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Antihyperglycemic Activity of *Syzygium cumini* (Jamun) in Diabetic Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Recently with the changes in population lifestyle, prediabetes is constantly on the rise. Management of prediabetes currently is with lifestyle modifications like weight loss, exercise and diet control. Better drugs with acceptable safety profile are needed for better control of prediabetes. This study was thus designed to evaluate the antihyperglycaemic effect of one such potential compound *Syzygium cumini* (SC) (Jamun) in comparison to conventional antidiabetic drug Metformin.
Methods: Rats were divided into four study groups (SC 100 mg/kg and 200 mg/kg, metformin 90 mg/kg and SC 200 mg/kg with metformin 90 mg/kg). The glycaemic changes were followed up for a period of 8 weeks.
Results: Streptozotocin (STZ) induced significant rise in blood glucose levels in the rats. SC 100 mg/kg and 200 mg/kg caused a reduction in BSL (192.50 ± 6.189 & 175.00 ± 6.782 respectively). SC 200 mg/kg alone and in combination with metformin caused a significant reduction in HbA_{1C} levels at the end of 8^{th} week (8.84 ± 0.65 & 6.86 ± 0.40 respectively) as compared to their baseline levels. Increase in dose had led to more significant reduction in BSL at the end of 8^{th} week in groups A & B ($p < 0.05$). However, reduction of BSL was superior with Metformin alone (159.17 ± 13.060) compared to *Syzygium cumini* administered alone. Also antihyperglycemic effect of

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Syzygium cumini administered along with metformin was significant ($p < 0.05$) compared to either doses of *Syzygium cumini* given alone.
Conclusions: *Syzygium cumini* demonstrated antihyperglycemic activity in diabetic rats but less significant when compared to metformin. Antihyperglycaemic effect of *Syzygium cumini* with metformin was significantly better than either drugs given alone. In prediabetic or diabetic individuals *Syzygium cumini* seed powder can be suggested as a potential add-on therapy with conventional antidiabetic drugs. However more non-clinical and clinical studies need to be conducted to confirm the findings.

Keywords: Syzygium cumini; prediabetes; type 2 diabetes mellitus; BSL; HbA_{1C}; metformin.

1. INTRODUCTION

Diabetes mellitus is a group of metabolic disorders arising from myriad pathogenic mechanisms, all resulting in hyperglycaemia. Genetic and environmental factors contribute to the pathogenesis and involves insufficient secretion of insulin, decreased response to insulin either endogenous or exogenous, raised glucose production, with or without abnormalities in fat and protein metabolism. The resultant hyperglycaemia might lead to acute symptoms and metabolic abnormalities [1].

Diabetes is also leading cause of non-traumatic lower extremity amputations, end-stage renal disease, and blindness in adults and also predisposes to cardiovascular disorders. With the rising incidence of diabetes worldwide, in future it would likely be a leading cause of morbidity and mortality [2].

Ayurveda, one of the oldest traditional system of medicine, is reported to have documented the management of diabetes [3]. Therapeutic agents have been used for its treatment before the discovery of insulin and several other plants have revealed antidiabetic activity [4]. Derivatives of plants with antihyperglycemic properties have been used in folk medicine from times unknown in the past [5].

Syzygium cumini (L.) Skeels. (*E. jambolana* Lam., Myrtaceae) is a plant used by traditional practitioners over centuries for the treatment of diabetes. Both animal and clinical studies have revealed that different parts of *Syzygium cumini* especially seeds, fruits and bark possess promising antidiabetic activity [6].

Due to the recent trends in lifestyle and food habits, prediabetes is a rising concern. Lifestyle modification is the best action to prevent the progression of prediabetes into diabetes. Being asymptomatic, patient of prediabetes tends to neglect the advice of lifestyle modification. One needs to stress the necessity of identifying it in early stages and plan lifestyle modifications. Also, another issue that needs to be kept in mind regarding lifestyle modifications is the long-term adherence. In a systematic review, it was noted that adherence in the long-term was an issue. The study stated that lifestyle modifications reduced the incidence of diabetes development more than standard treatment. Better glycaemic control, improved physical exercise capacity, and increased weight reduction were observed with lifestyle modifications over standard treatment. But, improvements over the long term deteriorated, highlighting problems with long-term adherence to lifestyle changes [7].

Therefore, there is a need for development of new drugs with better safety profile. In individuals with prediabetes, pursuit of naturopathy and reluctance starting on conventional antidiabetic drugs often promotes individuals into taking alternative therapies including dietary modifications and/or herbal supplements [8].

With need for development of new drugs with better safety profile and as a supplement to standard diabetic management, this study isdesigned to assess and compare the antihyperglycaemic effect of one such potential compound *Syzygium cumini* (Jamun) with standard antidiabetic drug Metformin in streptozotocin induced diabetic rats.

Objectives of the study are:

- To study the antihyperglycaemic effect of *Syzygium cumini* seed extract in dose dependent manner
- To compare the antihyperglycaemic effect of *Syzygium cumini* seed extract with metformin

2. MATERIALS AND METHODS

A total of 24 Sprague-Dawley rats of *Rattus norvegicus* species (either sex weighing 150-300

g) were procured from the animal house of Dr. D.Y. Patil Medical College, Pimpri, Pune. They were fed with commercially available feed and water ad libitum.

Ethanolic extract of *Syzygium cumini* seeds was used in this study. The seed powder obtained and the verification and extraction of the extract was done by Dr. D. Y. Patil College of Ayurveda and Research Centre, Pimpri, Pune. Dose of 100 & 200 mg/kg body weight was administered orally.

Metformin was used as the standard drug in the dose of 90 mg/kg body weight administered orally [9]. Both *Syzygium cumini* and Metformin and were administered once daily orally for a duration of 8 weeks. Streptozotocin (STZ) 45 mg/kg was administered intraperitoneal to induce diabetes in the rats [10]. Blood sample was collected from the rats after 3 days and fasting blood sugar levels were assessed using a glucometer. Rats having blood sugar levels above 200 mg/dl were included in the study.

The rats were divided into four groups with 6 rats in each group (n=6), distributed randomly (Table 1).

2.1 Parameters

Fasting blood sugar levels (BSL-F) were measured at baseline (3rd day post intraperitoneal injection of STZ), 2nd, 4th& 8th week of all the groups.

The glycated hemoglobin (HbA_{1C}) levels in groups B & D were measured at baseline (3rd day post intraperitoneal injection of STZ) and at the end of 8th week. Blood samples were collected from retro-orbital space.

2.2 Statistical Analysis

All values of results are presented as Mean ± SD. The statistical analysis within the group was evaluated by Paired Student's t-test. One-way analysis of variance (ANOVA) followed by Tukey's test was used for statistical comparison between various study groups. Statistical significance was accepted at $p < 0.05$ value. Data analysis was done using Primer for Biostatistics version 7.0.

3. RESULTS

Results are expressed as Mean ± SD. (Table 2).

The Mean ± SD of BSL after intraperitoneal injection of streptozotocin are given in the table. There was significant increase in blood sugar levels on 3rd day after injection which was statistically significant ($p < 0.05$) implying that diabetes was induced (Table 2).

3.1 Effect of *S. cumini* on Blood Sugar Levels

Syzygium cumini administration resulted in BSL reduction in group A administered 100 mg/kg at the end of 2nd week (251.17 ± 6.210), 4th week (230.3 ± 6.250) and 8th week (192.50 ± 6.189) respectively compared to baseline BSL (266.7 ± 6.5). BSL reduction was also observed in group B administered *Syzygium cumini* 200 mg/kg at the end of 2nd week (236.83 ± 7.960), 4th week (220.67 ± 9.459) and 8th week (175.00 ± 6.782) ($p < 0.05$) respectively compared to baseline (257.8 ± 10.1) suggesting a good diabetes control. (Tables 3 and 4) (Fig. 1).

The standard drug metformin 90 mg/kg administered to group C caused reduction of BSL at the end of 2nd week (241.83 ± 10.477),4th week (206.83 ± 8.773)and 8th week (159.17 ± 13.060) respectively compared to baseline BSL (260.3 ± 9.7).It was observed that the reduction in BSL in group C was statistically significant ($p < 0.05$) when compared reductions in BSLin group A at the end of 4th and 8th week. (Tables 3 and 4) (Fig. 1).

The reduction in BSL in group D administered both the study drugs *Syzygium cumini* 200 mg/kg and metformin 90 mg/kgwas at the end of 2nd week (243.83 ± 11.805), 4th week (202.50 ± 6.442) and 8th week (142.33 ± 9.913) compared to baseline BSL (260.3 ± 9.7) respectively.It was observed that reduction in BSL in group D at the end of 4thweek was statistically significant ($p < 0.05$) when compared to groups A & B. At the end of 8th week the BSL reduction in group D was statistically significant ($p < 0.05$) compared to all other groups. (Tables 3 and 4) (Fig. 1).

3.2 Effect on Glycated Hemoglobin (HbA_{1C})

The blood for glycated hemoglobin (HbA_{1C}) levels of groups B & D was collected from the retro-orbital space of the rats and assessed in the laboratory using high-performance liquid chromatography (HPLC) technique.

There was a statistically significant reduction in HbA_{1C} levels in group B (8.84 ± 0.65) ($p < 0.05$) and group D (6.86 ± 0.40) ($p < 0.05$) at the end of 8th week compared to their baseline levels. When the reduction in HbA_{1C} levels in these two groups were compared, it was observed that there was statistically significant reduction in group D (6.86 ± 0.40) ($p < 0.05$) administered the combination of *Syzygium cumini* 200 mg/kg with metformin 90 mg/kg, showing that there was better control of blood sugar levels in group D as compared to group B. (Table 5).

Table 1. Grouping of rats

Groups	Dosages
Group A	S. cumini 100 mg/kg (p.o.)
Group B	S. cumini 200 mg/kg (p.o.)
Group C	Metformin 90 mg/kg (p.o.)
Group D	S. cumini 200 mg/kg (p.o.) + Metformin 90 mg/kg (p.o.)

Table 2. Mean fasting blood sugar levels after induction of diabetes

Group	Treatment	BSL-F at baseline (mg/dl) Mean ± SD
A	SC 100 mg/kg (p.o.)	266.67 ± 6.532
B	SC 200 mg/kg (p.o.)	257.83 ± 10.128
C	Metformin 90 mg/kg (p.o.)	260.33 ± 9.688
D	SC 200 mg/kg (p.o.) + Metformin 90 mg/kg (p.o.)	267.50 ± 7.583

Table 3. Effect of *S. cumini* on blood sugar levels (mg/dl)

Group	Baseline	2nd week Mean ± SD	4th week Mean ± SD	8th week Mean ± SD
A	266.7 ± 6.5	251.17 ± 6.210	230.3 ± 6.250	192.50 ± 6.189
B	257.8 ± 10.1	236.83 ± 7.960	220.67 ± 9.459	175.00 ± 6.782*
C	260.3 ± 9.7	241.83 ± 10.477	206.83 ± 8.773*	159.17 ± 13.060*
D	267.5 ± 7.6	243.83 ± 11.805	202.50 ± 6.442*†	142.33 ± 9.913*‡

*$p < 0.05$ * when compared to Group A † when compared to Group B ‡ when compared to Group B & C*

Table 4. Comparison of effect of *Syzygium cumini* on fasting blood sugar levels (p values)

	Baseline	Group A	Group B	Group C	Group D
Baseline	Group A	-	0.313	0.589	0.998
	Group B	-	-	0.957	0.242
	Group C	-	-	-	0.49
	Group D	-	-	-	-
2 weeks	Group A	-	0.068	0.337	0.54
	Group B	-	-	0.792	0.577
	Group C	-	-	-	0.982
	Group D	-	-	-	-
4 weeks	Group A	-	0.178	< 0.001*	< 0.001*
	Group B	-	-	0.030*	0.004*
	Group C	-	-	-	0.776
	Group D	-	-	-	-
8 weeks	Group A	-	0.02*	< 0.001*	0.001*
	Group B	-	-	0.039*	<0.001*
	Group C	-	-	-	0.026*
	Group D	-	-	-	-

Table 5. Effect of *S. Cumini* on glycated hemoglobin (HbA_{1C}) levels

Group	Treatment	HbA_{1C} (%) Baseline	HbA_{1C} (%) 8^{th} week	p value
B	*S. cumini* 200 mg/kg	10.18 ± 0.58	8.84 ± 0.65*	p < 0.05
D	*S. cumini* 200 mg/kg + Metformin 90 mg/kg	10.54 ± 0.61	6.86 ± 0.40*†	p < 0.05

*p < 0.05: *compared to baseline †compared to Group B*

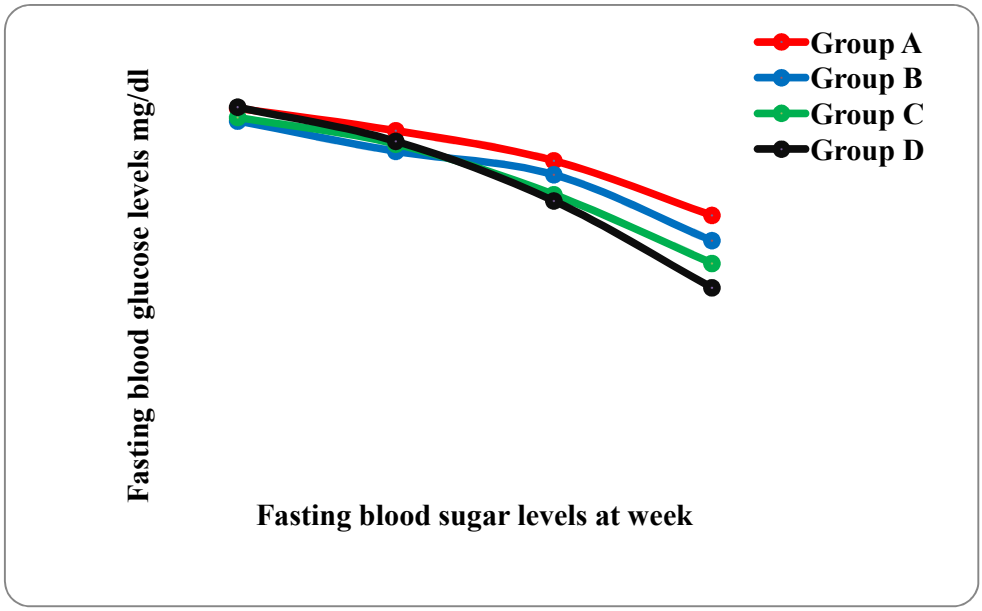

Fig. 1. Effect of *Syzygium cumini* on blood sugar levels (mg/dl)

4. DISCUSSION

Metabolic syndrome is a rising health concern among Indian population. International Diabetes Federation reports that in 2015 the number of adults with impaired glucose tolerance (IGT) or diabetes was 318 million and 415 million, respectively. It was also reported that the estimated count in 2040 would rise to 482 million and 642 million respectively [10,11]. Individuals with prediabetes when compared to normoglycemic individuals, were related to higher incidence of composite cardiovascular disorders including coronary heart disease, stroke, chronic renal disease, and all-cause mortality [12,13]. Available treatment modalities can control the disease progression but with several side-effects. Hence, there has always been a need for newer and effective pharmacotherapy with considerable safety profile.

With the recent lifestyle changes, prediabetes is constantly on the rise. Management of patients with prediabetes needs inclusion of various methods with special attention to lifestyle modifications like weight loss, exercise and diet control.Current pharmacological therapies for managing prediabetes are very few and cannot be justified due to their adverse effect profile. Better drugs with acceptable safety profile are needed which can be used for the treatment of prediabetes.

Many ayurvedic plants have been used for the treatment of diabetes. *Syzygium cumini* has been used in traditional ayurvedic medicine since ancient times to treat hyperglycaemia. Availability of many literatures in Ayurveda and modern medicine suggest antihyperglycemic activity of *Syzygium cumini*.

Various studies done to evaluate the antihyperglycemic effect of *Syzygium cumini* have found it to be effective in significantly reducing the blood glucose levels [14,15,16]. Its effect has been compared to various standard antidiabetic drugs, but very few have studied

antihyperglycemic action of *Syzygium cumini*in dose dependent manner and its effects when combined with a standard drug (metformin). This study was undertaken with the aim of assessing the effect of *Syzygium cumini*on BSL in a dose dependent mannerand comparing the results with the reduction in BSL with standard drugmetformin.

The results of our study indicated *Syzygium cumini* has definite antihyperglycemic effect in diabetic rats and thuscould have a role in the management of diabetes in humans which needs further extensive evaluation.

In our study, *Syzygium cumini* seed extract (100 mg/kg & 200 mg/kg) had significant antihyperglycemic activity from second week of observation in reference to the baseline ($p < 0.05$). Comparison between groups A & B showed a dose-dependent decrease in blood sugar levels at the end of 8th week. Higher dose of SC 200 mg/kg caused a significant reduction when compared to lower dose of SC 100 mg/kg at the end of 8th week.

Kumar A. et al, [14] reported *S. cumini* ethanolic and methanolic extracts (200 and 400 mg/kg) of *Syzygium cumini* caused a significant reduction ($p<0.05$) in blood sugar level. Sharma SB. et al. [15] reported ethanolic extract of *Syzygium cumini* caused dose-dependent effect on fasting blood glucose up to a dose of 100 mg/kg. However, the increase in doses to 200 mg/kg failed to show dose-dependent effect in their study.

In our study metformin had significant antihyperglycemic activity when compared to the study drug as expected. Combining SC (200mg/kg) with metformin was associated with more significant reduction than metformin used alone. Kumar A. et al. [14] reported SC(200 and 400 mg/kg)caused less reduction ($p<0.05$) in blood sugar level when compared to glibenclamide.

In our study *Syzygium cumini* significantly lowered HbA_{1C} levels in groups B & D. Combination of SC (200mg/kg) with metformin caused more significant reduction than *Syzygium cumini* or metformin given alone. Sharma SB. et al. [15] reported ethanolic extract of *Syzygium cumini* seed has shown significant reduction in HbA_{1C}levels in rabbits. Dusane M. et al. [17] reported sustained reversal in experimental diabetes evidenced by restoration of normoglycemia along with increases in plasma insulin and C-peptide levels in mice.

Syama HP. et al. [18] reported *Syzygium cumini* can potentially inhibit α-amylase, α-glucosidase, glycation, and DPP-IV enzymes. Ratsimamanga U. et al. [16] reported *Syzygium cumini* exerts hypoglycemic action like sulfonylureas by stimulating the surviving β-cells to release more insulin. Singh N. et al. [19] reported that dose of 75 mg *Syzygium cumini* over 30 days in alloxan diabetic rats achieved almost normal granulation in some partially damaged β cell islets except necrosed parts. Other studies have reported that it acts by increasing sensitivity and stimulation of surviving β cells to release more insulin.

Furthermore, clinical and toxicological studies to assess the antihyperglycemic effect and toxicities are needed. Clinical studies to assess the beneficial effect of *Syzygium cumini*in combination with conventional antidiabetic drugs and in patients with prediabetes also need to be evaluated. *Syzygium cumini* effects on beta cell regeneration, body weight, lipid profile in normal patients, patients with type 1 and type 2 diabetes and diabetic patients with co-morbidities need to be studied extensively.

Syzygium cumini seed powder can be used as a potential supplement in prediabetic patients reluctant to start conventional pharmacotherapy. Extensive studies with a larger sample size and administered for shorter & longer duration to check the antihyperglycemic effect and toxicities are needed. Clinical studies to assess the beneficial effect of *Syzygium cumini* in combination with conventional antidiabetic drugs and in patients with prediabetes also need to be evaluated. *Syzygium cumini* effects on beta cell regeneration,body weight, lipid profile in normal patients, patients with type 1 and type 2 diabetes anddiabetic patients with co-morbidities need to be studied extensively. However, lifestyle modification is still the mainstay of management.

5. CONCLUSION

The present study concluded that *Syzygium cumini* extract reduces blood sugar levels in diabetic rats. The antihyperglycemic effect of metformin with *Syzygium cumini* (Jamun) was significantly better than metformin or *Syzygium cumini* given alone. *Syzygium cumini* also caused decrease in HbA_{1c} levels but the reduction was more significant when used in supplementation with metformin. However more

non-clinical and clinical studies need to be conducted to confirm the findings.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Institutional Animal Ethics Committee (IAEC) clearance was obtained before starting the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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