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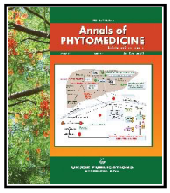

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Hypoglycemic activity of combined dried powder of *Andrographis paniculata* (Burm.) Nees whole plant and *Gymnema sylvestre* R. Br. leaves in experimental rat model

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Abstract

Naturally occurring plants, *Andrographis paniculata* (Burm.) Nees and *Gymnema sylvestre* R. Br. were selected and screened for antihyperglycemic potential against standard drug metformin HCl in an alloxan induced diabetic rat model. This study's main objective is to highlight the perspective in developing herbal antidiabetic formulations in the future. The natural components like flavonoids (quercetin) in plants were found to efficacious as compared with the marketed formulation. Alloxan-induced diabetic rat were treated with the oral administration of *G. sylvestre* dried leaves and *A. paniculata* decoction powder, either alone and in combination was studied. The use of the post-hoc Bonferroni multiple comparisons test revealed that after 3 and 5 h, metformin HCl (120 mg/kg) significantly lowers blood glucose levels (p<0.001). The combination of *A. paniculata* and *G. sylvestre* (100 mg/kg) and their dosage (200 mg/kg) also significantly reduced the blood glucose level after 3 and 5 h. After 5 h, a particularly substantial lessening of glucose level in plasma was monitored. The above investigation and prediction of the role of flavonoids may open new perspectives for the development of natural-based hypoglycemic products and their constituents and to fully understand the mechanism of action (MOA) underpinning flavonoids protective effects in diabetes and diabetic-like complications, more research is necessary.

1. Introduction

Natural products have tremendous potentials in lowering the plasma glucose level in mammals (Mahapatra *et al.,* 2015). It has been evidenced that with the passage of time, more and more people across the globe are being affected by this syndrome, which is now a day, popularly known as 'diabetes'. The changing lifestyle, reduced exercise, modern food habits (Patel *et al.,* 2011), and several miscellaneous factors have provoked the emergence among the masses (Kuhite *et al*., 2019). In this decade, it has been a matter of notice among the clinicians that the younger section of the society is also getting affected by this disease. By the end of 2050, it has been predicted that the patient population will be doubled up as compared to the present era. The type 2 form of diabetes mellitus is an alarming issue, whereas the cells do not properly exploit the formed insulin as a result of resistance in the body (Nagar *et al*., 2015). When the proper time comes, numerous antidiabetic drugs of synthetic origin have been in pharmacotherapy. In the developing nations, about 80% of the total global deaths from this metabolic disease have been reported (Mahapatra *et al*., 2017). Protein tyrosine phosphatase 1B, dipeptidyl peptidase-4, aldose reductase, peroxisome proliferator activated receptor-γ, and α-glucosidase, *etc*., are examples of inhibitor classes (Chhajed *et al*., 2017). With the long regimen of therapy, it has been evidenced by several complications, adverse effects, and several other issues. This has often led to shifting in the treatment approach among a prominent section of the society. The favored trend often displayed efficacious therapeutic potential with the administration of multiple doses along with very low toxicity and better tolerability (Gangane *et al*., 2018).

Mother nature indicated a privileged foundation for the investigation of several potential hypoglycemic molecules (Nagar *et al*., 2020). The alternative systems of medicine like Ayurveda, Unani, Siddha, Homeopathy, *etc*., have described numerous plants having a glucose lowering properties which are used either in the form of extract or phytoconstituents (Borikar *et al*., 2017). After getting inspiration from the nature, two Indian plant; *A. paniculata* (Family: Acanthaceae) and *G. sylvestre* (Family: Apocynaceae) were selected after thorough literature review and screened for anti-hyperglycemic potential against standard drug metformin hydrochloride in alloxan-induced diabetic rat model, with an objective to highlight the perspective in developing formulations in the future.

2. Materials and Methods

2.1 Chemicals and instruments

A generous gift sample of the common drug, metformin hydrochloride, was received from Zim Laboratories Ltd., Nagpur. HiMedia Ltd. supplied the diabetes-inducing substance, alloxan monohydrate, Mumbai, India. HiMedia Ltd. provided the analytical grade chemicals that were used in the study. The plasma glucose levels of the experimental rats were determined using One Touch™Select Simple

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Glucometer (Sample Volume 1 µl) and Glucose strips from Johson and Johnson, Mumbai, India. Shimadzu® AUW220D electronic balance was employed in weighing purpose during the study.

2.2 Animals

The Sprague dawley rats of age 5-6 weeks were utilized for screening the hypoglycemic potentials of the powdered herbal component. The animals were procured after obtaining permission from the CPCSEA (853/AC/04/CPCSEA) and housed properly under a hygienic condition in the controlled environment in animal house (25-26ºC, humidity 50-55%, and 12 h light/dark). Standard rodent pellets were fed to the two rats housed in a polypropylene cage, with unrestricted access to water.

2.3 Acquiring and analyzing plant material

The plants and their parts of *A. paniculata* and *G. sylvestre* were authenticated from Department of Botany, RTM University, Nagpur, Maharashtra, India. In October 2019, the entire *A. paniculata* and *G. sylvestre* plant was harvested from the Ramtek region of Nagpur, Maharashtra, India.

2.4 Phytochemical screening

Carbohydrates, flavonoids, saponins, and glycosides were detected in the hydroalcoholic extract of dried leaves from *G. sylvestre* and *A. paniculata*. The various phytoconstituents present in extract and decoction of plant material, as per (ST-1), specially the quercetin which shows absorbance at 415 nm (ST-2 and ST-3) after 30 min of incubation. As discusses previously, quercetin is the common flavonoid content found in *G. sylvestre* and *A. paniculata* possessing hypoglycemic activity (Borikar *et al*., 2018). With known concentrations, an SF-1 standard calibration plot was produced. Calculated from the calibration plot, the flavonoid concentration in the test sample.

2.5 Determination of flavonoids

The most significant natural phenols are most likely flavonoids, which are among the most varied and abundant classes of natural chemicals. These materials perform a variety of biological and chemical tasks, one of which is scavenging radicals. Using quercetin's usual plot (R^2 = 0.9911), the flavonoid contents of *P. granatum* flowers decoction and *A. paniculata* hydroalcoholic extracts was found to be 40, 18.75 mg (ST-4) quercetin equivalent/g of dry sample respectively.

2.6 Procedure for extraction

After adequately drying the entire plant of *A. paniculata* and *G. sylvestre* leaves for two weeks, a coarse powder was produced by grinding the contents. The contents (about 200 g) were further meticulously macerated using methanol for the duration of 15 days. After that, the solvent was dried using a rotator vacuum evaporator. *G. sylvestre* produced the solid light brown color mass (yield: 11.8%), while *A. paniculata* produced the solid dark brown color mass (yield: 12.3%). After then, the solid bulk was processed into an extremely fine powder.

2.7 Studies on oral acute toxicity

The OECD guideline, 423 was followed when conducting the acute toxicity tests in Sprague dawley rats for the plant dried powder in rising doses from 5 mg/kg to 5000 mg/kg to estimate the maximum *in vivo* safety limit (LD_{50} values) (ST-5 and ST-6) as well as the lowest quantity of drug (dose) that will endorse therapeutic action (therapeutic index) (Kanhed *et al*., 2016).

2.8 Statistical analysis

The number of animals employed was 6 in number. A triplicate of the experiment was conducted. The results were expressed as mean ± SEM. A p-value of <0.05 was seen as noteworthy. For statistical analysis, Prism program v5.0 software was used. The hypothesis was assessed using Bonferroni post-hoc tests and two-way analysis of variance (ANOVA).

3. Results

3.1 Determination of LD_{50}

The median lethal dose, or LD_{50}, is a metric used to assess a chemical's deadly toxicity. It is the dose at which the substance kills 50% of testers. Measured in milligrams of substance per kilogram of body weight, it is a widely used tool in toxicology to evaluate the possible harm caused by substances.

The plant powder materials presented well *in vivo* safety and therapeutic index. No signs of acute toxicity and mortality were observed despite the fact that the dose was increased between 5 and 5000 mg/kg. A final dose of 100 mg/kg body weight was chosen for the *in vivo* antidiabetic.

3.2 Evaluation of hypoglycemia potential

Alloxan monohydrate was made by dissolving it in physiological saline solution, which was then given intraperitoneally into rats who were malnourished and had no glucose to cause diabetes. After the lapse of 6 h, the rats were further administered 20% glucose solution intraperitoneally and further in order to prevent hypoglycemia, for the next 24 h, 5% glucose solution was administered. The animals demonstrating a blood glucose level of >250 mg/dl after 48 h of alloxan administration were subsequently selected for the antidiabetic screening study (Table 1). The ED_{50} of the plant powder material (ST-7) (whole plant of *A. paniculata* and leaves of *G. sylvestre*) were at a dose of 100 mg/kg for oral administration. After the dose administration, Digital glucose strips were used to measure the plasma glucose level after 1, 3, and 5 h. The potential (s) of the mixed powder in displaying hypoglycemic activity was calculated using the AUC method (Borikar *et al*., 2018).

3.3 Hypoglycemic potential

Oral delivery of dried leaves of *G. sylvestre* and powdered plant material of *A. paniculata* to rats with alloxan-induced diabetes (ethical approval-853/AC/04/CPCSF), either alone and in combination, resulted in a striking hypoglycemic activity ($F(4,60) = 12.92$, p <0.001). The post-hoc Bonferroni multiple comparisons expressed that metformin HCl (120 mg/kg) drastically reduce the blood glucose level after 3 h and 5 h ($p<0.001$). *A. paniculata* (100 mg/kg), *G. sylvestre* (100 mg/kg), and its combination (200 mg/kg) also appreciably lowered the blood glucose level after 3 h and 5 h (p <0.001) (Figure 1). The plausible chemical moieties present in the extract components may be the active polyphenols, alkaloids, or flavonoids which exhibited noteworthy anti-hyperglycemic activity by improving the blood glucose transportation capability in the secondary tissues or by elevating the insulin secretion levels from β-cells of the pancreas (Borikar *et al*., 2018; Nagar *et al*., 2010).

Following a 5 h oral dosage of *A. paniculata* whole plant powder and *G. sylvestre* leaves, a notably significant reduction in plasma glucose levels was seen. The anti-hyperglycemic potentials of the dried powder of *A. paniculata* and *G. sylvestre* are depicted in (Table 2).

Table 1: Effects of *G. sylvestre* dried leaves and *A. paniculata* dried plant powder in alloxan induced diabetic rats

S. No.	Groups	Dose (mg/kg)	Blood glucose level (mg/dl)			
			0 h	1 h	3 h	5 h
1	Dried *G. sylvestre* leaves powder	200	392.6 ± 26.56	370.2 ± 23.87	292.6 ± 20.03	203.4 ± 14.69
2	Dried *A. paniculata* plant powder	100	343.2 ± 17.72	319.4 ± 15.27	257.4 ± 11.75	202.4 ± 21.59
3	Combination of dried *A. paniculata* plant and *G. sylvestre* leaves powder	200	389.6 ± 14.61	359.8 ± 14.37	237.2 ± 16.15	141.4 ± 7.90

n = 6; ED_{50} values were found to be 100, 200 mg/kg b.w.; $p < 0.05$

Table 2: Hypoglycemic potential of combined decoction of *A. paniculata* dried plant and *G. sylvestre* dried leaves

Groups	Dose (mg/kg)	Blood glucose level (mg/dl)			
		0 h	1 h	3 h	5 h
Saline	1 ml	330.6 ± 25.19	364.6 ± 21.92	398.3 ± 25.97	433.4 ± 22.8
Metformin HCl	120	391.8 ± 5.86	316.5 ± 12.20	250.2 ± 13.66	188.2 ± 14.29
Dried powder of *G. sylvestre*	100	392.6 ± 16.56	368.7 ± 13.88	281.9 ± 10.03	214.4 ± 14.67
Dried powder of *A. paniculata*	100	346.1 ± 17.73	319.5 ± 14.27	242.8 ± 11.75	209.3 ± 11.59
Combined dried powder of *A. paniculata* and *G. sylvestre*	200	385.2 ± 14.61	341.7 ± 12.37	276.5 ± 16.21	203.8 ± 9.12

n = 6; ED_{50} values were found to be 100, 200 mg/kg b.w.; $p < 0.05$

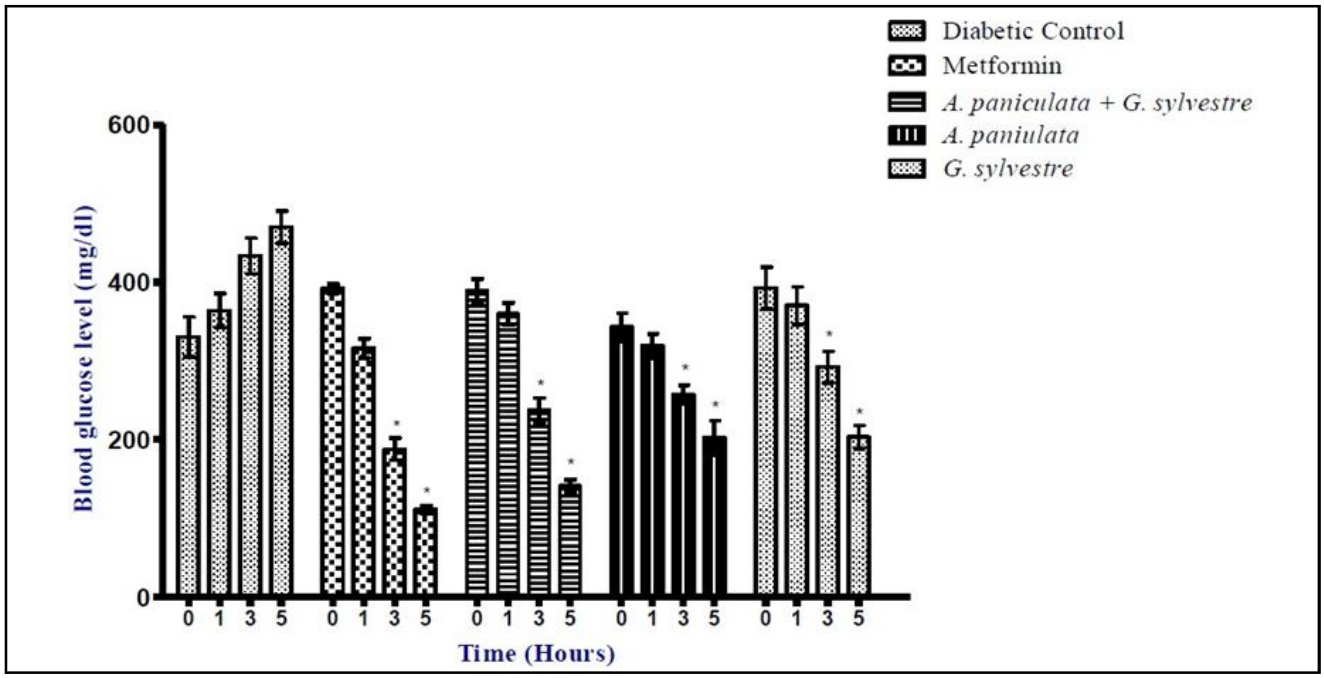

Figure 1: Effects of *A. paniculata* dried plant and *G. sylvestre* dried leaves decoction in alloxan induced diabetic rats.

The effect of oral administration of *G. sylvestre* (100 mg/kg) dried leaves and *A. paniculata* (100 mg/kg) dried plant powder to the alloxan-induced diabetic rats, either alone and in combination, resulted in a significant hypoglycemic activity [$F(4,60) = 12.92$, $p<0.001$]. The post-hoc Bonferroni multiple comparisons expressed that metformin HCl standard drug at the dose (120 mg/kg) drastically reduce the blood glucose level after 3 h and 5 h ($p<0.001$). Whereas, *A. paniculata* (100 mg/kg), *G. sylvestre* (100 mg/kg), and its combination (200 mg/kg) also appreciably lowered the blood glucose level after 3 h and 5 h ($p<0.001$ Vs diabetic control group) (Figure 1). After 5 h of oral administration of whole plant powder of *A. paniculata* and leaves of *G. sylvestre*, significantly reduction in of blood glucose level.

4. Discussion

Insulin is secreted by the β cells of the pancreatic islets of Langerhans, helping to regulate blood glucose levels. By destroying the β cells in the islets of Langerhans, alloxan significantly reduces the amount of insulin released, which leads to hyperglycemia. Rats with alloxan-induced diabetes showed a reduction in blood glucose levels when floral decoction powder was given orally. These may potentiate insulin secretion from the β-cell of the islets or increase blood glucose transport in the peripheral tissues, which would be the possible antihyperglycemic mechanism. It was thought that the flavonoid components of the decoction were essential in modulating the hypoglycemic effect. In addition phytoconstituents like glycoside or any alkaloid may be believed to impart the glucose lowering attribute. The natural components were found to be quite safe, have minimum toxicity and very efficacious as compared with the marketed formulation *A. paniculata's* main ent-labdane diterpenoid, andrographolide, is the main source of numerous pharmacological actions, including tiplatelet aggregation activity (Wu *et al*., 2008) immunomodulatory activity (Wang *et al*., 2009) and other myriad health benefits (Subramanian *et al*., 2012). Few published papers on pharmacology as well as other ent-labdane diterpenoids (including neoandrographolide and 14-deoxyandrographolide), flavonoids, quinic acids, and xanthones are reported for their noteworthy contributions (Wu *et al*., 2008). The present predicted studies of phytoconstituents like glycosides, saponin, and flavonoids (ST-1) containing quercetin may actively involve in significant antidiabetic potenital *via* specific mechanism.

In the documented research, the hypoglycemic evaluation of the whole plant decoction powder of *A. paniculata* and the hydroalcoholic extract of *G. sylvestre* leaves in fasting Zucker diabetic fatty rats demonstrated a strong inhibition of α-glucosidase (IC_{50} of 1.8 µg/ml), activation of peroxisome proliferator-activated receptor-γ, and enhancement of glucose sensitivity in the peripheral milieu, all of which effectively reduced the blood glucose level from 360 to 240 mg/dl (Aziza *et al*., 2013; Huang *et al*., 2005; Jafri *et al*., 2000; Li *et al*., 2005). Compared to the single dried plant powder treatment, the combination dried powder of *A. paniculata* whole plant and *G. sylvestre* leaves showed a rapid drop in blood glucose from 400 to 200 mg/dl, supporting the treatments potential for synergy. Furthermore, the powdered decoction demonstrated a significant alteration in catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase, and glutathione-S-transferase. This highlighted the hyperlipidemia, lipid peroxidation in pancreatic cells, and antioxidant properties that highlight the potential benefits of preventing diabetes as well as the likely mechanism (s) involved (Zhang and Tan, 2000). Similarly, the *G. sylvestre* extract's antidiabetic screening demonstrated robust antioxidant activity in the tests, such as TBA (56%), SOD-like (92%), and ABTS (54%). Because *G. sylvestre* extract contains antihyperglycemic ingredients as gymnemagenin and gymnemic acids, the blood glucose levels of the diabetic rats fed the extract dropped to normal levels. Furthermore, in the diabetic rats given the extract, lipid peroxidation levels were reduced by 31.7% in the serum, 9.9% in the liver, and 9.1% in the kidney (Kang *et al*., 2012). Blood glucose levels in the rats with diabetes in this investigation were higher, and after 5 h of oral medication delivery, the blood glucose levels significantly decreased.

5. Conclusion

The current investigation of the combined dried powder of *G. sylvestre* leaves and *A. paniculata* whole plant proved successful in significantly lowering the plasma glucose level in Sprague dawley rats that had been given alloxan. The investigation and prediction of role of flavonoids may open new perspectives for the development of natural based hypoglycemic products and their contituents. Still, additional investigation into the creation of formulations based on the mentioned principles may pave the way for novel approaches to the treatment of diabetes mellitus..

Conflicts of interest

The authors declare no conflicts of interest relevant to this article.

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