

ANTIOXIDANT AND PHARMACOLOGICAL EFFECTS OF TRIGONELLINE ON FREE RADICAL MEDIATED DISEASES

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ABSTRACT

Molecular oxygen helps in the process of oxidation that is the basic component of aerobic life and metabolism. A part of this oxygen is taken into living cells and converted to reactive oxygen species (ROS) as free radicals. Plant-derived materials have recently attained much importance in relation to the protection of cell membrane fluidity, protein denaturation, lipid peroxidation (LPO) and oxidative DNA damage caused by free radicals (FRs). Trigonelline, a major alkaloid component of various medicinal plants has many beneficial pharmacological activities i.e. hypolipidemic, hypoglycemic, neuroprotective, antibacterial, antiviral, anti-tumor activities, antimigraine, sedative and memory-improving properties. It has been also shown to reduce diabetic auditory neuropathy and platelet aggregation.

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INTRODUCTION

Trigonelline (TG) is a widely distributed plant hormone that also exists in several animal species, such as mammals, marine fishes, arthropods, coelenterates, crustaceans, echinoderms etc. It has been isolated from coffee (Allred *et al.*, 2009; Folwarczna *et al.*, 2016), fenugreek seeds (Ouzir *et al.*, 2016) radish (Kuroda *et al.*, 2018), peas, soybean and alfalfa (Mehrafarin *et al.*, 2012). A high level of TG is found in arabica coffee. It was first isolated from fenugreek seeds (*Trigonella foenum-graecum*), hence the name assigned to it is "trigonelline". Presence of TG in urine is a biomarker for consumption of coffee, legumes and soy products.

Excessive FRs production and LPO are involved in the pathogenesis of chronic diseases, including heart disease, cardiovascular disease, cancer, diabetes, Alzheimer disease, cataracts and age-related functional disorders (Singh *et al.*, 2014; Singh *et al.*, 2016). They also play a major role in the aging process (Khodr and Khalil, 2001). FRs cause damage in plasma membranes and can change the structure of macromolecules present in biological systems like lipid, nucleic acid, and protein. Various research studies highlighted the importance of consuming dietary products, rich in antioxidants, to prevent the chronic diseases caused by FRs. TG, which is an active compound of fenugreek and coffee, has high antioxidant activities, can be used to reduce the oxidative stress as well as in chronic diseases caused by FRs.

With the modern and competitive lifestyle and ever increasing stressful conditions, all types of diseases are becoming a big issue for human health. Due to the high cost and many side effects of synthetic allopathic medicines, more and more people are now inclining towards the use of natural products (nutraceuticals). Around 70% of the population in India depends on -

nutraceuticals for their primary health care. The term nutraceutical is made up of two words 'nutrition' and 'pharmaceutical' which exerts a curative or preventive effect on disease. These include various nutrients, dietary supplements, herbal products and functional foods. Nutraceuticals, of both plant and animal origin, hold great opportunities for food and pharma industries to bring out novel products for future needs. Nutraceuticals constitute an effective source of both traditional and modern medicines. They help in countering some of the serious health problems such as obesity, cardiovascular diseases, cancer, osteoporosis, arthritis, diabetes, atherosclerosis and overall health of the person.

CHEMICAL PROPERTIES

The chemical formula for TG is C₇H₇NO₂ (Figure 1). It is a methylation product of niacin (vitamin B₃), and hence it is also known as "methylated niacin". At higher temperatures, TG breaks down to niacin. TG can be readily extracted from its sources due to its high solubility in water.

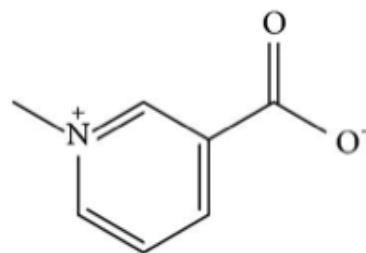


Figure 1. Structure of Trigonelline

PHARMACOLOGICAL EFFECTS OF TRIGONELLINE

Fenugreek plants and coffee are the main sources of TG. In the Fenugreek plant, seeds are the main source of TG. TG has been reported to have a number of pharmacological activities as summarized in Table 1. Coffee is one of the most commonly consumed beverages in the world whereas fenugreek plant is used as vegetable -

and spices. The pharmacological effects of TG have scientifically proved its healing effects in different disease conditions. The literature and research reports suggest that trigonelline (TG) can act as a protective compound against various liver disorders. Current research explores its mechanism of action in therapeutic potential. In one study, it was revealed that ethanol extract of fenugreek seeds, containing trigonelline, had a significant improvement in the oxidative stress parameters, that could be attributed to the flavonoid content of fenugreek (Hamadi, 2012). Experimental results showed that ethanol extract of fenugreek seeds and isolated trigonelline reduces lipid profile and blood -

glucose in alloxan induced diabetic rabbits. This effect may be due to the presence of trigonelline compounds that have antioxidant property (Velikii *et al.*, 1992). In another study from Brazil, coffee containing trigonelline and caffeic acid showed antimicrobial properties against enterobacteria. The IC(50) and IC(90) for the compounds determined by the microtiter plate method indicated that trigonelline had potential antimicrobial properties against *Salmonella enteric* (Almeida *et al.*, 2006).

According to the reports by Yoshinari *et al.* (2013) trigonelline has anti-diabetic effects in type 2 diabetic Goto-Kakizaki (GK) rats. Levels of

Table 1. Pharmacological properties of Trigonelline compound

Pharmacological properties	Effects	References
Antioxidant	Lower cellular ROS level; Lower blood and liver thiobarbituric acid reactive substances	Singh <i>et al.</i> , 2010; Hamadi, 2012; Zhou <i>et al.</i> , 2012; Yoshinari <i>et al.</i> , 2013
Hypoglycemic	Reduce blood glucose; Antidiabetic effect	Ouzir <i>et al.</i> , 2016; Yoshinari <i>et al.</i> , 2013; Tramontano <i>et al.</i> , 1986; Velikii <i>et al.</i> , 1992
Hepatoprotective	Protective role against Dimethylnitrosamine induced toxicity	Chaudhary <i>et al.</i> , 2010; Iqbal <i>et al.</i> , 2018
Antipyretic	Reduce body temperature	Iqbal <i>et al.</i> , 2018
Anti-Inflammatory	Suppress inflammation	Khalili <i>et al.</i> , 2018
Antibacterial	Decrease bacterial growth, antiseptic	Daglia <i>et al.</i> , 2002; Almeida <i>et al.</i> , 2006
Anticarcinogenic	Decrease the early apoptotic and late apoptotic cell death; Trigonelline interfere with Nrf2 activation	Hirakawa <i>et al.</i> , 2005; Boettler <i>et al.</i> , 2011
Anti-obesity	Inhibit fatty acid synthase and GLUT-4 transporter expression, Inhibit the adipogenesis	Ilavenil <i>et al.</i> , 2014
Hypolipidemic	Decrease serum and liver triglyceride levels	Ouzir <i>et al.</i> , 2016; Zhou <i>et al.</i> , 2012; Yoshinari <i>et al.</i> , 2013
Neuroprotective	Regeneration of the neuronal network	Zhou <i>et al.</i> , 2012; Khalili <i>et al.</i> , 2018; Tohda <i>et al.</i> , 2005
Antiviral Effect	Significantly inhibit the survival of herpes simplex virus	Zhou <i>et al.</i> , 2012
Reduced Platelet Aggregation	Inhibit platelet aggregation	Naito <i>et al.</i> , 2011
Gastroprotective	Significantly inhibit gastric lesions against indomethacin-induced toxicity	Antonisamy <i>et al.</i> , 2016

blood and liver thiobarbituric acid reactive substances and urinary 8-hydroxydeoxyguanosine could be lowered with trigonelline, compared to that of control rats (without trigonelline). These results suggest that lowering of diabetes by trigonelline is caused by reducing oxidative stress. A recent study was carried out to see the effect of TG on the renal function, morphological changes and renal apoptosis in neonatal diabetic rats. Result showed that TG treatment restored TNF- α levels and attenuated the oxidative damage. This was evident from the significant increase in the activity of endogenous antioxidants such as SOD, GST and GPx, the significant decrease in the activity of Na⁺K⁺-ATPase and the level of lipid peroxidation product, MDA. Recent investigation suggests that the change in mitochondrial transmembrane potential can switch the committed cells to apoptotic death with oxidative stress as the mediator. TG treatment, however, significantly decreased the early apoptotic and late apoptotic cell death (Ghule *et al.*, 2012). Medicinally, trigonelline has been used in antiseptic, antimigraine, and antitumor treatment (Chopra *et al.*, 2006).

CONCLUSION

Studies mentioned in Table 1 indicate that TG has many protective effects against lifestyle diseases caused by FRs due to its high antioxidant properties. We can conclude that TG compounds have a number of protective properties against toxicants. Hence, plants containing TG may serve as a good source of nutraceuticals which have potential for use in health care formulations.

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