Original Research Paper

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EVALUATION OF IN VIVO ANTIDIABETIC ACTIVITY OF COLEUS FORSKOHLII ROOT EXTRACT (COLEGEX®) BY DETERMINATION OF GLYCEMIC INDEX AND ORAL GLUCOSE TOLERANCE TEST (OGTT) IN WISTAR RATS

C A Anzar	Ingex Botanicals Pvt Ltd, Nelamangala, Bangalore-562123, Karnataka, India
Joseph M V	Ingex Botanicals Pvt Ltd, Nelamangala, Bangalore-562123, Karnataka, India
Dr. Sundaram R	Ingex Botanicals Pvt Ltd, Nelamangala, Bangalore-562123, Karnataka, India
Vadiraj G B*	Ingex Botanicals Pvt Ltd, Nelamangala, Bangalore-562123, Karnataka, India *Corresponding Author
Prasad C P	Ingex Botanicals Pvt Ltd, Nelamangala, Bangalore-562123, Karnataka, India
Bineesh Eranimose	Ingex Botanicals Pvt Ltd, Nelamangala, Bangalore-562123, Karnataka, India

ABSTRACT Diabetes is one of the most lethal metabolic illnesses, with high fatality rates across the globe. Many ailments, including diabetes and its complications, have been treated with the help of medicinal plants in traditional medicine since the dawn of time. These medicinal plants are widely accepted, inexpensive, and thought to have few unfavourable side effects. The Lamiaceae family is a possible source of medicinal compounds for the treatment of metabolic illnesses, such as diabetes. Based on the rise in postprandial blood glucose, meals high in carbohydrates are classified according to their glycemic index. The sudden increase in blood glucose that occurs right after eating is known as postprandial hyperglycemia. This study aims to investigate the glycemic index of Coleus forskohlii root extract (Colegex®) in Wistar rats. When compared to the pathological control group, the Colegex® group demonstrated a mid-level glycemic index of 63.72% and maintained the blood glucose levels. The effectiveness of Colegex® was evaluated in experimental rats using an oral glucose tolerance test to measure postprandial blood sugar levels. When compared to the pathological control group, the administered Colegex® demonstrated good glycaemic control as it was seen to maintain blood glucose levels. The glycemic index and OGTT (oral glucose tolerance test) results for C. forskohlii root extract (Colegex®) have demonstrated good glycaemic control and significant reduction in blood glucose levels compared to the pathological control group. Hence, Colegex® has the potential to be developed into a new oral antidiabetic drug for the management of diabetes mellitus.

KEYWORDS : Coleus forskohlii (Colegex®), Glycemic Index, Oral Glucose Tolerance, Antidiabetic Activity

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by a chronic disorder of carbohydrate, fat, and protein metabolism that results from defects in insulin secretions and insulin action, which cause hyperglycemia, lipoprotein abnormalities, an increase in basal metabolic rate, a defect in enzymes, and pancreatic beta cell damage from excessive oxidative stress [1]. The problem is associated with a lower quality of life and an increase in risk factors for morbidity and mortality. The development and progression of microvascular and macrovascular complications, such as cerebrovascular disorders [2,3], neuropathy, nephropathy, and cardiovascular degeneration [4], are significantly influenced by long-term hyperglycemia. It is possible to have many forms of diabetes mellitus, which are brought on by a complicated interplay between hereditary and environmental factors [5]. People have used medicinal plants to manage diabetes since ancient times, and according to the WHO, 80% of the world's population is currently utilizing herbal medicine as their primary source of healthcare [6]. Either by boosting insulin or preventing the absorption of glucose through the intestinal wall, anti-diabetic herbs can help damaged pancreatic tissue recover its function [7].

However, a few conventional plant remedies for diabetes have undergone extensive research. These treatments have been utilized for centuries [8]. Therefore, developing alternative agents with lower costs and greater efficiency has taken on significant importance. A valuable source for the development of novel compounds that may be utilized as pharmacological entities or straightforward dietary adjuncts to existing therapies could be found in the large number of plants that are used to care for diabetic patients [9]. As a result, herbal medicine is currently being prioritized as an appropriate anti-diabetic medication. The antidiabetic data is frequently anecdotal, so further research is required to support and promote the advantages of these plants over current medications. This research should also clarify their mechanism(s) of action and therapeutic effects [10].

Coleus forskohlii, the plant known as Native to India, has been used for many years in Ayurvedic medicine to treat a variety of conditions affecting the central nervous system, gastrointestinal tract, respiratory system, and heart [11]. It contains forskolin, a diterpene known to raise c-AMP content by activating adenylate cyclase, leading to a variety of pharmacological effects [12, 13]. The administration of forskolin promotes an increase in cAMP levels. The two signaling pathways PKA and guanine exchange via cAMP are further activated as a result of the higher cAMP levels [14]. Insulin is released as a result of a glucose-mediated reaction in pancreatic beta cells [15]. An in vivo investigation on rats provided support for the case for forskolin by showing that it reduced serum glucose levels, which in turn decreased the severity of fasting hyperglycemia [16]. Additionally, forskolin has demonstrated a reduction in retinal inflammation in diabetic rats through restricting glucose transport into the retina. It reduced inflammatory factor expression and downregulated glucose transporter 1 expression [17].

Even though there are currently several approaches, such as strict blood glucose control and ACE inhibitors (angiotensin-converting enzyme) use for the management of diabetic nephropathy, they were unable to satisfy the clinical need for the treatment of disease, which prompted research on alternative pathways, such as inhibition of the polyol pathway and formation of advanced glycation end products (AGEs). Because of this, a new category of medications that block the polyol pathway enzyme aldose reductase (AR) has developed [18–19]. Furthermore, there is an urgent need for the search for new ARIs (aldose reductase inhibitors) from natural sources due to the failure of several synthetic aldose reductase inhibitors (ARIs) due to their harmful effects and lack of sufficient efficacy [20]. Therefore, the objective of the current study was to evaluate various biochemical and physiological changes, with a focus on the involvement of the polyol pathway and AGEs (advanced glycation end products) in the treatment of diabetic nephropathy.

However, further investigations are required to determine the whole impact of forskolin on diabetic patients, including its benefits and drawbacks. The effects of forskolin on antidiabetic properties have been investigated in several studies using rats., In this study we investigated the efficacy of C. forskohlii (Colegex®) for its anti-diabetic effects. The outcome of the study will give inputs for designing a novel synergistic drug with strong antidiabetic properties.

MATERIALS AND METHODS

Preparation of C. forskohlii root extract (Colegex®)

C. forskohlii (Colegex®) is a standardized extract manufactured and registered by Ingex Botanicals Pvt. Ltd., Nelamangala, Bangalore, Karnataka, India.

Experimental Animals

Radiant Research Services Pvt. Ltd. in Karnataka, India, provided the male Wistar rats, which were ten weeks old and weighed 200 to 220 gm. The CPCSEA Registration Number 1803/ PO/ RcBi/ S/ 2015/ CPCSEA was used to supervise and regulate animal research studies. Picric acid has been used to identify each animal, and each has been given a unique number. The animal was housed in a standard polypropylene cage with a stainless steel top grill, common food, and water in bottles accessible to it. The bedding material used was sterilized paddy husk (source: Shree Balaji Rice Industries, Bangalore). The Aqua Guard service allowed free access to the water. Animals have always had access to clean, uncontaminated water for drinking. They were kept in these cages in standard laboratory conditions, which included a 12-hour light/dark cycle, a temperature of 22±3°C, and a relative humidity range of 30–70%. Under the guidance of skilled professionals, every procedure involving animals was carried out in an ethical manner. Radiant Research Services Pvt. Ltd.'s Institutional Animal Ethical Committee (IAEC) examined and approved the research protocol before the study's start.

Determination of Glycemic Index

Male Wistar rats that were ten weeks old and weighed 200 to 220 g were separated into 3 groups, with each group containing 6 animals. Group I served as the normal control and received a 0.5% carboxyl methylcellulose (CMC) solution. As a pathological control, Group II received 2 g/kg of glucose, while Group III received 2 g/kg of Colegex® dissolved in a 0.5% CMC solution. A basal glucose measurement was performed after 12 hours of fasting. After a basal glucose reading, Colegex® was administered. The blood sugar levels were measured at various intervals of 0, 15, 30, 60, 90, 120, 180, and 240 minutes after taking Colegex®. The ratio of incremental area was used to compute the glycemic index (GI) for Colegex®. Blood glucose response to the incremental area in less than two hours followed Jenkins et al.'s approach from 1981 and Wolever et al.'s method from 1991, [21,22] respectively, for the standard glucose solution under curve.

Glycemic Index

$$(GI) = \frac{\text{Incremental area under 2h blood glucose curve for food samples (2g)}}{\text{Incremental area under 2h blood glucose curve for glucose (2g)}} \times 100$$

Oral Glucose Tolerance Test

Male Wistar rats that were 10 weeks old and weighed 200 to 220 g were divided into 3 groups, with 6 rats for each group. The 0.5% carboxyl methylcellulose solution was given to Group I as a normal control. Group II served as the pathological control and received 2 g/kg of glucose, whereas Group III received Colegex® at a dose of 103.29 mg/kg along with 2 g/kg of glucose per body weight. Colegex® was administered 14 hours after the fasting basal glucose measurement, and glucose levels were assessed at various intervals of 0, 30, 60, 90, 120, 180, and 240 minutes following the administration of Colegex®. During the experimental period of 120 minutes, the postprandial blood sugar level was also measured concurrently.

Statistical Analysis

All the values were expressed as mean ± SEM and one-way ANOVA followed by a Dunnett test. $P < 0.05$ was considered statistically significant.

RESULTS

Glycemic Index

The Glycemic Index (GI) evaluates the foods' carbohydrate content in relation to how it affects blood glucose levels. In Table 1, the body weight of the rats' glycemic index was determined. The results of glucose measurements taken at various time points after the administration of Colegex®, including 0, 15, 30, 60, 90, 120, 180, and 240 minutes, are represented in Table 2 and Figure 1. The mid-level glycemic index for Colegex® was 63.72% (Table 3).

Table No. 1: Glycemic Index On Rat's Body Weight

Groups	Body weight
Group I Normal control	211.17±0.91
Group II Pathological control	212.00±1.44
Group III Colegex®	211.50±0.85

Values are expressed as mean±SEM (n=6);

Table No. 2: Effect Of Colegex® On Glycemic Index In Blood Glucose Level

Groups	0 min	15 min	30 min	60 min	90 min	120 min	180 min	240 min
Group I Normal control	84.7±3.0	100.5±1.6***	98.3±1.1***	97.2±1.4***	94.8±1.2***	93.3±1.4***	91.2±1.9***	81.8±1.4***
Group II Pathological control	85.0±1.8	140.5±1.2	161.7±1.7	165.5±1.4	167.0±0.9	162.0±0.9	133.0±2.1	111.0±2.4
Group III Colegex®	84.7±2.2	114.2±1.6***	116.5±1.2***	118.7±1.1***	111.0±1.2***	98.7±2.3***	92.8±2.8***	88.0±2.0***

Values are expressed as mean±SEM (n=6)

Table No. 3: Colegex® Glycemic Index

Colegex®	63.72%

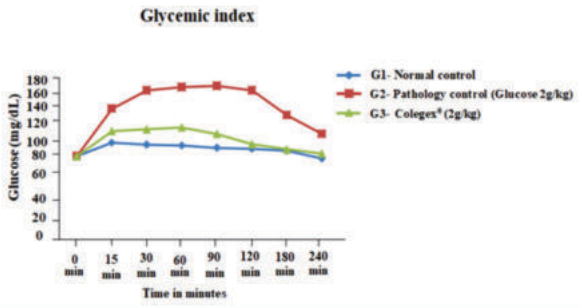

Fig. No. 1: Effect Of Colegex® On Glycemic Index In Blood Glucose Level

Oral Glucose Tolerance Test

In Table 4 and Figure 2, the impact of Coleus forskohlii root extract (Colegex®) on rat body weight is shown. The efficacy of given Colegex®, when orally treated in experimental rats, demonstrates significant improvements observed at 30, 60, 90, and 120 minutes of OGTT (Oral Glucose Tolerance Test) level when compared to the pathological control group (Table 5 and Figure 3). When compared to the pathological control group, Colegex®'s effect on feeding the rats showed inhibiting blood glucose levels at 30 minutes (9.15%), 60 minutes (7.15%), 90 minutes (4.93%), and 120 minutes (4.53%) (Table 6 and Figure 4).

Table No. 4: Effect Of Colegex® On Rat Body Weight

Group I	Group II	Group III
Normal control	Pathological control	Colegex®
206.11±0.91	210.10±1.12	208.30±0.45

Values are expressed as mean±SEM (n=6)

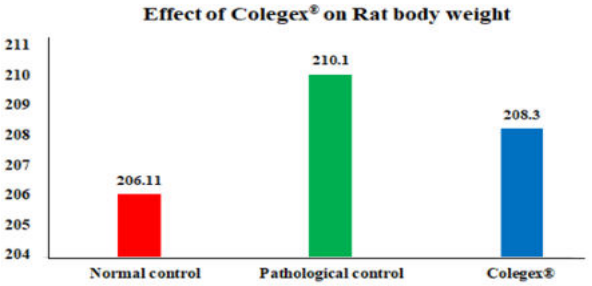

Fig. No. 2: Efficacy Of Colegex® On Rat Body Weight

Table No. 5: Effect Of Colegex® On Oral Glucose Tolerance Test On Blood Glucose Level

Groups	0 min	30 min	60 min	90 min	120 min	180 min	240 min
Normal control	77.33±0.71	80.50±0.56***	80.83±0.54***	78.67±0.49***	77.33±0.71***	74.83±0.60***	69.83±0.48***
Pathological control	76.83±0.31	153.00±1.03	156.17±1.40	151.83±0.91	147.00±1.26	110.83±0.22	78.33±0.76

Cole-gex®	77.17 ±0.75	139.00± 1.61***	145.00± 1.53***	144.33± 0.71***	140.33± 0.42***	108.00± 2.18	77.33± 2.04

Values are expressed as mean±SEM (n=6)

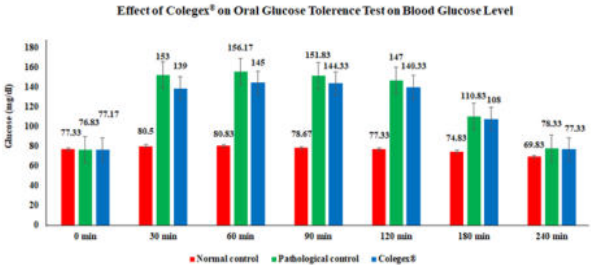

Fig. No. 3: Effect Of Colegex® On Oral Glucose Tolerance Test On Blood Glucose Level

Table No. 6: Percentage Inhibition Of Colegex® on Blood Glucose Level

Time (minutes)	Colegex® (% of Inhibition)
30	9.15
60	7.15
90	4.93
120	4.53

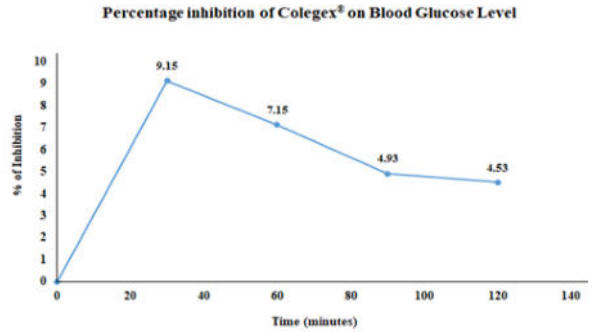

Fig. No. 4: Percentage Inhibition Of Colegex® on Blood Glucose Level

DISCUSSION

A significant therapeutic tool for treating human disorders continues to be medicinal plants and their byproducts [23–25]. It is a problem for the medical system to create drugs that can treat diabetes mellitus (DM) without causing side effects. As a result, there is a greater desire for medications that are recognized to have fewer side effects than the current generation of oral hypoglycemic medications. Natural anti-hyperglycemic remedies apparently have fewer negative effects than artificial oral hypoglycemic medications [26]. As a result, more research is being done on hypoglycemic plants, which may one day provide a natural solution for better clinical management of diabetes mellitus (DM).

A diterpene called forskolin is obtained from the Coleus forskohlii plant [27; 28]. Forskolin directly activates adenylate cyclase (AC), which raises intracellular cAMP levels in a variety of cells. The final consequences of cAMP generation depend on the adenylyl cyclase (AC) isoforms expressed in each type of cell and are as varied as the responses of forskolin-responsive cells [29]. Previous research on pancreatic beta cells has demonstrated that forskolin improves the glucose-mediated stimulation that causes beta cells to produce insulin [30]. The increase in cAMP, which opens up two major signaling pathways in beta cells, was responsible for this final result. Protein kinase A (PKA) mediates one route, whereas cAMP-regulated guanine nucleotide exchange factors are responsible for the activation of the other [31].

This study determined the glycemic index and the oral glucose tolerance test to demonstrate the plausible antidiabetic effect of C. forskohlii root extract (Colegex®) on rats. In this investigation, experimental rats were used to determine how well Colegex® performed in an oral glucose tolerance test to measure postprandial blood sugar levels. When compared to the pathological control group, Colegex® showed little effect on the glycaemic index as is was observed to maintain blood glucose levels. The Glycemic Index (GI) rates different types of carbohydrates in a diet based on how they affect blood sugar levels. Low-glycemic-index carbohydrates digest, absorb, and metabolize more slowly, resulting in a lower and more gradual rise in blood glucose levels. After a 12-hour fast, basal glucose was measured in this study. After a basal glucose reading, Colegex® was given. After the administration of Colegex®, glucose levels were assessed at various intervals of 0, 15, 30, 60, 90, 120, 180, and 240 minutes, respectively. The Colegex® showed a mid-level glycemic index of 63.72%. These findings suggest that Colegex® per se does not induce hyperglycaemia when compared to pathological control. Colegex® also demonstrated a good tolerance in the Glucose Tolerance Assay demonstrating its antidiabetic potential.

CONCLUSION

According to the glycemic index and oral glucose tolerance test results, Coleus forskohlii root extract (Colegex®) significantly lowers blood sugar levels. When compared to the pathological control group, Colegex® showed moderate effect on glycaemic index and was also observed to maintain blood glucose levels. When compared to the pathological control group, Colegex® demonstrated a mid-level glycemic index of 63.72% and sustained raised blood glucose levels. As the efficacy of Colegex® in Glucose Tolerance Test demonstrate good antihyperglycemic activity it is appropriate to conclude that Colegex® can be used as a therapeutic medication for the treatment of Diabetes mellitus.

Conflict Of Interest: None.

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