

## OVERVIEW ON EFFECTS OF VARIOUS ANTI-DIABETIC DRUGS – A COMPARISON

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### Abstract

Numerous scientific studies all over the world are being carried out to develop secure and reliable ways of treating Diabetes Mellitus, a common endocrine disorder that causes many other microvascular and macrovascular problems. Being a common and chronic health problem with various adversities, different medical procedures are utilized in this treatment to ensure better no side-effect recovery. In the present study, a balanced comparison is composed on the basis of significant existing researches and approaches done in the field of medicines for hypoglycemic effects via natural and synthetic drugs. Sole purpose of this review article is to assess efficacy of natural and synthetic drugs for diabetes treatment and sort their advantages and shortfalls. A comparative approach is utilized with an aim to provide optimal diabetes treatment model that brings fast recovery with no long term drug dependency or no possibilities of adverse associated damages as hypoglycemia as observed in certain diabetes cure processes.

**Materials and Methods:** The paper on hypoglycemic effects of natural and synthetic anti-diabetic drugs is entirely composed based on the existing authentic medical analyses and articles that as published. Genuine facts and information are gathered from trusted web libraries.

**Results:** In this review on natural remedies to avert hypoglycemic effects of synthetic anti-diabetic drugs, we have collected scientifically proven facts that solidify this factor. Additionally, natural products provide added nourishment through their bioactive components vital for stimulating human physical system, metabolic disorder like, diabetes mellitus.

**Keywords:** Diabetes Mellitus, anti-diabetic drugs, macrovascular disorder.

**Introduction:-**

Diabetes Mellitus, the disease caused from pancreatic malfunction is a health hazard with a large toll of world population as its victims. In the records, there were nearly 415 million adult diabetic patients worldwide during 2014. Projection says, the number may increase to around 642 million by 2040. Various reasons, such as, genetic abnormality, food habits and living patterns are responsible for its occurrence. Although, the disease can be controlled and cured with correct medication and right awareness, yet, basically due to ignorance and adverse side effects, the disease is keeping its menace graph steadily growing adding many other bad complications.

One such problem is hypoglycaemia, a health trouble that elevates due to ill monitored drug/anti-diabetic therapy as well as improper diet during the treatment course. This review paper on Benefits of Natural Therapies in Minimizing Hypoglycemic Effects explores better alternative medication procedures of synthetic Anti-Diabetic therapies with minimal hypoglycemic effects and clinical dependencies.

In the following sections, the selected subject of hypoglycaemia is explained including its originating history, types and symptoms, association with Diabetes and natural remedial options with minimal risk and NO side-effects.

### *2.1 Diabetes Mellitus – Its Brief Treatment History*

The disease, Diabetes Mellitus was identified in around 1500 BC Egypt, where the ancient medical texts suggest it to be detected with the symptom of 'Frequent discharge of urine'. The disease was called '*Madhumeha*' (Honey Urine) in India for its distinct trait of attracting ants towards it. Ancient physicians from India, Charaka and Shushruta (400 – 500 AD) classified the health trouble in two broad types, which we now call Type I Diabetes and Type II Diabetes [1]. Aretaeus the Cappadocian named it as 'Diabetes' ('Siphon' in Greek language) in First Century A.D. and 'Mellitus' ('Sweet like honey' in Latin language) was added with it by British Surgeon-General, John Rollo in 1798 to separate it from other Diabetes Type where urine is tasteless.

The two Diabetes types, as mentioned previously are characterized as, Diabetes Mellitus Type 1 (T1DM) to develop from dysfunction in insulin secretion and thus cured with insulin treatment. Type 2 Diabetes (T2DM) develops from poor response of cells to insulin and is not insulin dependent. Although detected long time ago, its effective cure has a critical history of successful formulation. Primitive treatments (Pre-Insulin Era) mostly included calorie restricted dietary and exercise based remedies later enhanced with specific drugs after the development of Insulin (by Dr Frederic Banting in 1922) and other subsequent medicines. [2]

Details of major synthetic Diabetes Mellitus drugs used currently are given below in the table (**Table- 1**) with their uses and side-effects:

**Table 1: Synthetic Anti-Diabetic Drugs with their uses and possible Side-Effects**  
[3],[11]

Class	Popular Drug	Year First Manufactured/Marketed	Advantages	Side Effects
Insulin	Regular Insulin	1923	Controls blood sugar, Antioxidant	Hypoglycemia, weight gain, insulin allergy, etc.
Sulfonylureas	Acetohexamide, Chlorpropamide, Tolazamide, Tolbutamide, etc.	1950	A1C reduction (Effective for type 2 Diabetes)	Hypoglycemia, cardiovascular problems, weight gain, etc.
Biguanides	Metformin, etc.	1959	Reduce hepatic glucose production, A1C reduction	Gastrointestinal (GI) problems, lactic acidosis
Glucagon-Like Peptide-1 Receptor Agonists	Exenatide, Liraglutide, etc.	1980	Weight Loss, A1C reduction	Gastrointestinal (GI) problems
$\alpha$ -Glucosidase Inhibitors (AGIs)	Acarbose, Miglitol, etc.	1995	A1C reduction	Gastrointestinal (GI) problems
Thiazolidinediones	Troglitazone, Rosiglitazone, Pioglitazone, etc.	1996	Skeletal muscle Insulin secretion, Reduction of hepatic Glucose production	Hypoglycemia, Myocardial infarction
Meglitinides	Repaglinide, Nateglinide, etc.	1997	A1C reduction	Hypoglycemia, Respiratory tract Infections and headache
Amylin Agonists	Pramlintide	2005	A1C reduction, Weight Loss, Reduction of postprandial glucose and glucagon	Nausea, Gastroparesis
DPP-4 Inhibitors	Sitagliptin, Alogliptin,	2006	Oral Drug, A1C reduction, non	Pancreatitis

	Vildagliptin, etc.		Hypoglycemic	
Colesevelam	-	2008	A1C reduction, LDL cholesterol reduction	Gastrointestinal (GI) problems, Increase in triglycerides
Bromocriptine	-	2009	A1C reduction	Nausea, Hypotension, Headache
Sodium Glucose Co-Transporter 2 Inhibitors (SGLT-2)	Canagliflozin, Dapagliflozin, Empagliflozin, etc.	2013	A1C reduction, Weight Loss, non Hypoglycemic	Urinary/genital infections

Keeping diabetes under control requires regular blood glucose level check, which is the process equally required to record level of Hypoglycemia.

## 2.2 Hypoglycemia in Diabetes Mellitus – Types and Symptoms

Hypoglycemia or Low Blood Sugar [3] is a side-effect, particularly observed with Type 1 Diabetes patients. Some cases, lower in number are also found with Type 2 Diabetes patients. Basically, Hypoglycemia develops due to ignorance, improper medication or their side-effects. The health hazard can be controlled and cured, yet, high diabetic disorders and mortality (overall about 4% to 10% due to cardiovascular complications) of Diabetic patients with Hypoglycemia is observed all over the world. Consequently, workable methodologies of diabetes cure to control Hypoglycemia are emphasized to serve better and ensured recovery.

The disease is typically connected with the adult Type 1 Diabetic patients who are under insulin treatment at the time mg/dl. Due to the reason, the disease is also called as 'Insulin Shock'. Among children and young diabetic patients [5], the disease is rare but still observed with some severe Type 1 cases. In some Type 2 diabetic or non-diabetic cases, lifestyle defects, wrong medications and lack of physical works can develop chances of low blood sugar.

### ***Hypoglycemia associated with Diabetes Mellitus can be detected with these symptoms:***

- (1) Growth of appetite, fatigue, frequent sweating, faster heartbeats, fainting – As autonomic signs and
- (2) Mood swing, irritation, problem in speech, anxiety, convulsion, etc - As neuroglycopenic signs.

*Levels of Hypoglycemia is classified as:*

**Table 2: Levels of Hypoglycemia (Descending Order of Severity from left to right) [4]**

Level	Severe Hypoglycemia	Documented Symptomatic Hypoglycemia	Asymptomatic Hypoglycemia	Probable Symptomatic Hypoglycemia	Pseudo-Hypoglycemia
<b>Physical Condition/ Control</b>	Strict control of plasma glucose level and professional healthcare assistance	Plasma glucose level is less or at 70 mg/dl and shows typical Hypoglycaemic symptoms	Plasma glucose level is less or at 70 mg/dl, but does not show any Hypoglycaemic symptoms	Plasma glucose level is less or at 70 mg/dl and shows typical Hypoglycaemic symptoms that can be usually controlled with self-treatment procedures	Plasma glucose level is more and nearby to 70 mg/dl and shows typical Hypoglycaemic symptoms

*Types of vulnerable patients of Hypoglycemia associated with Diabetes Mellitus are:*

**Table 3: Hypoglycemic Diabetic Patients and Root Reason [4]**

Vulnerable Hypoglycemic Diabetic Patients	Patients with severe renal dysfunction (Kidney damage)	Aged Patients	Hypoglycemia unaware patients
<b>Cause of Hypoglycemia</b>	Low need of insulin because of decreased renal insulin clearance, low rate of insulin reduction in peripheral tissues, lower rate of renal gluconeneosis	Unawareness, regular drug intake affecting kidney function and cognitive problems	Fear and anxiety if they are diagnosed with diabetes and increase the possibility of overdose of drugs or improper diet (Observed both in Type 1 and 2 Diabetes)

### *2.3 Channels that Increase Hypoglycemia Risk among Diabetic Patients*

These factors as given below are found as the common channels to increase Hypoglycemia Risk among Diabetic Patients (Both for Type 1 and 2). Even the non-diabetic people, if one or more of these channels are part of their daily life, may come under the chance of Hypoglycemia problems

[5], [12].

1. Lifestyle and Improper Diet, such as, carbohydrate rich diet, processed food, improper in treatment diet, etc.
2. Lack of Physical Work
3. Clinical Therapies, where mostly elderly patients develop low blood glucose due to over treatment and periodic drug intake, particularly, the insulin or Hypoglycemic drugs
4. Unawareness, where the patients are reluctant on regular exercise, medication timings, drug overdose, drug side-effects, diet, etc.
5. Fear of Hypoglycemia, caused due to the stress of regular check-ups, insulin injection trauma, apathy on diet, etc.

#### *2.4 Adversities of Anti-Diabetic Synthetic Drugs and Corresponding Advantages of Natural Therapies*

In the table given below, major Hypoglycemic Synthetic Drugs along with side effects other than Hypoglycemia are mentioned:

**Table 4: Hypoglycemic Synthetic Drugs and their Side-Effects (Other than Hypoglycemia) [8], [10]**

Hypoglycemic Synthetic Drug Class	Common Drug Under the Class	Side Effects (Other than Hypoglycemia)
Insulin	Regular Insulin	Insulin allergy, Weight gain, Lipodystrophy at the injection area
Sulphonylureas	Glibenclamide	Skin rashes, Weight gain, Heart trouble, Bone marrow impairment, Cholesterol jaundice, Photosensitivity
Meglitinides	Repaglinide	Sensitivity reactions
Amylin Analogues	Pramlintide	Allergy

For many reasons, modern diabetic treatments are utilizing Natural products as effective anti-diabetic remedies. Some of the major scientifically sanctioned reasons are given below [8]:

- **Preferred Option:** As per the survey, about 80 – 85% of the world population is found to prefer herbal and nature based drugs for various reasons, such as, affordability, easy for application, Availability and others.

- **Minimal Side-Effect:** Nature based products are well known and traditionally used in the society as food and health additives also. Common public trust is attached with these products and they are reliable for their non-toxic nature, which is an advantage to choose these products as convincing safe and healthy anti-diabetic medical alternative. Additionally, they do not interfere in any other medications that are utilized in the treatment process. Hence, are effective in combinational use. Some good examples are, Aloe Vera, Fenugreek, Curry Leaves and others.
- **Abundance:** Natural remedies, such as, aloe vera, ginseng and others for diabetes are easily available and grow widely in various parts of the world. That makes manufacturing process easy and can be easily procured for medicine manufacturing processes. These resources are compatible with the modern tools and procedures as applicable for standardized natural medicine making processes.
- **Cost Effective:** Due to vast abundance of natural anti-diabetic resources, medicines that are currently processed for this treatment are very cost effective. This is due to the lower manufacturing cost as applicable in their making. Moreover, with modern processing techniques, their shelf life and vitality are ensured through rigorous checks and authentic internationally accepted certifications, such as, WHO approval and national regulatory approvals and other relevant legal norms.
- **Natural Bioactive Resource:** Scientific studies confirm the presence of vital enriching resources, such as, flavonoids, glycosides, polypeptides and others that are present in the natural anti-diabetic remedies. These vital matters are essential to stimulate physical system in metabolic disorders, like Diabetes Mellitus.

**Table 5: Comparative Study between major natural and synthetic drugs based on their Hypoglycemic Effects on Diabetes Mellitus [8], [9]**

Scientific Name	Common Name	Potential anti-diabetic phytochemical components	Benefits	Better as Alternative of
Panax ginseng and Panax quinquefolium	Ginseng	ginsenosides	anti-hyperglycaemic effects, blood glucose level control	Insulin
Allium sativum	Garlic	Calenduloside E	Reduces Blood Glucose Level (Combination with metformin)	

Momordica charantia	Karela (Bitter melon)	sterols, glucoside mixtures, charantin polypeptides	Anti-Diabetic effects	
Gymnema sylvestre	Gymnema	triterpenoidic saponins	Reduces Blood Glucose Level (Combination with metformin)	Sulphonylureas
Berberis aristata	Tree Turmeric	Berberine	Anti-Diabetic effects, potential for hypoglycemia	
Sesamum indicum	Sesame seeds	Inositol	potential for hypoglycemia, antioxidant, anti-inflammatory, reduces hypolipidemic effects, effective for fat metabolism, cholesterol control	
Aloe barbadensis miller	Aloe vera	24-ethyl-lophenol, 24-methyl-lophenol, 24-methlene-cycloartanol, cycloartaol, lophenol	Antioxidant, Reduces Blood Glucose Level (Combination with glibenclamide)	Meglitinides
Silybum marianum	Milk thistle	silymarin	antioxidant, potential for hypoglycemia, reduces hypolipidemic effects	
Trigonella foenum-graecum	Fenugreek	saponins, alkaloid, high fiber, diosgenin, 4-hydroxyleucine/4-hydroxyisoleucine, trigonelline	antioxidant, Reduces Blood Glucose Level, potential for hypoglycemia	

**Note:** There are many herbal drugs that are used combing with synthetic drugs (e.g. metformin as mentioned above) to improve or minimize their side-effects [9].

### 2.5 Other Health Management Options of Hypoglycemia Remedy

Both Diabetes Mellitus and Hypoglycemia are controllable and recoverable diseases subject to proper awareness, discipline and therapy routine. Diabetes care standard provides these primary norms for the patients as well as caregivers and any other healthy individual to minimize risks associated with the disease.

- **Selecting health based therapy option:** Since Diabetes and Hypoglycemia are inter-related and both develop from dysfunction in cellular secretion, they are dependent of specific human genetic traits. Accordingly, drugs can be adverse as per a patient's health status. In such situation, consultation should be taken properly to follow patient specific diabetic treatment scheme of minimal side-effects. For example, simple therapeutic scheme, combination of natural and synthetic schemes, lifestyle approaches, etc.
- **Do regular health check as per medical guidelines:** The treatment of Diabetes includes an essential part and that is regular Blood Glucose level check up and other tests as per the level of complications. These tests should be done punctually along with the suggested health regime as prescribed.
- **Be aware on Self Treatments:** Diabetes needs an aware self-treatment procedure that a patient should follow strictly. Accordingly, the sufferer should be educated with time and correct diet schedule, exercise methods, medicine intakes, association with caregivers and others. Depending on the treatment phase, quality of this self-treatment procedure should be properly monitored and evaluated.
- **Overcome Hypoglycemia fear:** Usually, Diabetes creates a psychological trauma among the patients and that brings added harm to them. Over-treatment and excessive cautions are equally harmful as reluctance in following diabetic health regime. Diabetes care should incorporate right balance between maintaining lifestyle quality as well as clinical processes to avert risk of Hypoglycemia. Hence, fear of health status or any other cognitive weaknesses should be kept under control with natural healing methodologies.

### 3. Literature Review:

**Sanjay Kalra et al. (2013) [13]**, place grave concern towards the need of swift upgrade in treatment system keeping in view the rapidly rising patient rate of Hypoglycemic diabetic patients. The disease as an outgrowth of Diabetes Mellitus is easy to control, yet, has taken a major part of world population as its bad victim. Mortality numbers are shooting up fast giving shock and panic to the medical professionals as well as common mass. Lastly, Hypoglycemia, if stays for long brings several other major disorders, such as heart damage, sight damage, neurocognitive complications, myocardial infarction and others. Also, it has a close attachment with the quality of life of people from every level and categories. Thus, the researchers suggest awareness and conclusive remedial

solution to be made effective.

**DK Patel et al. (2012) [14]**, highlights the convenience and advantages of herbal drugs that are currently being studied at large scale to escape the side effects of synthetic drugs applied in Diabetes Mellitus therapies. Formulation of effective and NO-SIDE EFFECT fast remedy is a priority in the researches that are done in the field of Hypoglycemic Diabetic cure systems. So far, natural resources with potentiality of curing Diabetes with no/minimal risk of causing Hypoglycemia are proving to be of great benefits. In the study, such natural remedies are systematically categorized on the basis of scientific assessment. The major Diabetes cure plants with Hypoglycemic properties are from the families of Asteraceae, Araliaceae, Cucurbitaceae, Lamiaceae, Leguminosae, Liliaceae, Moraceae, Rosaceae. A number of bioactive components are found from the plants, such as, *Allium sativum*, *Citrullus colocynthis*, *Ficus bengalensis*, *Trigonella foenum greacum*, and others that can be utilized in the safe Hypoglycemic Diabetic treatment procedure.

**Jyoti Tara Manandhar Shrestha et al. (2017) [15]**, perform a case study on the bad effects of Oral Hypoglycemic Agents (OHAs) used in Type 2 Diabetes treatment for the Patients of Nepal. According to the study team, the endeavour is new and challenging. Also, allows possibilities for exploring novel local methods as effective alternative for the clinical OHA based procedures that are usually followed, but are causing associated problems, such as, nervous disorders, skin problems, etc.

**M. Kaur et al. (2014) [16]**, in their study discuss about the valuable benefits of Biological drugs that are currently analysed and included as alternative cure system for Diabetes Mellitus. Like the work of DK Patel et al. (2012), here also a systematic classification is done for the available biological drugs that can reduce the hypoglycemic side effects of synthetic drugs, such as, insulin and analogues, receptor agonists, glucagon-like peptide-1 (GLP-1), islet amyloid peptide (IAPP) analogues and others.

**Haixia Chen et al. (2021) [17]**, present a comparative study of synthetic and natural drugs of Diabetes care and evaluates their potency of curing the disease with no risk of Hypoglycemia. In the study, it is inferred that natural drugs with a number of benefits and for their easy availability and cost effectiveness are the better alternatives as considered in most parts of the world.

**Bahare Salehi et al. (2019) [18]**, make a detailed analytical observation on the potency of herbal Anti-Diabetic plants remedy in terms of their Hypoglycemic properties and classifies the bioactive components that produce the necessary antioxidant and preventive support against Hypoglycemic effects of synthetic diabetic drugs.

**Discussion:**

The previously developed methodologies, theories, studies and information as presented in this review paper on Hypoglycemic Effects of Natural and Synthetic Anti-Diabetic Drugs give a promising stage for large scale utilization of Herbal alternatives. Based on facts and literatures included here, the herbal Diabetes cure procedure can be either as combination or replacement for synthetic Hypoglycemic Diabetic treatment. Such inference is arrived considering the growing number of global patients affected with drug generated hypoglycaemia. As observed here, mostly the complication is caused by unregulated use of synthetic Diabetic therapies. Risk of this disease amplifies due to common misconceptions, imperfect treatment and indiscipline lifestyle.

**Conclusion:** The paper explicitly talks about the essence of herbal remedies as no side-effect better alternatives. And, it pays equal emphasis to acknowledge the importance of lifestyle managements, check-ups and self-treatments. This paper particularly advices the patients to be aware, learn and unfailingly practise self-management procedures to keep away fear or uncertainty and experience happy recovery from hypoglycaemia added Diabetes.

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