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REVIEW: PHARMACOLOGICAL AND THERAPEUTIC EFFECTS OF TRIGONELLINE

Astikta Ashok Bhondave*[1], Aditi Rajaendra Waghmare[2], Dr. Hemant. V. Kamble[3] and S. R. Ghodake[4]

[1,2]Student, Department of Pharmacology, LSDP College of Pharmacy, Pune, Maharashtra.
[3]Principal, Department of Pharmacology, LSDP College of Pharmacy, Pune, Maharashtra.
[4]Professor, Department of Pharmacology, LSDP College of Pharmacy, Pune, Maharashtra.

***Corresponding Author: Astikta Ashok Bhondave**

Student, Department of Pharmacology, LSDP College of Pharmacy, Pune, Maharashtra.

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ABSTRACT

Trigonelline (TRG), is an alkaloid predominantly found in the seeds of Trigonella foenum-graecum and coffee. Which has therapeutic efficacy as a neuroprotective, anticancer, hypoglycemic, hypolipidemic, sedative, memory-enhancing, antibacterial, antiviral, and antitumor agent. TRG's biological activities center around glucose and lipid metabolic regulation, as well as anti-inflammatory and oxidative stress modulation. It shows multidimensional effects, including neuroprotection from neurodegenerative disorders and diabetic peripheral neuropathy, neuromodulation, mitigation of cardiovascular disorders, skin diseases, diabetic mellitus, liver and kidney injuries, and anti-pathogen and anti-tumor activities. TRG has various therapeutic effects on multiple pathological conditions, including metabolic syndrome, neurodegenerative diseases, cancers, and inflammation-associated disorders.

KEYWORDS: Trigonelline (TRG), Pharmacological Activities, alkaloid, Therapeutic Effects.

INTRODUCTION

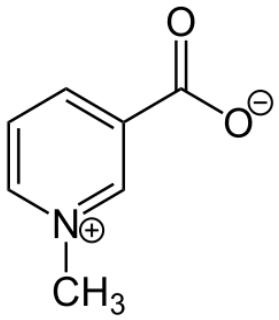
Trigonelline (TRG) was first isolated by Johns E. from fenugreek (Trigonella foenum-graecum) in 1885. Trigonelline is an alkaloid predominantly found in the seeds of Trigonella foenum-graecum and coffee. Which has therapeutic efficacy as a neuroprotective, anticancer, hypoglycemic, hypolipidemic, sedative, memory-enhancing, antibacterial, antiviral, and antitumor agent.[1]

It is synthesized by the methylation of nicotinic acid (niacin or vitamin
B3) and, thus, it is also called N-methyl nicotinic acid. S-adenosyl-l-methionine provides a methyl group for TRG synthesis.[2],[3]

Trigonelline is a plant hormone involved in regulating the plant cell cycle, nodulation, oxidative stress, and overall plant survival and growth. It is found in notable amounts in plants like coffee beans and fenugreek seeds. The name "trigonelline" comes from its initial isolation from fenugreek seeds.[4]

Trigonelline

chemical formula : C7H7NO2
molecular weight : 137.138 g·mol^{-1}
IUPAC Name: 1-methylpyridin-1-ium-3-carboxylate
Molecular Structure: Trigonelline is an alkaloid and a pyridine derivative that's
Formed when the nitrogen atom of niacin (vitamin B3) is methylated. It's also
Known as "methylated niacin".[4]



Structure of trigonelline[4]

Pharmacological Activities of Trigonelline

Safety Profile of TRG

- TRG has a good safety profile.
- No mortality or changes in behavior were observed in mice treated with TRG up to 5000 mg/kg.
- TRG did not affect the estrous cycle of rats or fertility in pregnant or non-pregnant female rats.
- A fetotoxicity study found no adverse effects on maternal parameters or fetal development.[5],[6]

Pharmacokinetics of TRG

- TRG has good bioavailability, with a biological half-life of ~3.5 hrs in rats.[7]

Regulatory Role of TRG in Glucose and Lipid Metabolism

- TRG regulates glucose synthesis and transport.
- TRG modulates lipogenesis and fatty acid metabolism.
- TRG can facilitate the maintenance and restoration of metabolic homeostasis.[8]

Therapeutic Effects of Trigonelline

Anti-diabetic effect

TRG exhibited anti-diabetic effects in both nonobese and obese T2DM animal models, significantly lowering blood glucose, insulin, TNF-α, HbA1c, TC, LDL-c, TG, and FFA levels.[65] It inhibited intestinal enzymes such as α-amylase, maltase, and lipase, leading to a 46% reduction in blood glucose levels. TRG improved glucose and lipid tolerance and protected liver and kidney functions in diabetic rats.[9] Molecular docking studies indicated that TRG could inhibit GSK-3α and GSK-3β, which are known to negatively regulate insulin sensitivity.[10] In the T2DM KK-Ay obese mouse model, TRG reduced plasma glucose and insulin levels, enhancing glucose tolerance and insulin resistance indices.[11] TRG-enriched yogurt in HFD-fed mice decreased fat accumulation and advanced glycation end products (AGEs) while improving insulin sensitivity.[10] A biomarker analysis in 3986 participants showed an association between serum TRG levels and decreased HbA1c levels over time.[10]

Effects on Alzheimer's Disease (AD)

TRG appears to mitigate the onset of AD primarily by reducing the accumulation of amyloid-beta (Aβ) peptides, which are known to contribute to neurotoxicity and the progression of the disease. TRG exhibits multiple mechanisms that contribute to its neuroprotective effects in Alzheimer's Disease, including reducing Aβ accumulation, enhancing cognitive function, and mitigating oxidative stress and inflammation. These findings suggest that TRG may hold promise as a therapeutic agent for AD, warranting further investigation into its efficacy and mechanisms of action.[12],[13]

Effects on Parkinson's Disease (PD)

TRG shows promise as a neuroprotective agent in the context of Parkinson's Disease, particularly in models that simulate the neurodegenerative processes associated with the disease.[14]

Effects of TRG on Cognition, Learning, and Memory

Trigonelline exhibits a multifaceted approach to improving cognition, learning, and memory by targeting inflammatory pathways, reducing oxidative stress, restoring neurotrophic factors, and enhancing neurotransmitter release. These findings suggest that TRG may be a promising candidate for therapeutic interventions aimed at cognitive impairments associated with aging and neurodegenerative diseases.[15],[16]

Effects of TRG on Stroke

TRG exhibits significant neuroprotective effects in stroke models by reducing inflammation and oxidative stress, interacting with MPO to mitigate inflammatory damage, and activating survival pathways in neurons. These findings suggest that TRG may be a promising therapeutic agent for stroke management.[17]

Anti-Depression and Anti-Epilepsy Effects of TRG

TRG shows promise as a therapeutic agent for both depression and epilepsy. Its ability to enhance hippocampal structure, modulate oxidative stress, and exert neuroprotective effects positions it as a potential treatment option for mood disorders and seizure management.[18],[19]

Neuromodulation Effects of TRG

TRG exhibits significant neuromodulatory effects, particularly as a sedative and potential sleep aid. Its interactions with various neurotransmitter receptors, including GABAA, GABAB, serotonin, and dopamine receptors, highlight its potential for influencing mood, anxiety, and cognitive functions. The findings suggest that TRG could be a valuable compound for developing therapeutic strategies aimed at managing sleep disorders, anxiety, and pain.[20]

Liver Protection Effects of TRG

TRG exhibits significant liver-protective effects by alleviating liver steatosis and NAFLD injury through the restoration of autophagy, reduction of lipotoxicity, and modulation of apoptotic pathways.[21] Additionally, TRG improves liver function by enhancing insulin sensitivity and reducing oxidative stress and inflammation. These findings suggest that TRG may be a promising therapeutic agent for liver-related disorders.[22]

Cardiovascular Protection Effects of TRG

1. Anti-Cardiomyopathy Effect: TRG reduced cell death (necrosis and apoptosis) in cardiomyocyte-like H9C2 cells exposed to H2O2, by regulating apoptotic and anti-apoptotic genes (such as caspase-3, caspase-9, Bcl-2, and Bcl-XL). It also inhibited the production of trimethylamine N-oxide (TMAO), a molecule linked to cardiovascular diseases, by reducing trimethylamine (TAM) production and FMO enzyme activity.[23]
2. Mitigation of Myocardial Injury: In animal models of diabetes and myocardial injury (induced by NICO, STZ, or ISO), TRG reduced myocardial necrosis, improved cardiac function, and normalized blood pressure. It did this by lowering levels of markers like creatine kinase isoenzyme, LDH, and AST.[24]
3. Alleviation of Fibrosis: TRG was shown to prevent fibrosis in the heart by inhibiting type I collagen self-assembly. In pulmonary fibrosis (PF) induced by bleomycin (BLM), TRG reduced inflammation, apoptosis, and fibrosis by targeting key signaling pathways (NF-κB/NLRP3/IL-1β) and promoting

autophagy. It also reversed epithelial-mesenchymal transition (EMT) and prevented the activation of profibrotic genes.[25]

4. Improving Endothelial Function: TRG intake from Sakurajima radish improved vascular endothelial function, as measured by enhanced flow-mediated dilation, indicating improved vascular health.[26]

Anti-Nephropathy Effects of TRG

1. Anti-Diabetic Nephropathy: TRG showed protective effects in diabetic kidney disease by preventing renal fibrosis, epithelial-to-mesenchymal transition, and oxidative stress. It improved kidney function in diabetic mouse models by regulating key pathways like Smad7, TNF-α, and Wnt/β-catenin, and enhanced autophagy. TRG also reduced kidney hypertrophy and apoptosis, suggesting potential for treating diabetic nephropathy.[27], [28]

2. Effects on Metal Exposure-Induced Renal Tubular Injury: TRG protected kidneys from iron-induced oxidative stress by suppressing ROS production and preventing damage to renal tubular cells. Chronic iron exposure could overwhelm the Nrf-2 antioxidant pathway, but TRG mitigated this, highlighting its role in managing metal-induced renal injuries.[29]

3. Preventive Effect against Kidney Stone Formation: TRG exhibited anti-lithiatic properties by reducing the size, number, and mass of calcium oxalate monohydrate (COM) crystals. It inhibited crystal growth and cell adhesion without affecting crystal aggregation, providing protection against kidney stone formation. TRG also prevented renal cell deterioration by blocking the overproduction of ROS, disruption of tight junctions, and the shift in cell cycle associated with crystal formation.[30]

Anti-Cancer Effects of TRG

TRG combats cancer by inhibiting the harmful hyperactivation of Nrf2, a factor that, when persistently active, promotes cancer growth and resistance to treatment. Inhibiting Nrf2 with TRG may make cancer cells more responsive to therapies.[31]

Anti-Head-and-Neck Cancer (HNC) Effects

TRG helps overcome ferroptotic resistance in head-and-neck cancer (HNC) by inhibiting the Nrf2–ARE pathway. It sensitizes resistant HNC cells to treatments like RSL3 and artesunate by enhancing ferroptosis and blocking the antioxidant systems that protect cancer cells, improving the effectiveness of therapies in resistant HNC cases.[32]

Anti-Lung Cancer and -Colon Cancer Effects

TRG inhibits Nrf2 activation in lung and colon cancers, blocking key signaling pathways, inducing cell cycle arrest, and promoting apoptosis. It also helps overcome drug resistance in colon cancer and reduces proteasome activity in pancreatic cancer cells, leading to increased cell death.[33],[34],[35]

Anti-Cancer Cell Migration and Anti-Lipoblastoma Effects

TRG, when incorporated into chitosan nanoparticles, effectively inhibits tumor cell invasion. It blocks hepatoma cell migration by downregulating the Raf/ERK/Nrf2 pathway and reducing MMP-7 expression. TRG-loaded chitosan nanoparticles also show anti-cancer effects in lipoblastoma (C6 glioma) cells.[36]

Antiviral, Antimicrobial, and Antifungal Effects of TRG

Antiviral Effects

TRG shows antiviral effects against various viruses, including RSV, HSV-1, PI-3, RVFV, EBV, and SARS-CoV-2. It reduces oxidative stress, inflammation, and viral replication, while also preventing lipotoxicity and cell damage caused by viral infections. Additionally, TRG may help reduce cancer risk associated with viruses like EBV and human gammaherpesvirus by inhibiting Nrf2 activation.[37]

Antimicrobial Effects

TRG shows antimicrobial activity with MICs ranging from 4 to 8 µg/mL against common bacterial strains and 32 to 64 µg/mL against isolated resistant strains, while ampicillin is less effective against the resistant strains with MICs >128 µg/mL.[37]

Antifungal and Antiparasitic Effects

TRG has antifungal effects against *Candida albicans* and *Candida parapsilosis* and shows antiparasitic activity against *Echinococcus granulosus*, causing damage to the parasite through increased caspase-3 activity and reduced Nrf2, NQO-1, and HO-1 expression.[37]

Other Protective Effects of TRG

Skin Protection Effects

TRG offers skin protection by inhibiting tyrosinase, preventing UV-B-induced damage, reducing oxidative stress, and protecting against collagen degradation and apoptosis.[38]

Anti-Allergic Inflammation Effect

TRG suppresses allergic inflammation by inhibiting mast cell activation, reducing lung tissue damage, and lowering serum IgE and T helper 2 cytokine levels. It also prevents the degranulation of IgE-sensitized mast cells, acting against allergic reactions.[39]

Gastroprotective Effects

TRG demonstrates gastroprotective effects by significantly reducing gastric ulcer formation in a rat model through increased PGE2 and antioxidant levels, while lowering pro-inflammatory molecules. It also mitigates colitis and cardiomyopathy in an inflammatory bowel disease (IBD) mouse model by reducing oxidative

stress, improving intestinal health, and alleviating cardiac symptoms.[40]

Phytoestrogenic Effects

TRG has phytoestrogenic effects, increasing testosterone levels and improving symptoms in testosterone deficiency. It stimulates MCF-7 cell proliferation through estrogen receptor activation and induces apoptosis in colon cells, suggesting novel estrogenic actions.[41]

Bone Density Regulation

TRG improves bone density and health in non-hyperglycemic rats, preventing osteoporosis. However, it worsens bone mineralization in diabetic rats, while it benefits bone strength in rats with slight blood glucose increases.[42]

Extending the Lifespan

TRG extends the lifespan of *Caenorhabditis elegans* by about 17.9%, demonstrating anti-aging effects. It also partially rescues Keap1-knockout zebrafish larvae from death by modulating the Keap1–Nrf2 pathway, which is involved in cellular defense against oxidation and electrophiles.[43]

CONCLUSIONS

TRG demonstrates significant anti-inflammatory and antioxidant properties, contributing to its wide-ranging benefits across various organs and tissues. Its key functions include:

- Metabolic Modulation: TRG plays a role in regulating glucose and lipid metabolism, which is crucial for maintaining overall metabolic health.
- Neurological Recovery: It aids in the recovery from neurological disorders, including neurodegenerative diseases, ischemic brain injuries, depression, cognitive impairments, and diabetic peripheral neuropathy.
- Diabetes Management: TRG helps alleviate conditions associated with diabetes mellitus (DM) and its complications, enhancing the quality of life for those affected.
- Cardiovascular and Organ Protection: The compound offers protective effects on the cardiovascular system as well as vital organs such as the liver, lungs, kidneys, gastric system, and skin.
- Anti-Cancer Properties: TRG has shown the ability to suppress tumor cell proliferation and migration, indicating its potential role in cancer prevention and treatment.

Overall, TRG stands out as a promising natural health enhancer with a favorable safety profile, making it a valuable addition to health and wellness strategies.

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