A Review on Phytochemicals as Potential Therapeutics for Diabetes

By

Sumaiya Tabassum Orchi
21346071

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Sumaiya Tabassum Orchi
Student ID: 21346071

Approval

The thesis titled " A Review on Phytochemicals as Potential Therapeutics for Diabetes" submitted by Sumaiya Tabassum Orchi (Student ID: 21346071), of Spring, 2021 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.).

Supervised By:

____

Dr. Humair Bin Md. Omer
Assistant Professor
School of Pharmacy
Brac University

Approved By:

Acting Chairperson:

____

Dr. Raushanara Akter
Acting Chairperson and Professor
School of Pharmacy
Brac University

Dean:

____

A.F.M. Yusuf Haider, PhD
Acting Dean, School of Pharmacy
Professor, Department of Mathematics and Natural Sciences
Brac University

Ethics Statement

This project does not involve any kind of animal and human trials.

Abstract

Diabetes mellitus is one of the major diseases that is seen in every corner of the world and it became a great challenge worldwide as the number of patients is increasing in a larger number. For managing diabetes, many pharmacotherapy and synthetic medicines has been developed but it is seen that those medicines are less patient compliant and holds limitations. So nowadays researchers are interested in plant derived medications which are known as phytochemicals. In this review article, detailed studies are provided about phytochemicals that are used as therapeutics for diabetes mellitus. This review gives scientific facts of phytochemicals such as- Flavonoids. Alkaloids, Terpenoids, and Phenolic acid which are antidiabetic potential. For using phytochemical derived medicines in mainstream, more research and clinical studies are required. This review aims to compile recent knowledge about phytochemicals used in diabetes management by emphasizing their therapeutic effectiveness, mechanism, challenges and advance treatment approaches.

Keywords: Phytochemicals; Anti-diabetic agent; Bioactive compound; Metabolites; Hyperglycemia, Bioavailability.

Dedication

I want to dedicate this project work to my beloved parents for their endless support, encouragement and to my niece whose arrival in this world coincided with the beginning of my university journey. Also, immense appreciation to my mentors and my faculties. Lastly, I dedicate this work to all Diabetes patients with the hope that advancements in Phytochemical studies will bring more effective treatments strategy and a better life.

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Chapter 1

Introduction to Diabetes and its prevalence

1.1 Background

Diabetes mellitus is a multidimensional and long-term metabolic dysfunction which is a condition that is marked by high blood sugar level. This can be caused when the body is unable to produce sufficient insulin by the pancreas or is unable to utilize it effectively, so that body becomes incapable to regulate blood glucose level for a long period of time. Insulin is a complex hormone which is directly responsible for carrying the glucose from blood into the cell, which is responsible for producing energy. Due to insulin dysfunction of insulin, the glucose remains in the bloodstream and leads to hyperglycemia- marked as diabetes. This hyper level of glucose can cause various complications such as- damaging different organs and tissues in the body.

Types of Diabetes

Predominantly there are three types of diabetes which are more common, those are: Type-1 diabetes mellitus (T1DM), Type-2 (T2DM) diabetes mellitus and Gestational diabetes mellitus, etc.

Type-1 diabetes is a type of a condition where it targets its own tissues or organs. Here in Type-1 diabetes the pancreas doesn’t produce any insulin or a smaller amount of insulin. It requires insulin therapy. It’s a chronic condition. Causes frequent urination, polyphagia, weight loss, fatigue, blurry vision etc. It is usually seen in young adults, children. It is not preventable.

In Type-2 diabetes the body becomes insulin resistant means the body fails to respond to insulin and deficiency of insulin is seen. It is usually seen in adults over 45 but increasingly seen in younger people too. This may cause complications such cardiovascular disease, renal failure, nerve dysfunction, less ocular vision etc. This type-1 diabetes condition is connected with one's lifestyle. Because of imbalance in diet, obesity, less physical exercise, also a strong reason for this can be generated from genetics. More than half of Type-2 patients require insulin therapy after 10 years of insulin resistance because of pancreatic damage of B-cell but in certain time it can be managed by changing the lifestyle, by oral medications or diet. According to (WHO, 2023) almost 90-95% of people are suffering from Type-2 diabetes.

Another type of diabetes is Gestational diabetes, which generally occurs during the time of pregnancy because of hormonal changes (like- lactose increases insulin resistance) and it rectifies after the childbirth. But it also can develop Type-2 diabetes later.

There are also some types of diabetes that exist, such as- Maturity onset diabetes of the young (MODY), Neonatal diabetes, cystic fibrosis diabetes, Steroid-induced diabetes, etc.

1.2 Prevalence of Diabetes

Worldwide diabetes became a top-most topic and a big health challenge of the 21st century. As per International Diabetes Federation around 537 million adults whose age is around 20-79 years are living with diabetes in 2021, this number will rise to 643 million by 2030 and 783 million by 2045 (IDF,2023). Bangladesh is one of the highest burdens of diabetes patients in the South Asian region. And there is evidence that this disease burden is increasing. The prevalence of diabetes in Bangladesh was around 13% in 2017-2018 increased from only ~5% in 2001, prevalence of undiagnosed diabetes was also found to be higher at 6% in 2017-2018. It is also seen that the current number of cases will be doubled (~15 million) by 2045. Although the prevalence of diabetes is increasing in Bangladesh. (Khan et al., 2022). Most recently, according to WHO over 800 people or adults are living with diabetes in 2024, a noticeable rise from 422 million in 2014 due to the increasing rate of Type-2 diabetes cases (WHO, 2024). Almost 445 million adults over 30 years old are not getting diabetes treatments (Lin et al., 2024).

Current data of Europe approximately 74 million adults live with diabetes from which 11.9% of men and 10.9% of women (WHO, 2024). The international prevalence of diabetes in adults in the year of 2021 is 537 people and it may increase to 783 million by 2045 which is assumed by the IDF.

Bangladesh is also holding among the highest 10th number. It became 8th number globally where adults aged (20-79) are suffering from diabetes. It was 13.3 million in 2021 and expected to raise to 22.3 million by 2045. But in Bangladesh the age rate is not specified and the growth is rapid, so it needs immediate actions and public concerns about health.

Table-1.1: Number of Diabetes cases in different countries by 2021. (Lin et al., 2024)

USA	32 million
Bangladesh	13.1 million
China	140.9 million
Indonesia	19.5 million
India	74.2 million
Pakistan	33.0 million

It is seen from 1990-2022 the rate of worldwide diabetes prevalence in adults has increased double (7%-14%),(Chan et al,2024). It is also seen that mostly suffering countries are low-middle income countries (IDF). To avoid this global problem, it requires global concerns as well as people themselves needs to be more aware about their health and the treatment strategies need a change, need to be strengthened to get rid of its long term effect.

Chapter 2

Methodology

The current review is based on a systematic search process undertaken to search, analyze, and synthesize pertinent scientific knowledge on the potential of using phytochemicals in the treatment of diabetes mellitus. Several databases established internationally were utilized to be able to cover a lot of published literature. These were PubMed, Scopus, Web of Science, and Google Scholar; these peer-reviewed resource sites are credible sources of biomedical and life science articles.

The search was conducted in a systematic procedure within [2000-2025]. A mixture of keywords and Boolean was used to encompass all the relevant articles. The main keywords were phytochemicals, plant-derived compounds, natural products, and bioactive compounds, coupled with diabetes, type 2 diabetes mellitus, insulin resistance, anti-diabetic effect, and glucose metabolism. Boolean operators 1 (AND, OR & NOT) were applied to narrow the search. Specific examples include a search term combination of phytochemicals AND diabetes and natural products AND insulin resistance.

The eligibility criteria to include articles of interest were as follows: (i) studies conducted in peer-reviewed journals; (ii) studies written in the English language; (iii) articles in which the focus was specifically on the antidiabetic property of phytochemicals either through in vivo, in vitro, or clinical studies; and (iv) review articles that provided valuable insight into the mechanism of action of the phytochemicals. Criteria of exclusion comprised abstracts of conferences with no full data, non-English studies, and papers with little relevance to the topic of phytochemicals applied in diabetes management.

Initially, the studies were carefully chosen to ensure that the studies used met the quality criterion of being published in high-impact journals and indexed either in PubMed or Scopus.

Reference lists of a selection of articles were also reviewed to identify any further studies not picked up in the initial database search.

Lastly, the retrieved articles were categorized, subjected to critical evaluation, and summarized into distinct topics, including but not limited to mechanism of action, the nature of the phytochemical being studied, and in diabetes management potentials.

Chapter 3

Introduction to phytochemicals, their application in medication historically

3.1 Introduction

Nature is the best in purpose of healing something, the one healer can be defined as phytochemicals, Phytochemicals that can be found in nature, from greenery sources. These are mostly physiologically potent compounds or the bioactive compounds, which includes-minerals, vitamins. These are not those essential compounds that are not necessarily important for a person to survive their lives but it may provide tons of benefits to the human body by its nature of prevention. Nowadays many health professionals are focusing more on this type of natural medication system because consuming this plant-based things or food routine may reduce the risk of different diseases. Its value has been established for years of civilization. It's been 5000 years from when people started using natural pants for treatments. Historical cultural countries like- China, Mesopotamia, Egypt, and India are seen to use herbal products for the remedies of medicine.

In Egypt at around 1550 BCE over 700 remedies are plant based including- Garlic, Aloe Vera, etc. (Crag and Newman, 2005)

3000 years ago Ayurveda was established in India. It includes Neem and Turmeric for treating different kinds of infections, or intestinal disorders.

In China, Ginger, Licorice were used as the remedy of traditional medicines, these are rich with secondary metabolites as like- Flavonoids, Terpenoids.

The middle Ages and in the renaissance the herbal texts and pharmacopeias got more exploration and new innovations.

The scientists have collected some active compounds from the whole plant-based products and converted it to pure substances. Some isolated plant-based compounds are-

1. Morphine- It's collected from opium poppy by Friedrich as first Alkaloids in 1804.
2. Salicylic Acid- From the Willow bark this salicylic acid was isolated. Its antecedent of Aspirin.
3. Digoxin- It's isolated from the foxglove plant, treats heart diseases.
4. Quinine- It was isolated from the bark of cinchona; it was the first curative medication of malaria.

It is seen that 10000 or more than of this number of phytochemicals are also there in nature but those are not still identified (salvin et al, 2012).

3.2 Classification of phytochemicals

Phytochemicals can be two types such as,

i) Primary metabolites: These are the compounds which mostly helps in plant growth. These primary metabolites are,

- **Proteins:** These are made from the smaller unit of amino acid, which helps in signaling pathway, essentials for enzymes, and for structure.
- **Amino acid:** This is important for cell activity. A large number of proteins together makes an amino acid compound.
- **Carbohydrates:** It supports the body's structure and by providing energy.

- **Lipids:** It stores the energy and helps the structure of the cell membrane.
- **Nucleic acid:** It helps by carrying the genetic information from mother to fetus.
- **Chlorophyll:** Helps in photosynthesis, plants make their foods by its help.

ii) Secondary Metabolites: It doesn't directly help the plant to grow but saves it from environmental complexity**.** There are different types of secondary metabolites, such as-

- **Alkaloids:** This contains Nitrogen in it. Example- caffeine, quinine, morphine etc.
- **Saponins:** It has foaming properties; cell membrane can be damaged by this. Saponins that improve cardiometabolic health and lower diabetes risk (Marinangeli, 2025).
- **Carotenoids:** Gives the protection to the plant from excess light, also helps in photosynthesis.
- **Terpenoids**: It has a defensive characteristic, it includes flavor, colors too. Example: rubber, menthol etc.
- **Polyphenol**: It has different types of phenolic group and it's a very large diverse compound. They also have some types, such as-

  1. Flavonoids- It's an antioxidant. It can be used in heart failure, as anti-cancer agent and anti-inflammatory (Panche et al., 2016). Citrus flavonoid such as naringenin also plays important role in hyperglycemic condition by lowering blood sugar level (Shilpa et al.,20230

  2. Lignans- It's also an anti-cancer agent also helps in lowering cholesterol level and balance the hormonal complexity (Thompson et al., 2005)

3. Phenolic acid- It is used as an anti-inflammatory, anti-oxidant agent.

3.3 Phytochemical in recent traditional medicines

In consideration of health safety, phytochemicals are the core to the initial way of treatment in the healthcare system in Asia and Africa. 80% of the population worldwide are dependent on traditional plant-based medication systems (WHO, 2013). Also, nowadays in western medication system is showing more interest in herbal or plant-based medication or treatment systems by different herbal therapies. For example, turmeric extracts like curcumin is also seen as managing metabolic disorders and anti-inflammatory substances. High consumption of vegetables and fruit is the key source of flavonoid, carotinoid and glucosinolates which reduces metablic disease risk (Avato & Argentriier, 2022; Wolfson et al., 2025)

3.4 Challenges

There is also some challenges that are seen using phytochemicals such as-

The standardization problem is one of them because herbal substances have different concentrations and it may vary. Then, some phytochemicals have toxic effects if it is used in a high dose. On other hand this plant-based compounds sometimes shows low bioavailability as poor or rapid metabolism and absorption took place. Sometimes it is difficult to get the desired result from the plant-based medications. Also can cause complex phytochemical interactions which act synergistically in plant but demonstrates reduced activity when isolated (Junejo et al., 2024, Misra et al., 2024)

These challenges can be overcome by using genetics for having active yield or nanotechnology and personalized nutrition strategy can be a better solution for it also for having effective results clinical trial is must (Junejo et al., 2024)

Chapter 4

Recent phytochemicals used as therapeutics for Diabetics

In low- and middle-income countries the prevalence of diabetes is seen more than other countries worldwide, so having an affordable and safer way of treatment which is easily accessible to anyone – phytochemical has taken the core place to treat diabetes. Phytochemical provides anti-diabetic, anti-oxidant properties also it works as anti-inflammatory as well.

Some recent phytochemicals which are used in the management of diabetics. Such as-

1. **Curcumin:** It was found in Turmeric (*Curcuma longa)*. Recently from a random trial it is seen that in fasting blood sugar curcumin lowered the blood sugar level, HbA1c and C-reactive protein level in a patient with type-2 diabetes mellitus, this trial was conducted over a 12-week period. (Panahi et al., 2018)

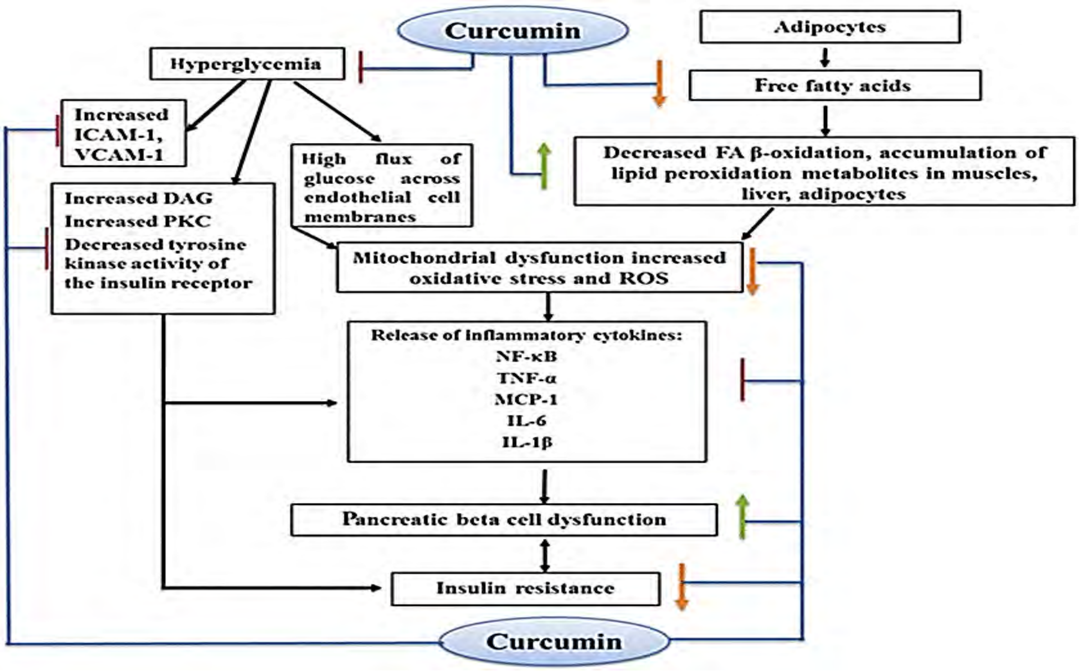

Figure 4.1: Mechanism of action of Curcumin in diabetes (Mohammadi et al., 2021)

By improving B-cell function and increasing the secretion of insulin curcumin helps in managing diabetes.

2. **Chlorogenic Acid:** The natural source of this acid is Apple, Pears, Caffeine, etc. In 2021 a result shows that this acid improves the postprandial sugar level and response of insulin is quite noticeable so, it provides supports by managing diabetes. (Ong et al.,2021)

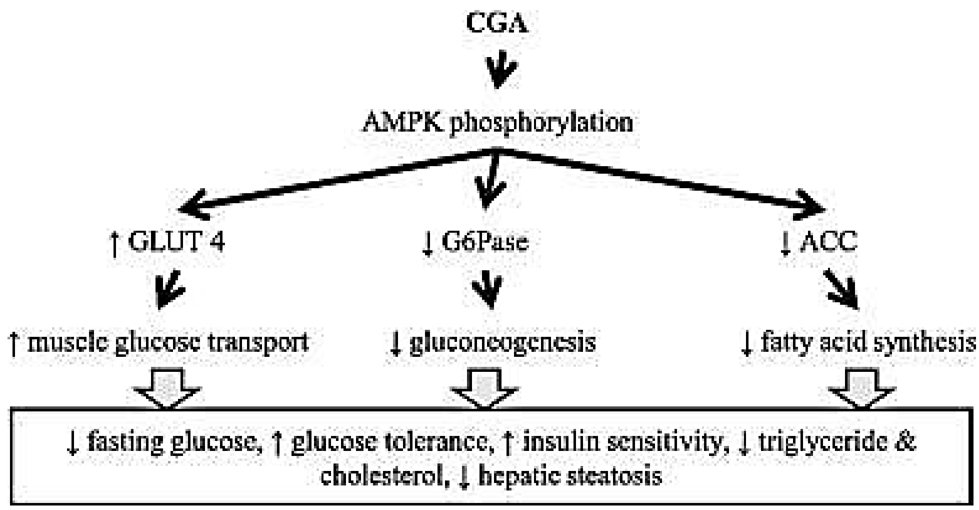

Figure 4.2: Mechanism of action of chlorogenic acid in diabetes (Ong, Hsu, & Tan, 2013)

Cholinergic acid lowers the hepatic glucose production by inhibiting glucose-6-phosphatase. It increases the insulin sensitivity and glucose tolerance is high by that time, this is how it manages diabetes.

3. **Resveratrol:** The main source of this metabolite is Grape fruit, Blueberries and peanuts. From a meta-analysis it is seen that it controls the insulin sensitivity and glucose control for the patients with TDM-2, who is suffering from obesity. (Tome et al.,2022)

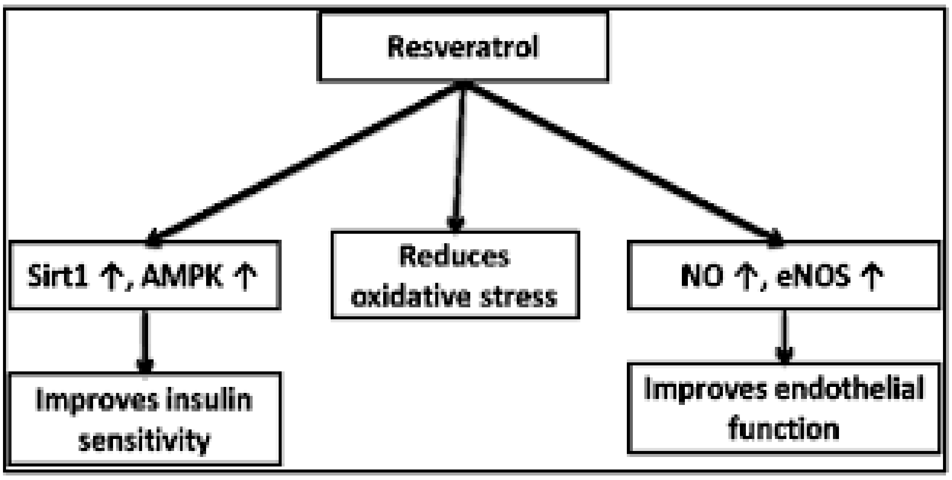

Figure 4.3: Mechanism of action of Resveratrol in Diabetics (Tome et al., 2022)

This polyphenol works by activating SIRT1 which helps by reducing oxidative stress thus the insulin signaling is increased.

4. **Berberine:** The source of these metabolites are *Berberis vulgaris, Hydrastis Canadensis etc.* A most recent clinical trials shows that Berberine can lower the blood sugar level, HbA1c and its insulin resistance with effects comparable to metformin. (Zhang et al.,2021)

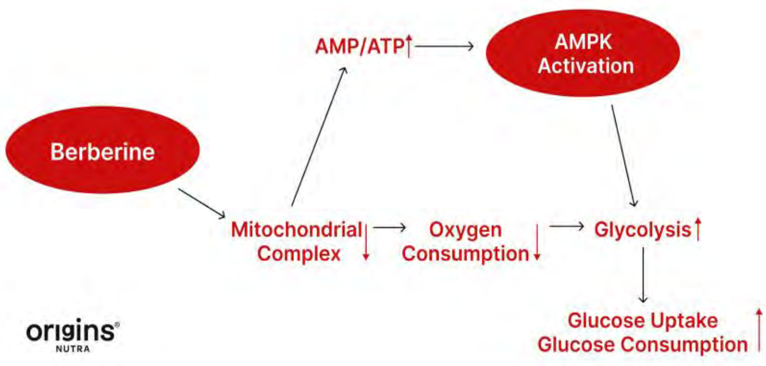

Figure 4.4: Mechanism of action of Berberine (Xu et al. 2021)

By activating Activated protein kinase, it regulates the glucose and lipid metabolism. It modifies insulin sensitivity and in peripheral tissue it increases glucose uptake thus lowers the gluconeogenesis in hepatic cell. (Zhou et al., 2022) And the glucose level is controlled in such manners.

5. **Epigallocatechin Gallate:** The one source of this metabolite is Green tea. A recent clinical trial shows the Epigallocatechin Gallate supplement helps in improving insulin resistance and in prediabetes individual it improves the lipid profile as well. (Rains et al.,2021)

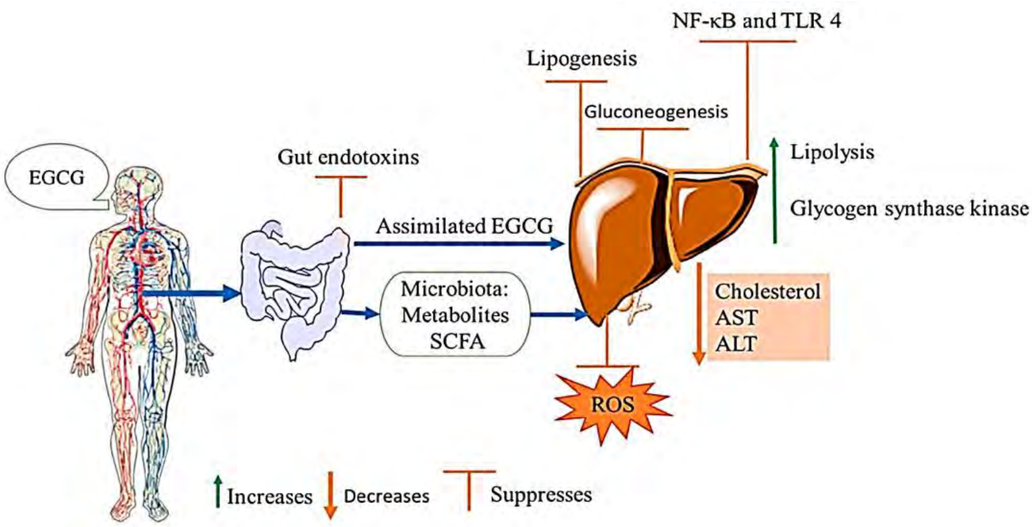

Figure 4.5: Mechanism of action of EGCG in diabetes (Liu et al., 2020)

By increasing the insulin sensitivity and inhibiting alpha-glucosidase and alpha-amylase it lowers the blood sugar level, on the other hand it shows the anti-oxidant characteristics (Liu et al., 2020). It also causes glucose uptake by GLUT4 expressions. This is how EGCG helps in managing diabetes.

6. **Quercetin:** The main source of these metabolites are Onion, Green leaves, Barries, kales and Apples, etc. In human studies some clinical trials reported that it improves HbA1c, lipid profiles and inflammation in patient with type-2 diabetes by quercetin supplements. (Egert et al., 2018). Also, a recent study shows quercetin protects pancreatic islets and improve glucose tolerance in animal model. (Liu et al.,2022)

In combination therapy it shows synergism with metformin, which is an anti-diabetic agent. It worked by controlling the glucose level. (Choi et al., 2020)

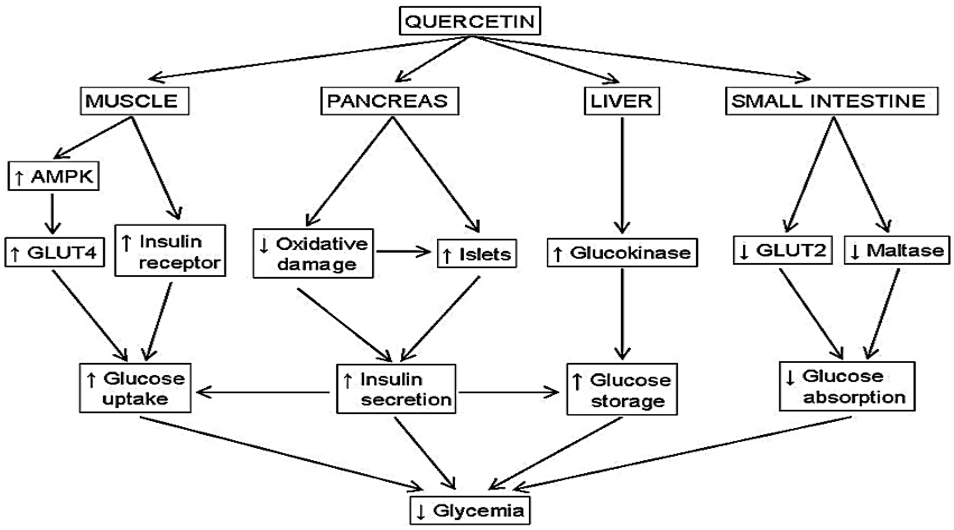

Figure 4.6: Mechanism of action of Quercetin in Diabetes (Zhao et al., 2022)

Quercetin works by inhibiting the carbohydrate digesting enzyme and enhances insulin secretion, reduce oxidative stress (Zhao et al., 2022)

7. **Kaempferol:** It is present in green leafy vegetables. An animal study shows Kaempferol supplements help to improve islets and reduces peroxidation of lipids.(Wang et al.,2021). In preclinical studies with highly obese diabetic mice kaempferol was given and it is seen that kaempferol reduced the blood glucose level, improved lipid level and insulin resistance (Zang et al.,2015).

   Kaempferol is a poor soluble and rapid metabolism substance that's why it shows low bioavailability.

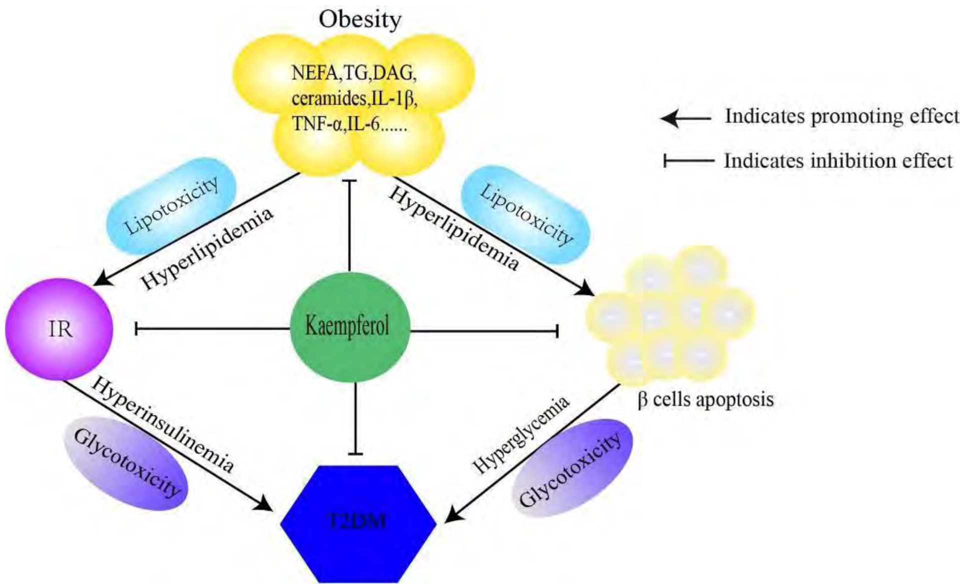

Figure 4.7: Mechanism of Kaempferol in Diabetes (Chan et al., 2018)

Kaempferol improves the insulin sensitivity by increasing IRS-1 actions and lowers the JNK activation. Provides protection to pancreatic B-cells. It inhibits hepatic gluconeogenesis.

Recently used phytochemicals that have been used to treat diabetes provided a strong border in the prevention of Diabetes management as well management of diabetes. These naturally occurring phytochemicals showed a strong anti-diabetic effect in many different processes this includes- Braberin, Kaempferol, Curcumin, and Resveratrol by glucose and insulin sensitivity, reducing the oxidative stress. This biologically active doesn't only act on hyperglycemia but also finds out the main reasons such as insulin prevention and B-cell disability.

These phytochemicals are mostly found in daily dietary and ancient herbal medicines. The challenges of using phytochemicals as a solution of diabetes can be overcome by pre-clinical trial, research, and phytopharmaceutical evolution for their correct therapeutic results.

Chapter 5

Extraction, Purification and Chemical characterization of phytochemicals for Diabetes.

For doing any research or for treatment purpose phytochemicals can be used and for isolating the phytochemical also for identification, extraction is the first step through which a compound can be identified, after completing its extracting procedure purification is must and then done the chemical characterization which gives the confirmation for the reason of its therapeutic effect.

5.1. Extraction procedure:

Selecting the Plant Material- This is a pre-extraction process mainly. The factors like plant root, leaves, bark etc. and the age of the plant also the geographical location may affect the contents of a phytochemical. Proper drying and mixing also grinding into an even powder promote larger surface area for an effective solvent perforation.

For an antidiabetic research purpose mostly used plants are, *Trigonella foenum-graecum, Gymnema sylvestre,Ocimum sanctum, Momordica charantia.* These contain mainly Alkaloids, Saponins, Flavonoids and Triterpenoids, etc.). For instance, grapes are used for resveratrol, coffee beans which are green used for cholorogenic acid and turmeric for curcumin.

Curcumin is extracted by using acetone or ethanol, Chlorogenic acid is extracted with water or methanol and Resveratrol is extracted by using 70% ethanol. These involves conventional extraction process that are:

- Soxhlet: It's a constant heating extraction procedure where ethanol is used for multiple hours (6-8 hours). (Handa et al., 2008). It is ideal for non-thermolabile compounds, but requires more time and more solvents.
- Maceration extraction: When plant is turned into a powder formation then the powder is soaked in a slightly high temperature such as 30-40 degree Celsius or in normal room temperature, with few shaking. Common solvents are used such as ethanol, methanol acetone and water. The order depends on solvents polarity, time, temperature and agitation (Sasidharan et al., 2011).
- Percolation: the powder materials are packed into a percolator. It's more efficient than maceration. But it requires more safety and precise solvent selection (Azwanida, 2015).

There are also some advanced extraction techniques such as UAE-Ultrasound Assisted Extraction, MAE-Microwave Assisted Extraction, SFE-Supercritical Fluid Extraction and PLE- Pressurized Liquid Extraction. UAE utilizes the ultrasonic waves which facilitated the plant cell wall disruption which is suitable for the extraction of flavonoids and alkaloid extraction (Wang & Weller, 2006). MAE is worked my heating the solvent mixture which improves the solvent extraction and increase the yield. It is ideal for the phytochemicals that are thermally stable (Eskilsson & bjorklund, 2000). SFE is best for non-polar compounds and it uses the CO2 as solvent. PLE increases the pressure and temperature which is ideal for the extraction of bioactive phenolic compounds (Mustafa & Turner, 2011).

The parameters such as solvent selection, temperature, time for extraction influences the significant yield and purity. Response Surface Methodology is used for fine-tuning these variables for increased phytochemical yield (Zhang et al., 2009).

The extraction procedures of phytochemicals that are used for diabetes management:

Curcumin- It is generally extracted from rhizomes. Solvent extraction is performed where ethanol is commonly used or acetone because of its polarity. Soxhlet and UAE- ultrasonic assisted extraction is used to increase the yield (Estbeyoglu et al., 2012). Recently it is seen that supercritical CO2 is used to preserve bioactivity (Paramasivam et al., 2009).

Resveratrol- Here solvent extraction is seen where methanol or ethanol is conventional. UAE & MAE increases efficiency (Zou et al., 2015).

Chlorogenic acid- It is increasingly found in green coffee, the extraction process includes aqueous ethanol and methanol solution and done under ultrasonic or MAE which improves yield (Farah et al., 2080)

Berberine- It is extracted with acidified methanol or ethanol with the addition of Hydrochloric acid which helps to improve solubility and the yield. UAE and Soxhlet techniques are used more (Kumar et al., 2015).

Epigallocatechin Gallate- The extraction process is performed by using aqueous ethanol under cold or sonicated conditions to prevent deterioration.

Quercetin- It is a flavonoid. Extracted by using methanol with hydrolysis liberates quercetin aglycone from glycosides. UAE gives an improved rate of extraction.

Kaempferol- Similar to Quercetin. Extraction is done by using ethanol or methanol, sometimes acid hydrolysis is used to eliminate the sugar moieties.

5.2. Purification of Phytochemicals:

After the extraction process, purification for isolating the phytochemicals which are responsible for the antidiabetic effect is very important. By this purification process the impurities and waste products are eliminated from the bioactive compound. It improves the virtue and therapeutic effectiveness of that compound.

This process commonly includes some methods such as TLC- Thin Layer chromatography, Column Chromatography, HPLC- High Performance Chromatography, gas chromatography, etc. The initial method is known as TLC; it's an analytical method which effectively separates the mixture based on their polarity differences. Column Chromatography is a stationary phase like alumina, silica gel, that isolates its phytochemicals based on size, partition and adsorption. HPLC is used on phenolic and flavonoid, due to their sensitivity, efficiency and versatility (Cimpoiu, 2006). Gas Chromatography is suitable for volatile and semi-volatile phytochemical purification which enables perfect identification and quantification of terpenes and essential oils which are bioactive (Sparkman et al., 2011). GC is always coupled with Mass spectrometry, GC-MS.

Progressive approach of compound isolation or purification techniques such as flash chromatography and HPLC increases the speed of purification, resolution and extensibility. In HPLC process, larger quantity of compounds can be purified with exceptional purity and is very crucial for bioactivity study and clinical trial (Miller, 2005). Flash Chromatography provides a swift and optimized purification of crude extracts, and thus it becomes easy and simple for isolating bioactive fraction with antidiabetic prospects (Still et al., 1978).

Purification process of phytochemical used for diabetes management:

Curcumin- Flash chromatography or HPLC is used as a purification process of curcumin. Curcumin is separated from Desmethoxycurcumin and Bisdemethoxycurcumin by this technique. Silica column chromatography can also be used by using solvents like chloroform-methanol for gradient elution (Jayaprakasha et al., 2006)

Chlorogenic Acid- Liquid-Liquid extraction is seen which is done by solid phase extraction. In HPLC using C18 columns with water acetonitrile gradients purifies it efficiently (Gouveia & Castilho, 2012).

Resveratrol- The purification is done by silica gel column chromatography and semi preparative HPLC. Hexane-Ethyl Acetate or methanol-water is used as solvent. Increased recovery can be possible if using Counter-Current chromatography (Sun et al., 2013).

Berberine- It uses preparative HPLC and Ion-exchange chromatography is used to isolate this bioactive compound. It also involves pH-based liquid-liquid separation by recrystallization.

Epigallocatechin Gallate- Purified by reverse-phase HPLC with a gradient of acidified water. SPE and gel filtration chromatography can also be used (Lee et al., 2000).

Quercetin- It is purified under Column chromatography by using Silica followed by HPLC and with high yield quercetin. Separation is facilitated using ethyl acetate-water gradient system.

Kaempferol- The purification process is done by using Silica gel chromatography and reverse-phase HPLC. Solvent gradients from water-methanol are common.

It may face some challenges such as co-elution, decreased yield of uncommon phytochemicals, the cost may be higher or solvent compatibility.

5.3. Chemical Characterization:

For the research purpose for phytochemicals chemical characterization is much important, especially for a chronic disease such as diabetes. It helps in identifying the bioactive compound or quantifying and elucidating the structure. For developing any medication, the accuracy of this process provides effective, consistent and safe bioactive compounds. As diabetes is connected with complex conditions such as insulin resistance, disrupted glucose metabolism and increased oxidative stress, it is very vital to explore and understand the chemical properties of phytochemicals with antidiabetic potential (Silverstein et al., 2005).

The compounds which are plant derived as like- flavonoids, alkaloids, terpenoids and phenolic acid shows glucose decreasing, insulin sensitizing and antioxidant effects. Chemical characterization fulfils the gap between pharmaceutical use and empirical use by doing verification of molecular identity, determining the concentration, linking structure to biological function, standardization, dosage formulation and establishing purity.

Analytical techniques for chemical characterization

1. UV-Visible Spectroscopy- It's an initial screening procedure. It helps detect the presence of aromatic rings and double bond. As an example, Curcumin shows absorbance at 420 nm with extended conjugation. Quercetin and Kaempferol shows strong absorbance in between 250-370 nm by indicating the phenolic nature (Esatbeyoglu et al., 2012).
2. Nuclear Magnetic Resonance (NMR) - It gives structural data in depth. ^{1}H NMR and ^{13}C NMR gives details on the environment of proton and carbon. As an example- The methoxy group and aromatic proton of Berberine are clearly recognizable (Claridge, 2009).

3. Mass Spectrometry- Structural fragments can be identified. Epigallocatechin Gallate shows molecular ion at m/z 459. It provides structural details for complex Flavonoids and Alkaloids (Lee et al., 2000).

4. Fourier Transform Infrared Spectroscopy (FTIR)- shows functional group by molecular vibration analyzation. Identifies O-H, C=O, and C=C stretches in phenolic and flavonoid compounds. Chlorogenic acid shows peaks at 3300 cm^{-1} and 1735 cm^{-1} (Griffiths & de Haseth, 2007).

Table-2: Chemical Characterization of Antidiabetic phytochemicals:

Phytochemical	Source	UV-Vis (λmax)	FTIR Functional Groups	NMR Highlights	MS (m/z)	Bioactivity
1.Curcumin	Curcuma longa	420 nm (Esatbeyoglu et al., 2012)	Keto, phenolic OH (Griffiths & de Haseth, 2007)	Methoxy & aromatic protons (Claridge, 2009)	368.4	Anti-inflammatory, hypoglycemic (Tiwari & Rao, 2002)
2.Chlorogenic acid	Coffee beans	325 nm (Farah et al., 2008)	Hydroxyl & ester C=O (Griffiths & de Haseth, 2007)	Caffeoyl quinic linkages (Claridge, 2009)	353	Antioxidant, glucose metabolism regulator (Tiwari & Rao, 2002)
3.Resveratrol	Grapes, peanuts	306 nm (Zou et al., 2015)	Trans C=C, phenolic OH (Griffiths & de Haseth, 2007)	Vinyl & aromatic signals (Claridge, 2009)	228 (Sun et al., 2013)	Insulin sensitizer, antioxidant (Tiwari & Rao, 2002)
4.Berberine	*Berberis* spp.	345 nm (Kumar et al., 2015)	Methoxy & aromatic rings (Griffiths & de Haseth, 2007)	Isoquinoline framework (Claridge, 2009)	336 (Wang et al., 2017)	AMPK activator, glucose reduction (Patel et al., 2012)

5.EGCG	Green tea (*Camellia sinensis*)	274 nm (Suzuki et al., 2006)	Catechol & galloyl ester (Griffiths & de Haseth, 2007)	Gallate & catechin protons (Claridge, 2009)	459 (Lee et al., 2000)	Improves glucose uptake, lipid metabolism (Tiwari & Rao, 2002)
6.Quercetin	Onions, apples	256 & 370 nm (Chirumbolo, 2013)	Hydroxyl & carbonyl (Griffiths & de Haseth, 2007)	Flavonol backbone (Claridge, 2009)	302 (Cimpoiu, 2006)	α-glucosidase inhibition, antioxidant (Tiwari & Rao, 2002)
7.Kaempferol	Broccoli, kale	266 & 366 nm (Calderón-Montaño et al., 2011)	Phenolic & carbonyl (Griffiths & de Haseth, 2007)	3,5,7,4′-OH substitution (Claridge, 2009)	286 (Cimpoiu, 2006)	Antioxidant (Tiwari & Rao, 2002)

Chapter 6

Advantages of Phytochemicals, Challenges and Future Direction of Phytochemicals

As the number of diabetes patients are increasing thus the plant derived compounds are getting more valuable for the treatment purpose as it mostly shows safe effects. In contrast to traditional synthetic drugs which mainly target a single pathway but phytochemicals show multifaceted effects by multiple effects such as reducing oxidative stress, reducing inflammation, and improving glucose metabolism. Sometimes these hampers by some factors like limited bioavailability, variability, limited evidence etc.

6.1 Advantages of Phytochemicals

Antioxidant anti-inflammatory effects are seen, which is because of inhibiting nuclear factor-kB activation, reducing proinflammatory cytokines thus reduces the inflammation and heart disease (Vauzour et al., 2010). They decrease carbohydrate digestion by inhibiting alpha-amylase and alpha-glucosidase and pancreatic beta-cell releases increased amount of insulin, increase glucose uptake through GLUT4 translocation also protects from glucotoxicity and damage (Bhattacharya et al.,2013). Curcumin, Quercetin, Berberine etc. shows antidiabetic effect or lowers the hyperglycemic condition. On the other hand, Reveratrol, catechins etc. improves endothelial activity and lipid metabolism, lowers the LDL oxidation and Blood pressure which helps to protect cardiovascular activity. (Scalbert et al., 2005). Combinations of resveratrol and Chlorogenic acid have safely been administered in the human body and also in animals in a combination (Farah et al., 2008). On the other hand, Resveratrol and metformin can control hyperglycemic conditions and lower the insulin resistance (Zhang et al., 2015).

In cancer treatment phytochemicals shows anticancer effects with diverse mechanisms including decreasing angiogenesis, promoting apoptosis of affected cell, suppressing tumor cells and modulating cancer signaling pathways. Such examples are thiocyanates, EGCG, Curcumin shows inhibitory effects towards cancer cell and tumor sites (Lamp, 2003).

Phytochemical also helps in neuroprotection. It decreases the oxidative stress and neuronal inflammation by initiating neurotransmitter and neuronal survival. Brain derived neurotrophic factor signaling can be increased by flavonoids, reduce excitotoxic damage and improve the cognitive system (Spencer, 2010). Also, phytochemical helps in shaping microbial diversity, influences gut microbiota, lowers the pathogenic bacteria and produces metabolites such as short chain fatty acid that improves the immune system and metabolic health (Selma et al., 2009).

Another advantage of phytochemicals is regulation of hormonal activity. Lignans from flaxseed, bioflavonoids and phytoestrogen can bind to estrogen receptors and give anti-estrogenic effects, this is beneficial for menopausal symptoms and decreases the probability of hormonal cancer (Messina, 2014). Also, some phytochemicals induce detoxification of enzymes by activating Nrf2, increasing the elimination of xenobiotic and damage mediated by toxins (kwak et al., 2004).

When phytochemicals are consumed as whole food it is generally well tolerated, and they are easy to excess, usually cost effective and also culturally accepted all over the world. Especially in low- and middle-income countries it has a wide range of acceptance because of their low access to costly pharmaceutical products (Ekor et al., 2014). They are devoted to traditional medicines such as Ayurveda medicines, traditional Chinese medicines and Unani – these all contain plant-based formulas and effectively manage metabolic, chronic diseases (Patwardhan, 2005).

6.2 Challenges of Phytochemicals

The first challenge of phytochemical is its bioavailability and limitations in pharmacokinetics. Some phytochemical has decreased water solubility, unstable in gastrointestinal environment, rapid metabolism and excessive hepatic clearance, thus shows poor bioavailability those are- curcumin, resveratrol and quercetin (Manach, 2005). Which reduces therapeutic effects and systemic absorption. As an illustration Curcumin has oral bioavailability lower than 1% which makes it difficult to gain plasma concentration without formulation enhancement (Kumar et al., 2015).

Table-3: Factors that cause impact on bioavailability (Ekor, 2014; Li et al., 2014)

Factors	Impact on Bioavailability	Example
Low solubility	Decreases absorption in gut	Curcumin
Chemical instability	Breaking down before absorption	EGCG
First-pass effect	Rapid excretion	Resveratrol
Efflux transporter	Pump back into the gut	Quercetin

Inadequacy of Standardization in formulation process is another challenge of phytochemical. A plant extract is influenced by its cultivation, species, storage, time of harvesting, extraction process, etc (Ekor, 2014). These all factors cause inconsistent phytochemicals. As an example, Green tea catechin contents can vary about 50% between marketed preparations (Li et al., 2014). Lack of standardized reference complicates the quality and dose thus there creates a difference in analysis.

Limited Clinical Validation- few effective phytochemicals evaluated on a large scale, RCTs remain less. Sample size is limited, few follow-ups, limited placebo control, weak evidence, moreover multifunctional effect where single phytochemical modulates more than two pathways which makes it more challenging to know the exact mechanism and exact therapeutic doses (Atanasov et al., 2015).

Policy and regulatory constraints- sometimes phytochemicals are marketed as dietary supplements leading to imbalanced regulation and quality control across regions (Wang, 2006).

Instability is another challenge of phytochemicals because it's easily degradable under environmental conditions such as heat, oxygen, air exposure which affects its shelf life and therapeutic effects (Dhanani, 2017).

Sustainability and intellectual property limitations can limit commercial investment in product development for research purposes. Sustainable biotechnological production, cultivation works as an eco-friendly solution for long term supply without degradation caused by environment.

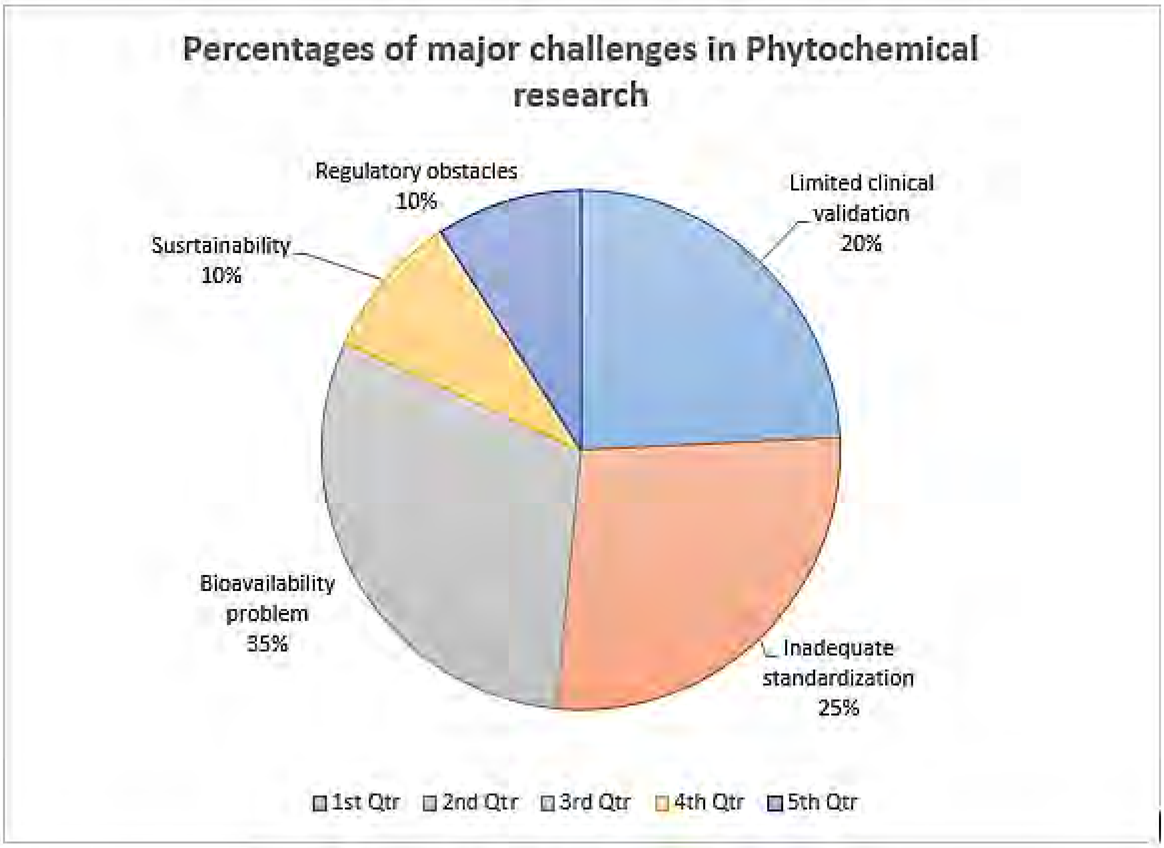

Figure 6.1: Distribution of major challenges in phytochemical studies based on trends report (Ekor, 2014; Li et al., 2014)

6.3 Future Direction of Phytochemical

1. Bioavailability Enhancement- Delivery system of nanoparticles such as polymeric nanoparticles, solid-lipid nanoparticles can enhance and improve the solubility and also give protection against degradation (Kumar, et al., 2015). On the other hand, the prodrug system and phospholipid complexes can help. Phospholipid complexes such as phytosomes helps to increase the membrane permeability or make it cross the biological membrane easily so that the increase in bioavailability and absorption can be achieved. Prodrug enhances the stability by changing the parent compound which ensures effective release at the target.

2. Synergistic Approaches with Conventional Treatments- For chemical fingerprinting development of analytical methods such as HPLC, LC-MS. ICH collaboration can be a helpful way for overcoming challenges. In future diabetes management may include synergistic approaches of phytochemicals with traditional allopathic medicines to increase effectiveness. Such example- Berberine with Metformin together for treatment shown more highly effective glucose lowering effect than it is used alone (Guo et al., 2020).

3. New Phytochemical Discovery- Advance technology such as Metabolomics, Bioinformatics and HTS can make it easy to discover antidiabetic bioactive compounds. These modern methods focus on: Unexplored phytochemicals, Marine medicinal plants, Endophyte metabolites. These advancements can facilitate novel phytochemicals with improved therapeutic effects, improved pharmacokinetic profiles. This will be safer and patient compliant (Rauter,perl et al., 2022).

4. Clinical and Mechanistic research and pathway mapping- Mechanistic study is lacking for development of phytochemical medications. For this future research should focus on, make clarification of biochemical pathways such as AMPK activation, PI3K signaling and translocation of GLUT4. Establish mapping of interaction between Gut microbiota and

phytochemical and see how it is initiated and modulate glucose absorption. Employing AI models to know the phytochemical target interaction.

5. Clinical Trials and Reform Regulatory Framework- Recently maximum phytochemical research are on preclinical trial so it needs well established human trial which can assess the effectiveness, safety profile and pharmacokinetics. Also standardization of traditional preparation as well as approval from FDA and EMA needed with proper labeling, health claims.

6. Viable Sourcing and production- Systemic cultivation of bioactive crops, Cell culture and biotechnological synthesis, Environment friendly extraction such as supercritical CO2 and UAE is much needed (Ghaasemzadeh, 2020).

Table-4: Challenges that need to overcome:

Challenges	Future Direction
Limited Bioavailability	Nano formulation process, development of prodrug
Limited clinical Data	Multifunctional trial, Human trial
Poor standardization	Using reference marker, chemical fingerprinting process
Phytochemical and synthetic drug interaction	Systemic toxicology study

In the coming years it is expected to see the advancement of science and technology for phytochemical studies and application. Next decade should experience the discovery of new phytochemicals by artificial intelligence. Also block chain supply for ensuring the authenticity and quality. Also, optimization of glucose monitoring and therapy needs to be initiated, also will witness in next decade the formulation of phytochemical based polypills for metabolic disorder.

Chapter 7

Conclusion

Phytochemicals are plausible. They act as multi-targeted bioactive agents for the treatments of diabetes. It isn't only used for a single purpose; rather it can focus on multiple pathways for metabolic disorders such as diabetes. The classes of phytochemicals including- Flavonoids, Terpenoids, Alkaloids, Phenolic acid, Coumarins, etc. are seen controlling the hyperglycemic condition in human body, such as they enhance GLP-1 signaling, activates AMPK, attenuates oxidative and inflammatory stress, lipid metabolism, modulating gut microbiome (Khan et al., 2022, Lin et al., 2024). These all multi targeted drug actions are similar to heart and kidney functions as well as it is more fitted with type-2 diabetes complexity and offers durable glycemic advantages in conjunction with modification of risk factors (Thomson, 2005). They can also be used with metformin, GLP-1 to reduce side effects and have synergism (Meng et al., 2019).

Nevertheless, while using these bioactive compounds for real world treatment purposes, this needs to be taken under continuous research and practice to close the traditional gaps. Quality controlled manufacturing system must be needed for ensuring consistency. In formulation the procedure needs to overcome the bioavailability as well as pharmacokinetics hurdles like solid-lipid, self-emulsification, and targeted delivery to the gut.

Safety needs to be evaluated and this includes phytochemical and drug interactions, undesired cellular effects, prolonged effects. In clinical purpose this phytochemical drug field needs highly designed research and studies as people nowadays looks for natural medications rather than synthetic one, so phytochemical studies should go beyond basic regular glucose level checking, blood sugar monitoring, weight related aspects and Bp effects, biomarkers, kidney also patient report improvement for a span of time.

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