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Antidiabetic and antihyperglycemic effect of citrus

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***Abstract*---**The tangerine fruit peels of Citrus reticulata contain significant amounts of three flavanones: hesperidin, naringin, and narirutin. Citrus is a rue group species of blooming trees and shrubs. In contrast to flavonol and quercetinRutaceae, citrus peel complex compounds quantities of flavonol and quercetinRutaceae. DM is one of most chronic diseases in the world. Citrus reticulata is a kind of citrus fruit with a various degrees of Hesperidin, a glycosylated flavanone of hesperetin, suppresses gluconeogenic pathways and diminishes intestinal glucose absorption in diabetes patients, leading in anti-hyperglycemic properties. Recent research looks into the efficacy of naringin to improve cholesterol levels by reducing HMGCoA reductase. Citrus sinensis, Citrus paradisi, and their combination have antihyperlipidemic and antiatherosclerosis properties. Hyperlipidemia is a collection of disorders characterized by elevated blood levels of lipids and lipoproteins, such as cholesterol, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), which can lead to atherosclerosis. Atherosclerosis and coronary heart disease (CHD) are the leading causes of death and sickness around the world.

***Keywords*---**citrus, chemistry citrus, pharmacological profile, diabetes mellitus, anti-diabetics effect, hyperlipidemia, anti-hyperlipidemia effects.

Introduction

Citrus is a genus of flowering trees and shrubs that belongs to the Rutaceae family of plants. Citrus fruits are produced by plants in the genus, which include major crops such as lemons, oranges, grapefruits, pomelos, and limes. South Asia, East Asia, Southeast Asia, Melanesia, and Australia are all home to the Citrus genus. Since ancient times, indigenous societies in these places have used and domesticated a variety of citrus species. The Austronesian expansion (c. 3000–1500 BCE) spread it to Micronesia and Polynesia, then to the Middle East and the Mediterranean (c. 1200 BCE) via the incense trade route, and finally to Europe. (Terol, *et al …,* 2018) (Fuller *et al …,*2017) *(*Zech-Matterne *et al …,2017)* (Langgut, 2017).

Citrus is a large collection of plants of the Rutaceae family, subfamily Aurantioideae, that belong to the Rutaceae family. Their commercial value is considerable, and their fruits, which are high in vitamin C, are used to make juices, wedges, preserves, jellies, and jams, as well as by-products for cosmetic and therapeutic purposes. (Nicolosi *et al ….,* 2005) (Inglese, and Sortino ., 2019).

Bitter orange, Citrus aurantium L. (Rutaceae), is a flavouring and acidifying compound commonly used in food (Karabıyıklı *et al ….,* 2014). In contrast to the active ingredient and its elements, the fruits of C. aurantium contains flavonoid-like substances with a number of pharmacological properties. According to the observations, flavonoid glycosides have also been found in the plant (Park *et al …,* 2014) . AS indicated by the data Biogenic amines and flavanones levels has also been identified. For its abundance of health-promoting secondary metabolites, C. aurantium is used to treat a wide range of disorders, such anxiety, lung and prostate cancers, gastrointestinal disorders, and obesity. C. aurantium has emerged as a viable replacement to Ephedra sinica Stapf.-containing rapid weight loss products on the market, as it contained psynephrine, a phenylethanolamine class alkaloid that is chemically similar to adrenergic drugs as a depressant (Suntar *et al ..,* 2018). Citrus is a tropical Asian plant native to everyone tropical and subtropical regions of the world. It's a common plant has a multitude of purposes in the treating a wide variety of problems. The most active biological substances in Citrus plants are flavonoids, specifically hesperidin and naringin, and alkaloids, particularly synephrine, which have significant medical impacts on human health. Its essential oil is often used in perfumes and cuisines. Citrus aurantium is also employed in herbal medicine as a stimulator and appetite reducer. It's also used to relieve nausea, indigestion, and constipation in traditional Chinese medicine, as well as cancer, cardiovascular effects, and sedative effects. The theory that bitter orange can substitute the banned ephedra stimulation even without negative effects of ephedra is what has made it popular. As a result, C. aurantium is a prominent weight-loss compound appear in a number of diet pills and fat-burning products. In "ephedra-free" herbal weight-loss remedies, nutritional supplements businesses have replaced bitter orange for ephedra. There is currently little proof that bitter orange is safer to use than ephedra, according to the National Center for Complementary and Alternative Medicine. It's simple to obtain and somewhat safe (Pellati *et al,*. 2002)

Chemistry composition

C. aurantium's chemical structure is fundamental for its health-promoting abilities. Vitamins, minerals, phenolic chemicals, and terpenoids build up the chemical profile (Khan *et al ..,* 2018). Flavonoids from the phenolic family have been identified as key chemical components in C. aurantium due to their physiological and pharmacological roles, as well as their health advantages. Flavones, flavanones, flavonols, and anthocyanins are the four different types of flavonoids found in C. aurantium (only in blood oranges) Citrus fruits mostly contain glycosyl derivatives of flavonoids. Aglycones are mostly found for certain parts of the fruit, such as with the peel and seeds, because to their lipophilic nature and hence limited water solubility (Khan , Nabavi *et al ..,* 2018). Flavanones are most numerous flavonoids discovered in C. aurantium. The most popular type flavanones reported are hesperidin 4′-methoxy-3′,5,7-trihydroxyflavanone and naringenin 4′,5,7-trihydroxyflavanone (Lee *et al ..,* 2015) . Hesperidin and naringenin are aglycones and/or glycosides having contain a structure with two hydroxyl groups in positions C-5 and C-7. (Jayaprakasha *et al ..,* 2008). The most widely distributed glycosides are hesperidin and neohesperidin, which are conjugates with rutinose and neohesperidose, alternately, but the most prevalent glycosyl analogues are naringin : naringenin-7-neohesperidoside and narirutin : naringenin-7-rutinoside (Lee *et al ..,* 2015) . The total polyphenol amount of peeled lemons and their peels is significantly greater than that of peeled oranges and grapefruit peels, according to numerous studies. Additionally total phenolics and total flavonoid percentages in the skin of all citrus fruits were still much larger than in the pulp, confirming previous findings (Guimarães *et al ..,* 2010).

Citrus peels have indeed been explored in detail , since they contain a broad range of biologically active molecules, such as : natural antioxidants like phenolic acids and flavonoids. Flavonoids, the most abundant phenolic chemicals are plentiful in citrus fruits. Peels contains ten times the amount of flavonoids present in juice. Flavone glycosides, as well as many other limited flavonoids such methylated flavones, flavone glycosides, and anthocyanin's, have been the most numerous. Fruit and citrus juice consumption has already been intensively explored for its potential involvement in boosting human health and illness management. These potential benefits are mostly due to flavones, polyphenols abundant in citrus (Mertz *et al ..,* 2009) (Khan and Dangles ., 2014) .

Pharmacological Profile and Applications Citrus

Therapeutically effective in application of different diseases includes : Anti-hyperlipidemia; Anti-hyperglycemic Activity; Antioxidant Effects ; Anxiolytic and Sedative effects; Effect on Microorganisms (Antimicrobial activity) ; It aid in digestion and relieves flatulence (Antiulcer Effects) ; Effects on the Cardiovascular System ; Cytotoxic and Anticancer Effects; Pesticides Effects ; Cosmetic uses. (Favela-Hernández *et al ..,* 2016) (Feitosa , *et al ..,* 2017) (Parham *et al ..,* 2020).

Anti-Diabetics Effect

DM is a heterogeneous group of syndromes characterized by the elevation of glucose levels due to a relative or absolute deficiency of insulin frequently inadequate insulin release is complicated by excess glucagon release lead disorders with carbohydrate, lipid, and protein metabolism, makes diabetes mellitus (DM) one of the most common diseases in the world. The American Diabetes Association identifies type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes (GDM), and many others types of diabetes (ADA). In humans, T2DM is actually more prevalent than T1DM, accounting for 90% of all forms of diabetes. T2DM is influenced by a mixture of insulin resistance and tissue insulin sensitivity, as well as pancreatic cell dysfunction (Mahmoud *et al* . ,2015). Insulin resistance is a characteristic of T2DM and is characterized by insulin receptor and/or postreceptor disorder. As a result of this impairment, glucose, lipid, and protein metabolism are all inhibited. T2DM patients have also increased hepatic glucose production, insulin insensitivity in skeletal muscle and adipose tissue, or a mixture of the two, as well as long-term persistent inflammation, all of which disrupt blood glucose control and contributes to the emergence of damaging metabolic disorders (DeFronzo *et al ..,* 2015) Long-term hyperglycemia in diabetics is associated with chronic malfunctioning of various organs (Giri, *et al ..,* 2018) Citrus reticulata , commonly described as : tangerine fruit peels, has significant amounts of three flavanones: hesperidin, naringin, and narirutin. Citrus peel also contains significant amounts of flavonol and quercetin (Puri *et al ..,* 2012) . Hesperidin, a glycosylated flavanone of hesperetin, diminishes intestinal glucose absorption and reduces gluconeogenic mechanisms, contributing in anti-hyperglycemic properties in diabetic people, thus according to Constantin et al. and Parhiz et al. (Constantin, *et al …,* 2014)

Vitamin C, flavonoids, phenolic chemicals, and pectin are all abundant in oranges. Hesperidin, narirutin, naringin, and eriocitrin are the most common flavonoids found in citrus. Citrus fruit peels include flavonoids such as hesperidin and naringin, which have anti-diabetic properties. It inhibits glucose-6-phospate and phosphoenol pyruvate activity. Orange peel's anti-diabetic properties appear to be mediated through anti-peroxidation, suppression of the a-amylase enzyme, which converts complex carbs to glucose, increased hepatic glycogen content, stimulation of insulin secretion, and repair of pancreatic b-cell secretory abnormalities. .(Abdelbaky *et al ..,* 2009)

Furthermore, active substances such as flavonoids and phenolic contents were responsible for both anti-diabetic and anti-hypercholesterolemia effects. Vitamin C, flavonoids, phenolic chemicals, and pectin are all found in abundance in orange fruits. Hesperidin, narirutin, naringin, and eriocitrin are the most common flavonoids found in citrus. (Guarnieri *et al ..,* 2007) (Ebrahimzadeh *et al ..,* 2010). Citrus fruit peels include flavonoids such as hesperidin and naringin, which have anti-diabetic properties. The activity is mediated by increased insulin levels in the blood, which has a direct or indirect influence on the improvement of pancreatic beta cells, as observed for other medicinal plant extracts. (Rama and Singh, 2006)

Pectin in orange fruit peel, according to Lallan and Shyam, can lower cholesterol levels in the blood and blood glucose levels. Hesperidin and naringin were the active chemicals that corresponded to the sample's anti-diabetic and anti-hypercholesterolemia properties. By inhibiting HMG-CoA reductase and acetyl-coenzyme A acetyltransferase, naringin and hesperidin considerably lowered cholesterol and triglyceride levels, according to Bok et al. Citrus fruits, according to a recent WHO report, protect against cardiovascular disease by lowering homocysteine levels. Vitamin C, carotenoids, and flavonoids, all found in oranges, have cardiovascular-protective properties. Limonene is responsible for the orange's cholesterol-lowering impact. Citrus fruit peel contains polymethoxylated flavones, which can decrease cholesterol more effectively than certain prescription medicines while causing no side effects (Milind, , and Dev,. 2012). Medicinal herbs medicine have characterized the investigation for anti-hyperglycemic drugs, possibly as they have less negative consequences than currently employed mainstream treatments. Flavonoids supplements appears to be associated to a decreased risk of certain serious diseases and a greater chance of recovery, according to previous studies (Chen *et al* .., 2012). Citrus fruit peels, or the upper covering of fruits likes lemons, oranges, mandarins, and grapefruits, have already been found to be rich in flavonoids. There are three types of flavonoids found in citrus fruits: Flavonoids include flavanones, flavones, and flavonols (Sharma *et al* .., 2019). Suppression of -amylase, an enzyme important in the breakdown of starch and glycogen, is being explored as a therapy for carbohydrate absorption disorders such diabetes and obesity. A broad range of various chemicals have demonstrated action, demonstrating that they may be efficacious in the management of diabetes. Many plants are known to also have -amylase inhibitory effects, implying that they could be useful in the reduction of diabetes. (Sales *et al .., 2012*). The probable significance of plant extracts as antagonists of -amylase has been repeatedly attributed to phenolic chemicals, which have different levels of antioxidant or free radical scavenging capabilities as well as therapeutic uses and have long been used as pharmaceuticals. Likewise, the degree of hydroxyl groups on the B ring of the flavonoid skeleton is linked to the strength of -amylase inhibition, thus according flavonoids, a prevalent class of natural phenolic compounds. (Piparo *et al .., 2008*)

Citrus lemon is a frequently consumed fruit due to its smoothness, fragrant flavor, and bioactive compounds. It is a part of the Rutaceae medicinal plant family. C. lemon is one of Algeria's most important fruit, and it's heavy in photochemicals like vitamin C and phenolic compounds, many of which have high antioxidant effects and are regularly utilized in culinary and medicinal therapy. Hesperidin, quercitrin, eriocitrin, didymin, and naringin are one of the flavonoids found in C. lemon. Naringin has been shown to have anti-diabetic benefits. C. lemon flavonoids also has been demonstrated to showing a wide range of antimicrobial, anticancer, and antiviral activities. The purpose of this study was to investigate the anti-diabetic and hypolipidemic in vitro inhibitory properties of EtOAc extract fruit of C. lemon employing -amylase and pancreatic lipase (Dhanavade *et al .., 2011*) .

Antihyperlipidemic Effects

Rafeeq Alam Khan, as reported by Neelam Mallick (Antihyperlipidemic effects of Citrus sinensis, Citrus paradisi, and their combinations) Hyperlipidemia is a collection of disorders characterized by elevated blood levels of lipids and lipoproteins, such as cholesterol, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), which can lead to atherosclerosis. (Linton *et al .,* 2019). Atherosclerosis and coronary heart disease (CHD) are the most likely reasons of illness and death around the world, though a variety of factors such as a high-fat diet, high blood pressure, family history, age, and lifestyle play a part in the development of ischemic heart disease. CHDs are caused by an increase in cholesterol levels, particularly total cholesterol (TC) and low-density lipoprotein (LDL). Cardiovascular problems are the leading cause of death in Western countries, and a 20% reduction in cholesterol levels can reduce the risk of CHD by 31% and the death rate by 33%. Hypercholesterolemia is the leading cause of cardiovascular disease (CVD), and maintaining cellular cholesterol homeostasis is critical for avoiding CVD. The plasma cholesterol level can be managed in a variety of methods, including decreasing dietary lipid absorption, increasing cholesterol elimination by feces excretion, decreasing cholesterol production, and removing cholesterol from circulation. Many studies have shown that HMG-CoA reductase inhibitors and acyl-CoA: Cholesterol acyl 9 transferase (ACAT) inhibitors have beneficial effects on hypercholesterolemia and atherosclerosis. Existing lipid-lowering medicines, on the other hand, have a number of side effects. Previously, a great deal of emphasis was placed on raising awareness about plant bioactive constituents. (Mallick and Khan ., 2016). Polyphenols, phytoestrogens, phytates, and polyunsaturated fatty acids are some notable nutraceuticals found in the herbal diet. Nutraceuticals are substances that are not considered nutrients yet play an important role in maintaining health. The positive role of dietary polyphenols, such as flavonoids in citrus fruit, in human health is a topic of increasing scientific attention. Naringin is a bioflavonoid found naturally in citrus fruits that has been shown to have antibacterial, antimutagenic, anticarcinogenic, and anti-inflammatory properties. The efficacy of naringin as a lipid-lowering and anti-atherogenic drug has gotten a lot of attention recently. (Bok *et al .,* 20002)

Recent studies have looked at the lipid-lowering properties of naringin, which was achieved by inhibiting HMGCoA reductase in rats. However, the animal model used to examine the efficiency of nutraceuticals in the prevention of certain diseases is critical. As a result, the current study examines whether this functional molecule can control diet-induced hypercholesterolemia as effectively as atorvastatin in rats predisposed to hypercholesterolemia and atherosclerosis. In rabbits, bioflavonoids' antihypercholesterolemic properties were shown to change plasma and tissue lipids, cholesterol-regulating enzymes, and tissue shape. (Liu *et al .,* 2012). The Rutaceae family includes sweet orange (Citrus sinensis) and grapefruit (Citrus paradisi), and its juice and pulp components have showed hypolipidemic effects in rats with diet-induced hypercholesterolemia. Vitamin C, dietary fiber, Vitamin A, potassium, folate, and Vitamin B5 are all found in grapefruit. It also has phytochemicals like limonoids and lycopene in it. (Gao *et al .,* 2006) . Naringin is the most important bioflavonoid in orange. Naringin has a wide range of pharmacological properties, including antioxidant,

lipid-lowering, anticarcinogenic, and enzyme inhibition, including CYP3A4 and CYP1A2, which are involved in a number of drug interactions in vitro. (Rogerio *et al .,* 2010). Many elements make up the essential oils found in orange juice (C. sinensis), including monoterpenes and sesquiterpenes, with d-limonene being the most prominent. In rabbits and people, orange juice or its flavonoid has been shown to decrease cholesterol levels. Its anti-inflammatory properties in a variety of diseases have also been widely demonstrated. Narirutin, also known as Naringenin 7-O-rutinoside, is another significant flavonoid found in large amounts in orange juice. It is well absorbed and has a high bioavailability. (Castranova *et al .,* 2011). Anti-inflammatory, anti-allergic, and anti-asthmatic characteristics have been discovered. Considering the reported biological activities of C. paradisi, C. sinensis, and their combinations in animals kept on a high cholesterol diet, a recent study was designed to explore the anti-hyperlipidemia effect of C. paradisi, C. sinensis, and their combinations in animals kept on a high cholesterol diet. (Ojeda de Rodríguez *et al .,* 2009) .

Conclusion

The anti-hyperglycemic and anti-hyperlipidemic properties of C. reticulata fruit peel hydroethanolic extract, hesperidin, and quercetin looked to be mediated by the antioxidative defense system, glucose metabolism, and insulin action improvement. Increased serum insulin and C-peptide levels, along with optimized calculated HOMA-cell function, demonstrated enhanced insulin release, whereas increased insulin action was has shown by a rise in HOMA-IS and a drop in HOMA-IR, as well as insulin receptor -subunit, GLUT-4, and adiponectin mRNA expression levels in adipose tissues have been rising exponentially. The hydroethanolic extract of C. reticulata fruit peel have a larger anti-hyperglycemic and anti-hypercholesterolemic efficacy than hesperidin and quercetin. C. reticulata orange peels hydroethanolic extract, hesperidin, and flavonoid exhibit significant antihyperglycemic and antihyperlipidemic properties. and effective ameliorative effects on liver and kidney activities, which may be secondary to significant improvement in the glycemic state, lipid profile, and antioxidant defense system.

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