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Citrus peel extract and powder attenuate hypercholesterolemia and hyperglycemia using rodent experimental modeling

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ABSTRACT

Objective: To investigate hypocholesterolemic and hypoglycemic potential of citrus peel extract and powder using rodent experimental modeling.

Methods: Considering the fact, rat feeding trial was carried out for a period of 56 d to access the prophylaxis of citrus peel flavonoids by employing normal (study I), hyperglycemic (study II) and hypercholesterolemic (study III) rats. Each study was further divided into three groups to ensure the provision of selected diets, *i.e.*, control, functional and nutraceutical diets. Each study was further divided into three groups to ensure the provision of selected diets, *i.e.*, control, functional and nutraceutical diets.

Results: Declining trend for total cholesterol was observed in all studies with maximum reduction (8.55%) in rat group fed on nutraceutical diet in study III. Likewise, levels of low density lipoproteins and triglycerides reduced 11.39% and 7.89% respectively in hypercholesterolemic rats. Moreover, nutraceutical diet alleviated the sera glucose level by 8.96% in study II.

Conclusions: Conclusively, inclusion of citrus peel bioflavonoids in dietary therapies is a promising strategy to modulate lipidemic and glycemic attributes without imparting any deleterious effect on hematological parameters.

1. Introduction

Globally, emerging trends are shifting consumer's cognizance towards the peculiar role of food in diseases management such as cardiovascular complications, cancer, arthritis and diabetes. This veracity has made gap between food and drugs very narrow in curtailing the life associated ailments [1]. In this reverence, dietary tools place emphasis on the dynamic facets of phytonutrients as they put beneficial effects on human health [2]. Taking in account the current scenario, novel health strategies assenting to the supplementation of phytochemicals to curb the onset of chronic disorders are dominating. Epidemiological studies have proved a healthy connection between functional ingredients of food and well-being of vulnerable group of the people [3]. This has drawn the concept of functional and nutraceuticals components in food, which wield beneficial effects beyond basic nutrition [4]. Amongst these ingredients of food, plant based functional components are extensively being employed for ameliorating non-communicable diseases owing to their ease to access, safety, acceptability and low cost [5,6].

Citrus peel, a byproduct of food processing industry, has a wide array of nutraceutical moieties that play significant roles against various physiological threats. It was noticed that citrus peel (orange) is a rich source of phenolic compounds that include phenolic acids and flavonoids constituting 147.6 mg/g of dry orange peel [7]. There are more than 4 000 structural variants of flavonoids that have been identified and characterized for their prophylactic potential. Among them, citrus peel derived

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flavonoids and their metabolites are of prime importance in providing therapeutic effects against various health related disorders [8]. There are two important glycosylated flavanones in citrus peel, namely, narirutin and hesperidin. However, hesperidin is more imperative for its therapeutic effects [9]. Considering numerous varieties of citrus family, *Citrus sinensis* is the major source of hesperidin ranging from 6.98 to 10.80 mg/g dried matter [10]. Studies have revealed its pharmacological and biological viewpoints such as hypolipidemic, hypoglycemic and anti-inflammatory perspectives. Due to its ease in accessibility of fruits by-products, citrus peel is one of the cheap sources of polyphenols for value added and designer food products [11].

In developing countries, hyperlipidemia resulting from fluctuations in lipid homeostasis, is the leading cause of cardiovascular diseases or atherosclerosis. Many factors are involved in the maintenance of blood cholesterol level that effect both intracellular and extracellular cholesterol metabolism [12]. Two important enzymes, 3-hydroxy-3-methyl-glutaryl-CoA 3 reductase as well as acyl CoA: cholesterol *O*-acyltransferase, present in the body that regulate cholesterol synthesis and modulate triglyceride level [13]. In this context, citrus peel flavonoids have ability to influence vascular endothelial cells in experimental models of hypercholesterolemia. In most animal species including human, inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA reductase are effective in lowering plasma cholesterol level thus normalize both intracellular and extracellular cholesterol metabolism. Furthermore, acyl CoA: cholesterol O-acyltransferase is involved in catalysis of cholesterol esterification, hepatic secretion of very low-density lipoproteins, cholesterol absorption and its accumulation in vascular wall. Similarly, acyl CoA: cholesterol O-acyltransferase inhibitors are being used in cholesterol lowering drugs due to its hypocholesterolemic potential [14]. It is revealed from the previous data that hesperidin (0.08%) reduces weight of fatty tissues & liver, hepatic steatosis, retinol binding protein (involved in lipid metabolism) and total plasma cholesterol [15]. Among polymethoxylated flavones, nobiletin (0.1%) restored plasma and hepatic high density lipoproteins (HDL) cholesterol level with simultaneous decrement in hepatic triglycerides in diet induced hypercholesterolemic rats [16].

Diabetes is the most common metabolic syndrome related with expansion of coronary diseases. It is a multifunctional disorder that is characterized by hyperglycemia, abnormality in lipoproteins and increased oxidative stress due to which insulin secreting pancreatic beta cells become damaged [17]. Research has confirmed that polyphenolic and flavonoids rich diet has a potential to alleviate blood glucose level [18]. Substantial facts have divulged the role of citrus peel as an anti-diabetic agent by the reason of its strong antioxidant potential. The citrus peel allied bioflavonoids: hesperidin and nobiletin, attenuate hyperglycemic state by alleviating activities of phosphoenol pyruvate, glucose-6-phosphatase and α amylase whilst ameliorating glucokinase action and insulin secretion in blood [19]. Interestingly, citrus peels are considered as agro-waste material and are thought to impart negative impact by aggravating the legal boundaries and hygienic status of metropolitans. Nonetheless, their exploitation in dietary regimen will not only offer as source of cost effective and innovative generation therapeutics but also enhance nutritional value of conventional edibles [20].

2. Material and methods

2.1. Procurement of raw material and powder preparation

The research project was conducted in Functional and Nutraceutical Food Research Section, National Institute of Food Science and Technology, University of Agriculture, Faisalabad (UAF), Pakistan. Citrus (Orange) was procured from local market, Faisalabad, considering the quality attributes like uniformity in color, size, shape and abrasion free trailed by washing. For the efficacy study, diagnostic kits were purchased from Sigma–Aldrich, Bioassay (Bioassays Chemical Co. Germany) and Cayman Chemicals (Cayman Europe, Estonia).

Citrus peels were separated from fruits and sun dried followed by grinding to a fine powder using grinder. Resultant peel powder was stored for the extraction of biomolecules and bioevaluation trial.

2.2. Preparation of citrus peel extract

Citrus peel extract was prepared using water and methanol (50% v/v) for time interval of 45 min at 50 °C using the guidelines of Sultan *et al.* [21], with some modifications trailed by filtration and rotatory evaporation.

2.3. Efficacy study

A rodent trial was conducted to explore the therapeutic potential of the representative citrus peel based functional and nutraceutical diets against lifestyle related metabolic syndrome *i.e.* hypercholesterolemia and hyperglycemia. For the intent, 60 male Sprague Dawley rats were acquired from National Institute of Health, Islamabad, Pakistan and adjusted in the Animal Room of National Institute of Food Science and Technology, UAF. The animals were adapted by feeding the control diet for course of 7 d and by maintaining temperature (23 ± 2) °C and relative humidity 55% ± 5% throughout the trial. At the beginning, some of them were slaughtered to obtain baseline values. In rat modeling, three independent studies were executed separately; study I, study II and study III. Rats were fed with control diet, diet containing citrus peel powder and diet containing citrus peel extracts in control, functional diet and nutraceutical diet groups respectively in all three studies. Study I was consisted of rats fed on normal diet, whereas in study II & III, high glucose & cholesterol rich diets were employed, respectively. In each study, three groups of rats were formed depending on variations in their diets; control, functional and nutraceutical diets were used to assess its effect on different biological attributes like total cholesterol, HDL, low density lipoproteins (LDL), triglycerides, glucose and insulin level.

2.3.1. Ethical approval

Ethics approval was given by the head of the National Institute of Food Science and Technology, UAF, Pakistan, by reviewing the suggestions of Animal Experimentation Ethics Committee, UAF. Animal experiments were conducted in accordance with the instructions for the care and use provided by the committee and instructed by the university.

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