

Antidiabetic and antihyperlipidemic effects of *Artemisia absinthium* L., *Citrullus colocynthis* (L.) Schrad. and *Gymnema sylvestre* (Retz.) R.Br. ex Sm. on type II diabetes hyperlipidemic patients

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Artemisia absinthium L., *Citrullus colocynthis* (L.) Schrad. and *Gymnema sylvestre* (Retz.) R.Br. ex Sm. have been used in Asian countries for thousands of years to treat diabetes. This study was conducted to evaluate hypoglycemic and antihyperlipidemic effects in type II hyperlipidemic diabetic patients. Study is blind randomized placebo-controlled clinical trials over 40 days. Individuals were divided randomly into 4 groups 1, 2, 3 & 4. Ten individuals were in each group. Group 1 was allocated for *G. sylvestre*, 2 for *A. absinthium*, 3 for *C. colocynthis* and 4 for placebo. Medication (1.0 g/day) was administered for 40 days. From each individual of each group on day 0, 10, 20, 30 and 40 blood samples were collected in fasting condition. Serum glucose values in group 1 dropped most considerably ($p < 0.05$). Diabetic individuals of all 3 groups as compared to control and placebo group, showed significantly lowered fasting serum glucose level ($p < 0.05$). Fasting serum triglycerides, cholesterol, HDL-cholesterol and LDL-cholesterol of all 3 groups were not reduced significantly at ($p < 0.05$) as compared to control and placebo groups. So it may be suggested that a type II diabetic patient can safely be switched from costly conventional antidiabetic medicine to cheap natural products.

Keywords: Clinical trials, Diabetes, Traditional medicine

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Diabetes mellitus being one the major and an ever increasing global grave health dilemma is causing massive economic burden and healthcare policy concerns¹. As of 2017, the number of diabetic individuals is 425 million in the world, with an assessed 5.0 million deaths each year as mentioned in a recent report of International Diabetes Federation². Based on its etiology and management diabetes mellitus may be divided into two main types. Type 1 or insulin dependent diabetes mellitus or juvenile on-set diabetes, it implicates autoimmune or idiopathic etiology. Type II or non-insulin dependent diabetes mellitus or old age on-set diabetes is mainly due to the predominant insulin secretory faults or insulin resistance. The treatment of Type 1 diabetes mellitus is only through Insulin therapy³. Type-II diabetes is also a disease with numerous facets including both a genetic factor and dynamic non-genetic component(s)⁴. With a worldwide rate of 5 % in the overall population, it has now reached an endemic

form. It is predicted that by the year 2045, world will have around 629 million adults with diabetes in contrast to the present 425 million in 2017. Current total global healthcare expenditures estimate for diabetes are USD 727 billion which will rise to USD 776 billion by 2045². Therefore, its control is a matter of pronounced concern for government as well as for general public. The management of diabetes using medicinal plants along side nutritional control has become matter of excessive deliberation for most scientists. The traditional usage of native flora to cure symptoms of human maladies or to improve certain features of the body conditions over look contemporary medicine. Natural sources constitute the foundation for a huge sum of contemporary drugs even now-a-days. So, in 25 % of whole prescriptions, one or more dynamic component is from them⁵. Thus in addition to present-day pharmacotherapy of diabetes mellitus, there is an unspeakable requisite for additional approaches for management of diabetes mellitus⁶. In the management of diabetes customary herbal mineral play a vital role. The herbal medicines

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in combination with allopathic drugs are frequently utilized as therapeutic remedies⁷. The reduction in cost of cure and prevention or treatment of numerous patients of type II diabetes and progress in some cases of type I diabetes can be achieved by use of suitable diet and alternative therapies. Predominantly when orthodox treatments are unable to control the ailment and patients need insulin, utilization of medicinal plants is incredible. Bio-active herbal constituents are blends of several biochemical substances like glycosides, alkaloids, polysaccharides, saponins and triterpenes, some of them possess renowned anti-diabetic properties⁸. Thus it is crucial to advance traditional and unconventional medicine because treatment of diabetes with synthetic medications is costly alongside extra side effects, normally due to this reason, it is not preferred. Orthodox medicine contains a substantial sum of herbal drugs and it is reported in literature that more than 400 plant species exhibit anti-diabetic activity⁹.

Artemisia absinthium L. (Family: Asteraceae, sub-family Asteroideae, and tribe Anthemideae) commonly known worm wood, is a perennial aromatic, small shrub distributed in Afghanistan, China, Europe, India, Japan, Kyrgyzstan, Kazakhstan, N Africa, North America, Pakistan, Russia and SW Asia. In Pakistan, it found in Chitral, Skardo, Ladakh, Parachinar, Naran and Kurram Agency^{10,11}. Phytochemical analysis showed that Thujones (40-70 %), trans-sabinyl acetate, cis-chrysanthenyl acetate and cis-epoxyocimene are the most common constituents in worm wood essential oils. α -pinene (6 %), nerol (3 %), p -cymene (4 %) and limonene (4 %) are also present in significant amount in worm wood¹². *Artemisia* species have been used in traditional medicines for the cure of diabetes, hypertension and digestive problems in many states of Middle East and Turkey^{13,14}. Ashraf *et al.*, 2010 reported in a survey study conducted in northern areas of Pakistan that powdered seeds of *A. absinthium* L. are used to cure gastric problems, intestinal worms and rheumatic pain¹⁵. Medicinal plants are used in traditional therapy to cure arterial hypertension and/or diabetes as mentioned in a report of survey conducted in Morocco. The total number of 626 subjects including 370 female & 256 male, were allocated into 3 groups: diabetics (61 %), hypertensive (23 %) and hypertensive diabetic (16 %). The 67.5 % of subjects commonly utilize curative herbs. This ratio is perceptibly the identical in almost all groups and is

independent of gender, age and socio-cultural level. The results of study showed that phytotherapy is broadly accepted in North eastern Morocco. For diabetes, *Artemisia herba-alba* Asso. (Compositae), was one of the most used 41 plants¹⁶. *A. absinthium* L. is utilized for treatment of indigestion, diabetes, tuberculosis, hypertension and also applied as an appetizer. In order to treat malaria young shoots are consumed whereas for cure of hypertension the leaves are chewed and leaves are applied to wounds for healing as well. It has been reported that decoction of leaves is used for the cure of diabetes and hypertension in traditional medicine in Kırklareli province of Turkey¹⁷.

It is suggested by World Health Organization (WHO) that a dose of 20 mg/kg (as divided) loading dose on the first day, then 10 mg/kg once daily for 6 days. Thus for a 60 kg adult, this works out as 1200 mg on the first day, subsequently 600 mg/day.

Citrullus colocynthis (L.) Schrad. is from Cucurbitaceae family, the common name is bitter cucumber or bitter-apple 'vine-of-Sodom'. It is herbaceous perennial vine originally from Africa and tropical Asia but it is now broadly scattered in Mediterranean region, Afghanistan, Egypt, India, Iran, Nubia, North Africa, Pakistan, Trieste, Turkey and also in Saharo-Arabian phytogeographic region in Africa. Main phytochemical constituents found in its pulp are pectin, colocynthein, colocynthin, colocynthetin and gum, whereas its seeds contain fixed oil and albuminoids. Due to presence of these therapeutically potential compounds, the fruit pulp and seeds are important medicinal part of this plant¹⁸. *C. colocynthis* has been used for treating bacterial infections and also have antidiabetic, anti-hypersensitive activities. It is one of the most used 41 plants for diabetes in oriental Morocco as reported in a survey study¹⁶. Ediriweera & Ratnasooriya (2009) reported a recipe used by Sri Lankan Ayurvedic and Traditional Physicians which describes that 500 mg powder of dried fruits or 1-3 g powder of dried roots are given to diabetic patients¹⁹. In another recipe used by the native populations of barren regions of Pakistan, it is mentioned that pickle of pulp of *C. colocynthis* is found active for diabetes. Local people pressed with feet slices of 1-2 kg of fruit placed in a clay pot until tongue taste become bitter for cooling purposes. For diabetes same recipe is used for seven days²⁰. In another recipe used in India to cure diabetes patients are recommended to press the fruits by legs in

morning and to eat roasted seeds on empty stomach²¹. The powder of bark of the dried red ripened fruit being taken (5-10 g) with water on empty stomach as mentioned in a recipe by Swargiary *et al.*²². It has been reported that *C. colocynthis* improved the glycemic profile with no severe antagonistic effects in type II diabetic patients²³⁻²⁵. Huseini *et al.*, carried out a 2 month clinical trial on 2 groups of 25 each of type II diabetic patients. Under standard anti-diabetic treatment, the patients were advised to take 100 mg *C. colocynthis* fruit capsules (experimental group) or placebos (control group) three times a day, respectively. *C. colocynthis* treated patients exhibited a remarkable reduction in HbA1c and fasting blood sugar levels²⁶. Rahbar & Nabipour reported that significant differences were observed within and between treated and placebo groups during the treatment with powdered seed of *C. colocynthis* (300 mg/day) in TG and cholesterol in non-diabetic hyperlipidemic patients²⁷.

Gymnema sylvestre (Retz.) R.Br. ex Sm. belongs to Asclepiadaceae family, generally famous as “miracle fruit” is a valuable herb widely found in Australia, South western region of China, India, Indonesia, Japan, Malaysia, Sri Lanka, Vietnam and tropical Africa²⁸. A group of oleanane type triterpenoid saponins called Gymnemic acid is one of the vital constituents of *G. sylvestre*. In addition to six known gymnemic acids, four new triterpenoidsaponins, gymnemasins A, B, C&D, obtained from the leaves of *Gymnema sylvestre* were recognized as 3-O-[beta-D-glucopyranosyl (1-->3)-beta-D-glucuronopyranosyl]-22-Otigloyl-gymnemanol, 3-O-[beta-D-glucopyranosyl(1-->3)-beta-D-glucuronopyranosyl]-gymnemanol, 3-O-beta-D-glucuronopyranosyl-22-O-tigloyl-gymnemanol and 3-O-beta-D-glucuronopyranosyl-gymnemanol, respectively. These Gymnemic acids are responsible for anti-diabetic action of *G. sylvestre*²⁹. A traditional polyherbal formulation “*Diabrid*” comprising of four indigenous plants namely, *G. sylvestre*, *M. charantia*, *E. jabolana* and *T. graecium* has been used to treat diabetes in Pakistan³⁰. *G. sylvestre* is also an important ingredient of a herbal formulation mentioned by Dr. Khurram in “Home remedies for weight loss and diabetes”. The recipe consists of *Gurmarbooti* (*Gymnema sylvestre*) – 50 g, dried bitter gourd (*Mamordica charantia*) – 50 g, *Jamun* (*Syzygium cumini*) dried seeds – 50 g, Fenugreek (*Trigonella foenum-graecum*) seeds – 50 g, Onion

seeds (*Allium cepa*) – 50 g and Black pepper (*Piper nigrum*) – 25 g. Mix well all of them, then take and mix ¼ teaspoon in milk, water or whey and take it. (www.pakladies.com). A traditional recipe used in Sri Lanka for diabetes described that 120 mL decoction of 120 g of fresh leaves of *G. sylvestre* is given twice a day¹⁹. A centuries’ old folk medicine recipe used in Puducherry UT, India describes that dried *G. sylvestre* leaf powder (2-3 g) is given with water along with seven fresh leaves are prescribed daily in the morning for 15 days for diabetes³¹. Two main tribal groups in South Tamil Nadu, India use *G. sylvestre* as a traditional herbal medicine for the cure of diabetes. The recipe is; fine powder (50 mg) of dried leaves is taken orally along with milk twice a day after food for 120 days to cure diabetes³². A traditional recipe used for curing diabetes in Kerala, India is that *G. sylvestre* leaf mercerized with water and the juice is taken daily. Recent studies have shown that Type-II diabetes is treatable by the extract of *G. sylvestre*. Its use is predominantly useful in regulating blood sugar. β -cells of pancreas are regenerated, secretion of insulin increases, which decreases the metabolic effects of sugar to a pronounced level by inhibiting the sugar absorption from intestine. Hence, it is a promising to opt natural choice to chemical sources for the regulation of blood sugar level^{24,25,33-35}. *G. sylvestre*, is also a cure of glycosuria and other urinary disorder. There is very little clinical indication to support the usage of *G. sylvestre* for diabetes because the studies that comprise humans are also not of appropriately high quality to demonstrate that *G. sylvestre* is effective to control blood sugar. Daily doses (400 mg) of GS4 (an extract of *G. sylvestre* leaves) reduced the quantity of insulin required by individuals with diabetes on insulin therapy. GS4 can also lessen cholesterol and triglyceride levels in people with diabetes³⁶. A substantial fall in blood glucose, glycosylated hemoglobin and glycosylated plasma proteins was observed in the patients taking GS4 (400 mg/day) for 18-20 months as supplement to the conventional oral drugs in a different study and conventional drug quantity could be condensed³⁷.

Only few studies have been scientifically confirmed, a lot more have yet to be discovered and verified. Research may target isolation, purification and description of bioactive compounds existing in these plants. The result of such studies may offer an opening point for progress of prospective antidiabetic medications³⁵.

This research was planned to observe the effects of *G. sylvestre*, *C. colocynthis* and *A. absinthium* on blood glucose and lipid profile in type II hyperlipidemic diabetic individuals.

Methodology

Locality of the study

The study was carried out in Lakki Marwat district. The subjects suffering from Type II Diabetes living in the area of the above localities were recruited for the study.

Selection criteria

The study was publicized using different ways including personal contacts, contacting diabetic individuals by telephone and also by visiting diabetic centers and neighboring villages. The questionnaire containing name, age, sex, address, type of diabetes, medicine for diabetes and drug for other diseases were filled. Accoutered GCT (glucometer) was used for determination of their fasting blood glucose. Those diabetic individual whose fasting blood sugars were 125 mg/dL or above and who were not taking insulin or any other medicines for any other diseases were registered for the study. The information about these 40 diabetic individuals on the day of screening in terms of age, Body Mass Index (BMI), serum glucose and serum triglyceride is given in Table 1. The mean age of diabetic individuals of groups 1, 2, 3 and 4 were 48±7, 51±9, 49±7 and 50±9 yrs, respectively. The BMI of group 1, 2, 3 and 4 were 29.1±7.1, 28.9±4.2, 26.9±4.1 and 27±6.2, respectively. The individuals of all the groups were overweight according to the criteria of WHO (1997). The serum glucose of the diabetic individuals in group 1, 2, 3 and 4 were 178±35, 170±30, 169±25 and 162±22 mg/dL, respectively. All the diabetic individuals were hyperlipidemic, the serum TGL of group 1, 2, 3 and 4 were 231±15, 219±42, 230±20 and 210±25 mg/dL, respectively.

Registration of Diabetic individuals for the study

The present study is a blind randomized placebo-controlled clinical trials over 40 days. The study was

Table 1 — Demographic data of diabetic persons on screening day

Groups	Age	BMI	Glucose (mg/dL)	TGL (mg/dL)
1	49±7	28.1±7.1	179±35	232±15
2	52±9	29.9±4.2	171±30	218±42
3	48±7	25.9±4.1	168±25	231±20
4	51±9	26±6.2	163±22	209±25

approved by the Ethics Committee of university and the reported investigations were conducted according to principles of Helsinki Declaration of 1975 as revised in 2008.

Based on the above criteria, 40 diabetic individuals of both sexes were selected for the study. The participants of the study were given written informed consent. The patients were randomized by the use of envelopes containing randomization codes prepared by independent statistician. These individuals were divided into four groups namely 1, 2, 3&4. Each group was having 10 individuals. Group 1 assigned for *G. sylvestre*, group 2 for *A. absinthium*, group 3 for *C. colocynthis*, group 4 for placebo group. The duration of study was 40 days. These people were permitted to use routine oral hypoglycemic drugs as per instruction of doctors and also routine dietetic food intake during the experimental period.

Preparation of *A. absinthium* L., *C. colocynthis* and *G. sylvestre* capsules

Specimens were collected from local market (freely available commercial crops or herbal products) and identified with the help of floristic materials³⁸⁻⁴⁰. The specimens were confirmed in the Herbarium of Quaid-I-Azam University, Islamabad by matching with already identified specimens. The plant name has been checked with www.theplantlist.org. The voucher specimen *A. absinthium* L. (Voucher No. ART 08), *C. colocynthis* L. Schrad. (Voucher No. Col 05) and *G. sylvestre* (Retz.) R.Br. ex Sm. (Voucher No. Gym 07) have been deposited in herbarium of Quaid-I-Azam University Islamabad (ISL) for future reference. The required amount of *G. sylvestre*, *C. colocynthis* and *A. absinthium* were grounded finely. The grounded *G. sylvestre* (shoots & leaves), *C. colocynthis* (whole fruit) and *A. absinthium* (shoots & leaves) were given to a pharmaceutical company to prepare the capsule containing 0.5 g of powder. The medicine capsules were stored in a cool and dry place.

Experimental protocol

The capsules of *G. sylvestre* were given 1.0 g doses/day for 30 days to group 1. *C. colocynth* 1.0 g doses/day in the form of capsules were given to group 2 and capsules of *A. absinthium* 1.0 g doses/day for 30 days to group 3. Each dose of *C. colocynth*, *A. absinthium* and *G. sylvestre* were spread over the day as breakfast (0.5 g) and dinner (0.5 g) doses; placebo 1.0 g doses/day for 30 days to group 4. From day 30 to day 40 (10 days) was the wash period and no dose

were given in those 10 days. However, blood samples were collected on day 40 to observe whether the effect of *C. colocynth*, *A. absinthium* and *G. sylvestre* is still there when the individuals are not using capsules. Patients from each group were excluded from study due to nonappearance on the day of blood collection, abnormality in herbal product intake and not ensuing the code of behavior of the study. Eight persons in each group accomplished the study.

Blood collection and analysis

Around 5 mL fasting blood samples were taken on day 0, day 10, day 20, day 30 and day 40 from each individual of each group, transferred to sterilized centrifuge tubes and allowed for clotting at room temperature. Samples were centrifuged for 5 min at 4000 rpm, separated serums were stored in freezer at 0°C for later analysis.

Blood glucose estimation

Glucose was estimated by the Spectrophotometric method using Randox Kit (CAT No. GL 2586/s).

Serum triglycerides determination

Triglycerides were estimated by Spectrophotometric the method of Tietz, 1990, using Randox Kit (REF TR 210)⁴¹.

Total cholesterol determination

Cholesterol was estimated by colorimetric method of National Cholesterol Education Program, (1988).

HDL cholesterol determination

The HDL- cholesterol content was estimated by procedure of Assmann, 1979⁴².

LDL cholesterol estimation

LDL Cholesterol will be determined using formula:

$$\text{LDL cholesterol (mg/dL)} = \text{Total cholesterol} - \text{TGL HDL cholesterol}$$

Data analysis

The data were analyzed using analysis of variance and LSD test using statistical software Mstat C. Mstat C with

MGRAPH by Russell-D-Freed M Stat Director Crop. & Soil Science Dept, Michigan State University Version.

Results and discussion

Effect of different medication on serum glucose level of diabetic persons

The day 0 values designate the fasting serum glucose of diabetic persons prior to the start of

medicine and were deliberated as control values for glucose. The average fasting serum glucose level of the diabetic persons of the group 1, 2, 3&4 on the starting day of the experiment (day 0), were 219±41, 211±57, 215±56 & 221±57mg/dL, respectively. The average fasting serum glucose level fell down steadily to 138±17, 143±30 and 140±35 mg/dL, respectively when the individuals of these groups (1, 2&3) used 1.0 g of drug doses/day for 30 days. However, the most significant lowering of glucose values was in group 1 at (p < 0.05) level. The average of fasting serum glucose level of diabetic individuals of group 1, 2 and 3 being significantly different (p < 0.05) from control and placebo group. The average fasting serum glucose level of the diabetic persons of group 1, 2, 3&4 on day 40 (when they were not taking respective medication for the last 10 days) were 181±38, 191±26, 213±69 & 225±57 mg/dL, respectively. The average fasting serum glucose level on day 40 of all 3 groups was statistically non-significant at (p < 0.05) because no clear alteration was detected between the mean fasting values on (0 day) and on (40 day). It is reported that *A. absinthium* is used to treat diabetes but it is based merely on survey reports¹⁷. Huseini *et al.*, (2009) reported similar results that there was a noteworthy reduction in HbA1c and fasting blood glucose levels in *C. colocynthis* treated patients²⁶. It is reported by Shanmugasundaram *et al.*, (1990) that daily GS4 (leave extract of *G. sylvestre*) doses of 400 mg decreased the quantity of insulin required by people with diabetes on insulin therapy³⁶. In another study carried out on humans by Baskaran *et al.*, (1990), it is mentioned that GS4 (400 mg/day) caused a marked decline in blood glucose, glycosylated hemoglobin and glycosylated plasma proteins and orthodox medication quantity might be decreased³⁷.

Effect of medications on serum TGL and cholesterol in diabetic persons

When the diabetic individuals of these groups (1, 2, 3&4) used 1.0 g doses/day of their respective medication for 30 days, their mean fasting serum TGL and cholesterol level dropped gradually but non-significant at (p < 0.05). It is mentioned by researchers that powdered seed of *C. colocynthis* (300 mg/day) produced a marked reduction in TG and cholesterol in non-diabetic hyperlipidemic patients²⁷. It is reported that GS4 also reduced cholesterol and triglyceride levels in the people with diabetes³⁷. The difference in the results may be attributed to the diverse fragments of the plant being used in the study.

Effect of different medications on serum HDL, LDL-cholesterol in diabetic persons

Average fasting serum HDL and LDL-cholesterol level of diabetic people of groups (1, 2, 3&4) used 1.0g doses/day of their corresponding drug for 30 days, fell down regularly but it was non- significant at ($p < 0.05$).

Conclusion

This study showed a remarkable reduction in glucose level due to medication as all the diabetic individuals were taking their usual medicine. This is certainly an incredible effect and it may be proposed that a type II diabetic patient can carefully be transferred from expensive conventional antidiabetic remedy to economical natural product.

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