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Unlocking The Potential Of Phytochemicals In Anti-Diabetic Therapy: Mechanisms, Challenges, And Future Prospects

Ankit Pal[1], Shreyoshi Pal[2], Saikat Manna[3], Semanti Ghosh[4], Bidisha Ghosh[5], Subhasis Sarkar[6], Suranjana Sarkar[7*]

[1]Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal700121, Email: pal334615@gmail.com, Ph:8348217452

[2]Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal700121, Email: shreyopal@gmail.com, Ph: 7449392966

[3]Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal700121, Email: saikatmanna547@gmail.com, Ph: 8327538480

[4]Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal- 700121, Email: semantig@svu.ac.in, Ph- 9432912893

[5]Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal- 700121, Email: bidishag@svu.ac.in, Ph- 8017314552

[6]Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal- 700121, Email: subhasiss@svu.ac.in, Ph- 960919374

[7]Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal- 700121, Email: suranjanas@svu.ac.in, Ph- 8981278415*

****Corresponding Author:** Suranjana Sarkar*

**Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal- 700121, Email: suranjanas@svu.ac.in, Ph- 8981278415*

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Abstract

Diabetes mellitus, a complex metabolic disorder, continues to pose a significant global health challenge. Conventional approaches to diabetes management primarily focus on pharmacological interventions, often accompanied by adverse effects and limited long-term efficacy. In recent years, the exploration of natural compounds, particularly phytochemicals derived from plants, has garnered increasing attention for their potential role in diabetes management. This comprehensive review synthesizes the current understanding of the role of phytochemicals in anti-diabetic therapy. Phytochemicals, bioactive compounds abundant in various plant sources, exhibit diverse biological activities that can impact key mechanisms underlying diabetes. They interact with cellular pathways involved in glucose metabolism, insulin sensitivity, and oxidative stress, thereby offering potential therapeutic benefits. We delve into the intricate molecular mechanisms through which phytochemicals exert their anti-diabetic effects. Flavonoids, polyphenols, alkaloids, and other classes of phytochemicals are discussed in terms of their ability to modulate glucose uptake, enhance insulin signaling, and mitigate inflammation. Moreover, their antioxidant properties are explored in relation to ameliorating oxidative stress-associated complications observed in diabetes. The review also highlights the challenges associated with

	translating phytochemical research into practical anti-diabetic interventions. Bioavailability, dose determination, and standardized formulations emerge as critical considerations for clinical application. Furthermore, we underscore the significance of interdisciplinary collaborations between pharmacologists, clinicians, and botanists to bridge the gap between traditional knowledge and modern evidence-based medicine.
	Keywords: Anti-diabetic therapy, Diabetes management, Insulin sensitivity, Plant-derived compounds, Photochemical

Introduction

Diabetes is a chronic condition that develops when the pancreas either generates insufficient amounts of insulin or when the body cannot properly utilize the insulin that it does. Insulin is a hormone that regulates blood glucose level. The three main types of diabetes are present. The first one is diabetes mellitus. Diabetes Mellitus (DM), one of the most common metabolic illnesses, is defined by elevated levels of glucose in the blood and inappropriate primary metabolism brought on by abnormalities in insulin production, insulin action, or both. One of the most prevalent medical conditions in the world, its incidence is rising quickly and is associated with microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke, and peripheral vascular disease) consequences (Firdous.,2014). Diabetes mellitus (DM) is a metabolic condition characterized by excessively increased blood glucose levels (Sapra&Bhandari., 2023). There are four main categories that may be used to classify the group of chronic illnesses that it encompasses. Type 1 diabetes mellitus (T1DM), type *2* diabetes mellitus (T2DM), gestational diabetes mellitus (GDM) and monogenic diabetes (Oliveira et al., 2023).Type 1 diabetes mellitus (T1DM), commonly referred to as autoimmune diabetes, is a chronic condition that causes hyperglycemia owing to an inability to produce sufficient amounts of insulin as a result of the death of pancreatic beta cells. Although symptoms often begin in infancy or teenage years, they can occasionally appear much later in life(Katsarou et al., 2017). Type 2 diabetes mellitus (T2DM), one of the most prevalent metabolic diseases. insulin-sensitive tissues' inability to react properly to insulin because to pancreatic beta-cells' imperfect insulin production. The molecular mechanisms involved in the production, release, and detection of insulin, as well as their detection, are closely controlled because these actions are crucial for maintaining glucose homeostasis. A metabolic imbalance that causes the illness to develop can be caused by flaws in any of the systems involved in these processes(Garcia et al., 2020). Gestational diabetes is when spontaneous hyperglycemia occurs during pregnancy, it is known as gestational diabetes mellitus (GDM), which is a frequent pregnancy problem. The most recent estimates from the International Diabetes Federation (IDF) for 2017 indicate that GDM affects around 14% of pregnancies globally, or 18 million births yearly. Overweight/obesity, a westernized diet, deficiency in nutrients, advanced maternal age, and a history of insulin resistance and/or diabetes in the family are risk factors (Plows et al., 2018). Neonatal diabetes, maturity-onset diabetes of the young (MODY), and different diabetes-associated syndromes are a few clinical disorders that are commonly defined by early-onset diabetes and are included under monogenic diabetes. Patients who appear to have type 2 diabetes mellitus, however, may have monogenic diabetes. In the absence of obesity, poor insulin secretion and reduced pancreatic islet function are the main causes of monogenic diabetes (Bonnefond et al., 2023). Large quantities of hypotonic urine are excreted when a person has diabetes insipidus (DI), a medical condition. Nephrogenic DI is caused by kidney resistance to the hormone arginine vasopressin (AVP), whereas central DI is caused by a lack of this hormone in the pituitary gland or the hypothalamus (Crain et al., 2019). Glulisine (Apidra), lispro (Humalog, Admelog, and Lyumjev), and aspart (Novolog and FiAsp), Metformin, Glibenclamideetc . Plants produce naturally occurring compounds termed phytochemicals. They are categorized as secondary metabolites and do not directly control the development, growth, or reproduction of fruits, vegetables, or mushrooms(Shen et al., 2022). Many phytochemicals are typically harmless, plentiful in basic dietary items, and have beneficial effects on health, thus they are being explored extensively with the aim of generating medications (Known et al., 2023) . Some of the phytochemicals are Aromatic acid, organic acid, phytosterols, flavonoids, terpenoids, saponins, alkaloids, carotenoids, essential oils, and protease inhibitors etc. . We are focusing on herbaltherapy since it has low levels of antibiotic resistance, inexpensive, easily producible, abundant in nature, and has minimal cytotoxicity.

Indian and Asian prospect:

Type1 diabetes –

In 2010 study it was seen that Saudi Arabia has 0.02752 incidence per 10000 type 1 diabetes rates from sample size of 1028.This is pretty concerning to the Asia. In 2002 study it was seen that Kuwait has 0.02018 incidence per 1000 type 1 diabetes rates from sample size of 760. This is pretty concerning to the Asia. In 2014 study it was seen that Asia has 0.0114 incidenceper 10000 type 1 diabetes rates from sample size of 433. This is pretty concerning to the Asia. In 2007 study it was seen that Australia has 0.0194 incidents per 10000 type 1 diabetes rates from sample size of 731.This is pretty concerning to the Asia and the more information present in (Table -1).

India now has three new T1DM cases for every 100,000 children aged 0 to 14 years. 3.0 cases/100,000 children in Chennai, 10.2 cases/100,000 children in Karnal (Haryana), and 17.93 cases/100,000 children in Karnataka, according to three sets of prevalence statistics. In 9% of instances of insulin insufficiency, T1DM is present and may be autoimmune or idiopathic in origin (Das et al., 2015).
Type2 diabetes:
In 100,000 people 5961 people are affected by type2 diabetes in Asia. In 100,000 people 6262 people are affected by type2 diabetes in China. In 100,000 people 4770 people are affected by type2 diabetes in India. In 100,000 people 6373 people are affected by type2 diabetes in Japan. In 1000,000 people 8835 people are affected by type2 diabetes in South Korea. In 1000,000 people 10,012 people are affected by type2 diabetes in Taiwan. In 1000,000 people 7661 people are affected by type2 diabetes in Saudi Arabia.

Region	Prevalence (cases per 100,000)	Burden of suffering (DALY per 100,000)
Asia	5961	729
China	6262	635
India	4770	663
Japan	6737	553
South Korea	8835	1044
Taiwan	10,012	294
Saudi Arabia	7661	623

Table 1: Disease burden of type 2 diabetes, 2017 (Khan et al., 2020).

8.4 % people are affected by type2 diabetes in Andhra Pradesh. 5.10% people are affected by type2 diabetes in Arunachal Pradesh. 5.5 % people are affected by type2 diabetes in Assam. 4.3% people are affected by type2 diabetes in Bihar. 13.6% people are affected by diabetes2 in Chandigarh. 7.1 people are affected by type2 diabetes in Gujarat and more information present in (Table-3).

Gestational Diabetes Mellitus :
However, the prevalence of GDM was generally higher in Asian immigrants (0.18%-24.2%). In 2019, it was predicted that 8.3% (463 million) of individuals in the world between the ages of 20 and 79 had diabetes, with 223 million of those people being women. According to projections, in 2045 it will exceed 700 million individuals and 343 million women alone. Prevalence of diabetes during pregnancy is also rising, which is dangerous for both the mother and the unborn child (Li et al., 2022).
Diabetes is a significant public health issue in India, where prevalence rates are estimated to range between 4.6% and 14% in urban areas and 1.7% and 13.2% in rural regions. According to reports, the prevalence of gestational diabetes varies by region, from 3.8% in Kashmir to 6.2% in Mysore, 17.9% in Tamil Nadu and 9.5% in Western Indi (Mithal et al., 2015).

Monogenic diabetes:
Among the Indian population, there is a dearth of literature on pediatric monogenic diabetes. In a South Indian tertiary care facility, 37 children with monogenic diabetes who were diagnosed between 2008 and 2019 had their case records retrospectively examined (Lakshmanan et al., 2021).

Age:
Type 1 diabetes may occur at any age, it does so in two distinct waves. Kids between the ages of 4 and 7 experience the first peak. The second affects youngsters between the ages of 10 and 14. The majority of persons with type 2 diabetes are over the age of 45, but it is becoming more common among kids, teenagers, and young adults. Pregnancy-related diabetes is more likely to occur in women over the age of 25 compared to younger

women. The majority of persons with monogenic diabetes are young, often 25 years or younger, and it manifests in a variety of ways. Diabetes insipidus occur between 10 and 20 years old.

Role of diet:
Eating a range of nutritious meals from all the food categories is essential to controlling diabetes: veggies and fruits. entire grains including quinoa, oats, brown rice, barley, and whole wheat. proteins, including tofu, lean meats, fish, eggs, nuts, beans, lentils, and poultry that controlling the diabetes mellitus.In case of diabetes insipidus If the condition is minor, a doctor or endocrinologist could advise reducing protein and salt in the diet to assist the kidneys generate less urine.

Genes:
The autoimmune death of pancreatic cells results in type 1 diabetes, a complicated condition with a significant hereditary component. More than 40 non-HLA susceptibility gene markers have been found, although the main susceptibility locus maps to the HLA class II genes at 6p21 (Steck et al., 2011). In case of type2 diabetes TCF7L2, a gene that regulates insulin release and glucose production, is one of the genes linked to type 2 diabetes risk. ABCC8, which plays a role in controlling insulin.In case of GDM When compared to pregnant women without GDM, both GDM groups had considerably reduced levels of methylation in the maternal imprinting MEST gene and the non-imprinting glucocorticoid receptor NR3C1 gene, both of which are linked to placental and fetal growth(Dalfrà et al., 2020). In case of diabetes insipidus the AVP gene is mutated, which results in diabetic insipidus. The antidiuretic hormone (ADH), also known as vasopressin, is made using the instructions from this gene.

Detection:
Plasma or blood glucose levels are currently used to diagnose diabetes mellitus. A person with the typical symptoms just has to have a random plasma glucose level > or = 200 mg/dL to be diagnosed(Lebovitz et al., 2001). In case of diabetes insipidus When there is evidence of plasma hyperosmolality (greater than300 mosm/l), urine hyperosmolality (less than 300 mosm/l or urine/plasma osmolality less than 1), and polyuria (urinary volume greater than 4 to 5 mL/kg/hr for two hours straight after surgery), central diabetes insipidus has been identified (Hui et al., 2023).

Treatment:
There are several medications that may be utilized to regulate and manage diabetes. Because each person is unique, each person's therapy will change based on their own needs. An insulin pump can be a useful alternative to using an insulin pen for treatment of Type 1 diabetic patients. If any patient carry Type 1 diabetes, for those patient might be able to have an islet cell transplant.
In order to control blood sugar levels in Type 2 diabetes, a patient may need medication. The most commonly used tablet is matformin, although there are several more varieties as well. Other treatment for Type 2 diabetic patient is diet and exercise, insulin, weight loss surgery, emotional support etc .

Symptoms:
Frequently urinate (pee) at night. Really thirsty,without exerting any effort, are extremely hungry, vision is hazy, are extremely hungry, extremely tired, Have tingling or numb hands or feet. Possess very dry skin, have wounds that heal slowly, Have more infections than normal, diabetes mellitus may be present as a result of these symptoms.
In case of diabetes insipidus for adult being extremely thirsty, producing a lot of pale urine, frequently preferring cold water, waking up frequently through the night to use the restroom and drink water this symptoms are present.
Symptoms of diabetes insipidus in a newborn or young kid may include: Fever, Headache, Vision problems, Problems sleeping, Vomiting, Irritability, being extremely thirsty, and preferring to drink cold drinks and water, Bed-wetting,pale urine in large quantity resulting in thick, wet diapers.

Alkaloids			Reference
Phytoconstituents	Plant Name	Part used	Dalfrà et al., 2020
Casuarine 6-o--glucoside	*Syzygiummalaccense*	Bark	Shen et al., 2022
Berberine	*Berberis spp. Tinosporacordifolia*	Roots, stem-bark	Lakshmanan et al., 2022

Cryptolepine	*Cryptolepissanguinolenta*		Plows et al., 2018
Catharanthine, vindoline and vindolinine	*Catharanthusroseus*	Leaves, stems	et al.
Calystegine B2	*Nicandraphysalodes*	Fruits	Mobasseri et al., 2010
Jambosine	*Syzygiumcumini*	Seeds, fruits, bark	Steck et al., 2014
Harmane , norharmane,	*Tribulusterrestris*		Rodrigues et al., 2023
			Li et al., 2022
Pseudoprototinosaponin AIII &prototinosaponin AIII	*Anemarrhenaasphodeloides*	Rhizome	Mithal et al., 2015
Perlargonidin 3-o-- l rhamnoside	*Ficusbengalensis*	Bark	Galicia-Garcia et al., 2020
Myrciacitrins I and II and myrciaphenones A and B	*Myrciamultiflora*	Leaves	Christ-Crain et al., 2019
Neomyrtillin	*Vacciniummyrtillus*	Leaves	Katsarou et al., 2017
Kalopanax	*Kalopanaxpictus*	Stem bark	Kwon et al., 2023
Galactomannan gum	*CyamopsistetragonolobusAmorphophalluskonjac*	Seeds Tubers	Das et al., 2015
Ganoderans A and B.	*Ganodermalucidum*	Fruit bodies	Mobasseri et al., 2020
Atractans A	*Atractylodes japonica*	Rhizomes	Christ-Crain et al., 2019
Aconitans A-D	*Aconitum carmichaeli*	Roots	Khan et al., 2020

Table 3: Phytoconstituents used in the treatment of Diabetes mellitus.

Challenges

There are many processes during the extraction of phytochemicals. The process can have error at any of the steps. The steps and concentration are very crucial. This is the first point of high chances of error in phytochemicals extraction.

The second point is concentration can be different in the same batch of extracts. So in this case if we extracts from various plants they have different concentration of phytochemicals and we cannot be sure that it is exactly same percentage as previous batch.

The third point is decrease in plant population due to the pollution and climate changes. So we need to prevent it.

The fourth point is we cannotpreserve the phytochemicals aswe have the methodology for this. We can preserve different types of phytochemicals for shorter period of time but for long time it is quite difficult for us.

The fifth one is the not equivalent infrastructure for phytochemicals production and maintenance for grand level.

Conclusion

The majority of medications have some adverse effect. So the opposite side phytochemicals have less side effect, easily producible, low levels of antibiotic resistance, natural resources are abundant,reduced cytotoxicity. So the several studies demonstrate that phytochemicals have very much effective for antidiabetic therapy.

Future prospect

Phytochemicals have good potentiality for antidiabetic therapy. The industrial infrastructure will improve in the future that will be available for large production of phytochemicals so for that reason we can treat

antidiabetic therapy due to the using of different phytochemicals.We can only hope that the appropriate dose will be determined in the future and another point is if we can safe the plant from extinction so, it will be better for us.

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