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Isopulegol: A Promising Phytochemical with Potential Therapeutic Benefits

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Abstract

Phytochemicals are naturally occurring biologically active compounds that provide promising options to existing therapeutic approaches and serve as vital resources for novel drugs. Essential oils derived from various medicinal plants contain a wide array of phytochemicals that exhibit diverse pharmacological properties. Terpenes are low molecular weight, volatile compounds that are abundant in essential oil of various plants and possess useful biological activity for treating diseases and ailments. Isopulegol is a monoterpene alcohol present in the essential oils of grape fruit, mint and rosemary. This mini review summarizes recent progress on the health benefits of isopulegol and discusses its potential mechanisms in the prevention and treatment of diseases in various experimental models.

Keywords: Phytochemicals; Essential oil; Terpenes; Isopulegol

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Introduction

Essential oils are complex mixtures of hydrocarbons and their oxygenated derivatives that are documented to exhibit a wide range of biological activities. Therapeutic properties of these oils are attributed largely to the presence of terpenoids and phenolic compounds that arises from two different isoprenoid pathways. Terpenes find extensive application in aromatherapy, medicaments, and disinfectants, insect repellent and in the production of cosmetics. Isopulegol (p-menth-8-en-3-ol), is a monoterpene alcohol present in the essential oils of various plant species [1]. Structural analysis of isopulegol reveals the presence of two linked isoprene units and an oxygen atom (**Figure 1**). It is a 3-oxygenated monoterpene of the p-menthane family, which is an intermediate in the preparation of (-) menthol and is used in the manufacture of fragrances. It is chiefly present in the essential oils of *Citrus acidavar, Citrus paradisi* and *Corymbia citriodora* (**Table 1**) [2-6]. The present review highlights the pharmacological properties of isopulegol on experimental models related to its gastroprotective, neuroprotective properties and its influence on diabetes mellitus.

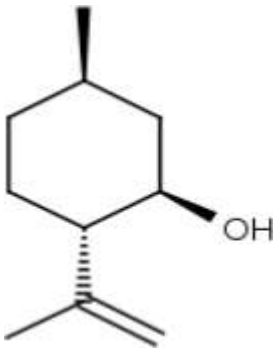

Figure 1 Structural analysis of isopulegol reveals the presence of two linked isoprene units and an oxygen atom

Role of Isopulegol on Peptic Ulcer Disease

Peptic ulcer is a benign lesion of the gastric or duodenal mucosa that results from an imbalance between gastric mucosal

protective and destructive factors. It is characterized by discontinuation in the inner lining of the gastric epithelium that extends into the muscularis propria layer. Several mechanisms are involved in the onset of peptic ulcer. The majority of cases are associated to H. pylori infection and the indiscriminate usage of non-steroidal anti-inflammatory drugs (NSAIDs). Currently, proton pump inhibitor (PPIs), triple regimen comprising two antibiotics and a proton pump inhibitor, prostaglandin analogs, bismuth quadruple therapy, mucosal cytoprotective agents are employed in the treatment of peptic ulcer [7].

S. No	Sources	Occurrence	Availability (%)	References
1	Citrus paradisi	Whole fruit	0.38	[2]
2	Eucalyptus Globulus	Essential oils of leaves	0.41	[3]
3	Cymbopogon citratu	Essential oil of whole plant	1.4	[4]
4	Citrus acidavar	Essential oil of fruit	1.4	[5]
5	Corymbia citriodora	Essential oil of Leaves	7.6	[6]

Table 1 Some important sources of isopulegol

Several studies have documented the relationship between natural products and their gastroprotective effects. In this context, the antiulcer effects of isopulegol on ethanol induced gastric ulceration were reported in experimental animals. Pre-treatment with isopulegol at various doses decreased ethanol induced gastric damage and exhibited direct cytoprotective effect. The depletion of GSH in gastric tissues was reversed on pre-treatment with isopulegol signifying its antioxidant property. In the gastrointestinal tract, KATP channels regulate diverse physiological effects such as contraction, acid secretion and blood flow. Modulators of these channels are of therapeutic importance and more specifically the channel openers exert healing effect in peptic ulcer disease. They initiate early restitution of the mucosal layer and rapidly enhance epithelial integrity and continuity. Isopulegol pre-treatment regulated prostaglandin levels in the gastric mucosa which is involved in the opening of KATP channels. By regulating endogenous prostaglandins levels, KATP channel opening and through antioxidant properties, isopulegol exhibits gastroprotective effects against ethanol and indomethacin induced gastric ulcers [8].

CNS Effects of Isopulegol

Epilepsy is a chronic neurological disease characterized by recurrent seizures caused by multiple factors. Imbalances between excitatory and inhibitory neurotransmitters in the central nervous system are presumed to be the major cause for convulsive episodes. The treatment goals are to prevent or prolong the latency of convulsion and create a balance between prevention of seizures and minimizing adverse effects. Gamma-aminobutyric acid (GABA) a naturally occurring amino acid serves as the main inhibitory neurotransmitter in the human cortex. There are two distinct classes of GABA receptors, GABAA and GABAB that differs in their biochemical, electrophysiological and pharmacological properties. Stimulation of GABAA receptors by GABA is associated with sedation, myorelaxation and anticonvulsant actions [9]. Recently GABA supplements and modulators of GABAA receptors are used to treat depression, insomnia, convulsion and anxiety. In this context, the anticonvulsant effect of isopulegol in pentylenetetrazole (PTZ) induced convulsions via selective blocking of GABA transmission was studied in mice. Pretreatment with isopulegol significantly prolonged the latency of PTZ induced convulsions similar to drugs with depressant effects on CNS. It has been reported that isopulegol acts as a positive modulator of GABAA and interacts with benzodiazepine site on the receptor thereby exhibiting anticonvulsant effects. Behavioural studies on animal models have also confirmed the CNS depressor activity of isopulegol [10]. Several lines of studies have confirmed the role of ROS on convulsion episodes and also documented the beneficial role of antioxidants as anticonvulsant agents. Pretreatment with isopulegol increased the activity of catalase, GSH and decreased lipid peroxidation in the hippocampus of mice. It is also known that convulsions followed by an increase in lipid peroxidation in brain tissue is curtailed by antioxidants and in this line the anticonvulsant property of isopulegol is related to its antioxidant properties [11].

CNS Effects of Isopulegol

Diabetes mellitus is a chronic metabolic disorder of multiple aetiology that arises due to total absence or insufficient secretion and action of insulin. It is associated with alterations in the activities of carbohydrate and lipid metabolism resulting in enhanced glucose production and decreased glucose utilisation with dyslipidemia. Isopulegol administration improved insulin secretion and action and ameliorated the metabolic alterations in high fat diet (HFD)/Streptozotocin (STZ) induced diabetic rats [12].

Pancreatic β-cell dysfunction (functional defect and decreased cell mass) and insulin resistance in peripheral tissues are recognised as hallmarks of diabetes mellitus. This change progressively leads to a greater degree of glycemic variability ultimately resulting in hyperglycemia. The role of hyperglycemia in the generation of oxidative stress has been well established. Increased flux of glucose through polyol pathway, hexosamine pathway, formation of advanced glycation end products (AGEs) and activation of Protein Kinase C (PKC) contributes to the overproduction of free radicals [13]. There are considerable evidences to show that these biochemical pathways, when activated by hyperglycemia, are associated with the generation of reactive oxygen species (ROS), ultimately leading to increased oxidative stress. Mitochondrion lies at the intersection of critical cellular pathways such as energy substrate metabolism, ROS generation, and apoptosis. Several

studies have highlighted structural and functional abnormalities in the mitochondria of pancreatic β-cells of diabetic subjects, especially with increased expression of electron transport chain (ETC) complexes I and V [14]. Disintegration of mitochondrial network in pancreatic β-cells was documented in diabetic animal models. Hyperglycemia increases ETC derived ROS in pancreatic β-cells and contributes to decreased glucose stimulated insulin secretion. Thus, hyperglycemia induced mitochondrial dysfunction and generates free radicals that exhaust the endogenous antioxidant defences resulting in disruption of cellular function and causes oxidative damage to membranes and tissues. In particular, oxidative stress is specifically deleterious to β-cells as they express only low levels of antioxidants that eventually alter their number and function.

As abnormally high levels of free radical generation and oxidative stress underlie the cellular changes and development of insulin resistance, scavenging or neutralizing free radicals and enhancing endogenous antioxidant defence is a potential therapeutic approach in curtailing the progression of diabetes mellitus and its complications. In this context, administration of isopulegol to HFD/STZ induced diabetic rats significantly improved the activities of enzymic antioxidants viz., superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione sulfur transferase (GST) in the pancreatic tissue. Similarly isopulegol administration increased the levels of low molecular weight antioxidants, vitamin C, E and reduced glutathione (GSH) and curtailed lipid peroxidation suggesting its antioxidative property. The study also confirmed the cytoprotective role of isopulegol in experimental animals confirming its potential role in preventing oxidative stress related complications in diabetes mellitus.

Impaired glucose utilization in peripheral tissues arising from insulin resistance results in chronic hyperglycemia. In diabetes mellitus, to normalize blood glucose levels pancreas responds by producing large amounts of insulin. Pancreatic β-cells are professional secretory cells and therefore possess a well-developed endoplasmic reticulum (ER), where native polypeptides undergo folding, assembly, glycosylation, disulphide bonding and post translational modifications to form mature proteins [15]. Proper functioning of the ER is essential to cell survival and any alteration in the ER environment can affect the protein folding process resulting in the production of misfolded proteins. Accumulation of misfolded proinsulin beyond a certain threshold interferes with the normal intracellular transport of proinsulin, leading to diminished insulin production and hyperglycemia [16].

To recognize and remove misfolded proteins, ER has evolved numerous signaling pathways that monitor its protein folding capacity. An overload of improperly folded proteins elicits a response called unfolded protein response (UPR). β-cells under normal conditions are continuously exposed to low threshold levels of UPR signaling that play major roles in ER biogenesis and expansion of the ER network. In diabetic state chronic stimulation by glucose increases insulin demand and initiate UPR. β-cells cannot properly attenuate translation to match ER protein folding capacity and hence they suffer from deposition of unfolded insulin in the ER, resulting in the activation of stress sensory pathways. The major stress sensor is pancreatic endoplasmic reticulum kinase (PERK), a Tran's membrane signaling proteins that act as a central regulator of ER stress [17]. PERK gets activated through direct or indirect binding of unfolded proteins and plays an important role in β-cell damage. Thus pro insulin is a potential ER stressor that activate PERK signaling pathway. Activated PERK undergoes auto phosphorylation and activates its downstream targets eukaryotic initiation factor (eIF2) and activated transcription factor 4 (ATF4) that governs the expression of chaperon (CHOP) an important pro-apoptotic downstream effector molecule resulting in apoptosis. Thus activation of PERK signaling results in a sustained reduction of insulin synthesis resulting in β-cell loss and diabetes. It has been proposed that many key components of UPR are rich and attractive targets for pharmacological intervention. Recent evidences emphasize the beneficial effect of antioxidant molecules against the induction of ER stress. Isopulegol, being an antioxidant, significantly decreased the expression of stress sensor protein PERK and its downstream targets eIF2 and ATF4 in the pancreatic tissue of HFD/STZ induced diabetic rats [18]. This confirms that Isopulegol is efficient in curtailing ER stress in diabetic animals.

Conclusion

From this review, the therapeutic potential of Isopulegol in the prevention and treatment of peptic ulcer disease, convulsions and in the management of diabetes mellitus are evident. Further validation in particular, clinical trials to investigate detailed mechanisms, adverse effects, drug interactions are necessary before including them in clinical practice. From this review, the therapeutic potential of Isopulegol in the prevention and treatment of peptic ulcer disease, convulsions and in the management of diabetes mellitus are evident. Further validation in particular, clinical trials to investigate detailed mechanisms, adverse effects, drug interactions are necessary before including them in clinical practice.

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