Review Article

Int J Life Sci Pharma Res., Vol: 15, Issue: 3, 2025; 31-43

IJLPR International Journal of Life science and Pharma Research

Content Available at www.ijlpr.com ISSN: 2250-0480

Polyphenols: A Promising Avenue for Diabetes Management

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Article History: Received: 19.Feb.2025 Revised: 04.Apr.2025 Accepted: 10.May.2025

Abstract

Diabetes mellitus (DM) is a pervasive metabolic illness that has a substantial influence on world health and is characterized by chronic hyperglycemia and an array of consequences. This paper investigates the potential of dietary polyphenols, natural substances in many plant-based foodsas a novel diabetes control strategy. Polyphenols have exceptional antioxidant and anti-inflammatory characteristics that can reduce oxidative stress and improve insulin sensitivity, ultimately improving glucose metabolism. The paper explores how polyphenols, including quercetin, resveratrol, and epigallocatechin gallate, promote pancreatic β-cell health and modulate inflammatory pathways. The essay also emphasizes the socioeconomic impact of diabetes, particularly in low and middle-income nations where access to healthcare and nutritional education is limited. By advocating for introducing polyphenol-rich foods into dietary regimens, this article hopes to give a comprehensive approach to diabetes care that addresses metabolic health and improves general well-being. The necessity for additional study into polyphenol absorption, appropriate doses, and long-term benefits is emphasized, opening the path for their use in clinical practice. Finally, this study underscores the importance of dietary treatments in diabetes management and improving health outcomes for those affected.

Keywords: Diabetes Mellitus, Polyphenols, Antioxidants, Glycemic Control, Nutritional value

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DOI: https://doi.org/10.22376/ijlpr.v15i3.2001

INTRODUCTION

Depiction

Metabolic illness known as chronic hyperglycemia, can arise from either inadequate insulin secretion reduced insulin action, or both. The anabolic hormone insulin plays a pivotal role in controlling carbohydrate, lipid, and protein metabolism. Adipose tissue, skeletal muscles, and the liver are the primary targets of metabolic complications caused by diabetes, which arise from insulin resistance.

Depending on the type and length of time that diabetes has been present, the severity of symptoms can vary. Symptoms of high blood sugar include increased hunger, polydipsia, dysuria, weight loss, and vision problems; these symptoms are more common in people with complete insulin insufficiency, which includesyoungsters. Some people with diabetes may not experience any symptoms at all, especially if their type 2 diabetes is in its early stages. Untreated ketoacidosis or nonketotic hyperosmolar syndrome can cause unconsciousness, disorientation, and, in extremely rare cases, death if left untreated. These consequences can arise from poorly managed diabetes [1-2].

People who are most economically and socially disadvantaged bear the greatest financial burden and burden of having diabetes. Its effects are measured by the increasing number of complications and fatalities as well as the annual increase in prevalence per capita. As life expectancy rises and technological advancements continue to reduce the prevalence of most infectious diseases, the effects of diabetes continue to worsen [3-4].

Although it is predicted that 366 million individuals had diabetes in 2011, this number is expected to increase to 552 million by 2030. Every country is seeing an increase in the number of people who have type 2 diabetes, with eighty percent of those who have diabetes residing in countries with low and intermediate incomes. In 2011, diabetes was responsible for 4.6 million fatalities. By the year 2030, it is anticipated that 439 million individuals will be diagnosed with type 2 diabetes. Because of environmental and behavioral risk factors, the prevalence of type 2 diabetes varies significantly from one geographical region to another. This is because the risk variables are different. It is anticipated that the prevalence of diabetes in adults, of which type 2 diabetes is becoming more prevalent, will increase over the next two decades. A significant portion of this increase will occur in developing countries, where most patients are between the ages of 45 and 64 years old [5-7].

The care of diabetes presently involves the use of antihyperglycemic agents (e.g., acarbose, metformin, sulfonylurea derivatives) and insulin therapy. Nonetheless, these methods are not entirely efficacious in averting the onset of complications and typically result in collateral effects, including vascular complications, hypoglycemia, flatulence, diarrhea, weight gain, weakness, fatigue, lactic acidosis, abdominal pain, and hepatotoxicity, among others. Moreover, many pharmaceuticals are prohibitively costly and inadequately accessible in impoverished nations. Consequently, the utilization of natural products abundant in phenolic compounds for the development of novel antidiabetic medicines presents a viable alternative, primarily owing to the efficacy, accessibility, and low toxicity of its phytochemicals.

Polyphenols are synthesized by several plant species. They safeguard the organism from harm inflicted by UV radiation and deter voracious microorganisms. They are especially prevalent in vegetables, fruits, whole grains, and legumes. Cocoa, coffee, tea, spices, and red wine are abundant in polyphenols. Researchers have found over 8,000 polyphenols in flora. Phenolic substances (e.g., catechin, myricetin, quercetin, delphinidin, cyanidin, gallic acid, ellagic acid, caffeic acid, etc.) have garnered significant interest within the scientific community in recent years owing to their substantial functional potential. The bioactivity of phenolics mostly stems from their capacity to suppress reactive species, donate electrons to free radicals, regulate gut flora, or activate antioxidant enzymes.

A wide variety of polyphenols, including isoflavones, anthocyanins, flavonoids, flavonols, flavanones, and flavones, make up your dailydiet.The relationships among polyphenols, glucose regulation, and diabetes mellitus are an area of active investigation. But there's growing proof that these plant components can help with blood sugar regulation and maybe even lower the risk of diabetes.

Table 01: Showing different classes of dietary polyphenols

Classification	Description	Key Examples	Health Benefits
Flavonoids	A group of polyphenolic compounds	- Quercetin - Kaempferol - Flavonols	Antioxidant, anti-inflammatory, heart health
Phenolic Acids	Compounds with a phenolic ring	- Caffeic acid - Ferulic acid	Antioxidant, may reduce cancer risk
Stilbenes	Compounds characterized by a stilbene structure	- Resveratrol	Cardiovascular benefits, anti-aging effects
Lignans	Plant compounds that can mimic estrogen	- Secoisolariciresinol - Matairesinol	Hormonal balance, may reduce risk of breast cancer
Tannins	Polyphenols that can precipitate proteins	- Gallotannins - Ellagitannins	Antioxidant, antimicrobial properties

Types of Diabetes Mellitus

Type-I DM

Early detection of type I diabetes (TID) begins with a consistent reduction in insulin output at least two years before diagnosis. During this time, β-cell sensitivity to glucose decreases. A lower first insulin response leads to a higher final insulin response, suggesting a compensatory mechanism. Early in the post-diagnosis phase, insulin responsiveness starts decreasing rapidly. In the first few years after diagnosis, insulin secretion declines biphasically, with the first year being steeper than the second. After a diagnosis, insulin secretion may diminish for years, finally resulting in little insulin production. Even within normal glucose levels, TID is indicated by elevated glucose levels. When TID develops, glucose levels significantly vary. Using metabolic markers like dysglycemia may help predict diabetes onset in at-risk individuals. Assessing glucose and C-peptide levels can enhance risk assessment and prediction [8-9].

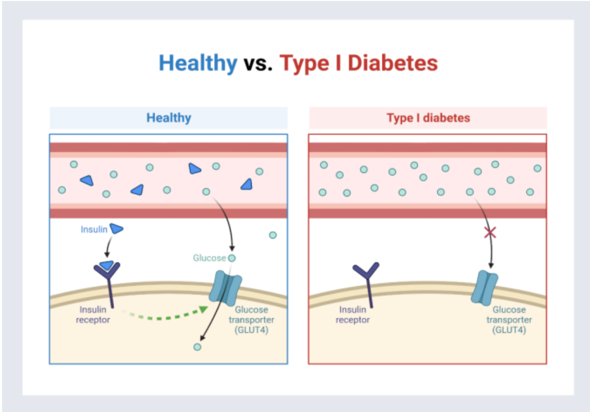

Fig 01: Health vs Type-I Diabetes

Type-2 DM

Insulin secretion defects are an important part of the pathophysiology of type 2 diabetes (T2D). Maintaining optimal glucose levels requires insulin secretion, the amount of which varies greatly depending on insulin sensitivity. One way to quantify the non-linear correlation between insulin sensitivity and secretion is with the disposition index. Moreover, because to their poor disposition index, patients with type 2 diabetes cannot effectively increase their insulin production to counteract insulin resistance. Due to the extreme nature of their insulin resistance, the insulin levels in obese type 2 diabetic patients who are insulin resistant are still inadequate, even when compared to insulin-sensitive lean control subjects. Stimulating glucose synthesis drastically reduces or eliminates insulin production (initial phase). There is an abnormally high ratio of proinsulin to insulin (C-peptide) in type 2 diabetics. There is a significant reduction in both the maximum insulin production and the hyperglycemia-induced enhancement of insulin responses to stimuli other than glucose. In most cases, hyperglycemia gets worse and harder to treat as time goes on. Another aspect of type 2 diabetes progression is the ongoing reduction in β-cell function [10-11].

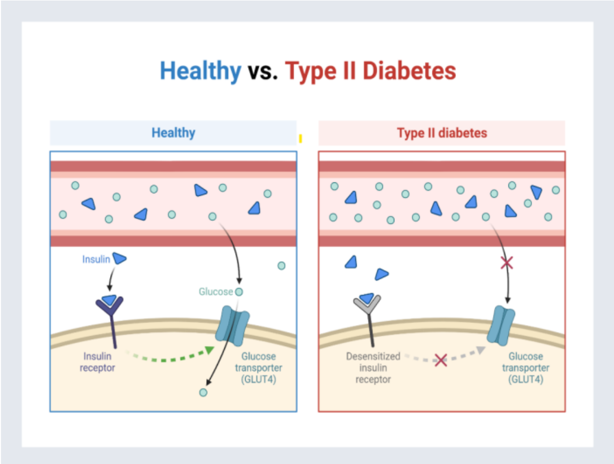

Figure 02: Healty vs Type I I Diabetes

Type 3 DM

Type 3 diabetes (T3D) is typically recognized as a neuroendocrine disorder that indicates the advancement of T2DM to Alzheimer's disease (AD). Throughout the TID, several signaling pathways undergo modifications, including insulin growth factor signaling, inflammatory responses, acetylcholine esterase activity, ApoE4A allele, and vascular dysregulation of brain capillaries. Recent studies have identified a connection between systemic dysfunction, such as diabetes, and neuro-cognitive impairment, which encompasses conditions like dementia, obesity, insulin resistance, and metabolic syndrome. Individuals diagnosed with Alzheimer's disease (AD) exhibit a decrease in insulin and neuronal insulin receptors when compared to age-matched controls. The presence of these defective pathways contributes to a gradual disruption in the entire insulin signaling cascade, ultimately leading to the advancement of insulin resistance [12].

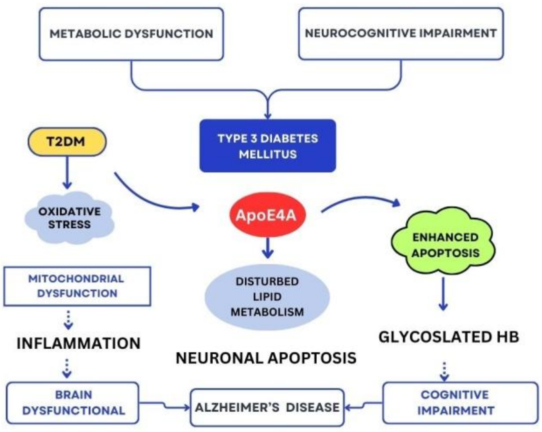

Figure 03: Mechanistic Pathways Connecting T2DM, Type 3 Diabetes

DIABETES IN INDIA

India, a country contending with an escalating health problem, is positioned at the forefront of the worldwide diabetes epidemic. India holds the unfortunate distinction of having the biggest number of diabetic patients globally, with a staggering 77 million individuals diagnosed with diabetes. This concerning trend results from multiple interrelated variables, such as genetic predisposition, lifestyle decisions, and the swift progression of urbanization and industry. The sedentary lifestyle, marked by extended durations of inactivity and a tendency towards convenience foods, has substantially contributed to the increase in diabetes incidence. Furthermore, the rising intake of processed meals, rich in sugar and refined carbs, has intensified the issue. Rapid urbanization and industrialization have resulted in a transformation of dietary preferences, with individuals increasingly opting for less nutritious and more calorie-dense foods. The ramifications of unmanaged diabetes are extensive, involving a range of devastating problems. Cardiovascular disorders, such as myocardial infarctions and cerebrovascular accidents, pose a substantial risk to the lives of patients with diabetes. Moreover, diabetes can result in chronic renal disease, a condition that gradually deteriorates kidney function and may ultimately require dialysis or kidney transplantation. Nerve injury, frequently presenting as numbness, tingling, or pain, especially in the limbs, is a prevalent consequence. Moreover, diabetes can compromise vision, resulting in disorders such as diabetic retinopathy, which may advance to blindness if not addressed. The economic impact of diabetes on India is significant, including expenses for medical care, diminished productivity, and early mortality. To address this important challenge, India must adopt a comprehensive and multifaceted strategy. Public awareness campaigns are crucial for educating the populace about the risk factors, symptoms, and preventive measures for diabetes. Advocating for healthy lifestyles, encompassing frequent physical activity and a balanced diet, is essential for preventing and managing the condition. Early detection via frequent screening programs is necessary for identifying at-risk individuals and commencing prompt interventions. Guaranteeing fair access to cheap, high-quality healthcare, including drugs, insulin, and vital medical services, is critical for optimizing diabetes management. Moreover, investing in research and innovation is essential for creating new therapies, technologies, and preventive measures to tackle the changing difficulties of diabetes. India may effectively alleviate the burden of diabetes and enhance its population's overall health and well-being by implementing a comprehensive strategy that integrates public health programs, personal lifestyle changes, and technological breakthroughs [12-13].

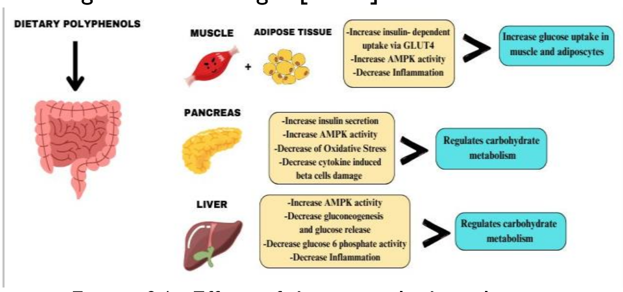

Figure 04: Effect of dietary polyphenols

USE OF POLYPHENOLS IN DM

Research suggests that polyphenols can play a crucial role in diabetes management by influencing several key pathways. They are significant in the management of diabetes mellitus (DM) owing to their antioxidant, anti-inflammatory, and glucose-regulating properties. Bioactive compounds mitigate oxidative stress, a significant factor in the pathogenesis of diabetes mellitus (DM), by neutralizing reactive oxygen species (ROS) and bolstering the body's inherent antioxidant defenses. This protection maintains the functionality of pancreatic β-cells, crucial for insulin synthesis and secretion. Polyphenols enhance insulin sensitivity by decreasing systemic inflammation via the downregulation of pro-inflammatory cytokines such as TNF-α and IL-6. They regulate glucose metabolism by inhibiting carbohydrate-digesting enzymes, including α-amylase and α-glucosidase, which delay glucose absorption and reduce postprandial blood sugar spikes. Polyphenols also improve glucose uptake in peripheral tissues, including muscle and adipose tissue, by influencing insulin signaling pathways and elevating glucose transporter (GLUT4) expression. Catechins, a class of polyphenols present in green tea, have demonstrated efficacy in lowering fasting glucose levels and enhancing postprandial insulin responses. Resveratrol and flavonoids have shown the potential to enhance glucose homeostasis and decrease insulin resistance markers in both preclinical and clinical studies.

The multifunctional properties of polyphenols position them as a promising natural adjunct in the management of diabetes mellitus. Their bioavailability is influenced by factors such as dietary composition, preparation methods, and individual metabolic responses. Recent developments in micro- and nanoencapsulation techniques present promising strategies to improve delivery and therapeutic efficacy, facilitating their integration into functional foods and supplements aimed at diabetes management14-16. The pathways are deciphered as:

❖ **Improved Glucose and Insulin Regulation**

Polyphenols have been shown to enhance insulin sensitivity and improve glucose tolerance. They protect pancreatic β-cells, the primary source of insulin production, thereby contributing to better blood sugar control. The process can be deciphered as:

Enhancement of Insulin Sensitivity

- **Activation of AMP-Activated Protein Kinase (AMPK):** Polyphenols such as epigallocatechin gallate (EGCG) from green tea activate AMPK, a key energy sensor that enhances glucose uptake in skeletal muscles and improves insulin sensitivity.
- **Improved Insulin Signaling:** Polyphenols reduce oxidative stress and inflammatory markers that impair insulin signaling, restoring the activity of insulin receptors.

Protection of Pancreatic β-Cells

- **Antioxidant Activity:** Oxidative stress is a major cause of β-cell dysfunction in diabetes. Polyphenols like quercetin and resveratrol enhance the expression of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase, reducing reactive oxygen species (ROS) levels.
- **Anti-Inflammatory Effects**
  Chronic inflammation damages β-cells. Polyphenols inhibit nuclear factor kappa-B (NF-κB) signaling, which regulates the expression of inflammatory cytokines, thereby preserving β-cell function.

Improvement in Glucose Uptake

- **GLUT4 Translocation:** Polyphenols increase the translocation of GLUT4 transporters to the cell surface in muscle and adipose tissues, facilitating efficient glucose uptake.
- **Inhibition of Digestive Enzymes:** Polyphenols such as chlorogenic acid inhibit α-glucosidase and α-amylase, slowing carbohydrate digestion and reducing postprandial glucose spikes.

Reduction of Insulin Resistance:

- **Adipokine Modulation:** Polyphenols improve the secretion of adiponectin (an insulin-sensitizing hormone) while reducing resistin, thus mitigating insulin resistance.
- **Reduction of Lipotoxicity:**Polyphenols prevent lipotoxicity-induced impairment of insulin signaling by reducing triglyceride accumulation in non-adipose tissues.

Gut Microbiota Modulation

- Polyphenols influence gut microbiota by promoting beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*. These bacteria produce short-chain fatty acids (SCFAs), which improve insulin sensitivity and reduce systemic inflammation.

Reduction of Advanced Glycation End Products (AGEs)

- AGEs are harmful compounds formed under hyperglycemic conditions and contribute to insulin resistance. Polyphenols like quercetin inhibit the formation of AGEs, thus alleviating diabetes-related complications [17-18].

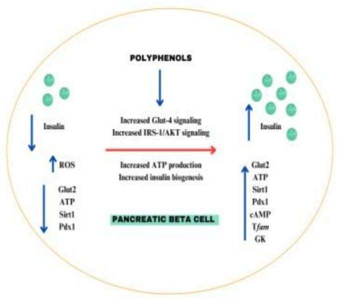

Figure 5: Role of Polyphenols in Enhancing Beta Cell Function via Glut4 and IRS-1/AKT Pathways

- **Inhibition of Carbohydrate-Digesting Enzymes**

  Studies indicate that polyphenols can inhibit enzymes like amylase and α-glucosidase, which are involved in carbohydrate digestion. This inhibition can lead to a more stable regulation of blood sugar levels.Postprandial hyperglycemia, hyperinsulinemia, and other hormonal and metabolic abnormalities are brought on by foods and drinks that contain a lot of accessible carbs, such as starch or sugar. Habitually consuming high-glycemic diets may raise the risk of obesity, diabetes, and cardiovascular disease because the regulatory mechanisms of glucose homeostasis are challenged by the quick absorption of glucose. Following high-carb meals, improving glycaemic control targets glucose absorption and carbohydrate digestion. The two main enzymes that break down dietary carbs into glucose are amylase and α-glucosidase. Through certain transporters, the released glucose is taken up by the intestinal enterocytes. Postprandial hyperglycemia would be suppressed by inhibiting the digestive enzymes or glucose transporters, which would slow down the small intestine's rate of glucose release and absorption [19]. The pharmacology involved can be emphasized as

  - **Inhibition of Carbohydrate Digestion**
    Polyphenols can inhibit the activity of digestive enzymes such as α-amylase and α-glucosidase, which are responsible for breaking down complex carbohydrates into glucose. By reducing the activity of these enzymes, polyphenols slow down the digestion of carbohydrates, leading to a more gradual release of glucose into the bloodstream, thereby mitigating postprandial hyperglycemia.
  - **Modulation of Glucose Absorption**
    The absorption of glucose across the intestinal wall is facilitated by specific transporters. Polyphenols may influence the expression or activity of these glucose transporters, thereby reducing the rate at which glucose is absorbed into the bloodstream. This action helps in controlling blood sugar levels after meals.

- **Stimulation of Insulin Secretion**
  Some studies suggest that polyphenols can enhance insulin secretion from pancreatic β-cells. This increased insulin release can help lower blood glucose levels by promoting glucose uptake in insulin-sensitive tissues.
- **Improvement of Insulin Sensitivity**
- Polyphenols have been shown to improve insulin sensitivity, which is crucial for maintaining glucose homeostasis. Enhanced insulin sensitivity allows the body to use insulin more effectively, facilitating better glucose uptake by cells and reducing blood sugar levels.
- **Modulation of Hepatic Glucose Release**: Polyphenols may also affect the liver's role in glucose metabolism by modulating the release of glucose into the bloodstream. This can involve altering the pathways that regulate gluconeogenesis (the production of glucose from non-carbohydrate sources).
- **Impact on Inflammatory and Oxidative Stress Markers**: Polyphenols possess anti-inflammatory and antioxidative properties, which can contribute to improved metabolic health. Chronic inflammation and oxidative stress are linked to insulin resistance and metabolic disorders, so reducing these factors can enhance carbohydrate metabolism.
- **Microbial Metabolism**: The metabolism of polyphenols by gut microbiota can also play a role in their effects on carbohydrate metabolism. The colonic microbiota can transform polyphenols into bioactive metabolites that may exert beneficial effects on glucose metabolism.
- **Epidemiological Evidence**: While in vitro and animal studies provide strong evidence for the beneficial effects of polyphenols on carbohydrate metabolism, the study emphasizes the need for more controlled human trials to confirm these findings and understand the underlying mechanisms better [20-21].

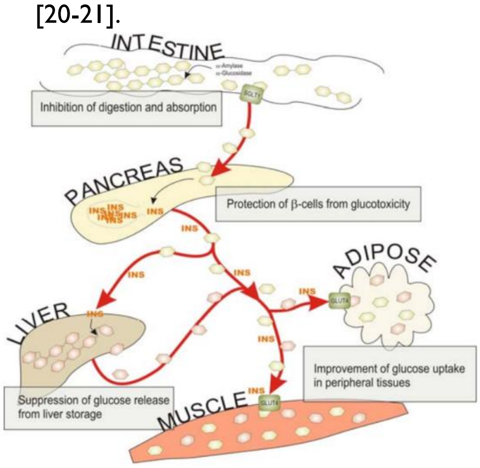

Figure 06: Effect of polyphenols on the carbohydrate-digesting enzymes

- **Anti-inflammatory and Antioxidant Effects**

Chronic inflammation and oxidative stress are hallmarks of diabetes and contribute to its associated complications. Polyphenols possess potent anti-inflammatory and antioxidant properties, mitigating these detrimental effects. By reducing reactive oxygen species generation and modulating inflammatory pathways, polyphenols can help prevent or manage diabetic complications such as nephropathy, neuropathy, and cardiovascular diseases.

Oxidative stress and inflammation are described as critical factors in the pathophysiology of diabetes mellitus. Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them with antioxidants. This condition is prevalent in diabetes and contributes to various complications, including insulin resistance and dysfunction of pancreatic β-cells, which are essential for insulin production. The article emphasizes that elevated oxidative stress can lead to cellular damage, exacerbating the metabolic disturbances associated with diabetes.

Inflammation is another significant aspect discussed in the article. Chronic low-grade inflammation is commonly observed in individuals with type 2 diabetes. This inflammatory state can further impair insulin signaling, increasing insulin resistance. The interplay between oxidative stress and inflammation creates a vicious cycle that worsens the overall metabolic condition, making it crucial to address both factors in diabetes management [22-23].

Regarding theapplications of polyphenols in improving antidiabetic therapy, the promising avenues can be described as:

- **Antioxidant Properties**: Polyphenols are known for their strong antioxidant capabilities. They can enhance the body's natural antioxidant defenses, helping to reduce oxidative stress. By protecting pancreatic β-cells from oxidative damage, polyphenols may improve insulin secretion and sensitivity, which is vital for effective glucose regulation.
- **Anti-inflammatory Effects**: The anti-inflammatory properties of polyphenols can help mitigate the chronic inflammatiossociated with type 2 diabetes. By reducing inflammatory markers and improving insulin sensitivity, polyphenols may play a role in alleviating the metabolic dysfunction seen in diabetic patients.
- **Dietary Interventions**: The article highlights that a diet rich in polyphenolic compounds is linked to better glucose homeostasis and a reduced risk of developing type 2 diabetes. This suggests that incorporating polyphenol-rich foods, such as fruits, vegetables, and certain beverages (like tea and red wine), could be beneficial for individuals at risk of or managing diabetes.
- **Microand Nanoencapsulation**: Innovative techniques like micro- and nanoencapsulation to enhance the bioavailability of polyphenols. These methods can improve the absorption and effectiveness of polyphenolic compounds when used as dietary supplements or functional foods, potentially leading to better outcomes in diabetes management.

Given these multifaceted benefits, polyphenols hold considerable promise for preventing and managing diabetes and its complications. Incorporating polyphenol-rich foods into dietary strategies can improve overall health and mitigate the burden of this widespread metabolic disorder [24].

Table 02: various polyphenols, class & biological functions

SL No.	Polyphenols	Type of Secondary Metabolite	Biological Function
1	Quercetin	Flavonoid	It has antioxidant effects, lowers inflammation, and may minimize the risk of chronic diseases.
2	Epigallocatechin Gallate (EGCG)	Catechin	It improves anticancer, metabolism, and antioxidants.
3	Kaempferol	Flavonoid	It has anti-inflammatory and antioxidant properties linked to a lower risk of cancer and cardiovascular disease.
4	Resveratrol	Stilbene	It has been linked to anti-aging benefits, cardiovascular protection, and possibly neuroprotective qualities.
5	Chlorogenic Acid	Phenolic Acid	Antidiabetic, promotes weight loss, lowers blood pressure.
6	Naringenin	Flavonoid	Reduces inflammation and improves metabolic syndrome.
7	Epicatechin	Flavonoid	Improves cardiovascular health and neuroprotection
8	Caffeic Acid	Phenolic Acid	It enhances antioxidant, antibacterial, and neuroprotective properties.
9	Gallic Acid	Phenolic Acid	It is associated with antimicrobial, anticancer, and anti-inflammatory properties.
10	Secoisolariciresinol	Lignan	It possesses both estrogenic and anti-cancer properties.
11	Matairesinol	Lignan	It has antioxidant properties and reduces the risk of cardiovascular disease.
12	Ellagitannins	Tannin	It has antioxidant, anticancer, and antimicrobial properties.
13	Proanthocyanidins	Tannin	It improves skin health and is involved in cardiovascular protection.

14	Curcumin	Curcuminoid	It consists of anti-inflammatory, antioxidant, and anticancer properties.
15	Ferulic Acid	Hydroxycinnamic Acid	It improves anti-aging and includes antioxidant and UV protection properties.
16	Cyanidin	Anthocyanin	Improves eye health, and anti-inflammatory and cardiovascular protection.
17	Delphinidin	Anthocyanin	Anti-inflammatory, supports eye health and cardiovascular protection.
18	Genistein	Isoflavone	It maintains hormonal balance and minimizes the risk of hormone-related malignancies.
19	Rutin	Flavonol Glycoside	It lowers pathological alterations.
20	Daidzein	Isoflavone	It maintains hormonal balance and promotes bone health.

4. Pre-clinical and Clinical Evidence

- The effects of resveratrol on various health parameters, including glucose homeostasis, insulin resistance, chronic inflammation, blood lipid profiles, diabetic hypertension, and oxidative stress, have been well-documented. There is some evidence that resveratrol can help reduce the risk of diabetes and its consequences. This phytoalexin appears to have a significant therapeutic effect on a variety of relevant metrics, including insulin sensitivity, blood glucose level modulation, cardiovascular protection, diabetic hypertension reduction, inhibition of oxidative stress and chronic inflammation, blood lipid profile improvement, and retinal health support [25].

- Investigation revealed that quercetin supplementation (250 mg/day for 8 weeks) led to a significant improvement in the total antioxidant capacity (TAC) among patients with Type 2 diabetes, suggesting an enhanced antioxidant status ($P=0.043$). Furthermore, a significant decrease in serum levels of oxidized low-density lipoprotein (ox-LDL), a marker linked to atherogenic risk, was observed, particularly in the quercetin group when compared to the placebo ($P<0.001$). Nonetheless, despite the favorable impacts observed on oxidative stress markers, the supplementation did not result in statistically significant alterations in glycaemic parameters, including fasting blood glucose, serum insulin, or glycosylated hemoglobin (HbA1c). Additionally, it did not influence lipid profiles or measurements of insulin resistance ($P>0.05$). The study found that quercetin supplementation may improve antioxidant defenses in diabetic patients; however, its effects on glycaemic control and lipid profiles appear to be minimal. This indicates a necessity for additional investigations into different dosages and durations to better understand the potential benefits [26].

- An investigation was conducted to examine how the timing of catechin and green tea polyphenol consumption affects postprandial glucose metabolism in both mice and humans. Significant findings indicated that the intake of epigallocatechin gallate (EGCG) or catechin-rich green tea during the evening, as opposed to the morning, led to a decrease in postprandial glucose levels and an enhancement in insulin secretion. The observed effects can be linked to variations in insulin sensitivity and β-cell functionality observed during morning and evening hours. The processes at play encompass the regulation of glucose transporters, the pathways of insulin signaling, and the suppression of carbohydrate-digesting enzymes like α-amylase and α-glucosidase. The timing-dependent glucose-lowering effects are likely influenced by the circadian rhythms of these enzymes and glucose transporters. The study presents certain limitations, such as the reduced fasting duration during evening trials in contrast to those conducted in the morning, as well as its brief overall duration, both of which could have influenced the outcomes observed. It is advisable to conduct long-term studies to validate these findings and investigate the chronic impacts of catechin consumption on glucose metabolism at various times throughout the day [27].

- A meta-analysis of seven randomized controlled trials examining green tea or green tea extract found no significant reduction in fasting plasma glucose, fasting serum insulin, 2-hour oral glucose tolerance test (OGTT), glucose, glycated hemoglobin (HbA1c), or HOMA-IR index levels. The authors noted that the limitations of the studies comprised small sample sizes, poor quality, and low evidence levels of the included research. A meta-analysis of 17 randomized controlled trials, comprising seven high-quality studies and ten low-quality studies, indicated that green tea significantly reduced fasting glucose and HbA1c by 0.09 mmol/L (95% CI 0.15–0.03 mmol/L; $p < 0.01$) and 0.30% (95% CI 0.37%–0.22%; $p < 0.01$), respectively. Subgroup analyses from studies with high Jadad scores indicated a significant reduction in fasting insulin (´1.16 μIU/mL, 95% CI ´1.91 to ´0.40 μIU/mL; $p = 0.03$) [91]. This study attributed these findings to glucose control or insulin sensitivity measures that did not derive from primary outcomes, the scarcity of high-quality studies, and the concealment of null findings in the majority of selected studies [28].

- Recent studies have established a scientific foundation for the conventional understanding of curcumin, affirming its significant role in the prevention and management of diabetes and related conditions. Curcumin may positively influence several critical facets of diabetes, such as insulin resistance, hyperglycemia, hyperlipidemia, and the processes of islet apoptosis and necrosis (Figure 2). Moreover, curcumin has the potential to avert the harmful complications associated with diabetes. While the multifaceted nature of this product suggests significant potential benefits, current clinical trial results for curcumin are limited to its application in treating diabetic nephropathy, microangiopathy, and retinopathy at this time. Rigorous studies must be conducted on human subjects to validate the potential of curcumin in mitigating diabetes and its associated disorders. Moreover, it is essential to employ various strategies to address the challenges posed by the limited solubility and inadequate bioavailability of curcumin. The endeavors encompass the synthesis of curcuminoids and the advancement of innovative formulations of curcumin, including nanoparticles, liposomal encapsulation, emulsions, and sustained-release tablets. The improved bioavailability and compelling outcomes from clinical trials of curcumin are poised to elevate this promising natural compound as a leading therapeutic agent for diabetes [29].
- The combination of berberine with hypoglycemic drugs, such as metformin and 2,4-thiazolidinedione (THZ), has been shown to enhance glucose uptake in myotubes, demonstrating an additive effect that can significantly improve diabetes management. Specifically, berberine can increase 2-deoxyglucose uptake by 4.1- and 4.7-times when paired with these medications, which is crucial for regulating blood glucose levels. This effect is largely attributed to berberine's ability to activate AMP-activated protein kinase (AMPK), thereby improving insulin sensitivity and glucose metabolism. While berberine's interactions are additive, the study also highlights that combining other phytochemicals like chlorogenic acid and ferulic acid with hypoglycemic drugs can produce a synergistic effect, further enhancing therapeutic outcomes. Overall, these combinations may help reduce diabetes mellitus by improving glucose uptake and potentially lowering the required doses of conventional medications, thus minimizing side effects [30].
- Ellagic acid (EA) has exhibited various preclinical effects that could potentially alleviate the challenges associated with diabetes mellitus, chiefly by improving glucose metabolism, augmenting insulin sensitivity, and decreasing fasting blood glucose levels. The robust antioxidant properties alleviate oxidative stress, a major factor in pancreatic β-cell dysfunction, while the anti-inflammatory effects contribute to the reduction of chronic inflammation linked to obesity and insulin resistance. Furthermore, EA has the potential to impede glycation processes, thereby safeguarding tissues from harm and averting diabetic complications like retinopathy and nephropathy. In summary, the complex mechanisms of EA indicate its potential as a valuable agent in the management of diabetes; however, additional clinical trials are essential to confirm these findings in human subjects [31].
- A double-blinded, randomized, crossover trial involving 32 subjects with type 2 diabetes demonstrated beneficial effects of 600 mg/day grape seed extract over four weeks on fructosamine, but no significant effect was observed.

  A separate study demonstrated the protective effects of grape polyphenols against fructose-induced oxidative stress and insulin resistance in first-degree relatives of individuals with type 2 diabetes.Following a six-day fructose loading period, the placebo group exhibited a 20% reduction in hepatic insulin sensitivity, which was correlated with an 11% decline in glucose infusion rate [31].

  The artifacts related to the clinical evidence of the role of polyphenols in the management of DM are remarkable. Substantial findings from epidemiological studies indicate that dietary polyphenols may play a role in the management and prevention of T2D, although there are also opposing viewpoints present. Significant consumption of total polyphenols, total flavonoids (particularly flavanones and dihydro flavonols), and stilbenoids correlates with a lower risk of diabetes among elderly individuals at elevated risk of cardiovascular disease, as demonstrated in the Prevencion con Dieta Mediterranea trial [32].
- Dietary flavonoids have been identified as a factor associated with a reduced risk of T2D. For instance, van Dam, Naidoo, and Landberg (2013) emphasized that anthocyanidins and flavan-3-ols may lower the risk of T2D. Additionally, a 20-year study conducted in the United States observed similar outcomes linked to higher consumption of anthocyanins or foods rich in anthocyanins. The consumption of dietary flavones is associated with a reduced prevalence of T2D among Korean women aged 30 and older [33].
- Additionally, research conducted with 4,186 Korean participants demonstrated that the intake of flavones and flavonols was negatively correlated with insulin resistance in male subjects. The intake of quercetin showed an inverse relationship with the prevalence of T2D among the Chinese population studied using a validated 100-item food frequency questionnaire. However, this study lacks conviction as it does not take into account the effects of co-existing

flavonoids. The consumption of flavonoids from fruits and vegetables during adolescence is associated with a positive risk factor profile for type 2 diabetes in early adulthood. Conflicting findings, however, suggested that the consumption of flavonoids may not be associated with a reduced risk of T2D [33].

- Aprospective cross-sectional study involving 38,018 women indicated that there was no association between the consumption of flavonols or flavones and the risk of T2D. Furthermore, the consumption of anthocyanidins showed no association with diabetes risk among women in Iowa. In conclusion, the findings from various epidemiological studies show a lack of consistency, potentially attributable to significant differences among populations and inaccuracies in dietary intake measurements [34].
- The interaction between ferulic acid and metformin is synergistic, as both compounds act on parallel pathways involved in glucose uptake. The synergistic interaction allows for a reduction in the metformin dose needed to achieve normoglycemia when combined with ferulic acid. Reducing the dose of metformin can decrease the associated side effects of metformin therapy [35].

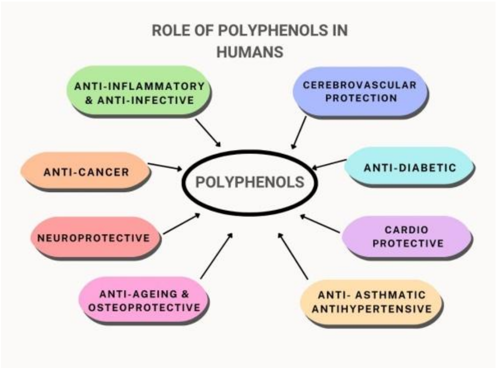

Figure 07: Illustration depicting the significance of polyphenols in human beings

SYNERGISTIC AND COMBINED THERAPIES

It has been documented that various groups of polyphenols exhibit distinct biochemical mechanisms and respond differently to various disease modes. Multiple studies indicate that treatment utilizing a range of polyphenolic compounds, whether as individual substances or in combinations, along with dietary consumption of natural sources abundant in polyphenols, has decreased the incidence of chronic diseases.

Polyphenols influence diabetes mellitus by a synergistic interaction of processes that address multiple facets of glucose metabolism, insulin sensitivity, and oxidative stress. Compounds like curcumin and resveratrol improve insulin sensitivity by regulating insulin signaling pathways, therefore diminishing insulin resistance, which is essential for the management of type 2 diabetes mellitus (T2DM). Their powerful antioxidant qualities alleviate oxidative stress, a major factor in β-cell dysfunction, by neutralizing free radicals and diminishing reactive oxygen species (ROS), thus safeguarding pancreatic cells and enhancing insulin release. Furthermore, polyphenols modulate glucose metabolism by blocking digestive enzymes such as α-glucosidase, resulting in reduced postprandial blood glucose levels. They also demonstrate anti-inflammatory properties by downregulating pro-inflammatory cytokines, including TNF-α, which are associated with insulin resistance and β-cell dysfunction. Moreover, polyphenols positively affect gut health by fostering good gut flora, which can improve their bioavailability and overall metabolic impact. The amalgamation of several polyphenols can result in improved therapeutic results, exemplified by catechin and quercetin, which collaboratively promote glucose metabolism and alleviate diabetes-related problems. These diverse activities emphasize the potential of polyphenols as adjunctive therapeutic agents in diabetes therapy, illustrating their contribution to enhancing metabolic health through a holistic approach.

A potential strategy for the treatment of diabetes mellitus involves the combined use of induced pluripotent stem (iPS) cells and spice polyphenols. To restore pancreatic function, iPS cells can be reprogrammed to develop into β cells that produce insulin, especially in cases of type I diabetes where β cells are injured. At the same time, polyphenols—found in a wide variety of spices—help control blood sugar levels and inflammation by increasing insulin secretion and improving insulin sensitivity while also providing antioxidant effects. By combining these two treatments, it is possible to enhance β cell mass and function, foster an environment that is favorable to β cell survival, and ultimately improve glucose homeostasis. A safer and more effective option for diabetes treatment could be a combination method that uses natural polyphenols to decrease some of the dangers associated with iPS cell therapy, such as immunological rejection and tumorigenicity.

Ferulic acid generates a resonance-stabilized phenoxyl radical that scavenges free radicals and diminishes oxidative stress. It enhances the glucose and lipid profiles in diabetic rats by increasing the activity of the antioxidant enzymes superoxide dismutase and catalase in pancreatic tissue. The combination of ferulic acid and metformin enhances both in vitro glucose absorption activity and the in vivo hypoglycemic efficacy of metformin. The metformin dosage can be decreased by fourfold (from 50 to 12.5 mg/kg body weight) when combined with 10 mg of ferulic acid/kg body weight in diabetic rats. Ferulic acid enhances glucose uptake via the PI3-K pathway, while metformin stimulates the AMPK pathway to facilitate glucose uptake.

Curcumin and other dietary polyphenols have been shown to work together to help fight obesity and diabetes, according to a new study. Curcumin is a polyphenolic substance that comes from turmeric. It has been shown to improve insulin sensitivity and resistance to high-fat diets (HFDs) in rodent models, which suggests that it could be used to treat metabolic disorders. Inflammation pathways are thought to be changed, endoplasmic reticulum (ER) stress is lowered, and adipokines, like rising adiponectin levels, are controlled. All of these things are important for metabolic health. Curcumin can also increase the production of fibroblast growth factor 21 (FGF21) in the liver, which shows that it plays a major role in maintaining energy balance and controlling metabolism. However, the results also show how hard it is to bring these benefits to people because of differences in absorption, metabolism that is affected by gut microbiota, and the difficulties in creating strong clinical studies. So, even though the preclinical evidence is positive, more study is needed to fully understand and use how curcumin and other polyphenols work together to improve metabolic health in humans [36-40].

CHALLENGES AND LIMITATIONS

The below explanation elucidates several challenges associated with the utilization of polyphenols in the treatment of Diabetes Mellitus:

- Limited bioavailability: Polyphenols exhibit poor absorption and rapid metabolic degradation, which diminishes their therapeutic efficacy. This limitation significantly impacts the potential effectiveness of polyphenol-based interventions, as the compounds may not reach their intended targets in sufficient concentrations to exert their beneficial effects.
- Structural complexity: The intricate molecular structure of polyphenols hinders the elucidation of their precise mechanisms of action and the determination of optimal dosages. This complexity poses a significant obstacle to researchers and clinicians attempting to develop targeted therapies and establish appropriate treatment protocols.
- Variability in outcomes: The inconsistent polyphenol content across different food sources, coupled with potential interactions with other dietary components or medications, contributes to heterogeneous results in clinical studies. This variability makes it challenging to draw definitive conclusions about the efficacy of polyphenols in diabetes management and complicates the development of standardized treatment approaches.
- Insufficient longitudinal data: There is a paucity of comprehensive long-term studies evaluating the safety and efficacy of polyphenol interventions in diabetes management. This lack of extended follow-up data limits our understanding of the potential long-term benefits and risks associated with prolonged polyphenol supplementation in diabetic patients.
- Lack of standardization: The absence of uniformity in polyphenol extracts and supplements impedes the conduct of reliable and reproducible research. This lack of standardization makes it difficult to compare results across different studies and hinders the development of evidence-based guidelines for polyphenol use in diabetes treatment.
- Translational challenges: Extrapolating findings from in vitro and animal studies to human subjects proves problematic, and human clinical trials have yielded conflicting or inconclusive results. This translational gap highlights the complexity of human physiology and the need for more robust, well-designed clinical trials to validate the potential benefits of polyphenols observed in preclinical studies.
- Dosage determination: Establishing optimal dosages for polyphenol interventions remains a significant challenge due to variations in individual metabolism, bioavailability, and the diverse array of polyphenol compounds. This difficulty in determining appropriate dosages further complicates the development of effective treatment strategies.
- Potential interactions: Polyphenols may interact with other medications commonly prescribed to diabetic patients, such as antihypertensive or lipid-lowering drugs. These interactions could potentially alter the efficacy or safety profiles of both the polyphenols and the conventional medications, necessitating careful consideration and monitoring in clinical practice.
- Regulatory hurdles: The classification of polyphenols as dietary supplements rather than pharmaceuticals in many jurisdictions presents regulatory challenges for their use in medical treatments. This classification may limit the scope of research and clinical applications, as well as the level of quality control and standardization required for their production and distribution.
- Individual variability: The response to polyphenol interventions may vary significantly among individuals due to genetic factors, gut microbiome composition, and overall health status. This variability complicates the development of generalized treatment protocols and highlights the need for personalized approaches in polyphenol-based diabetes management.

These problems highlight the need for more comprehensive study, improved standardization procedures, and novel approaches to overcome the constraints associated with polyphenol use in diabetes management. Addressing these challenges is critical to realizing polyphenols' full therapeutic potential in diabetes control [41-47].

RECENT TRENDS AND ADVANCEMENTS

The landscape of bioactive compound recovery has changed dramatically as a result of recent technological advancements in phenolic compound extraction, which emphasize sustainability, efficiency, and a decreased need on conventional organic solvents. Because of their health benefits and antioxidant qualities, phenolic compounds are becoming more and more sought after in a variety of industries, such as food, pharmaceuticals, and nutraceuticals. Increasing the yield and selectivity of these valuable chemicals from renewable resources has been made possible in large part by the development of unconventional extraction techniques.

Microwave-assisted extraction (MAE), which uses electromagnetic radiation to quickly raise the temperature of the solvent and the sample matrix, is one of the most noteworthy developments. Phenolic chemicals are released into the solvent more easily as a result of the rapid rupture of cell membranes caused by this process. When compared to conventional procedures, MAE is especially beneficial because of its speed and efficiency, which frequently result in better extraction yields. Similarly, cavitation bubbles are created in the solvent using ultrasonic energy in ultrasound-assisted extraction (UAE). These bubbles burst and produce shock waves that damage the plant material's cellular structure. Phenolic molecules can be extracted more successfully because of this mechanism, which also improves mass transfer and the solvent-analyte interaction.

Another cutting-edge method that has gained popularity is supercritical fluid extraction (SFE), especially when supercritical carbon dioxide (CO2) is used. The special qualities of supercritical fluids, which combine traits of gases and liquids, are exploited by SFE. Because of the reduced surface tension and increased diffusivity, the supercritical fluid can more easily pass through solid matrices. Because SFE works at lower temperatures than traditional techniques, it is especially useful for extracting chemicals that are sensitive to heat.

Deep eutectic solvents (DES) have become a viable substitute for conventional organic solvents in addition to these extraction methods. Because they are made of natural and biodegradable materials, DES are environmentally friendly and have low toxicity. When combined with cutting-edge extraction techniques, their distinct physicochemical characteristics increase the solubility of phenolic compounds, making them efficient solvents.

All things considered, these technical developments not only streamline the extraction procedure but also satisfy the growing need for environmentally benign and sustainable methods for recovering bioactive substances. A major advancement in the effective and responsible use of agricultural by-products is represented by the combination of unconventional extraction techniques with safer solvent substitutes, which will ultimately aid in the creation of nutraceuticals and functional foods that promote health and well-being [48-52].

DISCUSSION

For diabetic care, indexing polyphenols reveals a multitude of ways in which the metabolites promote metabolic health. Numerous plant-based diets contain naturally occurring substances known as polyphenols. These polyphenols possess powerful antioxidant properties that can combat reactive oxygen species (ROS), which are potentially dangerous. The significance of this lies in the fact that oxidative stress is a critical factor in the development of insulin resistance as well as the complications that accompany diabetes in its later stages. The consumption of polyphenols has also been linked to the modulation of inflammatory pathways, which has a role in the prevention of persistent low-grade inflammation, which may be present in individuals who have type 2 diabetes. Particular polyphenols, such as resveratrol, quercetin, and epigallocatechin gallate, are associated with enhanced glucose metabolism and increased insulin sensitivity, according to academic studies. By offering protective effects against oxidative stress, which is associated to damage to pancreatic β-cells, certain drugs have the potential to boost insulin production at the same time. The formulation of universal recommendations, on the other hand, is made more difficult by the complex features of polyphenols, which include individual differences in absorption and varied quantities in diets that come from a variety of diverse sources. Polyphenols have been demonstrated to have favorable effects overall in some clinical trials; however, other clinical trials have not consistently shown consistent findings. Therefore, additional randomised controlled trials are required to determine the full potential of polyphenols in the treatment of diabetes.

CONCLUSION

Overall, polyphenols represent an interesting path for improving diabetes control for a truly natural way to bolster your metabolic health. Hence, their antioxidant and anti-inflammatory potential makes them important nutritional adjuvants for diabetes-prone and diabetic individuals. Ultimately introducing higher levels of polyphenol-rich foods into diets such as berries, dark chocolate, green tea and a variety of fruits and veggies may result in better glycemic control and overall health. However, more research is necessary to properly utilize the advantages of polyphenols. To evaluate the long-term impacts of polyphenol consumption and establish the ideal dosages for therapeutic usage, longitudinal research is required. Furthermore, resolving the issues of polyphenol content fluctuation and possible drug interactions will be essential to creating successful treatment plans. Healthcare providers can better assist patients in making dietary decisions that promote their health and well-being by expanding their knowledge of polyphenols and their involvement in diabetes.

FUNDING

No funding was received for this study.

ACKNOWLEDGEMENT

Gupta College of Technological Sciences, Asansol, WB.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT AND ETHICAL STATEMENT

Not Applicable

AUTHOR CONTRIBUTION

Concept and design: Adib Hussain, Data collection: Kabirul Islam, Supervision: Arabinda Nayak

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