (Creatine Kinase-MB, Lactate dehydrogenase, etc.,) and restored antioxidant mechanisms in Isoproterenol (ISO)-induced myocardial injury in rats. Similarly, in rats with chronic alcohol-induced cardiac toxicity, oral dose of (50 mg/kg) TRG increased SOD, CAT, and GPx levels, while reducing MDA levels (Sekhar *et al.*, 2024). Therefore, there is some evidence that myocardial tissue is preserved with the aid of the cardioprotective antioxidant properties of TRG, playing a crucial role in cardiomyopathies, mitigating oxidative injury in cardiac tissue.

Anti-inflammatory activity

It is worth noting that TRG's novel anti-inflammatory effects are partly PPAR-α dependent. With the activation of this compound, NF-κB signaling pathways and pro-inflammatory cytokines are suppressed (Zhang *et al.*, 2024). Specifically, Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Inducible Nitric oxide synthase/Cyclooxygenase-2 (iNOS/COX-2) are dampened, reducing inflammation (Nguyen *et al.*, 2024). Thus, TRG would have beneficial effects in vascular inflammation, as well as in the stabilization of plaques.

Anti-fibrotic effects

TRG counteracts cardiac fibrosis and enhances vascular endothelial function by suppressing the spontaneous self-assembly of Collagen (Type I) in the heart (Nguyen *et al.*, 2024).

Anti-apoptotic effects

By inhibiting cardiomyocyte apoptosis, TRG mitigates cardiomyopathies. For example, in H9C2 cells exposed to oxidative stress, pro-apoptotic genes (cleaved caspase-3) were downregulated while anti-apoptotic gene (Bcl-2/Bcl-xL) expression was upregulated by the action of TRG (Nguyen *et al.*, 2024). In adult rats with ISO-induced myocardial dysfunctions, TRG also downregulated and prevented the activation of stress proteins (Hsp27, αB-crystallin). This preserves cell existence indicating the cardioprotective nature of TRG (Nguyen *et al.*, 2024).

Table 1: Classification of vasculopathies (Ramroth *et al*., 2023).

Vasculopathies	
Coronary Artery Disease	Decreased blood perfusion into cardiac tissue resulting in angina, myocardial infarction, and/or heart failure.
Cerebrovascular disease	Stroke and ischemic attacks.
Peripheral Artery Disease	Generally, involves the limbs, which may result in claudication.
Aortic atherosclerosis	Includes abdominal and thoracic aneurysms.

Table 2: Summary of Cardiopathies (Lopez *et al*., 2023).

Cardiopathies	
Ischemic heart disease	Unstable angina Myocardial Infarction (STEMI/ non-STEMI).
Valvular Heart Disease	Non-rheumatic and rheumatic valve disorders (Tricuspid, Mitral, Pulmonary and Aortic valves).
Cardiomyopathies and Heart Failure	Hypertrophic cardiomyopathy Dilated Cardiomyopathy Restrictive Cardiomyopathy.
Conduction defects	Atrioventricular blocks (1°, 2°, 3°) Bundle Branch Blocks (Right and Left) Bifascicular, Trifascicular blocks Atrial Flutter, Atrial Fibrillation Ventricular Tachycardia, Supraventricular Tachycardia.
Pericardial Diseases	Pericardial effusion Pericardial tamponade

Vascular/endothelial function

Based on research, upon consumption of TRG-enriched Sakurajima radish for 10 consecutive days, plasma TRG levels rose and caused a significant improvement in flow-mediated dilation of brachial arteries (an indicator of endothelial function), implying an enhanced nitric oxide bioavailability (Nguyen *et al.*, 2024).

PRECLINICAL AND EMERGING CLINICAL EVIDENCE

Evidence from experimental and limited human studies indicates potential cardioprotective effects of Trigonelline (TRG). In animal models, TRG pretreatment in rats exposed to chronic alcohol restored antioxidant enzyme activities, including Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx), and reduced Malondialdehyde (MDA) levels, with histological analyses suggesting preservation of myocardial tissue [Sekhar *et al.*, 2024]. In a separate model of Isoproterenol (ISO)-induced myocardial infarction in adult rats, TRG reduced infarct size, normalized cardiac biomarker levels, and downregulated stress-related proteins (Nguyen *et al.*, 2024). Supporting cellular evidence shows that in RAW264.7 macrophages, TRG suppressed nuclear translocation of NF-κB and decreased the production of pro-inflammatory cytokines, including Tumor Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6), demonstrating anti-inflammatory effects (Widjaja, 2025). In cardiomyocyte models, TRG reduced reactive oxygen species formation and attenuated apoptosis through modulation of Nrf2 signaling and caspase-3 pathways (Nguyen *et al.*, 2024). Human data remain limited; however, a dietary intervention involving a TRG-rich diet through consumption of TRG-enriched Sakurajima radishes was associated with improved endothelium-dependent vasodilation, suggesting a potential benefit on endothelial function (Nguyen *et al.*, 2024).

THERAPEUTIC POTENTIAL AND LIMITATIONS

Therapeutic Potential

TRG has a multi-targeted action, incorporating antioxidant, anti-inflammatory, lipid-modulating, endothelium, and cardiac tissue-preserving effects. Additionally, high dose animal studies do not show any acute toxicity (Nguyen *et al.*, 2024). Long-term evidence of tolerance is proven by coffee consumption. Furthermore, since TRG is a naturally occurring compound, it makes it accessible and more easily integrated into the diet, as a nutritive preventive strategy.

Limitations

One of the major limitations is the lack of large-scale, random, and controlled clinical trials involving isolated TRG. The current research and evidence is still preclinical and observational. Moreover, the effective dosage gaps in animal studies (40 mg/kg) is far greater in comparison to achievable intake from a regular diet which is approximately (1 mg/kg) from coffee. Additionally, while TRG is generally safe, a recent risk assessment highlights limitations in data on pharmacokinetics, and interaction with other compounds (Konstantinidis *et al.*, 2023).

CONCLUSION

TRG is an emerging natural compound with promising potential cardiovascular benefits. Preclinical research supports the action of TRG in improving antioxidant defenses, regulating serum lipid levels, suppressing inflammation, enhancing endothelial function, etc. These mechanisms directly target the root causes of cardiovascular diseases. On the other hand, several limitations persist. Clinical studies are required to determine certain crucial parameters including the effective dosage, interaction with other compounds, adverse effects, efficacy, etc.

With rigorous clinical research, TRG might evolve from a mere dietary element to a validated therapeutic agent in managing various cardiovascular diseases. Priority areas include dose-finding pharmacokinetic studies, randomized trials using standardized trigonelline formulations, and mechanistic human studies integrating endothelial function testing with cardiometabolic and gut-microbiome endpoints.

ABBREVIATIONS

CAT: Catalase; **COX-2:** Cyclooxygenase-2; **FMO3:** Flavin-containing monooxygenase 3; **GPx:** Glutathione Peroxidase; **IL-6:** Interleukin-6; **iNOS:** Inducible Nitric oxide synthase; **MDA:** Malonaldehyde; **NF-κB:** Nuclear Factor-kappa B; **Nrf2:** Nuclear Factor E2-Related Factor 2; **PPAR:** Peroxisome Proliferator-Activated Receptor; **SOD:** Superoxide Dismutase; **TMA:** Trimethylamine; **TMAO:** Trimethylamine-N-oxide; **TNF-α:** Tumor Necrosis Factor-alpha; **TRG:** Trigonelline.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AI DISCLOSURE STATEMENT

During manuscript preparation, the authors used ChatGPT (OpenAI) to assist with language refinement and improving clarity. All outputs were critically reviewed, edited, and verified by the authors, who take full responsibility for the content.

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