# Antidiabetic potential of flavonoids from *Artemisia macrocephalla* Jaquem in streptozotocin-induced diabetic rats: Pharmacological and biochemical approach

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**Abstract**: Plants belongs to Asteraceae family are reported to be rich in major phytochemical including flavonoids and are documented to acquire antidiabetic response. Antidiabetic effects of salvigenin, eupatilin and cirsilineol were screened on *in-vitro* enzyme inhibition and *in-vivo* streptozotocin animal models. Administration of salvigenin, eupatilin and cirsilineol (7.5 and 15mg/kg) produced antidiabteic responses in streptozotocin model for diabetes. All natural flavonoids reduces the blood glucose level to a significant level (*P<0.05, **P<0.01, ***P<0.001, n=8) but promising results were observed in eupatilin at dose of 7.5mk/kg (364.12±4.3 to 128.41±4.2mg/dL, n=8) and at dose of 7.5mk/kg 363.65±4.8 to 126.14±5.1mg/dL, n=8). Administration of salvigenin, eupatilin and cirsilineol (7.5 and 15mg/kg) for 28 days showed a substantial fall (*P<0.05, **P<0.01, ***P<0.001, n=8) in total cholesterol, LDL and triglcerides (TGs) in comparison to diabetic model. The isolated flavonoids reduced considerably the serum ALP, SGPT and SGOT in rats intoxicated with streptozotocin. The results indicate that the flavonoids may be useful in the development of new antidiabetic drugs.

**Keywords**: Artemisia, isolated flavonoids, enzyme inhibition, diabetes, streptozotocin.

## INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia that results from abnormal secretion of insulin, inappropriate action of insulin or both (Cernea and Dobreanu, 2013). This situation (chronic hyperglycemia) leads to micro vascular problems affecting the kidneys, eyes, nervous system and augmented the risk for cardiovascular complication (Skyler *et al*., 2017). In addition to this, hypertriglyceridemia and hypercholesterolemia are common complications of diabetes as well (Schofield *et al*., 2016). Approximately 4% of the worldwide general public is affected by DM and likely to rise by 5.4% in 2025 (Shoaib *et al*., 2018).

Diabetes mellitus has increasing prevalence worldwide with rising morbidity and mortality rate. According to a report, WHO estimated that diabetes has a worldwide prevalence of 347 million people in 2013. This report also anticipated that the prevalence is going to become double in between 2005-2030 and majority of the population would belong to the countries like Asia, South America, and Africa (Rowley *et al*., 2017). Claim has been put forward that more than 1200 plants contain diabetes mellitus remedies (Gothai *et al*., 2016) and studies have been carried out in detail for about 400 plants and compounds. Similarly, fats in the body may be beneficial and harmful which depends on the amount, location and disposition time. Body fats of older adults are harmful exceptionally it may provide resistance against loss or fractures of bones. While adults having fats in excess are at risk from diseases like diabetes mellitus type 2, arthritis, heart related disease, high blood pressure and stroke (Millstein, 2014).

Natural products are supposed to be an unlimited treasure of series of molecular bioactive entities and serve as scaffolds of novel drugs for the cure of various ailments (Riaz *et al*., 2018). Potentially active plant derived antidiabetic secondary metabolites that have the capability on multiple disease targets with safety profile are desirable for treating diabetes mellitus (DM) (Numonov *et al*., 2019). Bioactive compounds from natural source including flavonoids have been proven to have potent antidiabetic activity (Jaitak, 2019). An extensive review

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on the antidiabetic potential of Artemisia genus reveals that nine species including *A. herba-alba, A. afra, A. judaica, A. amygdalina, A. ludoviciana*, *A. dracunculus, A. sphaerocephala, A. absinthium and A. nilagirica* are reported to possess antidiabetic action (Dabe and Kefale, 2017).

Flavonoids are structurally diverse and most abundantly found polyphenols that are the essential constituents of our food (Williamson, 2017). More than 15,000 flavonoids have been separated and identified from plants and has been observed for diverse pharmacological applications (Xiao, 2017). Salvigenin, eupatilin and cirsilineol are bioactive natural flavonoids that are abundantly distributed among the species of genus Artemisia and have been well known for its medicinal importance including pronounced inhibitory activity against alpha-amylase and alpha-glucosidase (Olennikov *et al*., 2018). These natural secondary metabolites are well known for their diversified pharmacological properties including antioxidant (Nageen *et al*., 2018), anti-inflammatory and analgesic (Mansourabadi *et al*., 2015), anticancer (Nageen *et al*., 2018) and neuroprotective property (Sapkota *et al*., 2017).

Keeping in view the importance of Artemisia genus and especially flavonoids having the ability to exhibit antidiabetic activity both, *in-vitro* and *in-vivo* in various animal models (Jaitak, 2019), the present study was conducted to investigate salvigenin, eupatilin and cirsilineol from *Artemisia macrocephalla* Jaquem for antidiabetic activity.

## MATERIAL AND METHODS

Salvigenin, eupatilin and cirsilineol used in this study were isolated by our group from *Artemisia macrocephala* Jacquem and the spectroscopic data are in accordance with previous reported literature (Shoaib *et al*., 2016, Tashenov *et al*., 2013, Chu *et al*., 2014). DTNB (5,5-dithio-bis-nitrobenzoic acid), streptozotocin, Tween-80, α-glucosidase and substarte were purchased from Sigma Aldrich, Germany. Glibenclamide was taken from local pharmaceutical industry.

***In-vitro α-glucosidase enzyme inhibition activity***

The isolated flavonoids were assessed against α-glucosidase to determine the possible *in-vitro* antidiabetic potentials of these flavonoids. Salvigenin, eupatilin, cirsilineol and standard at various concentration were evaluated for possible *in-vitro* α-glucosidase enzyme inhibition activity by using spectrophotometric technique. Each analysis was repeated thrice and the $IC_{50}$ of isolated flavonoids and standard was calculated (Shoaib *et al*., 2018).

***Animals***

Balb/C mice (18-23g) and Sprague Dawley rats (160-180 g) were used in the study and kept in animal house with free access to food and *water ad libitum*. The animals were kept at room temperature around 22-25°C with light and dark cycle of about 12 h each (light on 6:00 am) and a relative humidity of 50-55%. Study was conducted as per approval protocols (notification no: FAB12/2018-44), in accordance with the animals byelaws 2008, Scientific Procedures Issue-I.

***In-vivo antidiabetic activity***

***Acute toxicity study***

Salvigenin, eupatilin and cirsilineol were screened for its possible toxicological effects using mice as model in two phases at different dose concentration ranging from 1 mg/kg to 250mg/kg b.w by intraperitoneal (*i.p.*) route. Mice were observed for abnormal behaviors, allergic manifestation and mortality for the next 72 h followed by 14 days observation (Shoaib *et al*., 2019).

***Oral glucose tolerance test and hypoglycemic activity***

The OGTT (oral glucose tolerance test) and hypoglycemic activity was carried out in normal overnight fasted rats with slight modifications. Rats in groups (n=8) were administered saline (0.9%, w/v), glibenclamide (0.5mg/kg, p.o), and isolated flavonoids (salvigenin, eupatilin and cirsilineol, 7.5 and 15mg/kg, i.p.) respectively. Glucose solution (1g/kg) was given 30 min after the administration of samples. Blood was withdrawn from the tail vein of rats at 0, 30, 60, and 90 min interval and the level of blood glucose was estimated using glucometer (Hasan *et al*., 2018). In another series of experiment, similar procedure was adopted except administration of glucose for hypoglycemic activity. Blood was withdrawn and estimated in similar fashion using glucometer (Hammeso *et al*., 2019).

***Induction of diabetes***

In order to induce diabetes, dose of 50mg/kg b.w of streptozotocin (STZ) in citrate buffer was given through intra peritoneal injection to the overnight fasted male rats. After three days (72 hrs) of STZ administration, the level of blood glucose was measured by one touch glucometer strips using SD glucometer (Korea) by collecting the blood from tail vein puncture. For further study, those animals were selected having fasting levels of blood glucose higher than 250mg/dL (Oguntibeju *et al*., 2016).

***Experimental design***

The animals were distributed into eight groups (n=8) randomly and kept on overnight fasting for 12 hrs. Normal saline were given to the control group (normal control, non-diabetic) while the group 2, the diabetic control received Tween-80 (2%). Glibenclamide which is a standard drug was received by group 3 at dose of (0.5 mg/kg, p.o.). Salvigenin, eupatilin and cirsilineol at a dose of 7.5 and 15mg/kg (i.p) was given to their respective groups assigned once daily for 28 days. Weight of the body and level of blood glucose was measured at 1$^{st}$, 4$^{th}$, 7$^{th}$, 10$^{th}$, 15$^{th}$, 21$^{st}$ and 28$^{th}$ day of treatment (Kumar *et al*., 2016).

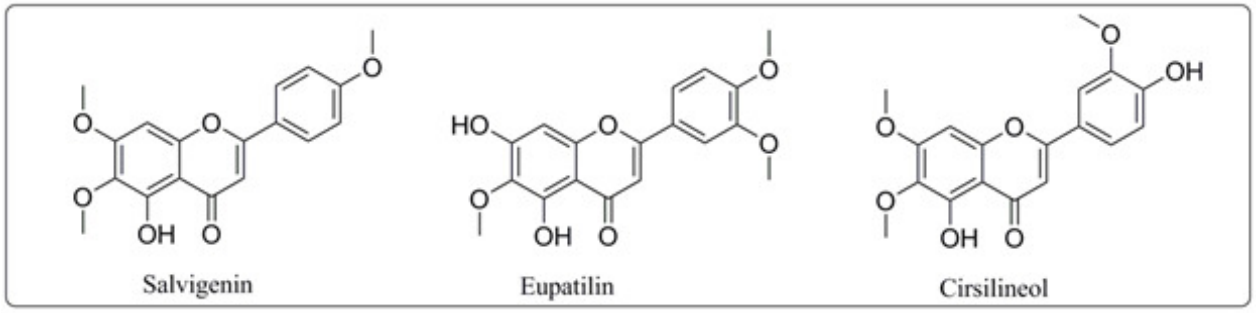


**Fig. 1**: Flavonoids used in study for antidiabetic activity

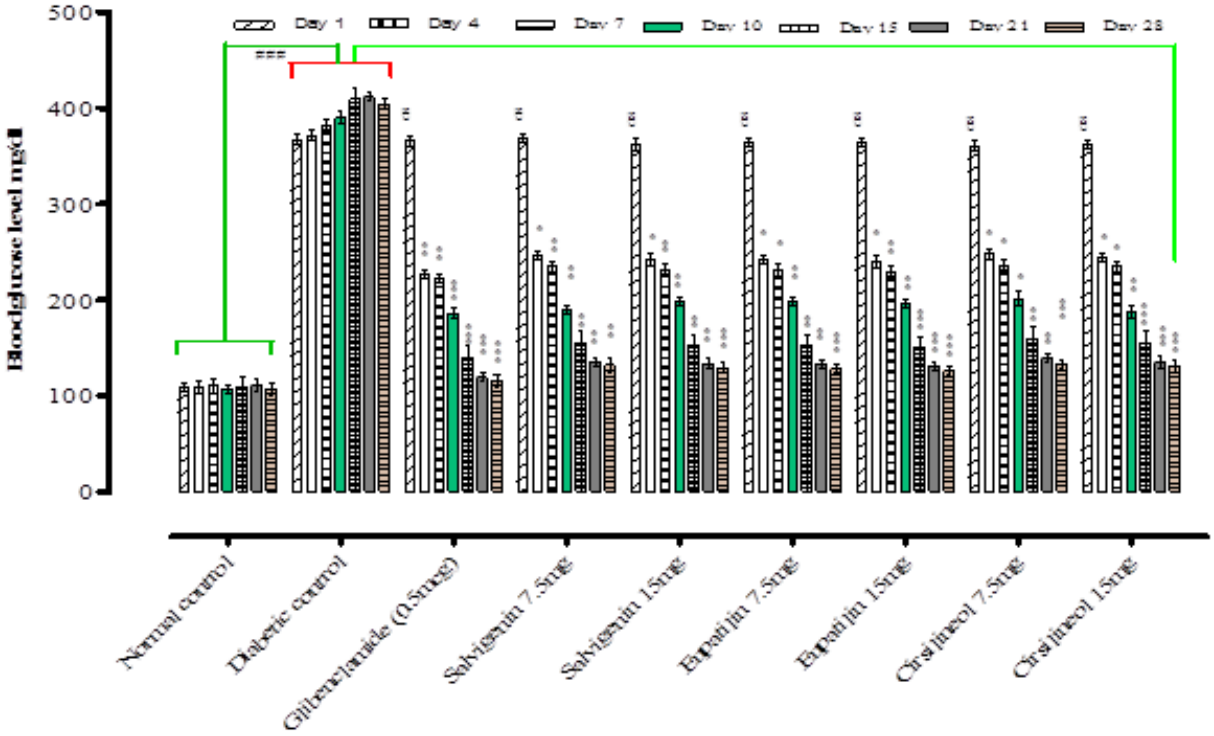


**Fig. 2**: Antidiabetic effect of flavonoids in STZ diabetic model. Mean ± SEM ($n$=8). $^{###}$P<0.001 vs control. $^{*}$P<0.05, $^{**}$P<0.01, $^{***}$P<0.001 vs diabetic group (One-Way ANOVA followed by Dunnett's bilateral comparisons).

***Assessment of serum lipid and liver physiological profile***

The blood samples from animals after study collected through cardiac puncture to analyze the biochemical parameters including serum total cholesterol (TC), high density lipoprotein (HDL), low density lipoproteins (LDL), triglycerides (TGs), hepatic enzymes like ALP, SGPT, SGOT and serum creatinine levels were determined (Doğan and Çelik, 2016).

## STATISTICAL ANALYSIS

Values are taken as mean ± SEM. One-way ANOVA followed by Dunnett's multiple comparison tests was used for statistical significance using GraphPad prism version 5.01. P value less than 0.05 was considered statistically significant.

## RESULTS

The structure of reported isolated flavonoids (salvigenin, eupatilin and cirsilineol) used in the antidiabetic study is given in fig 1.

**Table 1**: *In-vitro* α-glucosidase inhibition potentials of isolated flavonoids

| Sample | $IC_{50}$ µg/mL |
|---|---|
| Salvigenin | 51.65±2.91 |
| Eupatilin | 40.48±3.11 |
| Cirsilineol | 53.38±2.67 |
| Acarbose | 68.22±2.34 |

**Table 2**: Effect of salvigenin, eupatilin and cirsilineol on OGTT and hypoglycemic activity

| Groups | | | Blood glucose level in mg/dL | | | |
|---|---|---|---|---|---|---|
| | | | 0 min | 30 min | 60 min | 90 min |
| Oral glucose tolerance test | Normal control | | 105.21 ± 5.6 | 131.39± 5.1 | 170.39 ± 6.1 | 127.51 ± 4.1 |
| | Glibenclamide (0.5mg) | | 107.24 ± 5.7 | 114.23 ± 4.6### | 110.39 ± 5.3### | 109.11 ± 5.2### |
| | Salvigenin | 7.5 mg | 104.14 ± 4.9 | 119.67 ± 4.9* | 114.34 ± 4.5** | 111.28 ± 5.7** |
| | | 15 mg | 105.79 ± 5.1 | 117.11 ± 6.1* | 112.56 ± 5.6** | 110.51 ± 4.2** |
| | Eupatilin | 7.5 mg | 104.33 ± 4.7 | 116.39 ± 4.9* | 114.41 ± 6.5* | 110.38 ± 5.1** |
| | | 15 mg | 105.69 ± 4.9 | 114.18 ± 5.1* | 113.61 ± 4.5** | 110.03± 4.9** |
| | Cirsilineol | 7.5 mg | 107.76 ± 5.1* | 117.87 ± 4.3* | 116.76 ± 4.5* | 113.08 ± 6.2* |
| | | 15 mg | 106.14 ± 4.6** | 116.27 ± 5.5* | 115.61 ± 5.1* | 111.04 ± 6.1** |
| Hypoglycemic test | Normal control | | 104.21 ± 4.9 | 106.13 ± 4.7 | 106.15 ± 4.1 | 105.13 ± 5.5 |
| | Glibenclamide (0.5mg) | | 106.22 ± 5.1 | 94.01 ± 5.4### | 88.71 ± 5.1### | 87.19 ± 5.6### |
| | Salvigenin | 7.5 mg | 104.27 ± 4.7 | 106.11 ± 4.7 | 106.15 ± 5.7 | 105.22 ± 4.9 |
| | | 15 mg | 106.23 ± 4.1 | 105.87 ± 5.4 | 104.76 ± 4.4 | 106.16 ± 5.1 |
| | Eupatilin | 7.5 mg | 105.56 ± 5.8 | 106.12 ± 4.7 | 105.46 ± 5.7 | 105.34 ± 5.7 |
| | | 15 mg | 105.11 ± 5.3 | 104.71 ± 4.6 | 106.38 ± 5.9 | 105.51 ± 4.7 |
| | Cirsilineol | 7.5 mg | 106.51 ± 4.7 | 105.34 ± 5.5 | 105.68 ± 4.5 | 106.76 ± 4.1 |
| | | 15 mg | 105.11 ± 4.4 | 104.46 ± 5.3 | 106.92 ± 4.4 | 104.55 ± 5.1 |

Mean ±SEM (n=8). ###P<0.001, *P<0.05, **P<0.01 and ***P<0.001 *vs* standard

**Table 3**: Effect of salvigenin, eupatilin and cirsilineol on the body weight

| Groups | | Day 1st | Day 4th | Day 7th | Day 10th | Day 15th | Day 21st | Day 28th |
|---|---|---|---|---|---|---|---|---|
| Normal control | | 163.1±3.9 | 162.1±4.9 | 162.6±3.4 | 162.3±4.2 | 161.3±3.7 | 163.9±3.6 | 165.9±4.7 |
| Diabetic control | | 162.8±4.4 | 162.2±3.7 | 151.0±3.8# | 145.3±4.3## | 144.2±5.2## | 141.2±5.1## | 139.7±4.1## |
| Glibenclamide (0.5mg) | | 162.9±4.1 | 160.4±4.6 | 168.5±3.7* | 166.2± 4.1* | 168.1±4.3** | 167.7±4.8** | 163.1±4.2** |
| Salvigenin | 7.5 mg | 161.7±4.9 | 163.6±4.2 | 162.2±4.4* | 168.9±4.7** | 166.4±3.9* | 165.4±3.6* | 162.3±4.8** |
| | 15 mg | 164.5±4.0 | 163.2±4.7 | 161.7±4.2** | 167.0±4.6** | 163.5±5.1** | 161.8±4.7** | 164.1±5.1** |
| Eupatilin | 7.5 mg | 161.4±4.6 | 164.5±3.7* | 165.2±4.1* | 164.7±4.8** | 164.3±4.1** | 163.1±4.2** | 163.6±4.2 |
| | 15 mg | 162.1±4.9 | 163.6±3.4 | 163.3±4.2 | 164.9±3.6 | 165.6±4.4 | 166.9±4.7 | 165.1±5.1** |
| Cirsilineol | 7.5 mg | 163.5±4.0 | 164.2±4.7 | 163.7±4.2** | 166.0±4.6** | 163.5±4.3** | 162.8±4.7** | 166.1±5.1** |
| | 15 mg | 165.2±4.1* | 166.7±4.8** | 163.1±4.2** | 163.9±3.9 | 163.1±4.2 | 162.7±4.9 | 163.6±3.4 |

Mean ±SEM (n=8). #P<0.05, ##P<0.01 *vs* normal control test. *P<0.05, **P<0.01 *vs* diabetic group.

***In-vitro α-glucosidase inhibition activity***

The *in-vitro* inhibitory potentials of the salvigenin, eupatilin and cirsilineol on α-glucosidase enzyme were determined and $IC_{50}$ values are given in table 1. It is apparent from the results that all isolated flavonoids showed promising activity on α-glucosidase $IC_{50}$=51.65±2.91, 40.48±3.11 and 53.38±2.67µg/mL respectively.

***OGT and hypoglycemic effects of salvigenin, eupatilin and cirsilineol***

The effects of salvigenin, eupatilin and cirsilineol on the glucose level in plasma are given in table 2. The increase in level of glucose was noted in glucose control group after glucose administration. In rats treated with salvigenin, eupatilin and cirsilineol, there was a significant fall in level of plasma glucose in contrast to glucose control rats where the glucose level was increased. Similar type of results was noted in group treated with glibenclamide. In normoglycemic rats, all the three isolated flavonoids (salvigenin, eupatilin and cirsilineol) and glibenclamide significantly reduced the blood glucose at all time points (table 2).

***Estimation of biochemical parameters***

*Effect of salvigenin, eupatilin and cirsilineol on glycemia*

The effect of salvigenin, eupatilin, cirsilineol (7.5 and 15 mg/kg) and standard glibenclamide (0.5mg/kg) on variations in the level of blood glucose are tabulated in fig. 2. At the end of 28th day study, the administration of the salvigenin, eupatilin and cirsilineol (7.5 and 15mg/kg) significantly turn around the level of blood glucose compared to diabetic group.

***Effect of salvigenin, eupatilin and cirsilineol on body weight***

The effect of salvigenin, eupatilin, cirsilineol (7.5 and 15 mg/kg) and glibenclamide on alterations in body weight are shown in table 3. Diabetic group showed significant decrease in the body weight as compared to

**Table 4**: Antihyperlipidemic effects on STZ induced diabetes

| Groups | | Total CH (mg/dL) | HDL (mg/dL) | LDL (mg/dL) | TG (mg/dL) |
|---|---|---|---|---|---|
| Normal control | | 127.5 ± 6.1 | 39.3 ± 5.4 | 71.4 ± 4.9 | 131.4 ± 4.7 |
| Diabetic control | | 174.3 ± 6.5$^{###}$ | 27.3 ± 5.1$^{#}$ | 175.3± 4.6$^{###}$ | 166.3 ± 6.1$^{##}$ |
| Glibenclamide (0.5mg) | | 141.4 ± 4.5** | 41.5 ± 4.9** | 91.2 ± 5.2*** | 134.1 ± 4.8** |
| Salvigenin | 7.5 mg | 140.9 ± 4.9* | 37.2 ± 5.6* | 104.8 ± 4.7*** | 140.7 ± 5.1** |
| | 15 mg | 139.2 ± 4.7* | 38.1 ± 4.9* | 100.4 ± 4.5*** | 139.5 ± 5.7** |
| Eupatilin | 7.5 mg | 138.1 ± 5.1* | 39.2 ± 4.7* | 101.7 ± 5.5*** | 138.6 ± 4.9** |
| | 15 mg | 134.4 ± 4.7** | 40.9 ± 6.1** | 98.3 ± 5.1*** | 135.5 ± 4.3* |
| Cirsilineol | 7.5 mg | 142.1 ± 6.1 | 38.1 ± 4.7 | 103.5 ± 6.1 | 142.2 ± 5.1 |
| | 15 mg | 140.3 ± 5.2 | 39.4 ± 5.7 | 102.2 ± 5.7 | 140.7 ± 4.7 |

Mean ±SEM (n=8). $^{#}$P<0.05, $^{##}$P<0.01 and $^{###}$P<0.001 *vs* normal control test. $^{*}$P<0.05, $^{**}$P<0.01 and $^{***}$P<0.001 *vs* diabetic group.

**Table 5**: Effect of salvigenin, eupatilin and cirsilineol on serum profile

| Groups | | (ALP) IU | (SGPT) IU | (SGOT) IU | Serum creatinine (mg/dL) |
|---|---|---|---|---|---|
| Normal control | | 149.1 ± 4.5 | 20.6 ±5.1 | 19.5 ± 5.2 | 0.59 ± 0.6 |
| Diabetic control | | 278.4 ± 5.1$^{##}$ | 59.8 ± 4.8$^{###}$ | 58.0 ± 6.1$^{##}$ | 2.71 ± 0.7$^{##}$ |
| Glibenclamide (0.5mg) | | 144.3 ± 5.9** | 21.7 ± 6.2*** | 20.1 ± 4.5** | 0.62 ± 0.4*** |
| Salvigenin | 7.5 mg | 179.1 ± 4.7** | 31.1 ± 5.7** | 36.9 ± 4.7*** | 0.92 ± 0.7** |
| | 15 mg | 169.8 ± 4.2** | 29.6 ± 4.6*** | 33.1 ± 5.1* | 0.86 ± 0.3* |
| Eupatilin | 7.5 mg | 168.1 ± 4.7** | 28.2 ± 4.6** | 29.3 ± 4.3*** | 0.81 ± 0.7** |
| | 15 mg | 161.7 ± 4.2** | 23.5 ± 4.7*** | 23.1 ± 4.9* | 0.73 ± 0.3* |
| Cirsilineol | 7.5 mg | 181.3 ± 4.7** | 31.6 ± 4.9** | 37.1 ± 6.1*** | 0.93 ± 0.7** |
| | 15 mg | 173.8 ± 4.2** | 28.8 ± 6.1*** | 33.6 ± 4.9* | 0.89 ± 0.5* |

Mean ±SEM (n=8). $^{##}$P<0.01 and $^{###}$P<0.001 *vs* normal control test. $^{*}$P<0.05, $^{**}$P<0.01 and $^{***}$P<0.001 *vs* diabetic group.

normal control group and continued till the end of 28$^{th}$ day treatment. The isolated flavonoids salvigenin, eupatilin and cirsilineol (7.5 and 15mg/kg) significantly reversed the drop in body weight mediated by STZ and significantly increases the body weight of animals at the end of treatment.

***Assessment of serum lipid profile in diabetic rats***

The levels of parameters of lipid profiles including total cholesterol (TC), high density lipids (HDL), low density lipids (LDL) and triglycerides (TGs) in various groups are given in table 4. A significant increase in the level of TC, LDL and TGs was observed in diabetic group while a significant decrease in level of HDL was observed compared to normal group (table 4). The salvigenin, eupatilin and cirsilineol (7.5 and 15mg/kg) illustrated a significant fall in the level of TC, LDL and TGs as compared to diabetic group at the end of 28 days treatment. Furthermore, the salvigenin, eupatilin and cirsilineol (7.5 and 15 mg/kg) caused a significant increase in the HDL in diabetic group at the end of treatment.

***Effect of salvigenin, eupatilin and cirsilineol on the liver and renal functions***

The results of biochemicals like ALP, SGPT, SGOT and serum creatinine in the various groups are given in table 5. Diabetic group showed a significant increase in the levels of ALP, SGPT and SGOT as compared to the normal control. Salvigenin, eupatilin and cirsilineol (7.5 and 15mg/kg) significantly reduced the ALP, SGPT and SGOT in STZ-induced diabetic group. The salvigenin, eupatilin and cirsilineol (7.5 and 15mg/kg) also significantly turn down the serum creatinine in STZ-induced diabetic group. Similar type of results for ALP, SGPT, SGOT and serum creatinine was produced by the standard glibenclamide in STZ-induced diabetic group.

## DISCUSSION

The nature serves as a rich chemical bank to be explored for targeted bioactive agents having high therapeutic potentials (Mushtaq *et al*., 2018). As a mega biodiversity country, Pakistan has still a lot of potentials unexplored flora to be groom as a source phyto-pharmaca or modern medicine (Barkatullah *et al*., 2015). Exploring medicinal plants has provided opportunity for the development of herbal industry, herbal medicine and phyto-pharmaca. Hence, it was the first priority of researchers to explore plants species and families with anti-diabetic potential and ability to inhibit α-glucosidase. Therefore the selection of Asteraceae family was on the basis of their scientifically proved anti-diabetic activity in majority of the species (Belhattab *et al*., 2014). On the basis of kinship theory, plants belonging to the same family have generally similar chemical contents (chemotaxonomy).

Natural products are supposed to be an infinite treasure of series of molecular bioactive entities and serve as scaffolds of novel drugs for the cure of various ailment (Riaz *et al*., 2018). Potentially active plant derived antidiabetic secondary metabolites that have the capability on multiple disease targets with safety profile are desirable for treating Diabetes mellitus (DM) (Numonov *et al*., 2019). Bioactive compounds from natural sources including flavonoids have been proven to have potent antidiabetic activity (Jaitak, 2019).

As a result, flavonoids are currently considered as one of the most promising and significantly important class of natural products to enrich the current therapy choices against diabetes mellitus (Ahmed *et al*., 2018). Research on subclasses of flavonoids like flavonols (rutin, fisetin and morin), flavanones (hesperidin and naringenin), isoflavones (genistein and daidzein) and flavones (apigenin, luteolin, wogonin and baicalein) etc. demonstrated that they have the ability to prevent diabetes and its complications using *in-vitro* and *in-vivo* animal model studies. Utilizing flavonoids rich fruits and vegetables could help to lower blood glucose levels and to lessen the chance of developing diabetes (Al-Ishaq *et al*., 2019).

## CONCLUSION

The present research revealed that isolated flavonoids salvigenin, eupatilin and cirsilineol from *Artemisia macrocephala* Jacquem have significant *in-vitro* and *in-vivo* antidiabetic effects using STZ induced diabetic model. The findings suggest that flavonoids can be used as an effective candidate for development of antidiabetic agents.

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