



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH  
An official Publication of Human Journals

ISSN 2349-7203



Human Journals

Review Article

October 2020 Vol.:19, Issue:3

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## A Review on Trigonelline Containing Prodrugs

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|  <p>IJPPR<br/>INTERNATIONAL JOURNAL OF PHARMACY &amp; PHARMACEUTICAL RESEARCH<br/>An official Publication of Human Journals</p>   |  |
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**Keywords:** Trigonellin, Prodrug

### ABSTRACT

A prodrug is a drug or compound that after is metabolized or converted into a pharmacologically active drug. Inactive prodrugs are pharmacologically inactive drugs that are metabolized or converted to an active form in the body. Instead of administering a drug directly, a corresponding prodrug could be used instead to improve the way a drug is absorbed, distributed, metabolized, and excreted (ADME). Prodrugs are often designed to improve bioavailability when a drug itself is poorly absorbed from the gastrointestinal tract. A prodrug can be used to enhance the selective interaction of the drug with cells or processes that are not its target. This reduces the unwanted or unintended effects of a drug, especially important in treatments like chemotherapy, which can have serious unintended and unwanted side effects and adverse drug reactions. The design of the prodrug opens new doors in the difficult field of drug discovery and revolutionizes the art of drug development as they can overcome these challenges. Prodrugs are masked forms or bioreversible derivatives of active drug molecules that must undergo enzymatic and/or chemical transformation in vivo to release the parent active drug, which can then cause its desired pharmacological effect in the body. Prodrugs are the compound that undergoes biotransformation before presenting pharmacological effects. It is important to ensure that the prodrug must be pharmacologically inactive, quickly converted to its active drug, and a non-toxic fraction through metabolic reactions. The general terms related to prodrugs and the ways in which the prodrug strategy is used to overcome many pharmaceutical and pharmacokinetic problems such as low bioavailability by increasing or decreasing the lipophilicity of the parent drug, site selectivity. for higher absorption and less toxicity, short duration of action to increase patient compliance, rapid metabolism to increase oral bioavailability, and masking the bitter sensation of commonly used drugs, which is crucial for the compliance of geriatric and pediatric patients. The proposed review on trigonelline as a prodrug will be sufficient document evidence for the development of the application of prodrug.

## INTRODUCTION

Trigonelline is an alkaloid with chemical formula  $C_7H_7NO_2$ . It is a zwitterion formed by the methylation of the nitrogen atom of niacin (vitamin B<sub>3</sub>). Trigonelline is a product of niacin metabolism that is excreted in the urine of mammals.

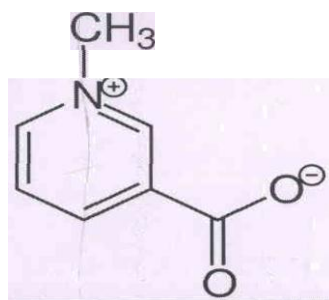


Figure No. 1: Structure of Trigonelline

### Names

IUPAC name: 1-Methylpyridinium-3-carboxylate

Other names

Nicotinic acid N-methylbetaine

Coffearine

Caffearine

Gynesine

Trigonelline

Properties

Chemical formula:  $C_7H_7NO_2$

Melting point: 230 to 233°C (446 to 451°F; 503 to 506K)

Trigonelline occurs in many plants. It has been isolated from the Japanese radish. [1](*Raphanus sativus* cv. Sakurajima Daikon), fenugreek seeds (*Trigonella foenum-graecum*, hence the name), garden peas, hemp seed, oats, potatoes, *S/achrs* species, *dahlia*, *Strophanthus*

species, and *Dichapetalum cymosum*. Trigonelline is also found in coffee. Higher levels of trigonelline are found in Arabica coffee. Holtz, Kutscher, and Theilmann have recorded its presence in several animals.

Trigonelline crystallizes as a monohydrate from alcohol in hygroscopic prisms (m.p. 130°C or 218°C *dry, dec.*). It is readily soluble in water or warm alcohol, less so in cold alcohol, and slightly so in chloroform ether. When trigonelline is heated in closed tubes with barium hydroxide at 120°C, it gives rise to methylamine and, if treated similarly with hydrochloric acid at 260°C creates chloromethane and nicotinic acid (a form of vitamin B<sub>3</sub>) as Trigonelline is a methyl betaine of nicotinic acid.

N-methyl nicotinate is an iminium betaine that is the conjugate base of N-methyl nicotinic acid, arising from deprotonation of the carboxy group. It has aroleasa plant metabolite, a food component, and a human urinary metabolite. It is an iminium betaine and an alkaloid. It derives from a nicotinate. It is a conjugate base of N-methyl nicotinic acid.

Traditionally the seeds are used as macerate for the treatment of diabetes, cough, and flatulence, to increase breast milk secretion, and for anti-inflammatory and aphrodisiac effects. The use is limited by its unpleasant smell and bitter taste which can be modified by adding mint leaves to the macerate. Antidiabetic properties are attributed mainly to galactomannan, 4-hydroxyisoleucin (4-OH-Ile), diosgenin and trigonelline. These substances demonstrate direct antidiabetic properties in clinical studies by increasing insulin secretion (4-OH-He), decreasing insulin resistance, and glucose resorption from the GIT (galactomannan) and improvement in B-cells regeneration (trigonelline). Besides this main effect, the herb improves blood lipid spectre (4-OH-He, diosgenin), and has reno-protective (4-OH-Ile, trigonelline), neuroprotective (trigonelline) and antioxidant (diosgenin, trigonelline) effects. Antidiabetic efficacy of trigonelline is comparable to glibenclamide treatment and more effective than sitagliptin therapy. Given the large body of evidence and promising results in comparison with Standard pharmacotherapy, fenugreek active substances have the potential to become a source of new antidiabetic medication.[2]

There is evidence that *Trigonella foenum-graecum* L. (fenugreek), a traditional Chinese herb, and its components are beneficial in the prevention and treatment of diabetes and central nervous system disease. The pharmacological activities of trigonelline, a major alkaloid component of fenugreek, have been more thoroughly evaluated than fenugreek's other

components, especially concerning diabetes and central nervous system disease. Trigonelline has hypoglycemic, hypolipidemic, neuroprotective, antimigraine, sedative, memory improving, antibacterial, antiviral, and anti-tumor activities, and it has been shown to reduce diabetic auditory neuropathy and platelet aggregation. It acts by affecting beta cell regeneration, insulin secretory activities of enzymes related to glucose metabolism, reactive oxygen species, axonal extension, and neuron excitability. However, further study of trigonelline's pharmacological activities and the exact mechanism is warranted, along with the application of this knowledge to its clinical usage.

This review aims to give readers a survey of the pharmacological effects of trigonelline, especially in diabetes, diabetic complications, and central nervous system disease. In addition, because of its pharmacological value and low toxicity, the reported adverse effects of trigonelline in experimental animal models and humans are briefly reviewed, and the pharmacokinetics of trigonelline are also discussed.[3]

The concentration-time curves of trigonelline in rabbits after iv administration were shown to fit one-compartment and two-compartment open model, respectively. The main parameters after iv administration of trigonelline were as follows:

$T_{1/2\alpha}$  was 10.8 min,  $T_{1/2\beta}$  was 44.0 min,  $K_{21}$  was  $0.044 \text{ min}^{-1}$ ,  $K_{10}$  was  **$0.026 \text{ min}^{-1}$** ,  **$K_{12}$**  was  $0.017 \text{ min}^{-1}$ , **AUC** was  $931.0 \text{ mg}\cdot\text{min}/\text{L}$ .

It was concluded that trigonelline showed a middlerate of absorption and a fast rate of elimination in the rabbit.[4]

Trigonelline is an alkaloid with chemical formula  $\text{C}_7\text{H}_7\text{NO}_2$  and CAS number 535-83-1. Trigonelline is a product of the metabolism of niacin (vitamin  $\text{B}_3$ ) which is excreted in the urine. It is also found in coffee, where it may help to prevent dental caries by preventing the bacteria *Streptococcus mutans* from adhering to teeth. Trigonelline occurs in many other plants, including fenugreek seeds, garden peas, hemp seed, oats, and potatoes. Trigonelline in the urine is a biomarker for the consumption of coffee, legumes, and soy products. Trigonelline, a betaine derivative of nicotinic acid, arrests cell division at the  $\text{G}_2$  phase after DNA transcription. It has some selectivity towards legumes, arresting cell division in root {tips of several leguminous species, while having no measurable effect on wheat or common sunflower.

The effects of both coffee components and coffee extract on the electrical responses of GABA(A) receptors expressed in *Xenopus* oocytes were studied by injecting cRNAs of the alpha(1) and beta(1) subunits of the bovine receptors. The aqueous extract of coffee dose-dependently inhibited the GABA-elicited responses, whereas the lipophilic extract of coffee by diethyl ether slightly potentiated it at low doses (0.1-0.4 uL/mL) but showed inhibition at high doses (0.5-0.8 uL/mL). Theophylline inhibited the response in a noncompetitive mechanism ( $K(i)=0.55\text{mM}$ ), whereas theobromine and trigonelline hydrochloride inhibited it in a competitive manner.[5]

Evidence accumulates that the transcription factor nuclear factor E2-related factor 2 (Nrf2) has an essential role in cancer development and chemoresistance, Thus pointing to its potential as an anticancer target and undermining its suitability in chemoprevention. Through the induction of cytoprotective and proteasomal genes, Nrf2 confers apoptosis protection in tumor cells, and inhibiting Nrf2 would therefore be an efficient strategy in anticancer therapy.

In the present study, pancreatic carcinoma cell lines (Pancl, Colo357, and MiaPaca2) and H6c7 pancreatic duct cells were analyzed for the Nrf2-inhibitory effect of the coffee alkaloid trigonelline (trig), as well as for its impact on Nrf2-dependent proteasome activity and resistance to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and anticancer drug-induced apoptosis. Chemoresistant Pancl and Colo357 cells exhibit high constitutive Nrf2 activity, whereas chemosensitive MiaPaca2 and H6c7 cells display little basal but strong tert-butylhydroquinone (TBHQ)-inducible Nrf2 activity and drug resistance. Trigonelline efficiently decreased basal and TBHQ-induced Nrf2 activity in all cell lines, an effect relying on a reduced nuclear accumulation of the Nrf2 protein. Along with Nrf2 inhibition, trigonelline blocked Nrf2-dependent expression of proteasomal genes (for example, *s5a/psmd4* and *a5/psma5*) and reduced proteasome activity in all cell lines tested. These blocking effects were absent after treatment with Nrf2siRNA, a condition in which proteasomal gene expression and proteasome activity were already decreased, whereas siRNA against the related transcription factor Nrf1 did not affect proteasome activity and the inhibitory effect of trigonelline. Depending on both Nrf2 and proteasomal gene expression, the sensitivity of all cell lines to anticancer drugs and TRAIL-induced apoptosis was enhanced by trigonelline. Moreover, greater antitumor responses toward anticancer drug treatment were observed in tumor-bearing mice when receiving trigonelline. In conclusion,

representing an efficient Nrf2 inhibitor capable of blocking Nrf2-dependent proteasome activity and thereby apoptosis protection in pancreatic cancer cells, trigonelline might be beneficial in improving anticancer therapy.[6]

Extension of dendrites and axons in neurons may compensate and rescue damaged neuronal networks in the dementia brain. Among the extracts of raw and roasted coffee beans, a methanol fraction of the ethanol extract (1 $\mu$ g/mL) of raw beans increased significantly the percentage of cells with neurites in human neuroblastoma SK-N-SH cells. Among subfractions of this methanol, fraction was a basic fraction (5  $\mu$ g/mL) which exhibited significant neurite outgrowth activity. Finally, trigonelline in the basic fraction was identified to be active as far neurite extension was concerned. Treatment with trigonelline (30  $\mu$ M) increased the percentage of cells with neurites at 3<sup>rd</sup> and 6<sup>th</sup> d after treatment. In addition, the number of neurites reacting positively to phosphorylated neurofilament-H was increased by treatment with 30 $\mu$ M trigonelline for 6days, suggesting enhancement of axonal extension. These results show that trigonelline promotes functional neurite outgrowth.[7]

Drinking coffee has been associated with the development of several endocrine-related cancers. The interpretation of these data has often been limited to the role that caffeine plays. Trigonelline (Trig), a niacin-related compound, is a natural constituent of coffee accounting for approximately 1% dry matter in roasted beans. Studies exploring the effects of this bioactive compound on mammalian cells are limited. The initial purpose of our studies was to determine whether trigonelline alters the actions of estradiol (E(2)), using the proliferation of estrogen-dependent human breast cancer (MCF-7) cells as a model system. When cells were cotreated with suboptimal doses of E(2) (10 pmol/L) and Trigonelline (100 pmol/L), an additive enhancement of MCF-7 growth was observed. In the absence of E(2), Trigonelline stimulated MCF-7 cell proliferation in a dose-responsive manner and significantly enhanced cell growth at concentrations as low as 100 pmol/L. Cotreatment of MCF-7 cells with Trigonelline and ICI182,780, an estrogen receptor(ER) antagonist, inhibited Trigonelline - induced cell proliferation. Trigonelline treatment also induced activation of estrogen response element reporter assays in MCF-7 cells and increased expression of ER target genes (pS2, progesterone receptor, and cyclin DI) similar to E(2). While our data demonstrate that Trigonelline activates the ER, competitive binding assays showed that Trigonelline does not compete for E(2) off of the ER at any concentration. This suggests that Trigonelline is activating the ER through a separate mechanism. Collectively, these data demonstrate that

Trigonelline even at low concentrations stimulates MCF-7 cell growth and that this effect is mediated through ER, clearly identifying Trigonelline as a novel phytoestrogen.[8]

## CONCLUSION

Trigonelline, an alkaloid with potential antidiabetic activity, is present in considerable amounts in coffee. It is used in biochemical research. Trigonelline promotes functional neurite outgrowth in human neuroblastoma cells. Trigonelline showed significant central nervous system (CNS) stimulant activities in rats. Trigonelline differentially affected the skeletal system of rats with streptozotocin-induced metabolic disorders, intensifying the osteoporotic changes in streptozotocin-treated rats and favorably affecting bones in the non-hyperglycemic (nicotinamide/streptozotocin-treated) rats. The results indicate that, in certain conditions, trigonelline may damage bone. In rats, estrogen deficiency caused a worsening of bone mineralization and mechanical properties of the tibial metaphysis, as well as increases in bone turnover markers. Administration of trigonelline did not affect the investigated parameters in non-ovariectomized rats, but it worsened the mineralization and mechanical properties of cancellous bone in ovariectomized rats. Unfavorable effects of trigonelline on the skeletal system depended on the estrogen status. They were observed only in the cancellous bone of estrogen-deficient rats. The results of bacteria mutation assays (*Salmonella typhimurium* strains TA98, YG1024, and YG1029) showed that trigonelline, alone or in combination with most of the single amino acids and mixtures of amino acids yielded potent mutagenic activity. However, in another study, it was found not mutagenic in the Salmonella plate incorporation assay and mouse lymphoma.

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