Functional Role of Ashwagandha *(Withania somnifera)* Leaves on Type 2 Diabetes Rat Induced by Streptozotocin.

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Abstract

This research examines the outcome of using Ashwagandha leaves to treat diabetes in rats with streptozotocin-induced diabetes. Two main groups of thirty mice weighing 180±5 grams (six mice per group) were used. 1st main group, which was given a basal diet as a Group of negative controls. 2nd main group, which consisted of 24 mice divided into four comparable subgroups, received a single injection of streptozotocin (STZ) at a dose of 100 mg/kg into the abdominal cavity. After that, the first subgroup was kept as a Group of positive controls. 2nd subgroup was fed a diet that included ashwagandha powder (100 g/kg), and 3rd subgroup was fed a diet that included ashwagandha powder (200 g/kg). The fourth subgroup was given a basal diet plus Ashwagandha powder (400 g/kg diet). Blood samples were taken from each mouse at the end of the trial, & the serum was separated & used to determine various biochemical analyses. Liver histopathology was performed. A chemical analysis of Ashwagandha powder was conducted. According to the results of Ashwagandha powder, there were noticeable differences in body weight, feed efficiency ratio, or feed intake, in the Group of positive controls and the groups that took Ashwagandha. Regarding blood fat levels, there was a noticeable change in the Group of positive controls in contrast to the Group of negative controls and the group fed Ashwagandha. A reduction in the glycemic index and insulin levels occurred in the groups fed with Ashwagandha, as there was an improvement in blood sugar and insulin levels in contrast to the Group of positive controls. Liver enzymes & kidney functions also reduced in the groups fed ashwagandha in contrast to the Group of positive controls. As a result, this study suggested Ashwagandha for the management of type two diabetes.

Keywords: Diabetes mellitus- Kidney functions- Ashwagandha- Lipids profile.

Introduction

Chronic hyperglycaemia caused by abnormalities in the secretion and function of the endocrine hormone insulin characterises diabetes, a chronic noncommunicable disease (CNCD) **(Unnikrishnan *et al.*, 2016) (Kharroubi and Darwish, 2015).** According to **Tabish (2007**), it is a class of metabolic illnesses & a major global health issue. Based on the aetiology & clinical characteristics, DM is typically dispersed into 3 types: type one, type two, & gestational diabetes **(Rayburn, 1997).** Diabetes is a severe public health issue that is spreading quickly around the world. The most prevalent kind of diabetes is type-2, which is characterised by problems in insulin production and insulin resistance. There is no therapy that doesn't have any negative side effects, despite the current advancements in therapeutic agents; as a result, new prevention tactics and improved therapeutic approaches must be developed **(Gheibi *et al.*, 2017).**

Due to its fast-rising rates and associated financial and societal consequences, type two diabetes mellitus (T2DM), a chronic endocrine & metabolic disease driven by genetic & environmental factors, has become a serious problem for people all over the world **(James *et al.*,2021).** Autophagy, oxidative stress, metabolic abnormalities with ongoing insulin resistance, inflammation, hypoxia, & other variables are all involved in the complex pathophysiology of this illness (**Li *et al.*, 2023)** that leads to this condition. As metabolic diseases can worsen inflammatory responses, impede the interaction of insulin receptors with glucose transporters, & impair -cell function, they are considered risk factors for the occurrence & progression of T2DM. Additionally, dyslipidemia can be caused by insulin resistance, which is a symptom of abnormal glucose metabolism, by raising the levels of free fatty acids (FFA) & TG in serum lipids **(Cheng *et al.*, 2022).** Although these results point to connections between lipid and glucose metabolism, the underlying mechanisms are still not fully understood **(Li *et al.*, 2021).**

DM, particularly type 2 (T2DM), is one of the most prevalent forms of disease. Stress and a change in lifestyle are linked to T2DM. Both the management of postprandial blood glucose levels and the use of some natural plant extracts with inhibitory activities against carbohydrate digesting enzymes like alpha-amylase are potential ways for inhibiting the absorption of carbs from the meal. These enzymes are responsible for breaking down carbohydrates. Natural plant extracts have less adverse effects than manufactured medications **(Gomaa *et al.*, 2021).**

Withania somnifera Dunal, an herb that corresponds to the Solanaceae family & grows to a maximum height of 150 cm, is a tiny woody shrub **Sapra and others (2020).** It is an adaptogenic herb, **Kulkarni and Dhir (2008)** describe how ayurveda and unani treatments use its roots, seeds, and leaves to promote "youthful vigour," increase muscle strength, & advance general health. For more than 3000 years, ashwagandha also referred to as Withania somnifera, Indian ginseng, & winter cherry has played a significant role in traditional herbal treatment (**Mishra *et al.*, 2005).**

The extract of W. somnifera is a complicated combination of several different phytochemicals, such as flavonoids and phenolic compounds. On the other hand, it is believed that the pharmacological action of W. somnifera roots is caused by withanolides, according to **Udayakumar *et al.*, (2010).** The largest class of phytochemicals is called polyphenols, and many of them have been discovered in foods made from plants. Researchers have discovered that powerful antioxidants known as polyphenols are able to neutralize free radicals by giving up an electron or a hydrogen atom **(Rice-Evans *et al.*, 2000).** Along with directly chelating metal ions like Fe+2 & reducing the rate of the Fenton reaction, polyphenols also scavenge radicals, which prevents the oxidation brought on by highly reactive hydroxyl radicals **Perron & Brumaghim (2009).**

Among these Withania somnifera is popularly known as Ashwagandha (AG) or winter cherry is one of the medicinal plants. The practitioners of traditional systems of medicines in India call it as Indian Ginseng [7].

It is widely classified as an adaptogen and shown to have wide range of activities including antidiabetic [8], antioxidant [9], hepatoprotective and antidepressant [10,11], anticancer, antistress, anti-inflammatory, immunomodulatory [12], and antibacterial activity [13]. The major biochemical constituents of W. somnifera are steroidal alkaloids.

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immunomodulatory [12], and antibacterial activity [13]. The major biochemical constituents of W. somnifera are steroidal alkaloids.

The plant Withania somnifera (WS) Dunal, which belongs to the family Solanaceae, is more commonly referred to as Ashwagandha. The Ayurvedic medicinal system makes extensive use of this herb **(Sangwan *et al.*, 2007).** Numerous research has demonstrated that this plant owns anti-inflammatory, antitumor, anti-stress, antioxidant, immunomodulatory, haematological, & rejuvenating characteristics in addition to its favourable effects on the endocrine, cardiac, & central neurological systems **(Widodo *et al.*, 2010).** In a current publication **(Anwer *et al.*, 2012),** revealed how Withania somnifera protected type 2 diabetic rats from oxidative stress and pancreatic beta-cell damage.

Ashwagandha is distinguished by its abundant phytochemical makeup. The raw material shows a varied constituents of chemical components depending on where it is found. Its active ingredients, alkaloids and witanolides, are essential to its pharmacological effect. The fundamental structure of witanolides is ergostane, a molecule with 6-membered lactone ring at either the C-8 or C-9 position. Witanopherin A, witanolides A-Y, witanone, witadomniferin A, and witasomniferols A-C are all members of the witanolides group. According to John (2014), the primary active components of alkaloids include Witanin, somniferin, tropin, somniferinin, pseudowitanin, pseudotropin, choline, kuskohigrin, isopeletierin, and anaferin. Anaferin is one of the several active chemicals that may be found in alkaloids. In addition, the raw material has flavonoids in it, such as 3-O-rutinoside, 6,8-dihydroxycemferol, quercetin, and a glycosidic derivative of 3-O-rutinoside called 3-O-rutinoside-7-O-glucoside.

The study's main objective was to show that WS has therapeutic potential for the management of T2DM.

Materials & Methods

Materials:

1- Plant and drugs:

- Ashwagandha was purchased from Imtenan Health Shop in Obour City, Egypt.
- El-Gomhoria Company provided streptozotocin to chemical, Egypt.

2- Chemicals:

DL Methionine powder, casein, cellulose, choline chloride powder, vitamins, & minerals. In Cairo, Egypt, the neighbourhood market was where we bought the oil and maize starch. The kits were provided by the Cairo, Egypt-based Bio Diagnostics Company.

2- Rats:

- The Agricultural Research Centre, Dokki, Giza, Egypt's animal house provided 30 adult males of the albino species Rats of the Sprague Dawley strain, weighing (180±5g).

Methods:

1- Experimental design:

The study used thirty mature male albino rats that weighed 180 g. The animals came from the Agricultural Research Center's animal house in Dokki, Giza, Egypt. In accordance with **Reeves *et al.*, (1993),** A standard diet was provided to rats for the whole week that they were housed at the animal home, where they were maintained in individual cages made of stainless steel and subjected to controlled environmental conditions. The experimental animals were split into two primary groups after adaption phase. Six rats made up 1st main group, which was given a basal diet as a control group. 2nd main group, which was made up of 24 rats divided into four similar subgroups, received injections of streptozotocin to cause diabetes mellitus in accordance with **Shinde and Goya's (2003)** description at a dose of one hundred mg/kg BW. Rats were given diabetes two weeks prior to beginning the medication. Following this, 1st subgroup was used as a positive control (+Ve), while 2nd subgroup was given a basal diet in addition to ashwagandha powder at a dosage of one hundred g/kg of diet, 3rd subgroup was given a basal diet in addition to ashwagandha powder at a dosage of two hundred g/kg of diet, & 4th subgroup was given a basal diet in addition to ashwagandha powder at a dosage of 400 g/kg. Every week during the six-week trial period, the weight & food intake of each rat were recorded. **Chapman *et al.*, (1959)** identified and described the food efficiency ratio (FER) & body weight gain percentage (BWG%). Rats were starved the night prior being sacrificed at the conclusion of the trial. Blood was then taken, separated by centrifugation, & maintained at -20° C for biochemical study.

2- Determination of nutritive value: The **A.O.A.C. (2010)** Ashwagandha's chemical makeup was analysed using a certain technique.

Streptozotocin-induction in rat's model:

Streptozotocin (STZ) was delivered into the rats at a dose of 100 mg/kg BW intraperitoneally. To avoid hypoglycaemia, the rats were subsequently preserved on five percent glucose solution bottles in their cages for the following 24 hours **(Prince *et al.*, 1998).** Sino-ocular puncture was used to collect blood samples from the eyes (venous pool) for the evaluation of glucose levels in the blood four days following STZ administration. The investigation employed rats with mild diabetes that suffered from hyperglycemia, with blood glucose levels among 260 & 300 mg/dL.

Biochemical Analysis:

Determination liver functions:

The levels of alanine amino transferase (ALT) & aspartate amino transferase (AST) in the serum were determined with the use of the methodologies outlined in **Hafkenscheid (1979) & Clinica Chimica Acta (1980)**, respectively.

Determination of kidney functions:

Henary, (1974), Patton & Crouch, (1977), and Han *et al.*, (1984) all used the enzymatic approach to determine the amounts of urea in the serum, serum creatinine, & uric acid, respectively.

Determination of lipid profile:

To ascertain the serum total cholesterol, triglycerides, & HDL, respectively, **Allain, (1974), Fossati & Principe, (1982), & Lopez (1977)** were consulted. LDL & VLDL values were calculated using the technique suggested by **Lee and Nieman (1996).**

Determination of Serum Insulin:

Straub and Sharp's (2002) techniques were utilized to assess the concentration of serum insulin.

Determination of Serum Glucose Concentration:

The technique of **Braham and Trinder (1972)** was utilized to determine the serum glucose concentration.

Statistical analysis

Utilising the computerised **SPSS, (1986),** statistical analysis of the given data was performed. According to **Snedecor and Cochran (1967)**, the impacts of various managements were examined utilizing the one-way ANOVA (Analysis of Variance) test and Duncan's multiple range test, with p0.05 utilized to denote significance across various groups.

Result and Dissection

Table (1): Nutrition value of ashwagandha leaves.

	Nutrients	Ashwagandha
Nutrients (gm)	Energy	239
	Protein	3.4
	Fat	0.5
	Carbohydrate	51
	Fiber	34
Minerals (mg)	Calcium	25
	Iron	3.5
Vitamins (mg)	Vitamin (A)	79.9
	Vitamin (C)	4.1

Table 1's chemical breakdown of ashwagandha reveals that it contains significant amounts of calcium, vitamin A, fiber, and calories. provide a decent amount of protein, iron, and vitamin C as well, low in content of fats, nevertheless. Ashwagandha's leaves & roots are mostly employed for medicinal purposes, yet they're also an excellent source of dietary fiber (28.8 percent) & minerals (10.1percent), not to mention aferine. A concentration of 0.16 percent **(Khanna *et al.*, 2006).** The roots of Ashwagandha, which contain a wide variety of biochemically distinct alkaloids, are rich in a number of essential elements, including anferine, iron, lactones, withanolids, acyl steryl glucosides, nitrate, potassium, sominine, somniferine, tannins, and tyrosine **(Kaul, 1957).**

Table (2): Effects of Ashwagandha *(W. somnifera* L.) Powder on BWG, Feed Intake & Feed Efficiency Ratio in Type 2 Diabetes Rat Induced by Streptozotocin.

Parameters / Groups	BWG (%)	Feed intake (g/day)	Feed efficiency ratio
(1) Control(-Ve)	221.80±9.60[a]	27.17±1.14[a]	0.82±0.01[a]
(2) Control(+Ve)	180.40±34.89[d]	20.88±4.42[c]	0.63±0.22[b]
(3) Diabetic + (ashwagandha 100 g/kg diet)	37.65±203.80[c]	25.86±4.47 [a]	0.81±0.00[a]
(4) Diabetic + (ashwagandha 200 g/kg diet)	211.40±30.16[b, c]	25.68±3.68 [a]	0.82±0.00[a]
(5) Diabetic + (ashwagandha 400 g/kg diet)	216.20±23.70[b]	26.68±2.96 [a]	0.80±0.00[a]

*Values are expressed as means ±SE.

*Values at the same column with different letters are significant at P<0.05.

The effects of powder on rat BWG, feed intake & feed efficiency ratio are revealed by data in Table 2. The average BWG of the Group of positive controls (+Ve) was significantly lesser than that of Group of negative controls (-Ve), with values of 180.40±34.89 and 221.80±9.60, respectively. Additionally, as in contrast to the positive control (+Ve), the average values of groups three, four, & five each showed a significantly higher rate of body weight growth, with average values of 203.80±37.65, 211.40±30.16, and 216.20±23.70, respectively. The group (5) that consumed a baseline diet with ashwagandha powder at level 3 saw the best results with an average value of 20.88±4.42 and 27.17±1.14, respectively. The feed intake table demonstrated that average value of the Group of positive controls (+Ve) was much lower than that of the Group of negative controls 20.88±4.42 and 27.17±1.14, respectively.

The current statistics agree well with a number of studies that have been evaluated by **(Raakhee *et al.*, 2009 and Ali, 2021).** They found that ashwagandha strengthens the immune system, which refocuses attention on losing weight. Antioxidants, which are essential for both weight loss and general health, are also included in it. Additionally, a few earlier studies found that the high concentration of various bioactive components, including carotene, flavonoids, alkaloids, triterpenoids, tannins, phenolics, and saponins, may be the reason for the beneficial effects of ashwagandha root powder (ARP) on controlling obesity **(Gad Alla, 2023; Elhassaneen *et al.*, 2023-b & Elhassaneen *et al.*, 2023-a)**. Prior research has demonstrated that ARP's anti-obesity effects may be ascribed to multiple mechanisms, such as anti-inflammatory, antioxidant, decreased fat accumulation, lowered levels of leptin and resistin, elevated lipolysis, elevated adiponectin, inhibited adipocyte differentiation, and decreased adipogenesis **(Raakhee *et al.*, 2009).**

The detrimental consequences of STZ, such as DNA alkylation, hyperglycemia, and necrotic lesions, manifested in a loss of body weight and an overall degeneration of appearance in the animals that were given to STZ therapy. The findings that we have right now are in agreement with those of **Habibuddin *et al.*, (2008) and Piyachaturawat *et al.*, (1988).**

Table (3): Effects of Ashwagandha (*W. somnifera* L.) Powder on Organ Relative Weight in Type 2 Diabetes Rat Induced by Streptozotocin.

Groups \ Parameters	Spleen	Liver	Kidney	Heart
	(%)			
(1) Control(-Ve)	0.40±0.08^{c}	3.16±0.31^{c}	0.64±0.03^{d}	0.33±0.03^{e}
(2) Control(+Ve)	0.57±0.22^{a}	3.49±0.65^{a}	0.98±0.01^{a}	0.50±0.03^{b}
(3) Diabetic + (ashwagandha 100 g/kg diet)	0.46±0.17^{b}	3.30±0.98^{b}	0.83±0.40^{b}	0.45±0.16^{c}
(4) Diabetic + (ashwagandha 200 g/kg diet)	0.51±0.30^{a}	3.28±0.62^{b}	0.78±0.12^{c}	0.55±0.04^{a}
(5) Diabetic + (ashwagandha 400 g/kg diet)	0.38±0.06^{c}	3.09±0.19^{d}	0.75±0.06^{c}	0.38±0.05^{d}

Table (3) displays outcome of changes in the relative organ weight. Rats in the Group of positive controls with type 2 diabetes experienced an elevation in the average value of the relative weights of their hearts, spleens, livers, and kidneys in contrast to the (-ve) group. other than for the rats group fed Level (2) ashwagandha (200 g/kg diet), which significantly increased the relative weight of the heart in contrast to the Group of positive controls, supplemented diet with ashwagandha induced a reduction in the average relative weight of the spleen, liver, kidneys, & heart in comparison to the (+ve) control.

When animals in group E were contrasted with those in group A, weight of the liver increased (hypertrophy) relative to the body weight, even though the average weight of all animals in treatment group E reduced. It may be linked to elevated triglyceride buildup that results in an enlarged liver. This may be brought on by an increased fatty acid infusion into the liver brought on by hypoinsulinemia and a decreased ability of the liver to excrete lipoprotein secretion due to a lack of apolipoprotein B synthesis. The current study's findings concur with those of **Ohno *et al.*, (2000) & Merzouk *et al.*, (2000).**

According to **Ichinose *et al.*, (2006),** elevated kidney weight is linked to increased renal expression of angiogenic factors, containing fibrogenic factor transforming growth factor (TGF)-beta-1 induced by high glucose, angiopoietin (Ang) -2, & vascular endothelial growth factor (VEGF) - A. According to reports from several other researchers **(Habibuddin *et al.*, 2008 & Malatiali *et al.*, 2008)**, mice handled with STZ had rise in kidney weight relative to body weight.

Table (4): Effects of Ashwagandha (*W. somnifera* L.) Powder on Serum Kidney Function in Type 2 Diabetes Rat Induced by Streptozotocin.

Parameters / Groups	Uric acid	urea	Creatinine
	(mg/dl)		
(1) Control (-Ve)	1.96±0.15[c]	25.68±2.40[d]	0.56±0.02[e]
(2) Control (+Ve)	2.59±0.57[a]	65.92±6.75[a]	0.99±0.02[a]
(3) Diabetic + (ashwagandha 100 g/kg diet)	2.00±0.12[b]	40.68±8.36[b]	0.89±0.01[c]
(4) Diabetic + (ashwagandha 200 g/kg diet)	1.98±0.20[c]	35.54±4.06[c]	0.92±0.02[b]
(5) Diabetic + (ashwagandha 400 g/kg diet)	2.14±0.20[b]	37.28±0.77[b]	0.83±0.03[d]

The data in Table (4) demonstrated that there was a substantial difference between the average values of uric acid in the Group of positive controls (+Ve) and Group of negative controls (-Ve), which were 2.59±0.57 & 1.96±0.15, respectively. When contrasted with positive control (+Ve) group, all rats fed at different dosages of ashwagandha powder showed significant variations in the average values.

The average value of urea level in the control (+Ve) group, conversely, however, elevated significantly when in contrast to the Group of negative controls (-Ve); the values were 65.92±6.75 and 25.68±2.40, respectively, with a significant variance. The average values of all rats fed a diet supplemented with ashwagandha powder varied significantly from the control (+Ve) group. Group 4 supplemented on level 2 from ashwagandha powder produced the best results when compared to the Group of positive controls, with average values of 35.54±4.06 and 65.9±26.75, respectively. The creatinine level table showed that, at 0.99±0.02 mg/dl & 0.56±0.02 mg/dl, respectively, the average value of positive group was More than that of negative group.

According to **Grunz-Borgmann *et al.*, (2015),** who hypothesised that ashwagandha would be a botanical strategy in order to administer renal failure treatment, the current investigation supports their hypothesis. Additionally, **Rasheed *et al.*, (2020)** shown by the renal function analysis (serum urea & creatinine levels) that ashwagandha root extract may be used to treat cisplatin-induced renal damage in albino wistar rats. Because of the phenolic and flavonoid content, which facilitates the elimination of nitrogenous waste products such ammonia, urea, uric acid, non-protein nitrogen, & creatinine, as well as protect against hyperammonaemia and nephrotoxic conditions, Ashwoganda has the ability to improve kidney function **(Harikrishnan *et al.*, 2008).** Additionally, according to **Govindappa et al.'s research from 2019**, ashwagandha considerably reduces the side effects of gentamicin thanks to its antioxidant action. It also lowers levels of MDA, total protein, BUN, and Cr.

Table (5): Effects of Ashwagandha (*W. somnifera* L.) Powder on Serum Liver Function in Type 2 Diabetes Rat Induced by Streptozotocin.

Parameters / Groups	AST	ALT
	(U/L)	
(1) Control (-Ve)	27.60±2.07[b]	21.20±2.86[c, d]
(2) Control (+Ve)	40.00±4.18[a]	43.80±4.49[a]
(3) Diabetic + (ashwagandha 100 g/kg diet)	33.20±2.58[a]	25.40±3.20[c]
(4) Diabetic + (ashwagandha 200 g/kg diet)	27.00±1.00[b]	32.60±3.13[b]
(5) Diabetic + (ashwagandha 400 g/kg diet)	18.60±1.51[c]	15.80±1.83[e]

As shown in Table (5), ashwagandha (W. somnifera L.) powder has an impact on the serum liver function of type 2 diabetes-induced rats. When contrasted with negative group control (-Ve), the average levels of liver enzyme AST were substantially higher in the Group of positive controls (+Ve), with average values of 40.00±4.183 and 27.60±2.074 u/l, respectively. Rats fed diets supplemented with ashwagandha powder showed a substantial decline in the average values when contrasted with the control (+Ve) group. The level of AST liver enzyme at which level 5 fed on a basal diet with Ashwagandha powder received the best treatment was reported.

The average values of the Group of positive controls (+Ve) were substantially greater than those of the Group of negative controls (-Ve), which were 43.80±4.49, 21.20±2.86 and (u/l), respectively, according to the ALT enzyme results. Conversely, however, the treated groups' mean values 25.40±3.20, 32.60±3.13, and 15.80±1.83 (u/l), respectively were lower than those of the Group of positive controls when they were fed Ashwagandha powder at three doses.

These findings are backed by research by **Ichikawa *et al.*, (2006)** who discovered that Ashwagandha root extract includes withanolides, an anti-inflammatory compound that may help prevent liver damage and reduce weight. Additionally, **Sultana *et al.*, (2012)** obtained that rats treated with gentamicin and Ashwagandha possessed blood levels of AST and ALT that were much lower and near to normal, suggesting that this root extract may have hepatoprotective effects against gentamicin toxicity. The existence of certain active compounds in ashwagandha root that have antioxidant properties is most likely the cause of all these effects.

Our findings were in line with those of **Saxena *et al.*, (2007),** who investigated the hepatoprotective impact of ashwagandha & discovered a reduction in the activity of liver enzymes, indicating significant part that ashwagandha has in enhancing liver function. Ashwagandha may have positive hepato-protective benefits, according to **Sabiba *et al.*, (2013)** & **Jamuna *et al.*, (2018).** AST, ALT, & ALP changes in diabetic rats handled with ashwagandha root extract were returned to normal levels **(Swamy *et al.*, 2019).** Ashwagandha's high antioxidant content may be the cause of its hepatoprotective effects **(Harikrishnan *et al.*, 2008).** Diabetes treated with streptozotocin resulted in tissue damage from lipid peroxide in the pancreas, liver, kidney, & heart. According to **Prince and Menon (1999),** the leaking out of these enzymes from the tissues & subsequent migration into the blood stream may be the cause of the increase in these enzyme levels in diabetes.

According to **Udayakumar *et al.*, (2009),** DM affected the AST, ALT, ACP, & ALP activities in serum. Changes in the metabolism that the enzymes are a part of in diabetic animals are directly correlated with changes in AST, ALT, ACP, and ALP levels. Because of the availability of amino acids in diabetes patients' blood, transaminases become more active & are also responsible for enhanced gluconeogenesis & ketogenesis **(Gokce and Haznedaroglu, 2008; Batran *et al.*, 2006).** The WSREt & WSLEt treated groups showed the restoration of AST & ALT to their respective normal levels. This is in line with our earlier findings on Chinese juniper berry extracts. Restoration of the normal level of these enzymes implies that the liver is working normally because AST & ALT levels are also indicators of liver function. Alloxan-induced diabetes in rats has been linked to increased blood ACP and ALP activity **(Bhavapriya *et al.*, 2001).** According to **Prince and Menon (2000),** the migration of these enzymes from the tissues into the bloodstream may be the cause of the growth in levels of these enzymes in diabetes.

Table (6): Effects of Ashwagandha (*W. somnifera* L.) Powder on Serum Lipid profile in Type 2 Diabetes Rat Induced by Streptozotocin.

Groups \ Parameters	TC	TG	HDL-c	LDL-c	VLDL-c
(1) Control(-Ve)	93.22±5.74[b]	94.66±4.15[e]	68.08±2.53[a]	54.58±1.87[c, d]	21.18±2.12[b]
(2) Control(+Ve)	112.04±8.18[a]	159.84±2.36[a]	38.48±1.11[d]	70.54±2.75[a]	32.04±0.55[a]
(3) Diabetic + (ashwagandha 100 g/kg diet)	91.50±1.49[b]	144.08±4.33[b]	63.40±1.80[b]	61.12±2.71[b]	28.34±2.94[b]
(4) Diabetic + (ashwagandha 200 g/kg diet)	72.88±4.31[c]	111.48±3.85[c]	57.60±3.65[c]	58.60±3.11[c]	22.32±0.76[b]
(5) Diabetic + (ashwagandha 400 g/kg diet)	71.42±3.35[c]	102.04±7.22[d]	50.76±3.31[c, d]	63.54±2.68[b]	20.14±1.56[b]

Table (6) reveals levels of blood TC, TG, HDL-c, LDL-c, & VLDL as well as their relationship to the administration of Ashwagandha. The obtained data demonstrated that, at 112.04±8.18 and 93.22±5.74 mg/dl, respectively, average of TC of the Group of positive controls (+Ve) was substantially higher than that of the Group of negative controls (-Ve). When compared to the Group of positive controls (+Ve), groups fed on Ashwagandha showed improvement in all three tested levels of TC.

Triglyceride levels were also examined, and the results revealed that the Group of positive controls (+Ve)'s average serum triglyceride level was significantly greater than the Group of negative controls (-Ve), coming in at 159.84±2.36 and 94.66±4.15 mg/dl, respectively. Group (5) received the best outcome. However, the average HDL-c values for the Group of positive controls (+Ve) and the Group of negative controls (-Ve) were significantly different, coming in at 38.48±1.11 and

68.08±2.53 mg/dl, respectively. Comparing the average values of the treatment groups three, four, & five to the Group of positive controls (+Ve), a significant variance was seen. The average value for the Group of positive controls (+Ve) was significantly greater than the Group of negative controls (-Ve), coming in at 70.54±2.75 and 54.58±1.87 mg/dl, respectively, according to the LDL-c data. Results for VLDL-c obtained that Group of positive controls (+Ve) had an average value that was substantially greater than Group of negative controls (-Ve). which were, respectively, 32.04±0.55 and 21.18±2.12 mg/dl.

These results align with those of **Mishra *et al.*, (2009),** who found that a drop in serum triglyceride levels indicates a decrease in creation and an increase in utilisation of VLDL. Ashwagandha alone may improve the body's ability to use triglycerides, which would result in a drop in blood triglyceride levels. Our findings are in line with those of **Anwer *et al.*, (2017),** who found that withania somnifera (WS) (200 & 400 mg/kg) given orally one time per day for five weeks caused a significant (P<0.001) decrease in glucose, TC, TG, LDL-c, and VLDL-c levels with a significant increase of HDL-c values.

According to **Jha & Paul (2020),** (Withania Somnifera) was given orally for four weeks at a dose of 1000 mg/Kg body weight. The lipid profile investigation revealed that following exposure to endosulfan, levels of total cholesterol (1176.686 mg/dl), cholesterol (LDL) (78.834.151 mg/dl), & triglycerides (60.832.613 mg/dl) increased, whereas levels of cholesterol (HDL) (13.501.33 mg/dl) decreased. However, after W. somnifera therapy, the levels of the lipid profile significantly improved (P< 0.001) contrasted with the endosulfan-treated group.

Since insulin suppresses the hormone-sensitive lipase synthesis, the abnormally high blood lipid concentration is mostly caused by an rise in mobilisation of free fatty acids from peripheral fat depots.

Diabetes-prone rats receiving Withania somnifera root extracts (WSREt) & leaf extracts (WSLEt) typically see a return to values that are close to normal. As a result, although boosting HDL-c, WSREt and WSLEt treatments showed impacts on triglyceride, phospholipid, and cholesterol levels. The antioxidant capabilities of W. somnifera may lessen the susceptibility of lipids to oxidation & stabilise the membrane lipids, both of which would lessen oxidative stress **Udayakumar *et al.*, (2009).**

In accordance with **Leite *et al.*, (2007)**, coronary heart disease risk is increased in DM due to the raised level of serum lipids. It is generally known that DM modifies the normal metabolism of tissues like the heart, liver, and kidney.

As insulin suppresses the hormone-sensitive lipase synthesis, the abnormally high blood lipid concentration is mostly caused by an rise in mobilisation of free fatty acids from peripheral fat depots.

Diabetic rats receive WSREt and WSLEt, which tends to return the levels to close to normal. As a result, although raising HDL-c, WSREt & WSLEt therapy showed hypocholesterolaemic, hypotriglyceridaemic, & hypophospholipidaemic results of. Antioxidant activities of W. somnifera are well documented and may lessen the susceptibility of lipids to oxidation & stabilise the membrane lipids, lowering oxidative stress (**Bhattacharya *et al.*, 1997)**.

According to **Swamy *et al.*, (2019),** the administration of ashwagandha root extract to diabetic rodents reversed alterations in serum lipids, excluding HDL-bound cholesterol (C), as well as restored lipid levels in tissues such as the liver, kidney, as well as heart to baseline. These findings indicate that ashwagandha root extract might produce hypolipidemic effects in rodents with alloxan-induced DM. According to **Verma and Kumar's (2011)** findings, when the effects of ashwagandha root's hypocholesterolemic properties were tested on human volunteers, there were significant drops in serum cholesterol, triglycerides, & low-density lipoproteins**. Pal *et al.*'s (2015)** study also showed how ashwagandha root powder was able to lower total lipids, cholesterol, and triglycerides in hypercholesteremic rats. Conversely, however, the liver's bile acid content and plasma HDL-cholesterol levels were both markedly elevated by the extract.

Both the cholesterol levels & the antioxidant impacts of Withania somnifera were found to decrease in a study using white albino rats that had hypercholesterolemia **(Udayakumar *et al.*, 2010).** In a research by **Agnihotri *et al.*, (2013),** intriguing outcomes were obtained in changing the lipidemic profile, body weight, & blood pressure in the context of clinical trials on diabetes, but not demonstrating result on blood sugar levels. According to **Usharani *et al.*, (2014),** administering a standardised ashwagandha extract under the brand name SENSORIL enhanced the lipidemic profile and antioxidant parameters while also proving the raw material's safety and tolerability. Despite its safety and acceptability, Usharani *et al.*, showed that it had an impact on the lipidemic profile and altered the reflection index (RI).

Table (7): Effects of Ashwagandha (*W. somnifera* L.) Powder on Serum Insulin & Serum glucose Type 2 Diabetes Rat Induced by Streptozotocin.

Parameters / Groups	Insulin (m U/L)	gloucose (mg/dl)
(1) Control (-Ve)	5.02±0.78[c, d]	95.56±3.87[e]
(2) Control (+Ve)	11.87±0.25[a]	250.48±3.67[a]
(3) Diabetic + (ashwagandha 100 g/kg diet)	5.74±0.42[c]	160.56±5.55[b]
(4) Diabetic + (ashwagandha 200 g/kg diet)	6.12±0.49[b]	103.18±1.43[d]
(5) Diabetic + (ashwagandha 400 g/kg diet)	6.19±0.57[b]	110.82±2.20[c]

With average values of 11.87±0.25 and 5.02±0.78, respectively, for insulin level as demonstrated in table (7), it is obvious that the Group of positive controls significantly improved in contrast to negative group. When contrasted with diabetic group, the treated groups' insulin levels significantly decreased. The group three diet supplemented with 100 mg of ashwagandha had the highest results. When contrast to normal control rats, streptozotocin-induced diabetic rats had significantly greater blood glucose levels, with average values of 250.48±3.67 and 95.56±3.87, respectively. Rats fed at various ashwagandha dosage levels exhibit a considerable drop in blood sugar contrasted with the Group of positive controls, with average values of 160.56±5.55, 103.18±1.43, 110.82±2.20, and 250.48±3.67.

Khalili's (2009) findings, which showed that ashwagandha may be taken into consideration as a viable therapy for painful diabetic neuropathy, lend support to these findings. **Belal *et al*.'s (2012)** research also demonstrated that ashwagandha uses a variety of ways to achieve its hypoglycaemic effects and contains phytocomponents that can prevent stress-induced hyperglycaemia. **Nagaraj and Veeresham (2018)** discovered the same pattern of change and observed that pretreatment with ashwagandha resulted in much lower blood glucose levels than glimepiride alone treated diabetic rats. The impact of ashwagandha may result from the liver microsomes' suppression of the drug metabolising enzyme CYP2C9.

Withaferine A & Withanolide A are 2 primary withanolides that have been linked to the pharmacological activity of Withania somnifera. The powdered root of ashwagandha can be utilised to create low-GI foods with good sensory qualities. It can also be beneficial in treating and/or preventing insulin resistance, impaired glucose uptake, and blood sugar regulation. As a result, it is essential to have wholesome and nourishing goods that may help prevent and treat Type II Diabetes.

Biscuits made with ashwagandha root powder were determined to be more suited than churan balls made with the powder, while beverages made with the powder were not very well received. Value-added goods made with powdered ashwagandha root were more well-liked. Because ashwagandha has a bitter taste, it cannot be consumed in its raw form even though it has great therapeutic value. Therefore, it is necessary to standardise & develop more value-added products based on ashwagandha root powder to promote its health benefits **(Singh *et al.*, 2014).**

The anti-diabetic benefits of ashwagandha are also taken into consideration when using it. There aren't many reports about this problem, though. In a review publication, **Durg and Shivaram (2018)** provided an interesting description of the raw material's antidiabetic effects. The preclinical studies yielded encouraging outcomes. Its capacity to decrease blood glucose levels has been demonstrated in investigations on animals **(Kyathanahalli and Manjunath, 2014 & Thakur *et al.*, 2015)**. Furthermore, **Tekula *et al.*, (2018)** verified that Withaferin A has substantial therapeutic promise since it can effectively regulate type 1diabetes in rats that has been produced by modulating Nrf2/NFκB signalling. Molecular docking has also been used in in silico research to validate the potential of withaferin A (**Surya Ulhas and Malaviya, 2022)**. Only one clinical research, conducted in 2000, demonstrated a direct decline in blood glucose levels **(Andallu & Radhika, 2000).**

The observations & conclusions of this research demonstrate that streptozotocin was actual in inducing severe hyperglycaemia in experimental rats **(Habibuddin *et al.*, 2008; Kim, 2006; Heidari *et al.*, 2008).** Diabetic glomerular hypertrophy is an early stage of glomerular disease development when mesengial enlargement is absent **(Malatiali *et al.*, 2008)**. Even though the exact cause of the ailment is unknown, there is evidence to suggest that regional shifts in the synthesis of single or more growth factors &/or their receptors play an important role in the progression of renal hypertrophy. The development of insulin-dependent diabetes mellitus (IDDM) is associated with renal hypertrophy was hypothesised by Sharma and **Ziyadeh (1995)** to be connected to the overexpression of transforming growth factor (TGF)-beta 1 in the kidney, specifically in proximal convoluted tubules (PCT) cells & glomerular mesengial cells.

To produce low glycaemic index (GI) food product with favourable sensory characteristics and to prove to be positive in the healing and / or hindrance of impair glucose acceptance, insulin resistance and in addition being an effective means of controlling glucose levels. Therefore, it is a vital role for healthy and nutritious products which may be beneficial in avoidance and managing of Type II Diabetes.

Histopathological examination of liver:

A liver section examination under a light microscope on rodents from group one demonstrated that the hepatic lobules exhibited a typical histological structure (Figure 1). In contrast, liver of rats from group two demonstrated hepatocellular vacuolar degeneration (Figs.2). In contrast, the hepatocytes of rodents in group three exhibited hydropic degeneration. & hepatocellular vacuolar degeneration and sinusoidal leukocytosis (Fig. 3). Furthermore, liver of rats from group 4 exhibited Kupffer cells activation & slight fibroplasia in the portal triad (Fig. 4). Moreover, liver of rats from group 5 exhibited Kupffer cells activation & slight vacuolization of some hepatocytes (Fig. 5).

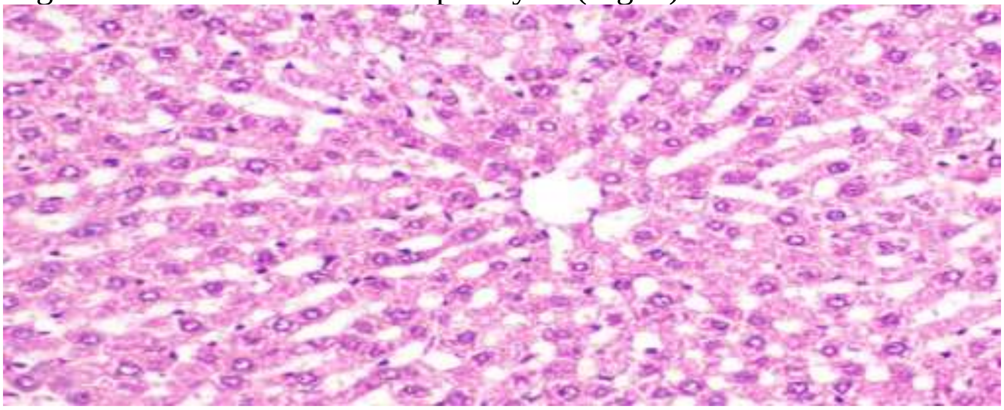

Fig. (1): Liver of rat from group one demonstrating the normal histological architecture of hepatic lobule (H & E X 400).

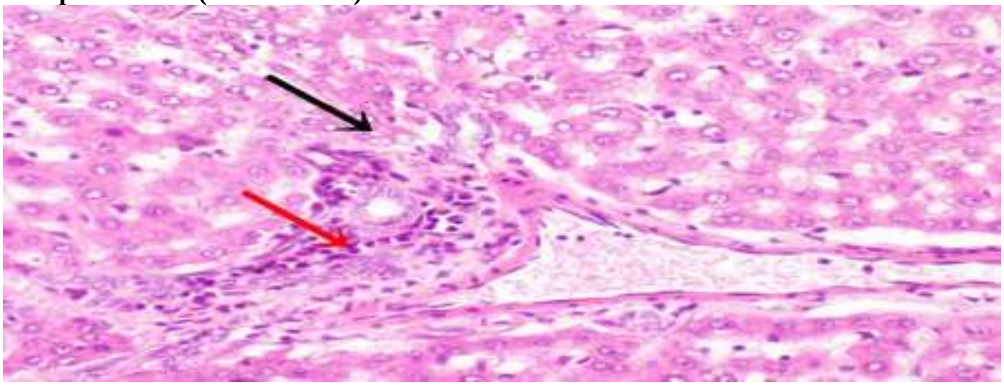

Fig. (2) Liver of rat from group two demonstrating hepatocellular vacuolar degeneration (black arrow) & portal infiltration with inflammatory cells (red arrow) (H & E X 400).

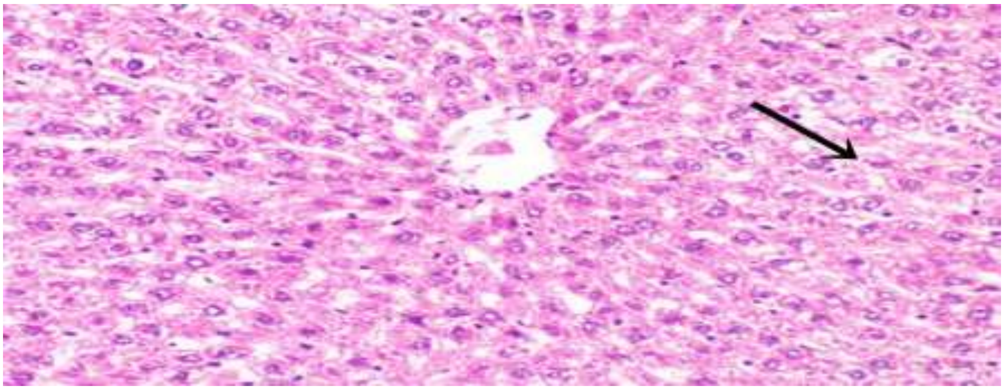

Fig. (3): Liver of rat from group 3 demonstrating hydropic degeneration of hepatocytes & hepatocellular vacuolar degeneration & sinusoidal leukocytosis (black arrow) (H & E X 400).

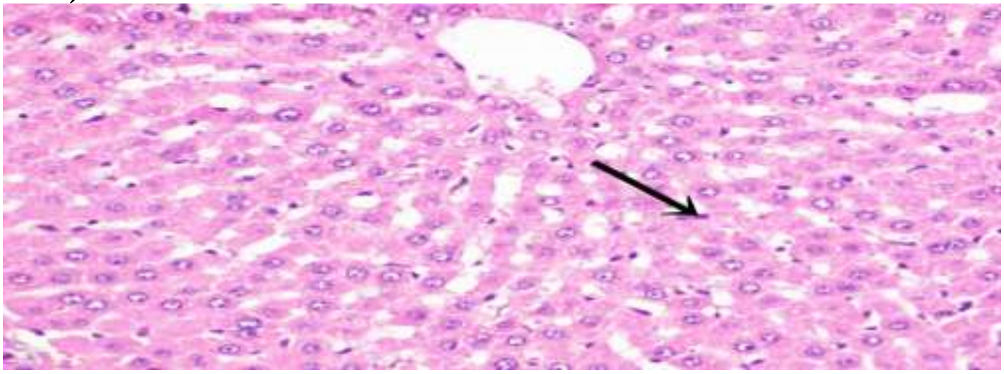

Fig. (4): Liver of rat from group 4 demonstrating Kupffer cells activation & slight fibroplasia in the portal triad (black arrow) (H & E X 400)

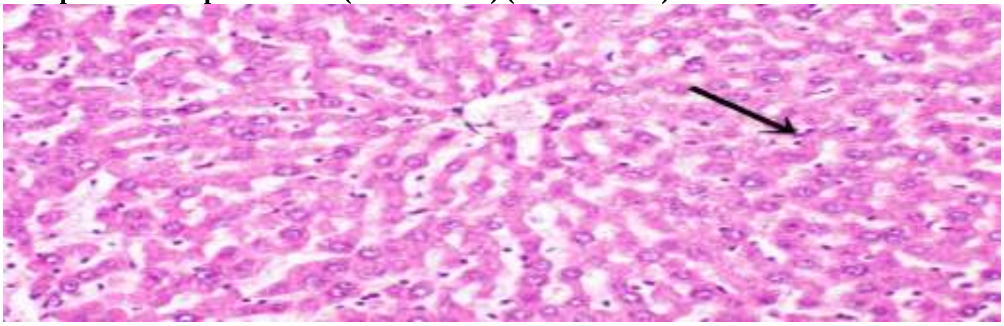

Fig. (5): Liver of rat from group 5 demonstrating Kupffer cells activation & slight vacuolization of some hepatocytes (black arrow) (H & E X 400).

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الدور الوظيفي لأوراق الأشواجندا على النوع الثاني لمرض السكر في الفئران المحدث بواسطة الاستربتوزين

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الملخص:

تبحث الدراسة الحالية تأثير استخدام أوراق نبات الأشواجندا لعلاج مرض السكري في الفئران المصابة بداء السكري المستحدث بواسطة الستربتوزوتوسين. تم إنشاء مجموعتين أساسيتين من ثلاثين فأرا بوزن 180±5جم. (ستة فئران لكل مجموعة) المجموعة الرئيسية الأولى تم إعطاؤها نظامًا غذائيًا أساسيًا كمجموعة ضابطة سالبة. تلقت المجموعة الرئيسية الثانية، والتي تكونت من 24 فأراً مقسمة إلى أربع مجموعات فرعية قابلة للمقارنة، حقنة واحدة من الستربتوزوتوسين بجرعة 100ملجم/كجم في تجويف البطن بعد ذلك، تم الاحتفاظ بالمجموعة الفرعية الأولى كعنصر كمجموعة ضابطة موجبة، وتم تغذية المجموعة الفرعية الثانية بنظام غذائي يتضمن مسحوق الأشواجندا (100جم/كجم)، وتم تغذية المجموعة الفرعية الثالثة بنظام غذائي يتضمن مسحوق الأشواجندا (200جم/كجم). تم إعطاء المجموعة الفرعية الرابعة نظامًا غذائيًا أساسيًا بالإضافة إلى مسحوق الأشواجندا (400جم/كجم من النظام الغذائي). تم أخذ عينات الدم من كل فأر في نهاية التجربة، وتم فصل المصل واستخدامه لتحديد التحاليل البيوكيميائية المختلفة. تم عمل هستوباثولوجى للكبد. تم عمل تحليل كيميائي لمسحوق الأشواجندا. وفقا لنتائج مسحوق الأشواجندا كان هناك فروق ملحوظة في وزن الجسم، أو نسبة كفاءة التغذية، أو تناول العلف، في المجموعة الضابطة الموجبة والمجاميع التي تناولت الأشواجندا. بالنسبة لمستويات الدهون في الدم، كان هناك تغير ملحوظ في المجموعة الضابطة الموجبة مقارنه بالمجموعة الضابطة السالبة والمجاميع التي تغذت على الأشواجندا. حدث انخفاض مؤشر نسبة السكر في الدم والأنسولين في المجاميع التي تغذت على الأشواجندا حيث وجد تحسنا في مستويات السكر في الدم والأنسولين مقارنة بالمجموعة الضابطة الموجبة. وانخفضت إنزيمات الكبد ووظائف الكلى في المجاميع التي تغذت على الأشواجندا مقارنة مع مجموعة الضابطة الموجبة. ونتيجة لذلك، اقترحت هذه الدراسة الأشواجندا لعلاج مرض السكري من النوع 2.

الكلمات المفتاحية: داء السكري - وظائف الكلى - أشواجاندا - تحليل الدهون.