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 avonoids, 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 benets 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.

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


*Corresponding Author:
Tayyiba Afzal
Department of Botany, PMAS Arid Agriculture University, Rawalpindi, Pakistan
tayyibaafzal3@gmail.com

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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,
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 100 g [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 phenolics 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. paradisi 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.
<table>
<thead>
<tr>
<th>Citrus Species</th>
<th>Plant Part</th>
<th>Experimental Model</th>
<th>Effective Dose</th>
<th>Pharmacology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. reticulata</em></td>
<td>Immature Fruit</td>
<td>Adult Human</td>
<td></td>
<td>Metabolize fat by adipogenesis</td>
<td>[26]</td>
</tr>
<tr>
<td><em>C. sudachi</em></td>
<td>Peel extract</td>
<td>Japanese People</td>
<td></td>
<td>Improve the ratio of visceral fat to subcutaneous fat</td>
<td>[27]</td>
</tr>
<tr>
<td><em>C. aurantifolium</em></td>
<td>Aqueous Fruit extract</td>
<td>Alloxan induced Diabetic rat</td>
<td>Garlic + C. aurantifolium 150 mg/kg</td>
<td>Improved Insulin level</td>
<td>[28]</td>
</tr>
<tr>
<td><em>C. japonica</em></td>
<td>Fruit powder</td>
<td>Diabetic rat</td>
<td>6% fruit powder</td>
<td>Hypoglycemic effect, improve thyroid hormones</td>
<td>[29]</td>
</tr>
<tr>
<td><em>C. maxima</em></td>
<td>Leaf extracts</td>
<td>Albino diabetic mice</td>
<td>Ethanol Extract of C. Maxima Leaves 200 mg/kg BW</td>
<td>Improve complications of DM associated with oxidative damages</td>
<td>[30]</td>
</tr>
<tr>
<td><em>C. aurantiifolia</em></td>
<td>Aqueous extract of Limes and lipton tea</td>
<td>Albino rats</td>
<td>2ml/kg body weight</td>
<td>Ameliorate hyperglycemia</td>
<td>[31]</td>
</tr>
<tr>
<td><em>C. maxima</em></td>
<td>Fruit segment, juice</td>
<td>STZ induced diabetic rats</td>
<td>Paranthas containing 7.5% of fruit segment and 7 g/kg</td>
<td>Improving the enzymes involved in phosphorylation of glucose</td>
<td>[32]</td>
</tr>
<tr>
<td><em>C. sinensis</em></td>
<td>Fruit juice</td>
<td>Obese and diabetic rats</td>
<td>200 mL of pure Moro orange juice/day</td>
<td>Decrease body mass and improve biochemical profile</td>
<td>[24]</td>
</tr>
<tr>
<td><em>C. reticulata</em></td>
<td>Fruit juice</td>
<td>Fat Diet Feed Rats</td>
<td>High Fat + Mandarin juice</td>
<td>Improve mitochondrial membrane potential, reduced visceral adipose tissue</td>
<td>[33]</td>
</tr>
<tr>
<td><em>C. clementina</em></td>
<td>Fruit juice</td>
<td>Fructose fed rat</td>
<td>Citrus concentrate enriched with β-cryptoxanthin, hesperidin and pectin</td>
<td>glucose tolerance, dyslipidemia and blood pressure</td>
<td>[34]</td>
</tr>
<tr>
<td><em>C. aurantiifolia</em></td>
<td>Fruit peel methanol extract</td>
<td>Alloxan induced diabetic rats</td>
<td>28 days, 41% reduction in glucose</td>
<td>Anti-hyperglycemic effect</td>
<td>[35]</td>
</tr>
<tr>
<td><em>C. aurantiifolia</em></td>
<td>Fruit extract</td>
<td>Aldose reductase and sorbitol dehydrogenase inhibitory assay</td>
<td>138.66 and 47.21µg/mL</td>
<td>Inhibition of aldose reductase and sorbitol dehydrogenase</td>
<td>[36]</td>
</tr>
<tr>
<td><em>C. reticulata</em></td>
<td>Fruit peel hydroethanolic extract</td>
<td>Type 2 Diabetic Wistar Rats</td>
<td>100mg/kg b.w./day</td>
<td>Improved glucose tolerance, decreased elevated liver lipid peroxidation</td>
<td>[37]</td>
</tr>
<tr>
<td><em>C. maxima</em></td>
<td>Peel extract</td>
<td>Alloxan induced diabetic Rat</td>
<td>600 mg</td>
<td>70% decrease in blood glucose level</td>
<td>[38]</td>
</tr>
<tr>
<td><em>C. bergamia</em></td>
<td>Nutraceutical containing Polyphenol Fraction and Cynara Cardunculus extract</td>
<td>liver steatosis patients</td>
<td>300 mg/day</td>
<td>78% Reduction in liver fat content</td>
<td>[39]</td>
</tr>
<tr>
<td><em>C. limon</em></td>
<td>Peel oil</td>
<td>Diabetic Rat</td>
<td></td>
<td>Diabetes-induced Ulcer treatment</td>
<td>[40]</td>
</tr>
<tr>
<td><em>C. aurantium</em></td>
<td>Peel extract</td>
<td>Mice</td>
<td></td>
<td>reducing plasma total cholesterol (TC) and triglyceride (TG) levels</td>
<td>[41]</td>
</tr>
<tr>
<td><em>C. reticulata</em></td>
<td>Alkaloids</td>
<td></td>
<td></td>
<td>downregulating inflammatory cells growth, immunoglobulin, and cytokines</td>
<td>[42]</td>
</tr>
<tr>
<td><em>C. maxima</em></td>
<td>Peel</td>
<td>Alloxan induced diabetic Rat</td>
<td></td>
<td>Prevention of oxidative stress</td>
<td>[43]</td>
</tr>
<tr>
<td><em>C. pomace</em></td>
<td>Water extract</td>
<td>Vero cells and zebrafish</td>
<td></td>
<td>Protects against oxidative damage</td>
<td>[44]</td>
</tr>
</tbody>
</table>

**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 anti diabetic 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
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

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

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. reticulata* 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. reticulata* 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. reticulata* 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].
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 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. Naringenin reduced the expression of ER Stress inducible pseudokinase. Insulin resistance, apoptosis and glycogen accumulation decreased. Increased glucose tolerance.

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

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