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Original article

Ameliorative effect of borneol, a natural bycyclic monoterpene against hyperglycemia, hyperlipidemia and oxidative stress in streptozotocin-induced diabetic Wistar rats

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ABSTRACT

Diabetes mellitus is a major public health problem worldwide. Oxidative stress plays a pivotal role in the pathogenesis of diabetes as it is one of the inevitable outcomes of the cellular process. The present study aims to investigate the putative antihyperglycemic, antihyperlipidemic and antioxidant efficacy of a monoterpene borneol, in comparison with glibenclamide, a standard drug for therapy of diabetes. Diabetes was induced by a single intraperitoneal injection of 40 mg/kg body weight. The results of the present study showed a significant increase in the biochemical indices viz., fasting blood glucose concentration, glycated hemoglobin, urea, alanine aminotransferase, aspartate aminotransferase, malondialdehyde concentration, total cholesterol, triglycerides, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol and atherogenic index, with a significant decrease in body weight, plasma insulin, HOMA-β-cell functioning index, glycogen, high-density lipoprotein cholesterol and antioxidant enzyme activities, viz., superoxide dismutase, catalase and reduced glutathione in diabetic rats when compared to controls. In addition, histology of the normal architecture of pancreas was affected in diabetic rats when compared to controls. The results for the first time reveal that oral administration of borneol for thirty days significantly attenuated the above mentioned alterations near to controls. Therefore, it is suggested that borneol could be a potential therapeutic antidiabetic molecule of biological relevance.

1. Introduction

Diabetes is one of the major endocrine disorders of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels [2]. Diabetes is becoming the third “silent killer” of mankind, after cancer and cardiovascular diseases, because of its high prevalence, morbidity and mortality [3]. All over the globe, around 200 million people suffered from diabetes in 2010 and it is anticipated to reach 300 million by 2025 [4]. In spite of immense developments in drug discovery, the control of diabetes is problematic and represents a major challenge in the medical field [5]. Although insulin and synthetic oral hypoglycemic drugs such as thiazolidinediones, sulfonylureas, and α-glucosidase inhibitors currently used in clinical practice are associated with a number of serious undesirable side effects. Therefore, scientists have focused on herbal sources for innovative antidiabetic agents that retain the therapeutic efficacy and are devoid of side effects [6,7]. A medicinal plant, *Galega officinalis* led to the discovery and synthesis of metformin. Metformin exemplifies an efficacious oral hypoglycemic drug to treat diabetes and currently is on the list of WHO essential medicines [8].

Streptozotocin (STZ) is widely employed in experimental studies to induce diabetic models [9,10]. The STZ-diabetic rat serves as an excellent model to study the molecular, cellular and morphological changes in tissues during diabetes [11]. STZ [2-deoxy-2-(3-methyl-3-nitrosourea)-1-D-glucopyranose] is an antibiotic synthesized from a gram positive soil bacterium, *Streptomyces achromogenes*. After intraperitoneal or intravenous administration, STZ selectively accumulates in pancreatic islet β-cell via glucose transporter-2 and causes the alkylation of DNA [12]. The methylnitrosurea group of STZ alkylates DNA and liberates toxic amounts of nitric oxide, which inhibits aconitase activity both causing DNA damage which in turn induces the activation of poly-ADP ribosylation involved in DNA repair [13]. The

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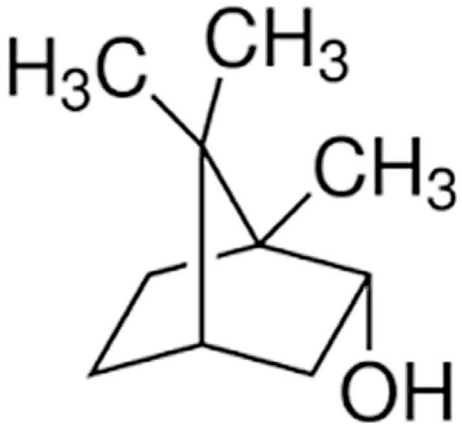

Fig. 1. Molecular structure of borneol.
IUPAC name: 1,7,7-Trimethylbicyclo [2.2.1] heptan-2-ol.
Molecular formula: $C_{10}H_{18}O$.
Molecular weight: 154.253 g/mol.

subsequent activation of poly-ADP ribosylation leads to depletion of cellular NAD+ and further reduction of ATP [14]. The enhanced ATP dephosphorylation supplies a substrate for xanthine oxidase resulting in the formation of superoxide radicals and thus increasing oxidative stress. In addition, STZ is a source of free radicals that might also contribute to DNA damage and subsequent cell death [15]. The key factor underlying the diabetogenic effect of STZ is free radical-generated β-cell destruction which is mediated through oxidative stress [16]. Since pancreatic β-cells possess low transcription rate and these cells seem to be more vulnerable to free radical attack when it is exposed to oxidative stress, thus causing low levels of antioxidant enzymes [17]. As a result of the STZ cytotoxic action, β-cells undergo partial destruction by necrosis, which reduces the β-cell mass, thereby subsequent inhibition of insulin synthesis and secretion [18].

Borneol (Fig. 1) is a bicyclic monoterpene alcohol, which occurs in essential oils of the numerous medicinal plants of the families from *Dipterocarpaceae* (e.g. *Dipterocarpus turbinatus*), Lamiaceae (e.g. *Rosmarinus officinalis* or *Salvia officinalis*), Valerianaceae (e.g. *Valeriana officinalis*) and Asteraceae (e.g. *Matricaria chamomilla*), etc. [19]. Borneol exerts a wide array of therapeutic properties such as radical scavenging properties [20], antioxidant and antimicrobial [21], antifungal [22], antiepileptogenic [23], antihypertensive and antioxidant [24], antithrombotic and antiplatelet [25], immunomodulatory [26], antinociceptive and anti-inflammatory [27], vasorelaxant effect on rat thoracic aorta [28], and neuroprotective effects [29]. Besides, borneol can accelerate the opening of the blood-brain barrier, improving the penetration and bioavailability of other drugs [30,31]. Administration of borneol protects primary rat hepatocytes against exogenous oxidative DNA damage [32]. Recently several monoterpenes have shown potent antidiabetic properties such as carvacrol [33], carvone [34], D-limonene [35], citronellol [36], thymoquinone [37,38], thujone [39], safranal [40], geraniol [41], myrtenal [42] and menthol [43]. To the best of our knowledge, there are no scientific reports on borneol as an antidiabetic molecule till date. In this regard, the current study aims to investigate the hypoglycemic potential of borneol by assessing their effects on biochemical indices, hypolipidemic activity and antioxidant enzyme status with their associated pathological changes in STZ-induced diabetic Wistar rat model.

2. Materials and methods

2.1. Chemicals

Borneol (99%) and STZ were purchased from Sigma-Aldrich (St. Louis, Missouri, USA). The diagnostic kits were supplied from Swemed Biomedicals Pvt. Ltd., Bengaluru, India for the estimation of biochemical parameters. All the other chemicals used in this study were of analytical grade obtained from standard commercial suppliers.

2.2. Experimental animals

The experimental procedures were conducted according to the ethical norms approved by Institutional Animal Ethical Committee (IAEC) of the University of Mysore (Approval number- **UOM/IAEC/18/2012**) and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines were followed for the treatment of animals. Adult male healthy albino rats of Wistar strain with a body weight ranging from 180 to 200 g were procured from the Central Animal House Facility, Department of Zoology, University of Mysore. The rats were acclimatized to the environment before the initiation of the experiment and maintained in an air conditioned room (25 ± 1 °C) with a 12-h light/12-h dark cycle. The rats were provided standard laboratory chow supplied by Amrit feeds Pvt. Ltd, Bengaluru and water *ad libitum*.

2.3. Experimental design

A total of thirty animals were divided into six groups, comprising a minimum of five animals in each group as follows.

Group I: Control
Group II: Vehicle control received 0.5% dimethyl sulfoxide (DMSO)
Group III: Diabetic control
Group IV: Diabetic rats received borneol (25 mg/kg body weight/day) dissolved in 0.5% DMSO
Group V: Diabetic rats received borneol (50 mg/kg body weight/day) dissolved in 0.5% DMSO
Group VI: Diabetic rats received glibenclamide (0.1 mg/kg body weight/day) dissolved in 0.5% DMSO

The oral intubation method was employed throughout the experimental period by using rat gavage to administer the borneol, glibenclamide and DMSO once in a day.

2.4. Experimental induction of diabetes

The experimental diabetes was induced in overnight fasted rats by a single intraperitoneal injection of STZ (40 mg/kg body weight) dissolved in a freshly prepared 0.1 M citrate buffer (pH 4.5). The animals injected with STZ exhibited hyperglycemia and the onset of diabetes was confirmed by measuring the elevated fasting blood glucose (FBG) 72 h after STZ injection. Rats with an FBG level above 250 mg/dL [33] were considered to be diabetic and selected for the experiment. The treatment of the diabetic rats was started on the fourth day after STZ injection. This was considered as the first day of treatment, and the treatment was continued for twenty eight days.

2.5. Assessment of body weight

The body weight was recorded of all the different groups before the commencement of the treatment period (0 day) is considered as initial body weight, also on weekly intervals and on the termination of treatment period (28^{th} day) is considered as final body weight.

2.6. Estimation of biochemical indices

At the termination of the treatment period, the rats were fasted overnight with free access to water and sacrificed by mild ether anaesthesia. The blood was collected from the carotid artery with and without anticoagulants for plasma and serum separation, respectively. The blood was centrifuged at 1000 rpm for 10 min and the separated serum was used for various biochemical analyses. Biochemical indices, especially FBG level was monitored at weekly intervals by glucometer