Review Article

Hypoglycemic Effect of *Andrographis paniculata* Extract in Alloxan Induced Albino Wistar Rats: A Systematic Review

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ABSTRACT

Diabetes or Diabetes Mellitus (DM) is recognized as part of the top leading causes of mortality rates around the globe. The disease is involved with the pancreas which produces insulin. Insulin is crucial in regulating glucose, and as well as fat from the food individuals consume. DM can occur when limited amounts of insulin is produced by the pancreas. It can also occur when insulin is not regulated properly. DM is threat to people of all ages as it can be acquired no matter how old or young a person can be, approximately 90–95 % of people are at risk to have this type of diabetes, due to their imbalanced lifestyle. Therefore, the researchers aim to investigate the effects of *Andrographis paniculata*; also known as Serpentina, on biochemical parameters of blood sugar level in both alloxan and STZ-induced rats. Experimental and scientific studies conducted on *Andrographis paniculata* were reviewed from the year 2000 to 2020. A total of ten (10) studies were included in this review, which revealed significant hypoglycemic effects of Serpentina in both alloxan and STZ-induced rabbits and rats. The hypoglycemic activity of Serpentina was due to the active compound (Andrographolide) of the plant and which proved its use in decreasing blood glucose level in all of the reviewed experimental research. Regardless of the presence of known oral hypoglycemic drugs in the market, remedies made from this medicinal herb have been undoubtedly successful to help aid DMII and markedly decreased complications due to lessened side effects.

Key words: Alloxan-induced, *Andrographis paniculata,* Blood glucose level, Diabetes Insulin Resistance, Serpentina.

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INTRODUCTION

Diabetes milletus (DM) is a worldwide health disorder which threatens the life of an individual when left untreated.[1] People diagnosed with diabetes has increased dramatically, starting from the year 1980 with only 108 million people, to 422 million people in 2014.[1,2] The dramatic rise of diabetic patients ultimately intensifies treatment costs. Subsequently, many health professionals stressed on diabetic care.[3] The disease has no known cure, and because of its life-threatening complications, various practices are strictly followed. However, modification of lifestyle is often not enough to reduce blood glucose levels to normal levels. Thus, the disease is aided with various hypoglycemic drugs and insulin.[4]

The production of insulin is estimated to be $9.5 billion yearly,[5] which is undoubtedly expensive, leaving those with financial issues struggle to purchase the treatment they ultimately need. According to Spero; insulin has become a multibillion-dollar global market ranging at $24 billion per year, which would continue to increase as there is an apparent demand in supply, as diabetic patients drastically rises yearly. Therefore, making it much more expensive for the masses.[5]

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The prevalence of diabetes, specifically diabetes mellitus II; among younger people, has led to the increased of interest in developing medicinal practices in diabetes.[2,4] Aside from conventional antidiuretic and antioxidant treatment, in which were concluded by various literatures that many plants and herbs possess hypoglycemic effect.[6-9] The authors of these literatures still recommend for a thorough study, concerning the medicinal benefits in diabetes. The plant '*Andrographis paniculata*' is found in Asian countries especially in India, and was reported that it possesses various health uses specifically in the prevention of many diseases.[7-10]

Andrographis paniculata, is generally called *Serpentina* in the Philippines. Serpentina has been historically used to treat inflammation and bacteria.[8-10] It contains a chemical called 'Andrographolide', which is an active ingredient in Serpentina. Andrographolide possess various pharmacological benefits, targeting inflammation, cancer, obesity and diabetes.[9,10] The researchers are focused on Serpentina extract in contrast to an already known oral hypoglycemic drug; Glimepiride.

Thus, the researchers aim to determine whether Serpentina has the potential for lowering blood glucose levels, and as well as treating the disease. Hence, the researchers aim to determine significant differences among the Control Group, the Oral Hypoglycemic Drug (Glimepiride) Group and the Serpentina Extract Group of the study, in terms of their height, weight and blood glucose levels. Hence, the objective of the researchers is to quantitatively evaluate the effects of the Serpentina extract in terms of height, weight and blood glucose levels.

The findings from the various literary reviews will contribute greatly to the benefit of the society considering that medicine in our modern world undoubtedly continues to evolve day by day. Thus, college medical students and future medical researchers, will be able to use this literary review to aid them with their studies. Alongside with medical experts and patients diagnosed with DM will be able to broaden their knowledge with the use medicinal herbs as alternative practice for DM.

MATERIALS AND METHODS

The objective is to identify the most reliable and replicable study on the effectiveness of Serpentina on DM. Articles were identified on PubMed (July 2018), National Center for Biotechnology Information (NCBI), Research Gate. Keywords used were the following: Diabetes Mellitus, Diabetes Mellitus Type 2, Insulin, Alloxan Induced, Hypoglycemic Effect, Oral hypoglycemic agent, *Andrographis paniculata*, Serpentina, Antidiuretic Effect, Andrographolide, Decrease Blood glucose and Pharmacology of *Andrographis paniculata*. The abstracts of articles from each of these searches were thoroughly reviewed and selected those which met the criteria made for this study. Scholar articles on Google was also used for possible articles that may be included in the study.

The included studies summarized in Table 1, used alloxan or streptozotocin (STZ) as induced to animals; subjects must be *Andrographis paniculata*, randomized complete block design and test animals should either be rats or rabbits. All studies included were rigorously and thoroughly reviewed and appraised by researchers prior to the inclusion of the studies, Figure 1 demonstrates the guide and series of phases which ultimately formed the 'inclusion studies' included in the review.

Figure 1 demonstrates the inclusions needed for the studies to be approved. Detailing the research design, test animals, test subjects, and the ways to induce diabetes.

The 'Selection Guide' PRISMA flowchart diagram demonstrates the phases taken prior to the inclusion of studies. Detailing the number of studies searched in databases, the number of titles and abstracts screened, full-text reviews, assessment using 'Inclusion Criteria' and studies included for the final analysis.

RESULTS

There were vast studies that involved the plant *Andrographis paniculata,* but very few have met the standards with this specific review. Originally, there were eighty-five (85) articles in total involving Hypoglycemia and *Andrographis paniculata,* unfortunately there were duplicates hence the researchers excluded those articles. Which led to only a total of twenty-three (23) articles successfully passed a few phases prior to inclusion. After critically appraising these articles, only ten (10) articles fulfilled the inclusion criteria for the review. The article demonstrated either an Alloxan Induced or STZ induced animals; Test subjects are Serpentina in contrast to a known oral hypoglycemic drug/ treatment or another plant; Randomized complete block design were used; and Test animals are either rats or rabbits. Table 1.1 demonstrates the list of included studies for the review. However, among the 11 selected articles; the study made by Noble1 presented the most ideal experimental model for the researchers. The study is titled; "Hypoglycaemic Activity of *Andrographis paniculata* Crude Extract". They have monitored the blood glucose level after every 1st, 2nd, 4th hr and 7th day period of observation, after administering insulin orally and different amounts of *Andrographis paniculata* crude extract.[13] The diabetic rats were

Table 1: List of Included Studies.

Included Studies	Author (s)	Date	Significant Finding (s)
"Evaluation of Beneficial Effects of Antioxidant Properties of Aqueous Leaf Extract *of Andrographis paniculata* in STZ- Induced Diabetes",	Aniikumar M. Dandu, Naseeruddin M. Inamdar	2009	Compared to diabetic animals, those treated *with Andrographis paniculata* demonstrated significantly lower fasting blood glucose levels on the 15th and 45th days of diabetes
"Experimental and clinical pharmacology of *Andrographis paniculata* and its major bioactive phytoconstituent andrographolide",	Thanasekaran Jayakumar, Cheng-Ying Hsieh, Jie-Jen Lee, and Joen-Rong Sheu	2013	The treatment of *Andrographis paniculata* to diabetic rats at a dosage of 400 mg/kg body weight twice daily for 2 weeks resulted in a 49.8% decline in fasting serum triglyceride levels
"Antidiabetic and antihiperlipidemic effect of *Andrographis paniculata* (Burm. F.) NEES And ANDROGRAPHOLIDE In high- fructose-fat-fed rats",	Agung Endro Nugroho, Mohamad Andrie, Ni Kad-ek Warditiani, Eka Siswan-to, Suwidjiyo Pramono, and Endang Lukitaningsih	2012	Compared to the control group, the purified extract and andrographolide significantly (P0.05) de-creased blood glucose, triglyceride, and LDL levels.
"Blood Glucose Reduction by Combination of *Andrographis paniculata* (Burm. F.) Ness Herbs and Azadirachta indica A. Juss Leaves in Alloxan-Induced Diabetic Rats",	Anwar, Wigati, Sudarsono, and Agung Endro Nugroho	2014	Treatment with *Andrographis paniculata* Ethanolic Extract (APEE) and *M. Citrifolia* Ethanolic Extract (MCEE) for 14 days, both demonstrated decreased pre-prandial and post-prandial blood glucose levels.
"Antidiabetic effect of a combination of andrographolide-enriched extract of *Androgpraphis paniculata* (Burm F.) Nees and asiaticoside-enriched extract of Centella asiatica L. In high fructose-fat fed rats",	Agung Endro Nugroho, Novena Yety Lindawati, Kyky Herlyanti, Lina Widyastuti, and Suwidjiyo Pramono	2013	Andrgrapholide-enriched extract of *A. Paniculata* (AEEAP) leaves and asiaticoside-enriched extract of *C. Asiatica* (AEECA) both demonstrated significantly decreased blood glucose. Hypglycemic effect were 61.21% and 61.12% respectively.
"View of *in vitro* Alpha-glucosidase and alpha-amylase Enzyme inhibitory effects of *Andrographis paniculata* extract and andrographolide",	Rammohan Subramanian, M Zaini Asmawi, and Amirin Sadikun	2008	At 60 min, there was a substantial (P 0.05) decrease in blood glucose. Ethanolic extracts of *Andrographis paniculata* had no significant effect on glucose absorption in the small intestine
"Hypoglicemic and beta cell protective effects of andrographolide analogue for diabetes treatment",	Zaijun Zhang, Jie Jiang, Pei Yu, Xiangping Zeng, James W. Larrick, and Yuqiang Wang	2009	Alloxan-induced rats treated with andrgrapholide-lipoic acid conjugate (AL-1) resulted to a lowered blood glucose levels, increased blood insulin levels and preserved beta cell mass and function
"Anti-diabetic property of ethanolic extract of *Andrographis paniculata* in streptozotocin in diabetic",	Zhang X. And Kwong Huat Tan	2000	Fasting serum triglyceride levels were reduced by 49.8% with the *Andrographis paniculata* extract, compared to 27.7% with metformin.
"Anti-Diabetic activity and metabolic changes induced by *Andrographis paniculata* plant extract in obese Diabetic Rats",	Muhammad Tayyab Akh-tar, Mohamad Syakir Bin Mohd Sarib, Intan Safinar Ismail, Faridah Ab-as, Amin Ismail, Nordin Hj Lajis, and Khozirah Shaari	2016	The metabolic profile of obese and obese–diabetic rats can be restored to normal using 200 mg/kg of *Andrographis paniculata* extract.
"Hypoglycaemic Activity of *Andrographis paniculata* Crude Extract",	Dr. Victoria M. Noble, Dr. Cherry C. Favor, and Mrs. Erlinda O. Panganiban	2020	500 mg/kg dose of *Andrographis paniculata* can be used as alter-native hypoglycemic treatment for insulin

administered with 0.10 ml/kg insulin and the Andrographis paniculata crude extract in 250, 500, and 750 mg/dl dosages.[13]

The diabetic rats in the experiment were administered with 0.10 ml/kg insulin and the *Andrographis paniculata* crude extract in 250, 500, and 750 mg/dl dosages.[13] As stated previously, the blood glucose level (BGL) were monitored after every 1st, 2nd, and 4th hr of the day, also on the 7th day period of observation. The experimental model made by the researchers presented significant decreases in BGLs of the rats after taking different doses of *Andrographis paniculata* crude extract. In table 2, the model and results presented were able to highlight the decrease among the test groups of the experiment. As well as it demonstrated clear and organized results, which also satisfies the selection of articles.

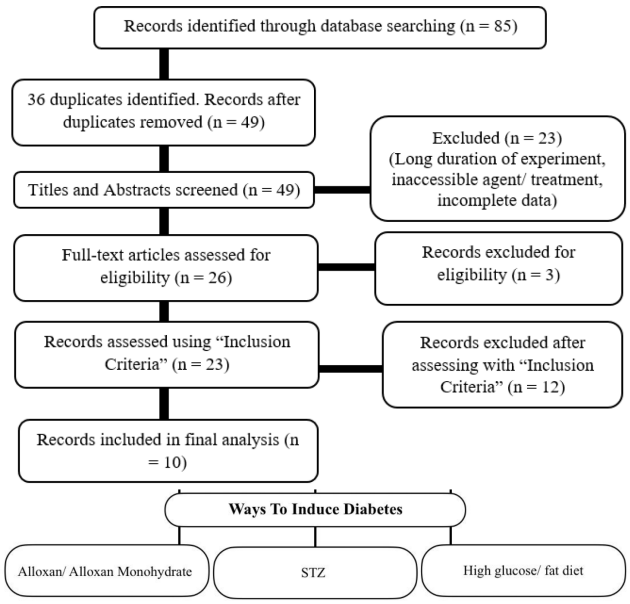

Figure 1: Flowchart for inclusion criteria. Remove the apostrophes.

The study also displayed an ANOVA table which demonstrated that the f-value of the reduced blood glucose level among the different groups is 0.876, with a 0.504 in *p*-value. With a *p*-value is < 0.05, reveals for no significant difference between blood glucose level among the categorized groups.[13] The ANOVA table is presented in Table 2.1. Lastly, in Table 2.2 of the study demonstrates the multiple comparison tests of the different groups using Least Significant Difference (LSD) with Insulin (control group). The table presents that mean difference of decreased BGL of rats using Insulin with specific doses or treatment of *Andrographis paniculata* crude extract are 120.00 mg/dL, 39.33 mg/dL

Table 2: Blood Glucose Levels (BGLs) of Rats Before, During and After the Oral Administration of Insulin and Doses of *A. paniculata* Crude Extract.

Group Sample	Dose	Rat No.	Weight, kg	Blood Glucose Level Results					
				Before Alloxan	After Alloxan	1st hour	2nd hour	4th hour	7th day
Group 1 Positive Control Insulin	0.10 mg/kg	1	0.153	96	>600	>60	>60	>57030	Died
		2	0.131	64	410	188	62	<32378	148
		3	0.152	98	215	131	55	<26180	48
		4	0.144	81	>600	336	203	<36564	Died
		5	0.187	84	600	550	233	311	30
Group 2 *A.paniculata* Extract	250 mg/kg	1	0.183	104	323	326	298	311	30
		2	0.163	97	>600	>600	>600	>600	Died
		3	0.144	97	212	255	233	235	79
		4	0.143	103	378	400	386	467	Died
		5	0.179	86	395	456	485	449	Died
Group 3 *A.paniculata* Extract	500 mg/kg	1	0.162	104	336	468	355	354	54
		2	0.162	110	352	393	365	373	15
		3	0.167	86	286	444	388	373	24
		4	0.155	76	>600	>600	>600	>600	Died
		5	0.163	83	588	>600	>600	>600	Died
Group 4 *A.paniculata* Extract	750 mg/kg	1	0.158	102	396	467	370	444	104
		2	0.199	94	>600	>600			Died
		3	0.162	95	330	461	581	461	Died
		4	0.175	91	261	424	501	341	382
		5	0.161	64	430	458	510	430	Died

Table 2.1: Comparison of the Reduced Blood Glucose Level of Diabetic Induced Rats with the Different Doses of *A. paniculata* Crude Extract with Insulin as Control Group.

	Sum of Squares	DF	Mean Square	*f*-value	*p*-value
Between Groups	83,192.933	3	27,730.98	0.876	0.504
Within Groups	189,867.167	6	31,644.53		
Total	273,060.100	9			

Table 2.2: Multiple Comparison Test of the Different Groups using Least Significant Difference (LSD) with Insulin as Control Group.

Treatment (I)	Treatment (J)	Mean Difference (I-J)	Std. Error	*p*-value
Insulin	250 mg/kg	120.00	162.39	0.488
	500 mg/kg	39.33	145.25	0.796
	750 mg/kg	247.50	162.39	0.178

and 247.50 mg/dL.[13] It is presented in the table that the *p*-values are <0.05, hence concluded no significant difference between the reduced blood glucose level using insulin and the different doses of *Andrographis paniculata* extract.[13] The literary study made by Noble, established that 500 mg/kg dose of *Andrographis paniculata* crude extract has the same hypoglycemic activity with insulin, when it comes to reducing the BGL on the rats. Thus, concludes that 500 mg/kg dose of *Andrographis paniculata* can ultimately be used as alternative hypoglycemic treatment for insulin.[13]

DISCUSSION

The researchers were able to conclude from these literary reviews that Serpentina is widely used as a hepatoprotective and hepatostimulative agent in Asian traditional medicine. The extract derived from the leaves of this plant has lengthy been used as a remedy for a variety of liver ailments.[7-9] These numerous studies have shown that Serpentina is made up of Andrographolide. Andrographolide is a key compound in Serpentina, by these findings, it is revealed as the largest contributor to most of the plant's medicinal properties.[12] An extract of Serpentina that contains at least 15% andrographolide can be used as a hypoglycemic agent.[7,17] On top of that, the plant widely recognized for being an effective treatment for various respiratory illnesses.[14-17] Moreover, these studies revealed that Serpentina contains hypoglycemic and renal-protective properties.[14-17]

Despite of known advanced treatment and medications, numerous researchers are especially drawn to herbal remedies. Various plants have been rigorously and thoroughly studied especially for its medicinal use in treatments of diabetes. The increased interest among herbal remedies are due to the known side effects, high cost and scarcity of modern anti-diabetic drugs for rural areas, as well as in developing countries.[9,16] The results and findings of this review is consistent with results of studies conducted on Serpentina across different countries. The blood glucose level obtained from these studies strongly indicates that extracts of Serpentina demonstrated significant hypoglycemic effects in agents of alloxan, STZ and well as high glucose induced animals. This figure displays the critical process which takes place after treatment with *Andrographis paniculata* extract. It shows the beginning of the process from High Fat Diet and Inducing Alloxan to the end, which results to the Improved Glucose Levels. This figure summarizes the antidiabetic effect of the extract to the experimental rats.

CONCLUSION

Serpentina is widely used as traditional remedy in Asia, especially in India, it is majorly used in treating many inflammatory and respiratory diseases. Based on the various studies reviewed, the researchers can conclude that Serpentina possess anti-diabetic activities therefore, it has the potential to replace costly treatments and medications in treating DM. This systemic review has provided an understanding and gave an insight regarding the pharmacological activity of Serpentina. The study should be conducted in various countries and used different population groups such as those that are just diagnosed with DMII and those that are diagnosed for more than a decade. As well as, possibilities of underlying side effects in these experimentations may occur. For that reason, the researchers recommend other

agents to induce diabetes, to determine whether there are significant changes with the results, and if there will be abnormal reactions from the plant extract due to the use of different agents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUMMARY

All authors contributed to the data extraction and analysis, draft, and revision of the review. All of them gave final approval of the version to be passed and agreed to be accountable for all aspects of the work.

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