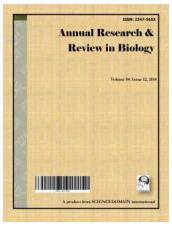

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The Protective Effects of Safranal against Diabetes Mellitus and Its Complications

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Authors' contributions

This work was carried out in collaboration between both authors. Author MS designed the study and wrote the draft of the manuscript. Author FB managed the analyses of the study and literature's search. Both authors read and approved the final manuscript.

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ABSTRACT

The increasing incidence of diabetes mellitus in all over the world is considered as a serious threat for human health. Oxidative stress is responsible for occurrence of diabetes by generation of oxygen free-radical, glycosylation of non-enzymatic protein, auto-oxidation of glucose, impaired glutathione metabolism, alteration in antioxidant enzymes, and formation of lipid peroxides. Oxidative stress also causes systemic inflammation, endothelial dysfunction, impaired secretion of pancreatic β cells and impaired glucose utilization in peripheral tissues. Recently, antioxidants have been focused as a therapy for diabetes. The present study has been designed to gather experimental *in vitro* and *in vivo* investigations on the anti-diabetic effects of safranal; however, the application has not fully understood. This review indicated the anti-diabetic effects of safranal related to its antioxidant and anti-inflammatory activities.

Keywords: Safranal; diabetes; oxidative stress; inflammation.

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1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease recognized by insulin deficiency or insulin resistance that induces chronic hyperglycemia and disturbed lipids, carbohydrates, and proteins metabolism [1-12]. Oxidative stress is a main factor in the development and progression of various diseases including of diabetes and its complications, while on the other hand, hyperglycemia generates free radicals, and it also disturbs the antioxidant defense system such as catalase, glutathione peroxidase and superoxide dismutase [8-15]. Anti-hyperglycemic drugs have main adverse effects and cannot always prevent diabetes complications [16-20]. Thus, alternative anti-diabetic medicine is needed due to its low risk beneficial effects [21-23]. The protective effects of natural antioxidants against chemically induced toxicities have been focused in recent years [4,24-27,5]. Antioxidant therapy may play great role for diabetic patients; therefore, it can be considered for treatment of oxidative stress in DM and may be good choices for diabetes therapy [28]. Phenolic compounds are natural antioxidants abundant in many plants such as saffron [29-33]. The antioxidant properties of medicinal plants are responsible for anti-diabetic activity [34-40]. However, there are many controversies on the role of antioxidant therapy for diabetic patients [40-43,32]. Thus, this review provides an overview of experimental studies on the biological activities of safranal, especially focusing on their anti-diabetics effect.

2. METHODS

Online literature resources were checked using different search engines such as Medline, Pubmed, Iran medex, Scopus, and Google Scholar from 2009 to 2017 to identify articles, editorials, and reviews about the anti-diabetic effects of safranal.

2.1 General Information of Safranal

Safranal ($C_{10}H_{14}O$) is one of the main ingredients of saffron which is produced from natural de-glycosylation of picrocrocin [39-41]. 60% of the volatile components of saffron is related to safranal [42]. Safranal, with molecular weight 150. 21 g/mol is the major volatile oil responsible for the aroma of saffron [43,32,44,14]. The stability of safranal is also dependent upon temperature, light and humidity on degradation of potency under storage conditions. Safranal should be stored under -20℃ and pharmacological activities as a supplement remain unaltered for at least 2 years or even longer [2,27,9,24,21].

2.2 Biomedical Findings of Safranal

Several studies have been indicated that safranal may be useful as a treatment for neurodegenerative disorders [5,7,12,3231,34], age-related diseases [42,43,1,3,4], cardiovascular diseases [36,37,38,35,39,40,41], respiratory failures [6], gastrointestinal diseases [8], renal failures, etc. In addition, antioxidant and anti-inflammatory activities of safranal have been recognized as main mechanisms involved in the occurrence and developments of diseases such as diabetes [11]. These findings were approved by other studies in which safranal had protective effects against tissue oxidative damage. It has been indicated that safranal has tumoricidal, anti-genotoxic, and anti-aging via modulating oxidative stress [13,16,17,18].

2.3 Anti-diabetic Effects of Safranal

Medicinal herbs and their active ingredients contain bioactive substances that act through antioxidants activities [6-8]. Recent studies have been indicated that safranal can affect hyperglycemia in a variety of *experimental* models [19,20]. One of the main mechanisms involved in the ani-diabetic effects of safranal is inhibitory effect on free radical production [22]. The radical scavenging activity of safranal is related to donate hydrogen atoms for 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical stabilization [2,27]. Safranal modulated antioxidant gene expression and upregulate mitochondrial anti-oxidant genes, leading to a lower mitochondrial oxygen radical generation, which may be responsible at least in part for the improved hyperglycemia, hyperlipidemia and oxidative stress in experimental diabetic model [30,9]. It was also reported that safranal may be effective in the treatment of diabetes by modulating of oxidative stress in STZ diabetic rats [23]. The antihyperglcemic activity of safranal was also confirmed in alloxan diabetic rats [25]. The findings of one study indicated that safranal may have anti-hyperglycemic effects without hepatic and renal toxicities in the alloxan-diabetic rats [27]. Based on these results, the protective effect of safranal on pancreas of diabetic rats might be related to its scavenging activity [25].

Diabetes mellitus usually induces lipid abnormalities by increasing free radicals generation, especially reactive oxygen species (ROS) [26,31]. Lipids when react with free radicals, they undergo peroxidation to form lipid peroxides [12,7]. The increase in the level of ROS in diabetes could be due to their increased production and/or decreased destruction by non-enzymic and enzymic catalase (CAT), reduced glutathione (GSH), and superoxide dismutase (SOD) antioxidants [12,32,2]. Several mechanisms such as modulatory effects on the oxidant-antioxidant system and inhibitory effect on pancreatic lipase have been suggested for the hypolipidemic effects of safranal [7]. In this regard, Samarghandian et al. indicated the stimulating effect of the formation of GSH. The GSH reacts with free radicals and is a crucial substrate for glutathione peroxidase (GPx) and glutathione-S-transferase (GST) which involve in the cellular defense mechanisms against intermediate oxygen products. The ratio of GSH/GSSG plays a main role in glucose homeostasis of diabetes because thiol groups are critical in intracellular and membrane redox state.45 Safranal induced an increase in serum GSH level, which might increase the GSH/GSSG ratio and decrease lipid peroxidation, and thus ameliorate serum glucose regulation [7]. Samarghandian et al. also indicated that safranal inhibits elevation of the serum lipid level by controlling oxidative and nitrosative systems. Lipids change to form lipid peroxides when it reacts with free radicals [7]. Samarghandian et al. also indicated that safranal might prevent the occurrence of atherosclerosis by reduction of serum NO content [23]. The effects of safranal on the inflammation in the STZ-diabetic with high-fat diet (HFD) have been studied. Results indicated that safranal decreased the inflammation both in the plasma and pancreas tissue, by decreasing the tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β levels. Additionally, safranal decreased the oxidative stress increased due to type 2 diabetes in the plasma and pancreas tissue [34]. Therefore, safranal is an effective agent for curing of arthrosclerosis by controlling lipid profile through correction of insulin resistance, oxidant-antioxidant system and inhibition pancreatic lipase [36].

3. CONCLUSION

This review suggested that the anti-diabetic effects of *safranal* may be related to the antioxidant and anti-inflammatory activities.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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