DOI: https://doi.org/10.54393/df.v4i03.78

DIET FACTOR
Journal of Nutritional & Food Sciences
https://www.dietfactor.com.pk/index.php/df
Volume 4, Issue 3 (Oct-Dec 2023)

Review Article

Potent Hypoglycemic Phytochemicals from Citrus

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ARTICLE INFO

Key Words:
Citrus, Diabetes, Naringenin, Metabolism, Hesperiden, Fruits

How to Cite:
Afzal, T., Bibi, Y., Mashwani, Z. ur R., Gilani, S. S., Naheed, N., Jabeen, A., & Afzal, R. N. (2023). Potent Hypoglycemic Phytochemicals from Citrus: Citrus for Diabetes. DIET FACTOR (Journal of Nutritional &Amp; Food Sciences), 4(03). https://doi.org/10.54393/df.v4i03.78

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Received Date: 8th September, 2023
Acceptance Date: 28th November, 2023
Published Date: 31st December, 2023

ABSTRACT

In particular, when it comes to the cure and management of chronic diseases, consuming a diet that contain natural products such as; plants is crucial for health promotion. Citrus fruit has been widely consumed and possess nutritional components that supports the management and cure of various disease conditions and the underlying metabolic changes that leads to development of long term serious diseases. Multiple citrus fruit species are analyzed for their curative effect particularly for the diseases that are associated with metabolic alterations such as diabetes, heart burn and dyspepsia. Diabetes is found to be effectively cured and allied health problems are managed by the use of citrus fruits and the specific secondary metabolites found in citrus fruits such has; hesperidin, naringenin and nobiletin. Citrus fruits primarily contain flavonoids, which have a number of advantageous properties for health promotion, especially anti-diabetic effects. Present review enlightened the specific curative potential of citrus fruits and phytochemicals on the living organisms, the potential anti-diabetic efficacy and the metabolic pathway of citrus bioactive compounds hesperidin and naringenin is explained. Mechanistic regulation of metabolic disturbances owing to various disease conditions that are root caused by diabetes are effectively done by the bioactive compounds of citrus fruits. Citrus fruits have matchless benefits when it comes the issues of hyperglycemia, while their antidiabetic effects and have ameliorative effect on diabetes related health problems remain to be verified in detail at molecular and clinical level in forthcoming studies.

INTRODUCTION

Phyto-therapeutics are safe alternatives to treat many acute and chronic diseases including diabetes, at traditional level remedies are prepared from plants to treat various disease [1]. Fruits are a vital part of the human diet because they consist of necessary nutritional components such as; amino acids, dietary fiber, lipids, carbohydrates, vitamins, and minerals [2]. Phenomenal medication efficacy of fruits of many Citrus species is reported and attributed to the presence of bioactive secondary metabolites [3]. Obesity, a prevalent element of the metabolic disorders in modern sedentary life styles, was the fifth most important causative background for death worldwide. Diabetes, chronic illnesses, ischemic heart disease, and cancer can all be brought on by obesity [4, 5]. A crucial energy providing molecule for carrying out typical functions of metabolic pathways and regulation of physiological reactions is glucose. The quantity of glucose in blood is typically controlled by glucose-regulating hormones like insulin and glucagon, which are released by the pancreatic beta- and -cells, respectively [6]. A collection of metabolic illnesses known as diabetes mellitus, a dangerous condition marked by long term hyperglycemia, the elevated level of glucose in blood. It is common throughout the world [7]. Chronic hyperglycemia is associated with several disorders like ketoacidosis, dysfunction, and failure of organs like the eyes, kidney,

DOI: https://doi.org/10.54393/df.v4i03.78

nerve, and heart [8]. One of the most dangerous side effects of diabetes mellitus is diabetic retinopathy (DR), which is also the main factor in vision loss and blindness in advanced countries. High levels of sugar in blood leads to health damage of eye as both the neuronal and vascular components of the retina that may occur by the given pathway Figure 1 [9, 10].

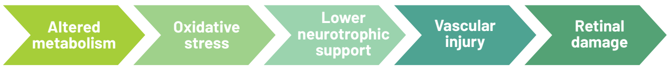

Figure 1: Process of retinal damage caused by Hyperglycemia

Diabetes has been now seen a global epidemic disorder due to more advancement in industrialization and increasing obesity in individuals. According to recent surveys it is predicted that diabetes will be increased from 4% in 1995 to 6.4% in 2025. By the year 2025 the most affected countries are predicted to be China, USA and India. No. of individuals suffering will be increased from 194 million to 380 million. Diabetes may largely classify into four classes. [11-13]. Drinking sugar-sweetened beverages increases the chance of acquiring chronic pathologies including type II diabetes mellitus and cardiovascular diseases, which can be avoided by consuming fruit juices and beverages, which are high in bioactive substances with known health advantages [14].

Potent Hypoglycemic Citrus Fruits

Fruits are a highly suggested food option because of their nutritional worth and health-improving properties. A significant source of carbohydrates that directly increase postprandial blood glucose and insulin response is fruit, which is another benefit. Fruits often have a low to medium GI (GI = 30 to 60 percent) [15]. Traditional medicine suggests citrus fruits as a treatment for diabetes [16]. Most common and widely available, citrus fruit belongs to the angiospermic family Rutaceae and contains significant amounts of helpful secondary metabolites [17, 18]. With 16 species, Citrus is a genus that includes a wide range of plant life forms. All across the world, citrus fruits are grown and eaten. Numerous citrus fruits, including bergamots, grapefruits, lemons, limes, mandarins, oranges, and pomelos, contain flavonoids. Flavones, flavanones, flavonols, isoflavones, anthocyanidins, and flavanols are some of the flavonoids found in citrus [19, 20]. Citrus fruits (orange, tangerine, and grapefruit) have low glycemic index, 10 per 100 mg. A reduced incidence of gestational diabetes mellitus was seen when fresh fruit was consumed. The 1-h and 2-h plasma glucose readings fell by 0.050 mmol/L (95 percent confidence interval [CI] -0.081 to -0.019) and 0.035 mmol/L (95 percent CI] -0.059 to -0.012), respectively, when the overall consumption of fruit is increased by 100g [21]. Citrus fruits are excellent source of high quantity of Myo-inositol content that is proved effective to reduce levels of high blood glucose in the people diagnosed with Gestational Diabetes Mellitus [22]. Naringenin and gallic acid are found in *C. aurantium* fruit residues that have inhibitory effects on α-glucosidase and α-amylase at the effective concentration of 332 μg/mL. Aqueous Ethanol extract of fruit peel was loaded with phenolocs and flavonoids, hence control/repress post-prandial hyperglycemia [23]. *Citrus sinensis* (L.) Osbeck's Moro variety of blood oranges are grown because, when grown at low temperatures, high levels of anthocyanins, ascorbic acid, and hydroxycinnamic acids have been reported. These chemical elements may regulate a variety of physiological processes, including body mass regulation [24]. Different parts of *C. paradisia* are known to have low glycemic index which support the effectiveness of plant for curing diabetic complications and reducing elevated blood sugar level [25]. Targeted pharmacological potentials of different citrus species are well-known as explained in Table 1.

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Table 1: Proximate analysis of beet root powder

Citrus Species	Plant Part	Experimental Model	Effective Dose	Pharmacology	Reference
C. reticulata	Immature Fruit	Adult Human		Metabolize fat by adipogenesis	[26]
C. sudachi	Peel extract	Japanese People		Improve the ratio of visceral fat to subcutaneous fat	[27]
C. aurantifolium	Aqueous Fruit extract	Alloxan induced Diabetic rat	Garlic + C. aurantifolium 150 mg\kg	Improved Insulin level	[28]
C. japonica	Fruit powder	Diabetic rat	6% fruit powder	Hypoglycemic effect, improve thyroid hormones	[29]
C. maxima	Leaf extracts	Albino diabetic mice	Ethanol Extract of C. Maxima Leaves 200 mg/kg BW	Improve complications of DM associated with oxidative damages	[30]
C. aurauntifolia	Aqueous extract of Limes and lipton tea	Albino rats	2ml/kg body weight	Ameliorate hyperglycemia	[31]
C. maxima	Fruit segment, juice	STZ induced diabetic rats	Paranthas containing 7.5% of fruit segment and 7 g/kg	improving the enzymes involved in phosphorylation of glucose	[32]
C. sinensis	Fruit juice	Obese and diabetic rats	200 mL of pure Moro orange juice/day	Decrease body mass and improve biochemical profile	[24]
C. reticulata	Fruit juice	Fat Diet Feed Rats	High Fat + Mandarin juice	improve mitochondrial membrane potential, reduced visceral adipose tissue	[33]
C. clementina	Fruit juice	Fructose fed rat	Citrus concentrate enriched with β-cryptoxanthin, hesperidin and pectin	glucose tolerance, dyslipidemia and blood pressure	[34]
C. aurantifolia	Fruit peel methanol extract	Alloxan induced diabetic rats	28 days, 41% reduction in glucose	Anti-hyperglycemic effect	[35]
C. aurantifolia	Fruit extract	Aldose reductase and sorbitol dehydrogenase inhibitory assay	138.66 and 47. 21µg/mL	Inhibition of aldose reductase and sorbitol dehydrogenase	[36]
C. reticulata	Fruit peel hydroethanolic extract	Type 2 Diabetic Wistar Rats	100mg/kg b.w./day	improved glucose tolerance, decreased elevated liver lipid peroxidation	[37]
C. maxima	Peel extract	Alloxan induced diabetic Rat	600 mg	70% decrease in blood glucose level	[38]
C. bergamia	Nutraceutical containing Polyphenol Fraction and Cynara Cardunculus extract	liver steatosis patients	300 mg/day	78% Reduction in liver fat content	[39]
C. limon	Peel oil	Diabetic Rat		Diabetes-induced Ulcer treatment	[40]
C. aurantium	Peel ectract	Mice		reducing plasma total cholesterol (TC) and triglyceride (TG) levels	[41]
C. reticulata	Alkaloids			downregulating inflammatory cells growth, immunoglobulin, and cytokines	[42]
C. maxima	Peel	Alloxan induced diabetic Rat		Prevention of oxidative stress	[43]
C. pomace	Water extract	Vero cells and zebrafish		Protects against oxidative damage	[44]

Therapeutic Efficacy of Citrus Phytochemicals

According to global statistics, majority of the world population depends largely on herbal medicines and ethnobotanical treatments, such as the antidiabetic allicin. Terpenoids, alkaloids, and phenolics are the three categories into which secondary metabolites have been categorized based on the biological effects they have been found to have. With more than

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40,000 compounds, terpenoids are the plant metabolites that consist of highest diversity, whereas phenolics comes next to terpenoids and make up close to 8000 chemicals [45]. Plants are the source of 40% drug formulations [46]. The four primary kinds of diabetic neuropathy are mononeuropathy, diabetic polyradiculopathy, autonomic neuropathy, and peripheral neuropathy. Diabetes neuropathy affects 50% of diabetic individuals (Focal neuropathy). In type 1 diabetes, glucose management significantly slows the development of neuropathy; however, herbal treatments for type 2 diabetes show less success in this regard. Hesperidin's antioxidant, anti-inflammatory, and anti-glycation capabilities are proven to be useful in treating diabetic neuropathy [47]. In diabetic animal models, quercetin, a main flavonoid present in citrus fruits, particularly in fruit peels, was known to exhibit anti-diabetic effects at doses of 10, 25, and 50 mg/kilogram body weight (kg b.w.) [48]. It is a glycone of rutin, and it is present in a number of various flavonoids as a central component [49]. It has also been demonstrated that citrus flavonoids exhibit DPP-4 inhibitory activity, with rutin being the most potent inhibitor with an IC50 of 485 M. Orange peel contains a lot of naringin, which has been demonstrated to inhibit DPP-4 in vitro and in vivo as well as to increase levels of insulin. As a result, it is thought to be a potential low-cost treatment for diabetes [50, 51]. The therapeutic values of some prominent citrus phytoconstituents, viz., Flavonoid, Flavanone, Phenol, Flavonoid glycoside and Polymethoxyflavanone [52] are discussed below in Table 2.

Table 2: Pharmacological Potential of Citrus Bioactive Compounds

Class of Secondary Metabolite	Citrus Bioactive Compound	Experimental Model	Pharmacological Potential	Reference
Flavonoid	Hesperiden	Human	Improve inflammatory and oxidative stress	[53]
Flavonoid	Naringeen	Rat	Improve Glucose Tolerance	[29]
Polymethoxyflavone	Nobiletin	Rat	Oxidative stress diminution	[54]
Phenol	Chlorogenic acid	Streptozotocin induced diabetic rats	Reduce diabetes related cardiovascular risks	[55]
Flavonoid	Novel Nano-Hesperidin	Diabetic rats	Enhance insulin production from β-cells	[56]
Flavanone	Naringenin	Diabetic mice	Decreased blood glucose level	[57]
Flavanone	Naringenin	Mice	Diabetic Nephropathy	[58]
Flavonoid glycoside	Didymin	HepG2 Cells	Inhibition of Aldose Reductase	[59]
Flavonoid	Hesperidin	Rat	Lowering of blood glucose level	[60]
Flavanone	Hesperidin	retinal pigment epithelial cells	Improved CAT, GSH, SOD levels, glutathione peroxidase activities and cell viability	[61]
Flavanone	Naringenin	STZ treated diabetic rats	Increased GSH, Bcl-2, TrkB, BDNF and synaptophysin levels	[9]
Flavonoid	Chrysin	Hyperglycemic goat lens	Anti-cataract activity	[62]

Mechanism of Action of Citrus Bioactive Constituents

Flavonoid

1. Hesperidin

Peels of *C. reticulata* fruit have been shown to be highly concentrated with the phytoconstituents of flavanones group and hesperidin is among the predominant bioactive compounds [63]. Citrus peel is enriched with important phytochemicals such as flavonol and quercetin [64]. Advanced characterization protocols revealed the presence of hesperidin in *C. reticulate* hydroethanolic fruit peel extract. Elevated serum glucose levels were observed in NA/STZ-induced diabetic rats so these rats were used in Oral Glucose Tolerance Test (OGTT) for testing antihyperglycemic efficacy of hypoglycemic agents. Following actions are mediated by the tested compounds and plant extract as shown in Figure 2;

- The hydroethanolic fruit peel extract from C. reticulate is more effective than any of the individual phytochemicals at enhancing OGT and lowering the level of elevated fructosamine.
- Homeostatic model assessment (HOMA) of insulin resistance (IR), insulin sensitivity (IS), and β-cell function showed that treatment of diabetic rats with C. reticulate fruit peel extract, hesperidin, and quercetin successfully promoted working efficiency of cellular components even under stressful conditions of disturbed metabolism.
- Similar to this, the tested substances and peel extract caused a notable rise in liver glycogen content together with a significant decrease in the activity of the liver enzymes G-6-pase and glycogen phosphorylase. These enzymes work in the liver and muscles to activate glycogen synthetase while inhibiting glycogen phosphorylase [37].

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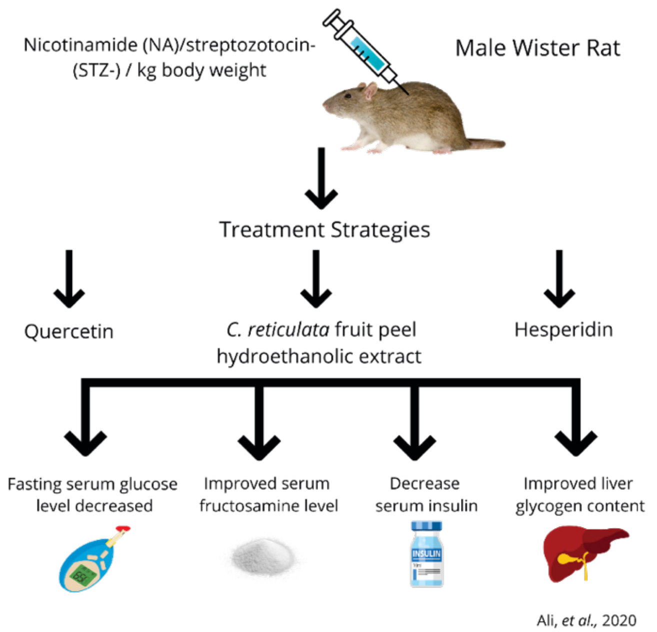

Figure 2: Metabolic improvements in diabetic rat treated with Citrus fruit extract and phytochemicals[37]

Hesperidin is considered useful to treat cognitive deficit but the low bioavailability makes its restricted to be used for the treatment of dementia. Because of their low toxicity and biocompatibility, gold nanoparticles are a perfect mechanism of drug translocation for the brain. So hesperidin gold nanoparticles (HSP-AuNPs) were synthesized and tested at diabetic in-vivo rat model for the purpose of analyzing potential and targeted effects of HSP-AuNPs on the ability of memory boost up as shown in Figure 3. Nanoparticles increased the bioavailability thus showed significant anti-oxidant and have protective function on various organs[65].

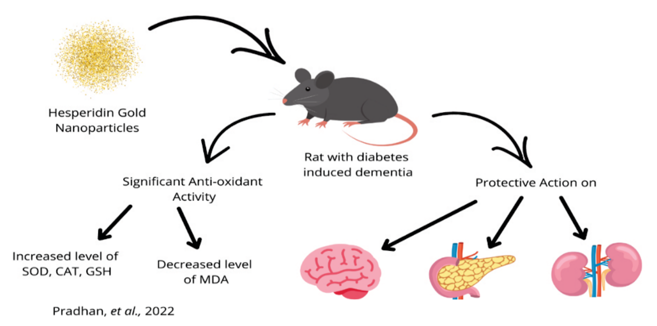

Figure 3: Efficacy of Hesperidin Nanoparticles in reversing damages of different organs in memory impaired rat[65]

2. Naringenin

It belongs to the flavanones of the class flavonoids. Hyperglycemic nephrotoxicity occurs when the normal functioning of Endoplasmic reticulum (ER) is not maintained. To regulate kidney physiology efficiently in diabetic patients, an important citrus flavonoid has great importance. ER dysfunctioning in kidneys of diabetes induced model rats is maintained by using Naringenin. The translational regulations occur by the several changes at the molecular level such as activation of marker proteins that alter the integrity of ER. Some of these proteins are ER protein kinases, initiation and transcription factors in diabetic kidneys that exhibited initiation of ER stress response due to damaging changes in nephrons. Along with all these proteins synthesis and activation of targeted transcription factors, modifications at structural level in the ER of hyperglycemic renal cells is controlled by Naringenin that ultimately assures that it has anti-ER stress potential as given in Figure 4[66].

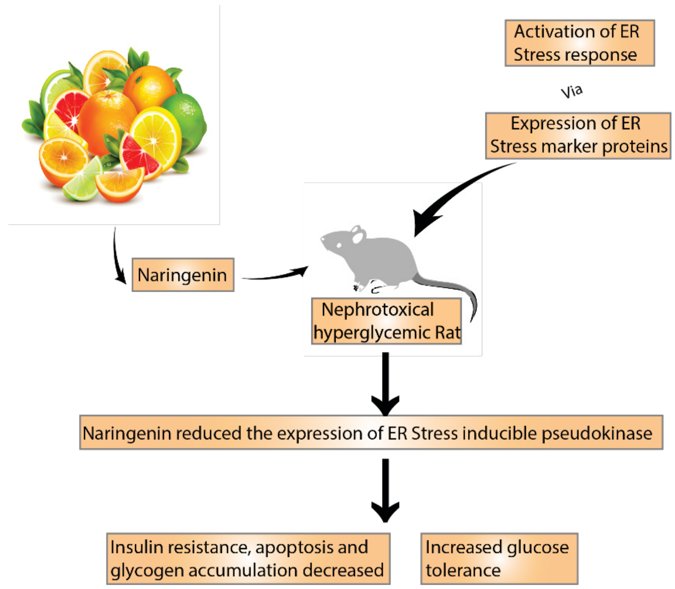

Figure 4: Hypoglycemic effect of Naringenin[66]

CONCLUSIONS

The usefulness of citrus fruit in traditional medicine and the pharmacy industries was covered in the current review, along with the therapeutic relevance of citrus fruit for the treatment of diabetes. It is widely appreciated that citrus fruits have health promoting abilities and it is attributed to the existence of valuable group of secondary metabolites flavonoids (hesperidin, naringenin, didymin) limonoids, alkaloids, essential oil and pectin. The beneficial nature of citrus fruits are most likely due to the flavonoids. Hesperidin, a predominant part of citrus metabolic chemistry, gives citrus a place to stand in pharmacology and it has shown protective effect against many diseases, such as diabetes, hypertension, cancer, inflammatory and other chronic diseases caused by oxidative stress. The therapeutic and medicinal value of the citrus fruit is high and it is in limelight for the search of targeted compound for the relief of diabetic complications. Citrus fruit as a whole and also the secondary metabolites of citrus are well

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known for the cure and management of disease symptoms related to diabetes and associated health problems. For the betterment of the diabetes treatment, there is a need to encourage the usage and research exploration of active compounds for diabetes.

Authors Contribution

Conceptualization: TA, YB, ZURM
Writing-review and editing: SSG, NN, AJ, RNA, TA
All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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