ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Antidiabetic potential of Triphala Guggul - an ayurvedic formulation in alloxan-induced diabetes animal model

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Article History:

Received on: 02.07.2019
Revised on: 06.10.2019
Accepted on: 11.10.2019

Keywords:

Alloxan monohydrate, Antidiabetic activity, Diabetes mellitus, Triphala Guggul

ABSTRACT

The purpose of this study was to evaluate the potential antidiabetic drug Triphala guggul (TG), an indigenous polyherbal Ayurvedic formulation in an alloxan-induced diabetes rat model. Diabetes mellitus was induced in rats. The rats were divided into nine groups, including the groups of normal control which received the vehicle, the standard group (Glibenclamide) and rats with induced diabetes were treated with the tablet of Triphala guggul and Triphala guggul churna in doses of 100, 200, 400 mg/kg body weight, respectively. They were administered orally for 28 days on a single dose. Blood was collected from the vein in the tail on days 7, 14, 21 and 28. Biochemical estimates were made using blood serum. Acute toxicity studies did not reveal toxicity in rats. For 28 days, Administration of Triphala guggul tablet and Triphala guggul churna formulations improved oral glucose tolerance in diabetes-induced rats and after 28 days, resulted in a significant reduction in serum glucose level compared to normal control rats. These formulations do not affect the kidney, adipose tissue, and liver. The Triphala guggul formulation has a promising antidiabetic property and is effective in the treatment of diabetes.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i1.1823

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Diabetes mellitus is a systemic metabolic disease characterized by hypo-insulinemia, hyperglycemia, hyperlipidemia, and hyper aminoacidemia resulting in decreased insulin secretion and insulin action. Diabetes mellitus is becoming a global challenge in the XXI century. According to estimates by the International Diabetes Federation (IDF, 2015), about 415 million people suffer from diabetes (with a global prevalence of 8.8 percent), of which 75 percent live in low-and middle-income countries. With this trend, in 2040, the world could have 642 million people affected by diabetes. Type 2 diabetes mellitus is the predominant clinical form in place of type DM. Globally, the population of Type 1 diabetes increases by about 3% every year. Worldwide, India has the second-largest diabetic population in the world (~69 million as of 2015). With this trend, India will have 123.5 million people with diabetes by 2040 (IDF, 2015).

The word diabetes was coined by the Greeks, Dr. Aristaeus, in the First Century AD. DM has been known for years, and the sweetness of urine has been mentioned in Ayurveda by Sushruta. His drug

therapy is 80 years old. The presence of sugar in the urine of diabetics was proved by Dobson in 1755 (Wadkar *et al.*, 2008). Every year more than 4 million people die of diabetes, and tens of millions of people can move and suffer from critical complications such as stroke, kidney failure, blindness (American Diabetes Association, 2004). In daily practice, the majority of patients using antidiabetic drugs such as sulfonylurea, Biguanides, etc., these drugs have some side effects, such as nausea, vomiting, abdominal pain, diarrhea, headaches, etc., and then, the search for a new formulation antidiabetic safe herbs are essential in order to overcome these problems.

Triphala guggul is one of those formulation polyherbal compound with 5-medicinal plants (*Emblica Officinalis, Terminalia chebula, Terminalia belerica Linn* (Triphala) (Rajan and Antony, 2008), *Commiphora Mukul*, (Ulbricht *et al.*, 2005) *Piper longum*. These plants are famous for having antidiabetic, antihyperlipidemic and antioxidant activity (Sabu and Kuttan, 2002) According to the traditional Indian system of medicines, a mixture of drugs is used to increase the specific activity and eliminate unwanted side effects. In light of the above information, this study was conducted to assess the hypoglycaemic activity of Triphala guggul and its effect on creatinine, cholesterol, SGOT, SGPT, and glucose in diabetic rats.

MATERIALS AND METHODS

Chemicals and Drugs

Triphala guggul (tablets) gutika was elected from the local pharmacy. Triphala churna, (Bhardwaj P nautical works, Rau, Indore) Guggul churna and Pippali churna were collected by Manakarnika Asuhadhalaya and Alloxan monohydrate Chemicals Pvt. Ltd. Pune, chemicals, and solvents were analytical.

Instrumental-Accu-check Active Glucometer-Roche Diabetes Care, Germany. Centrifuge-Abbexa Ltd, double beam spectrophotometer, UV — V630 JASCO (Tokyo, Japan).

Animals

Healthy Wistar rats of both sexes between 8 and 10 weeks of age with a Bodyweight of 120 to 250 g were housed in polypropylene cages at 25 $\pm$ 2 $^{\circ}$ C with a light-dark cycle for 12 hours in the Animal House of Pharmacy college of RD's. It was acclimatized for seven days. Animals fasted the night before experimenting. The experiments were carried out after the approval of the protocol (registration No RDCOP / Pcol-01 / IAEC / 2018-19 / 01) by the IAEC, and the care of the animals was carried out according to the rules of CPCSEA, Govt. of India. Formulation of the TGT indication in Table 1.

The formulation of Triphala guggul chruna was developed in the laboratories of the Pharmacy college of the RD's and were analyzed for its antidiabetic activity in this study report (3: 5: 1) (Sharangdharacharya, 1988). The TGC formulation is given in Table 2.

Phytochemical preliminary examination

The presence of several phytochemical constituents in the formulation was determined by TLC, total phenolic content, and total flavonoid content according to standard methods (Patel *et al.*, 2009).

Acute oral toxicity test

Acute oral toxicity of the polyherbal formulation was performed in accordance with OECD 423 guidelines (Parasuraman, 2011; OECD 425, 2001).

Induction of diabetes

Animals fasted for 18-24 hours; diabetes was induced by a single intraperitoneal injection of freshly prepared alloxan monohydrate (150 mg/kg) dissolved in 0.9% Normal Saline.

Oral Glucose Tolerance Test

For the study, Wistar rats of both sexes weighing 130-250g were taken. Rats were fasting at night (18 hours) with free access to water. Rats were divided into eight (8) groups of six rats in each group.

Group 1-Normal control-0.5% CMC sodium

Group 2-Standard-Glibenclamide (5 mg/kg orally)

Group 3-low test - Triphala Guggul 100 mg/kg tablet

Group 4-Medium test - Triphala guggul tablet 200 mg/kg

Group 5-High test - Triphala Guggul tablet 400mg / kg

Group 6-Low test -Triphala Guggul Churna 100 mg/kg

Group 7-Medium Test-Triphala Guggul Churna 200 mg/kg

Group 8 - High Test-Triphala Gugul Churna 400mg / kg

Groups 3 to 8, the animals were treated orally with a single dose of Triphala Guggul Gutika and Triphala guggul Churna 100 mg/kg, 200 mg/kg and 400 mg/kg orally, respectively. Glucose (2 G / kg) was administered orally through the orogastric tube 30 minutes after administration at the dose of formulations (Shirwaikar *et al.*, 2006). The normal control animals were administered with the same volume of vehicle. Blood was taken from the vein in the tail at

Table 1: Composition of the formulation (Triphala Guggul Gutika)

Sr. No.	Botanical name	Quantity is taken
1.	Terminalia chebula	27.77g
2.	Terminalia ballerina	27.77g
3.	Emblica Officinalis	27.77g
4.	Commiphora Mukul	138.88g
5.	Piper longum	27.77g
6.	Preservative	q.s

Table 2: Compositionof the formulation. (Triphala Guggul Churna)

Sr. No.	Botanical name	Quantity is taken
1.	Terminalia chebula	1g
2.	Terminalia ballerina	1g
3.	Emblica Officinalis	1g
4.	Commiphora Mukul	5g
5.	Piper longum	1g

0,1,2,3, and 4 hours of glucose administration and blood glucose levels were interrupted using the glucometer (Accucchek active) (Ahmed *et al.*, 2010).

Experimental Procedure

All diabetic rats were randomly divided into nine groups of six rats in each group.

Group 1-Normal control-0.5% sodium CMC (vehicle)

Group 2- Diabetic group-alloxan 150 mg / kg i. p.

Group 3-Standard-alloxan 150 mg / kg i. p. + Glibenclamide

Group 4-Low test-alloxan 150 mg / kg i. p. + Triphala guggul tablets 100 mg/kg

Group 5-medium test-alloxan 150 mg/kg i. p.+ Triphala guggle tablet 200 mg/kg

Group 6-High test-alloxan 150mg / kg i. p. + tablet Triphala Guggul 400mg / kg

Group 7-Low test-alloxan 150 mg/kg i. p. + Triphala Guggul churna 100 mg/ kg

Group 8-Medium test-alloxan 150 mg/kg i. p. + Triphala Guggul churna 200 mg/kg

Group 9-High test alloxan 150 mg/kg i. p. + Triphala Guggul churna 400 mg / kg

The formulation was suspended at 0.5% w / v sodium carboxymethylcellulose (Sod. CMC) in distilled water and orally administration of once daily for 28 consecutive days (Tomy *et al.*, 2015). Blood samples were collected on 1st, 7th, 14th, 21st and 28th day of treatment, through the tail vein and to estimate blood glucose with a glucometer. The weekly change in body weight of all experimental animals was recorded.

Estimation of hematological and biochemical parameters

The serum was separated by mandatory centrifugation at 3500rpm below 30°C for 20 minutes. The collected serum was used to estimate total proteins, SGOT, SGPT, creatinine, triglyceride, and cholesterol, etc. (James *et al.*, 2011).

Histopathology

After 28 days of Treatment, on 29^{th} day, the animals were anesthetized by injection of ketamine and Xylazine (Nurdiana *et al.*, 2017). Rats were sacrificed after blood collection (Parasuraman *et al.*, 2010). All tissues (pancreas, liver, and adipose tissue) were stored in neutral formaldehyde solution for histopathological examination.

RESULTS AND DISCUSSION

The presence of markers like gallic acid, quercetin, guggulsterone E, and Z was confirmed by TLC, where the pre-filled plates of TLC as a stationary phase. The mobile phase used for Toluene: ethyl acetate: formic acid: methanol (3:3:0.8:0.5 v/v/v/v) as the mobile phase.

TLC chromatogram of TGT has confirmed the presence of markers with Rf 0.48, 0.56, and 0.29 for the Quercetin, Gallic acid, Guggulsterone, respectively, in the same way the TLC chromatogram of TGC confirmed the presence of markers with Rf 0.46, 0.54 and 0.35 for the Quercetin, Gallic acid, Guggulsterone, respectively. The percentage of the phenolic

content of TGT and TGC was 297 μg / ml and 67 μg / ml, respectively. The Flavonoidal content of TGT and TGC rates were 219 μg / ml and 367 μg / ml, respectively.

Acute Oral Toxicity Studies

In an acute toxicity study, animals treated with the formulation Triphala Guggul Gutika and Triphala Guggul Churna showed a sign of toxicity is not observed for the parameters during the first 4 hours. And followed by daily observations for 14 days, no mortality was observed, the drugs were found safe at the proven dose of 2000 mg/kg body weight. One-tenth of this dose level was taken as an effective dose, such as 100 mg/kg, 200 mg/kg and 400 mg/kg, respectively.

Oral Glucose Tolerance Test

The in vivo study was conducted 28 days after the initiation of the formulation and administration of the standard drug (glibenclamide). For each of the seven days, OGTT was carried out by collecting the blood of rats and recorded blood glucose levels, after 28 days of study the percentage of inhibition was calculated and compared with the standard drug of inhibition.

Antidiabetic activity of TGT, TGC formulation

After the administration of the formulation, OGTT was done. Effect of Triphala Guggul Gutikas and Triphala Guggul Churna formulation of normal blood sugar level and diabetic fasting rats, after a glucose load of 2g / kg, the blood sugar level increases $\frac{1}{2}$ h rapidly after administration of glucose and then decreased gradually. The Standard drug Glibenclamide and three different doses of the formulations (100 mg/kg, 200 mg/kg and 400 mg/kg) were administered orally 30 minutes before administration of glucose. In normal control groups animals, a gradual increase in blood glucose was observed after glucose loading and within 2 hours. Diabetic groups of animals showed a gradual increase in blood glucose levels and stabilized in 2 hours. 100 mg/kg, 200 mg/kg Triphala Guggul Gutikas and Triphala Guggul Churna formulation showed a minimum decrease in blood glucose concentration, but at 400 mg/kg TGT and TGC showed a maximum decrease in blood glucose concentration. The same procedure was followed, and similar results were observed on 14, 21, and 28, respectively. The values were expressed as mean $\pm$ S. E. M. and the help of prism graphics software, and the values are compared using two-way ANOVA paths. (Bonferroni post-tests) The result of the antidiabetic activity of the TGT and TGC formulation is shown in Table 3 and Table 4, should and in Figure 1 and Figure 2. The graph shows the difference between plasma glucose (mg/dl) from initiation of treatment and 28 days after treatment.

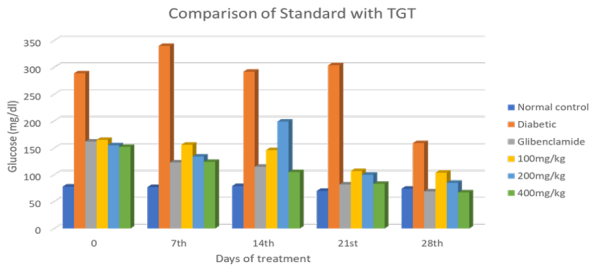


Figure 1: Effect of TGT and glibenclamide on plasma glucose levels on days 7, 14, 21, 28 of treatment

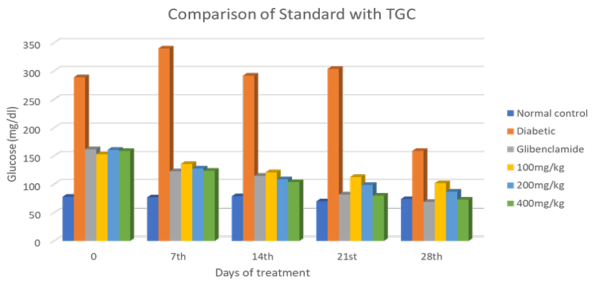


Figure 2: Effect of TGC and glibenclamide on plasma glucose levels on days 7, 14, 21, 28 of treatment

Percentage of Inhibition

The percentage of inhibition is measured by taking the results from the day of treatment to the end of treatment. Figure 3 shows a comparison between the standard and the different doses of the formulation (TGT and TGC), such as 100 mg/kg, 200 mg/kg, and 400 mg/kg. 100 TGT and 200 TGC show a linear inhibition of glucose and can be used as the dose is maintained. 400 TGT and TGC show drastic inhibition of glucose level to be used in severe Hyperglycaemia as a loading dose.

Histopathological parameter

Figure 4 shows that sections of the pancreas, liver, and adipose tissue in rats treated with TGT and TGC showed a protective result of the formulation. A marginal decrease in pancreatic β cell size was observed in rats Figure 4 (b) that was once more normalized in rats treated with TGT and TGC Figure 4 (c, d) approximately parallel to normal control rats Figure 4 (a) when histopathological features of adipose tissues were analyzed, a vital increase in adipocyte size was observed in diabetic rats Figure 4(f) relative to the normal control group Figure 4(e) in total treatment with TGT and TGC, a significant reduction in adipocyte size was observed

Table 3: Plasma glucose values (mg/dl) determined on days 7, 14, 21, and 28 of treatment, respectively, and as a TGT formulation compared to the standard drug

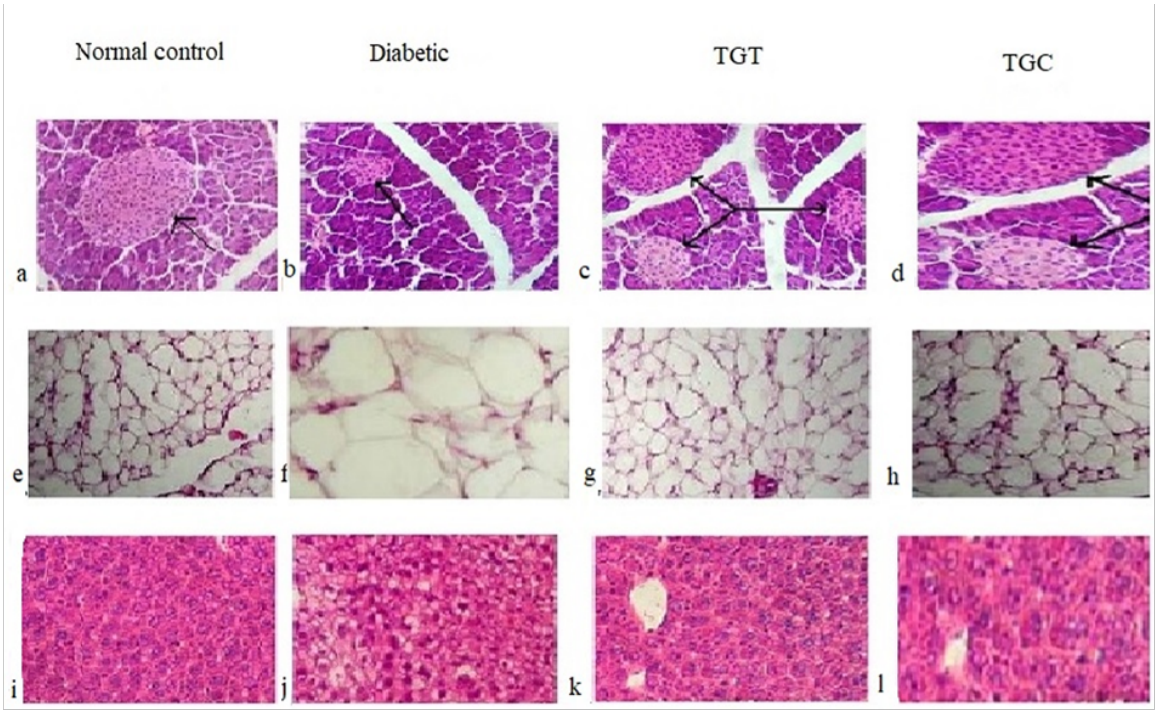
	Normal control	Diabetic	Standard (Glibenclamide)	100mg/kg TGT	200mg/kg TGT	400mg/kg TGT
0	78±1	159±4	162 ±4	165±5	155±3	152±3
7th	77±0.6	289±5	123±1	156±2*	134±2*	124±1*
14th	79±1	340±2	115±1	146±2*	119±2	105±1**
21st	70±2	292±4	82±4	107±1	100±3	83±2
28th	74±3	304±8	69±5	104±1*	85±2	67±4*

The values are expressed as mean ± SEM of(n-6). * P<0.05 less significant, * * p < 0.01 significant, * * *p<0.001 more significant.

Table 4: Plasma glucose values (mg/dl) determined on days 7, 14, 21, and 28 of treatment, respectively, and as a TGC formulation compared to the standard drug

	Normal control	Diabetic	Standard (Glibenclamide)	100mg/kg TGC	200mg/kg TGC	400mg/kg TGC
0	78±1	159±4	162 ±4	153±2	161±5	159±5
7^{th}	77±0.6	289±5	123±1	137±2	128±1**	124±1
14^{th}	79±1	340±2	115±1	121±1*	109±1	104±1*
21^{st}	70±2	292±4	82±4	113±1	99±3	80±2
28^{th}	74±3	304±8	69±5	102±2	87±2*	73±6

The values are expressed as mean ± SEM of(n-6). * P<0.05 less significant, * * p < 0.01 significant, * * *p<0.001 more significant.



Photomicrograph of the section from the pancreas (a-d), adipose tissue (e-h), and liver (i-l) of various groups of rats. The arrow indicates the islet region of the section.

Figure 4: Effect of the TGT and TGC formulation on the pancreas, liver, and adipose tissues

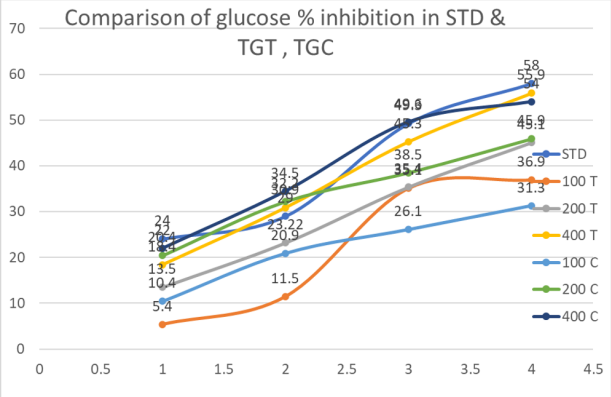


Figure 3: Percentage inhibition of glucose on treatment with Glibenclamide, TGT, and TGC formulations

Figure 4(g, h). Similarly, liver tissues in diabetic animals showed signs of severe steatosis, that is, accumulation of lipid drops that were noticeable within the type of vacuoles Figure 4(j) In relation to the liver of normal control animals Figure 4(i). However, treatment with TGT and TGC not only reversed this deformity but at a similar time, showed no signs of toxicological effects compared to the normal control group Figure 4(k, l).

Diabetes mellitus can be a major international health problem, with at least 171 million people worldwide suffering from diabetes in 2000, according to the World Health Organization, or 2.8 percent of the population. Its incidence is increasing rapidly, and it is estimated that by 2030, this range can almost double (Wild *et al.*, 2004), in traditional practice, medicinal plants are used in different countries to regulate diabetes mellitus. The hypoglycaemic action of these medicinal plants is the subject of a thorough study (Hernandez-Galicia *et al.*, 2002), plant medicine is often considered less toxic and free of the many side effects than the synthetic drugs (Pari and Umamaheswari, 2000).

In a wide range of animal models, alloxan monohydrate induces diabetes. Alloxan and its dialuric acid reduction product establish an oxidation-reduction cycle with the formation of superoxide radicals. These radicals undergo the disposal of hydrogen peroxide. Highly reactive hydrogen radicals are formed by the Fenton reaction. This action of reactive oxygen species with a simultaneous massive increase in the concentration of cytosolic calcium causes the rapid destruction of beta cells. Therefore, decrease insulin secretion (Szkudelski, 2001). The mechanism of Glibenclamide is used as a standard drug that acts by binding and inhibiting the sensitive channels of potassium ATP in pancreatic beta cells. This inhibition results in depolarisation of the cell membrane and opening of calcium channels and increased intracellular calcium within the pancreatic beta-cell and resulting stimulation of insulin secretion or release (Serrano-Martin *et al.*, 2006).

Triphala Guggul is an Ayurvedic drug-containing Shuddha Guggulu, Triphala, and Pippali Churna. Its advantages include its use in Ayurveda for weight loss, constipation, fistula, internal abscess, liver abscess, infectious wounds of soft tissues. Flavonoids and phenolic contents are natural antidiabetic agents, which interfere with the production of free radicals, due to the reduction of oxidative stress and inhibition of the digestive enzyme, thus, the reduction of postprandial sugar level. Trifala guggul tablet has a greater total phenol content than Trifala Guggul Churna. Trifala Guggul Churna has a higher flavonoid content than Trifala guggul tablet. The formulation of TGT and TGC contains several phytoconstituents, as observed in TLC studies. The thin-layer chromatographic analysis revealed the presence of constituents such as quercetin RF value 0.48, gallic acid: 0.56, guggulsterone in TGT: 0.29, and quercetin RF 0.42, gallic acid: 0.50, guggulsterone in TGC: 0.35.

Acute toxicity studies of TGT and TGC for 14 days had no effect on the behavior or overall appearance of the animal, and therefore, rats survived the trial period. There were no signs and symptoms such as restlessness, shortness of breath, diarrhea, convulsions, and coma.

The TGT and TGC formulations were investigated for hyperglycaemic action in the animal glucose model induced by hyperglycaemic events at a dose level of 100, 200, and 400 mg/kg, respectively, the selected formulation showed significant anti-hyperglycaemic activity. Comparative study of glucose inhibition % in the standard and experimental drug. Among all the formulations TGT and TGC, polyherbal formulations 100mg / kg TGT and 200mg / kg TGC show a linear glucose inhibition of 36.9% and 45.9% and can be used as a maintenance of the dose. 400 mg/kg TGT and 400 mg/kg TGC show drastic inhibition of 55.9 %, and 54% glucose will be used in severe hyperglycemia as a loading dose.

After the treatment of the formulation, the level of total cholesterol decreased significantly in comparison with the group of diabetics. Treatment with the polyherbal formulation significantly reduced cholesterol levels, triglycerides, and LDL. Triglycerides and cholesterol are the main carriers of diabetes. The polyherbal formulation is also attributed to an increase in clearance and a decrease in the production of cholesterol and triglycerides due to

the stimulation of insulin secretion. Increase insulin secretion to achieve desired pharmacological activity and elimination of side effects, obtained through the combination of a variety of herbal medicines together.

Therefore, the results of this analysis work indicate that the formulation is also effectively used in the treatment of diabetes mellitus. Due to the mechanism of action of the formulation may be due to inhibition of free radical generation after oxidation. In addition, increasing the effect of insulin in plasma by increasing pancreatic secretion of insulin from existing beta cells or its release from the improvement in glucose and protein levels, such as insulin, inhibits gluconeogenesis from the protein. Diabetic animals showed an increase in the level of triglyceride, cholesterol, LDL cholesterol, and low levels of HDL-cholesterol, whereas administration of TGT and TGC have shown a reduction in significant and dose-dependent levels of triglycerides, cholesterol, LDL-cholesterol and an improvement in levels of HDL-cholesterol. This result is implicating in its usefulness in DM with hyperlipidaemic complications.

However, TGT and TGC not only reversed this abnormality but at a similar time, showed no toxicological signs compared to the normal control group. After examining the histopathological characteristics of adipose tissues, a vital increase in adipocyte size was observed in diabetes affected rats compared to the normal control group. In total treatment with TGT and TGC, a significant reduction in adipocyte size was observed. Similarly, liver tissues in diabetic rats showed signs of severe steatosis compared to normal control rats. Triphala guggul formulations have a promising antidiabetic property, as demonstrated by the results of the study, and are useful in the management of DM.

CONCLUSIONS

In conclusion, oral administration of the TGT and TGC formulation shows a significant reduction in blood sugar in each normal control group and in hyperglycaemic alloxan-induced rats. Both formulations have significantly restored all parameters to almost normal in alloxan-induced diabetic rats. The antidiabetic activity of the formulation of TGT and TGC can be attributed to the presence of phenolic and flavonoid contents. The Triphala guggul formulation has a promising antidiabetic property and proves useful in the management of diabetes.

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