



OVERVIEW ON HYPOGLYCEMIC EFFECTS OF NATURAL AND SYNTHETIC 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 informations 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.



1. 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 Hypoglycemia, 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 Hypoglycemia is explained including its originating history, types and symptoms, association with Diabetes and natural remedial options with minimal risk and NO side-effects.

1.2 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. [1], [2]

2. Literature Review:

- 2.1 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 distorders, 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.
- 2.2 **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, Leguminoseae, 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.
- **2.3 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.

- 2.4 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.
- **2.5 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.
- **2.6 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.

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 [1], [2],[11]

Class	Popular Drug	Year First	Advantages	Side Effects
		Manufactured/M		
		arketed		
Insulin	Regular Insulin	1923	Controls blood	Hypoglycemia,
			sugar, Antioxidant	weight gain,
				insulin allergy,
				etc.



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Sulfonylureas	Acetohexamide,	1950	A1C reduction	Hypoglycemia,
	Chlorpropamide,		(Effective for type	cardiovascular
	Tolazamide,		2 Diabetes)	problems, weight
	Tolbutamide, etc.			gain, etc.
Biguanides	Metformin, etc.	1959	Reduce hepatic	Gastrointestinal
			glucose	(GI) problems,
			production, AIC	lactic acetosis
			reduction	
Glucagon-Like	Exenatide,	1980	Weight Loss,	Gastrointestinal
Peptide-1	Liraglutide, etc.		A1C reduction	(GI) problems
Receptor Agonists				
α-Glucosidase	Acarbose,	1995	A1C reduction	Gastrointestinal
Inhibitors (AGIs)	Miglitol, etc.			(GI) problems
Thiazolindinedion	Troglitazone,	1996	Skeletal muscle	Hypoglycemia,
es	Poglitazonerosig,		Insulin secretion,	Myocardial
	Litazone, etc.		Reduction of	infarction
			hepatic Glucose	
			production	



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, Vildagliptin, etc.	2006	Oral Drug, A1C reduction, non Hypoglycemic	Pancreatitis
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.

4.1 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 when the level of blood glucose goes down under 60 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	Documented	Asymptomatic	Probable	Pseudo-
	Hypoglycemia	Symptomatic	Hypoglycemia	Symptomatic	Hypoglycemia
	,	Hypoglycemia		Hypoglycemia	
Physical	Strict control	Plasma glucose	Plasma glucose	Plasma glucose	Plasma glucose
Condition/Co	of plasma	level is less or	level is less or	level is less or	level is more
ntrol	glucose level	at 70 mg/dl	at 70 mg/dl,	at 70 mg/dl	and nearby to
	and	and shows	but does not	and shows	70 mg/dl and
	professional	typical	show any	typical	shows typical
	healthcare	Hypoglycemic	Hypoglycemic	Hypoglycemic	Hypoglycemic
	assistance	symptoms	symptoms	symptoms that	symptoms
				can be usually	
				controlled with	
				self-treatment	
				procedures	





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

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

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

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.





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 antidiabetic 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



Allines anti	Conlic	Colondulacida E	Dadwass Di- 1	
Allium sativum	Garlic	Calenduloside E	Reduces Blood	
			Glucose Level	
			(Combination with	
			metformin)	
Momordica	Karela (Bitter	sterols, glucoside	Anti-Diabetic	
charantia	melon)	mixtures, charantin	effects	
		polypeptides		
Gymnema	Gymnema	triterpenoidic saponins	Reduces Blood	Sulphonylureas
sylvestre			Glucose Level	
			(Combination with	
			metformin)	
Berberis	Tree Turmeric	Berberine	Anti-Diabetic	
aristata			effects, potential	
			for hypoglycemia	
Sesamum	Sesame seeds	Inositol	potential for	
indicum			hypoglycemia,	
			antioxidant, anti-	
			inflammatory,	
			reduces	
			hypolipidemic	
			effects, effective	
			for fat metabolism,	
			cholesterol control	
Aloe	Aloe vera	24-ethyl-lophenol, 24-	Antioxidant,	Meglitinides
barbadensis		methyl-lophenol, 24-	Reduces Blood	
miller		methlene-cycloartanol,	Glucose Level	
		cycloartaol, lophenol	(Combination with	
			glibenclamide)	



Silybum		silymarin	antioxidant,
marianum	Milk thistle		potential for
			hypoglycemia,
			reduces
			hypolipidemic
			effects
Trigonella	Fenugreek	saponins, alkaloid, high	antioxidant,
foenum-		fiber, diosgenin, 4-	Reduces Blood
graecum		hydroxyleucine/4-	Glucose Level,



hydroxyisoleucine,	potential	for	
trigonelline	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].

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

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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.

4. Result

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 Hypoglycemia. 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 indisciplined lifestyle. Thus, 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 Hypoglycemia added Diabetes.

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