Original Research Article

Comparative study on antidiabetic effect of ethanolic extract of jute leaf on neonatal streptozotocin- induced Type-2 diabetic model rat

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ABSTRACT:

Aim: Functional food and their bioactive compounds have been considered as a new approach for the prevention and management of type 2 diabetes and its complications. According to this approach current study was carried out as an elucidation of antidiabetic properties of *Corchoruscapsularis* and *Corchorusolitorius*varieties of jute leaf (ethanolic extract) on nSTZ-induced type-2 diabetic rats.

Methodology: The type-2 diabetic model rat was developed by a single *intraperitoneal* injection of freshly prepared STZ (90mg / kg / 10ml) in sterile citrate buffer (0.1 M, pH 4.5) to rat pups (48 hour old). After three months, OGTT was performed to select diabetic (FSG > 6.5mmol/L and after 90min of glucose load > 14 mmol/L) experimental rats. The rats were randomly divided into four groups [DWC, GT, Ext-1 and Ext-2 represent, diabetic water control, glybenclamide treated (20mg/5ml/kg body weight), *C capsularis* treated and *C olitorius* treated group (1.25g/10ml/kg body weight) respectively].One group was kept with normal rats[normal water control, NWC]. The treatment was given once daily or 28 cosecutive days. Fasting serum glucose, liver glycogen and lipid profile were estimated by using standard methods.

Results: The results showed that Ext-1 and Ext-2 treated groups gradually decreased serum glucose level (7.15 ±0.67 to 5.94 ± 1.19 and **7.20 ± 0.93 to 5.28 ±1.03** respectively) and reducing effect by Ext-2 was significant (p=0.001). Both extract showed lower liver glycogen level compared with GT group [**5.0±2.5 Vs 17.7±6.5** (Ext-1 *vs* GT) and 7.5±6.4 Vs 17.7±6.5 (Ext-2 *vs* GT)] and even Ext-1 manifested significant effect (p=0.05). Additionally, lipid profile estimation revealed no significant improvement by the consumption of both the extracts. **Conclusion:** On the basis of current investigations, it may be concluded that both varities of jute's leaf demonstrated hypoglycemic properties in Type 2 diabetic model rats; further in-depth studies are recommended to explore the exact mechanism(s) of hypoglycemic effect.

Keywords:*Jute leaf, hyperglycemic, lipid profile, STZ, glibenclazide, T2DM*

ABBREVIATIONS

FST = Fasting serum glucose, GOD-PAP = Glucose oxidase, HDL= High density lipoprotein, LDL = Low density lipoprotein, ip = intraperitonial , OGTT = Oral glucose tolerance test, TG = Triglycerides, T2DM = Type 2 diabetic model rats, nSTZ= neonatal streptozotocin

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies distinguished by chronic hyperglycemia with abnormal metabolism of carbohydrate, fat and protein resulting from defects in insulin secretion, insulin action, or both [1]. DM develops either when the pancreatic β-cell is unable to secrete enough insulin or when the body fails to utilize insulin properly [2-3]. Moreover, the high production and imbalance scavenging of reactive oxygen species play an integral role in the development of DM [4-6]. Diabetes is becoming the third "killer" of the health of mankind along with cancer and cardiovascular diseases and leads to serious damages of vital body systems, especially the nerves and blood vessels [7]. Over the time, diabetes is becoming a remarkable cause of damaging internal organs like heart, blood vessel, eye, kidney, and nerve [8].

Plants have always been a potential source of active drugs. According to the ethnobotanical survey, about 800 plants have been identified as antidiabetic potentials [9]. Moreover, people are using many plants as well as herbs for treating several diseases including diabetes without any scientific knowledge on their proper functions and constituents as dietary adjuvant [10-11]. This practice may be attributed to the uncompromised cost and side effects of synthetic hypoglycemic agent. Although numerous synthetic drugs has developed for the treatment of diabetes but the safe and effective treatment paradigm is not yet to be achieved [12]. From the previous reports on plant potentials against diabetes, it is assumed that the phytochemicals play a major role in the management of diabetes, which needs further exploration for the development of novel antidiabetic drugs and nutrition [13]. Jute leaf (genus: *Corchorus*, family: Tiliaceae) have been possessed many medicinal values including diabetes [14-15]. In Bangladesh, jute leaf of two cultivated species, *Ccapsularis*and *Colitorius* is used as vegetables mainly as a byproduct of thinning jute fields at the seedling stage [16-17]. Previous scientific report established that jute leaf contain several nutritional values like lipids, protein, crude fibre, carbohydrate, vitamins (A,C,E) and minerals including calcium, sodium, potassium, phosphorus and iron.[17-20]. For example, 100g of the fresh leaves contained 43-58 calories, 4.5 – 5.6g protein, 0.3g fat, 7.6 – 12.4g total carbohydrate , 80.4 – 84.1g water, 1.7 - 2.0g fibre, 2.4 g ash, 266 -366mg Ca, 97 – 122mg P, 7.2 -7.7mg Fe, 12mg Na, 444mg K, 6,410 - 7,850 µg beta carotene equivalent, 0.13 – 0.15mg thiamine (Vitamin B_1), 0.26 – 0.53 mg riboflavin (Vitamin B_2) , 1.1 – 1.2 mg niacin and 53 - 80 mg ascorbic acid (Vitamin C) [21-23]. The biochemical properties of jute leaf with high heritability and genetic advance transmitted from wild gerplasm to cultivated species through crossing and agronomical practices [24]. Jute leaf contains hundreds of different beneficial compounds known as phytochemicals such as polysaccharide (acidic polysaccharide), sitosterol, scopoletin and fusidic acid, anthocyanin, alkaloids, terpenoids, tannins, flavonoids, glycosides, caffeine, catechine, p-coumaric acid, ferulic, caffeic, vanillic, p-hydroybenzoic, protocatechuic, vanillic acids and β-sitosterol those shows health promoting effect against cardiovascular diseases, some forms of cancer and other degenerative diseases [25-30]. The most important action of these chemicals (specially, phytol and monogalactosyldiacylglycerol) are, the function of antioxidant that react with the free oxygen molecules or free radicals in the body [31-32]. However, there is dearth of information on possible mechanisms of action by which these leaves exert their health benefits. Therefore, this study sought to investigate the possible mechanisms of action of this vegetable leaf in type 2 diabetic model rats.

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2. MATERIAL AND METHODS

2.1 Place of study

The study was conducted in the department of pharmacology at Bangladesh University of Health Sciences (BUHS), Mirpur, Dhaka, Bangladesh Jute Research Institute (BJRI), Nashipur ,Dinajpur and the department of chemistry at Hajee Mohammad Danesh Science & Technology University, Dinajpur, Bangladesh.

2.2 Plant collection and Extraction

Fresh early mature leaf from two jute varieties *C capsularies* (accession number: CVL-1) and *C olitorius (*accession number: O-9897) was collected from sub-station of BJRI, nashipur, Dinajpur, Bangladesh. After collection, jute leaves were washed by fresh water thoroughly and sun dried accordingly. For ethanolic extract preparation, sun dried leaves were grinded to make fine powder by a grinding machine. The grinded powder was dissolved in absolute (96%) ethanol for overnight at room temperature. This procedure has repeated for three times. After the completion of extraction, dried extract was prepared using a rotary evaporator (BUCHI R-114, Switzerland) at 45°C and in a freeze drier (HETOSICC, Heto Lab Equipment, Denmark) at -55°C. Finally, dried extract stored in a reagent bottle at 8°C refrigerator until further use.

2.3 Animals

Adult Long Evans rats (body weight 170 -220 g) were used in this experiment. The animals were maintained at a constant temperature (22 ± 1 ° C) on a 12 h light / dark cycle with free access to water. Standard commercial food pellet was provided for their nutrition at Bangladesh University of Health Sciences (BUHS) animal house. Current investigation was done according to the guide for the care and use of laboratory animals (1996). All the sections of this manuscript is based on the ARRIVE guidelines for reporting animal research [33]. All efforts were made to minimize the sufferings of the experimental animals.

2.4 Development of Type-2 diabetic model rats

Type-2 diabetic model rats were developed by a single intraperitoneal injection of streptozotocin (STZ) to 48 hr old rat pups at a dose of 90mg/kg/10ml and the preparation was freshly prepared in sterile citrate buffer (0.1 M, pH 4.5) just before the induction. After 3 months of STZ induction, type-2 diabetic model rats were confirmed (fasting serum glucose level >6.5mmol/ L and after the 90min of glucose load serum glucose level >14mmol/L) by OGTT and selected for the investigation of antidiabetic effect of ethanolic extract of jute leaf.

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2.5Doses preparation of glybenclamide and jute leaf extract

The standard drug glybenclamide was prepared at a dose of 20 mg per 5 ml of solvent (water + few drops of 1 N Sodium hydroxide) per kg body weight. Ethanol extract of *C capsularis* and *C olitorius*are administered intragastrically at a dose of 1.25g per kg body weight during the experimental period.

2.6 Experimental design

To elucidate the antidiabetic effect of *C capsularis*and *C olitorius* on STZ-induced type 2 diabetic model rats, current investigation was performed with 26 Long Evans rats and all rats were selected randomly to make fourdifferent groups (group 2-group 4).Group-1 consisted of normal rats (n = 6): normal water control (NWC); group-2 (n = 6): diabetic water control (DWC), group 3 (n =7): glybenclamide treated GT), group 4 (n = 6): *Ccapsularis* treated (Ext-1), group-5 (n = 7) : *C olitorius* treated (Ext-2).

2.7 Biological sample collection

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During the experiment, fasting blood glucose level was monitored at 1st, 21st and 28th day's. Blood samples (1 mL) were collected by cutting the tail tips of the rat at baseline as well as on day 21. At the end day of the experiment the rats were decapitated under the mild ether anesthesia after an overnight (12hr) fast and the blood was rapidly collected (5ml) by following cardiac puncture. The liver was collected in ice cold condition for glycogen measurement.

2.8 Biochemical Analysis

Serum glucose was measured by Glucose Oxidase (GOD-PAP) method using micro- plate reader (Bio-Tec, ELISA) [34]. Total cholesterol in serum was determined by colorimetric (CHOD-PAP) method [35]. Serum triglyceride (TG) was determined by enzymatic colorimetric (GPO-PAP) method [36]. Serum HDL cholesterol was determined colorimetric method [37]. The LDL cholesterol was computed mathematical Friedewald's equation: LDL = TC –HDL-TG/5 [38] and liver glycogen was measured by anthrone-reagent method [39].

2.9 Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, version 12, Chicago, IL, USA). Results ware expressed as mean ± SD. Statistical evaluation of data was performed by using one-way analysis of variance (ANOVA) and paired t test. The level of significance was considered at p = 0.05.

3. RESULTS AND DISCUSSION

3.1 Effect of *Ccapsularis*and *C olitorius* extract on the body weight

During the experimental period the body weight of different rat groups was recorded once a week. Initial body weight was 213 ± 22, 193 ± 32, 190 ± 18, 193 ± 20, 186 ± 14 (mean ± SD) of NWC, DWC, GT, Ext-1, Ext-2 treated groups respectively and at the last day of experiment, the body weight was (M±SD;g) 236 ± 26 (↑10.7%), 224 ± 56 (↑24%), 195 ± 19(↑2.6%), 260 ± 24 (↑34.7%), 236 ± 14 (↑26.8%) as well (Figure 1). No significant body weight changes were observed compared with base line value as well as among different treated groups. All experimental rats increased their body weight gradually (2-35%) throughout the study period.

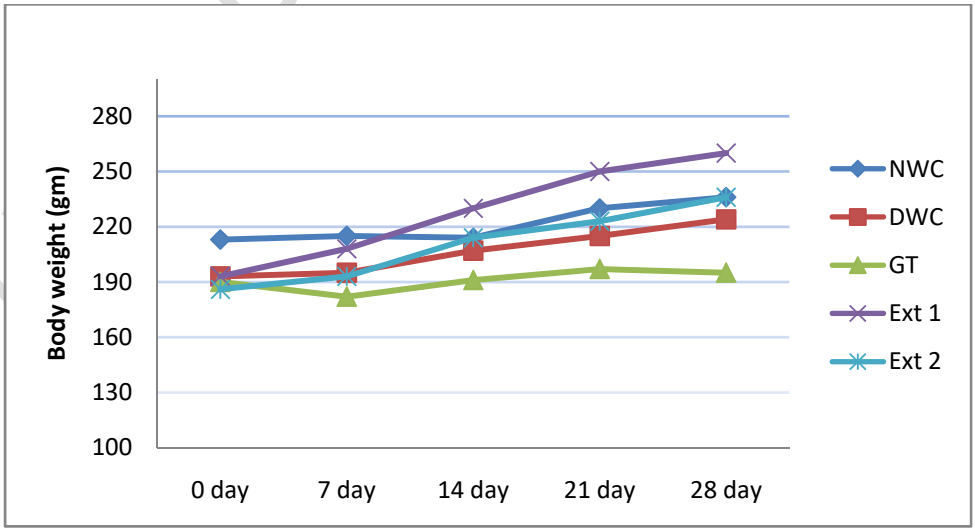

Figure 01: Effect of *C capsularis* and *C olitorius*extract on the body weight of normal and type 2 diabetic model rats.

Group NWC, DWC, GT, Ext-1 and Ext-2 represent normal water control rat, diabetic water control rat, Glybenclamide treated diabetic rat, C capsularis treated diabetic rat and C olitorius treated diabetic rat respectively. Data represented as mean ± standard deviation (M ± SD). Statistical comparison between groups was performed using one way ANOVA and pair sample t test.

3.2 Effects of *C capsularis*and *C olitorius* extract on fasting serum glucose level

At baseline, FSG (Fasting Serum Glucose) level of NWC, DWC, GT, Ext-1 and Ext-2 treated groups were 5.36±0.28, 6.95±0.45, 7.36±0.62, 7.15±0.67 and 7.20±0.93 (mean±SD, mmol/L) respectively. There was no significant difference of FSG level among several treated groups except NWC group. After 28 days of consecutive oral feeding of *C capsularis*and *C olitorius*leaf extract,the FSG level was 5.45±0.55(↑2%), 6.96±2.48, 6.77±2.07(↓8%), 5.94±1.19 (↓17%) and 5.28±1.03 (↓27%) respectively. Moreover, Ext-2 showed significant (p=0.001) reduction of FSG level compared to base line value.

Table 01: Effect of *C capsularis*and *C olitorius*extract on fasting serum glucose level

Groups	Fasting serum glucose level (mmol/l) (M ± SD).		
	O day	**21 day**	**28 day**
NWC(n=6)	5.36±0.28 (100%)	5.43±0.39	5.45±0.55 (102%)
DWC(n=6)	6.95±0.45 (100%)	6.90±2.60	6.96±2.48 (100%)
GT (n=7)	7.36±0.62 (100%)	7.14±0.98	6.77±2.07 (92%)
Ext-1 (n=6)	7.15±0.67 (100%)	7.02±0.34	5.94±1.19 (83%)
Ext-2 (n=7)	7.20±0.93 (100%)	5.60±0.82	**5.28±1.03 (73%)**

Group NWC, DWC, GT, Ext 1 and Ext 2 represent normal water control rat, diabetic water control rat, Glybenclamide treated diabetic rat, C capsularis treated diabetic rat and C olitorius treated diabetic rat respectively. Data represented as mean ± standard deviation (M ± SD). Statistical comparison between groups was performed using one way ANOVA and paired sample t test.

3.3 Effect of *C capsularis* and *C olitorius*extract on the blood glucose levels after simultaneous glucose feeding

Figure 2 depict the effect of oral administration of *C capsularis*and *C olitorius* extracts to type 2 model rats with glucose solution simultaneously on 21st day of the experiment. The simultaneous administration of leaf extracts showed the inability to cope with glucose load by the treated animals. After the 30 min of glucose load, the increment of serum glucose level was 14%, 83%, 159%, 114% and 165% in NWC, DWC, GT& Ext-1 & Ext-2 treated groups respectively. At 60 min glucose level was 40%, 126%, 129%, 121% and 163% and at 90 min 26%,110%,103%, 103% and 149% respectively compared to their 0 min value. The result showed that Ext-1 and Ext-2 were unable to oppose the rise of serum glucose arising out of glucose load in T2DM rats. DWC group showed the highest blood glucose level compared to other groups.

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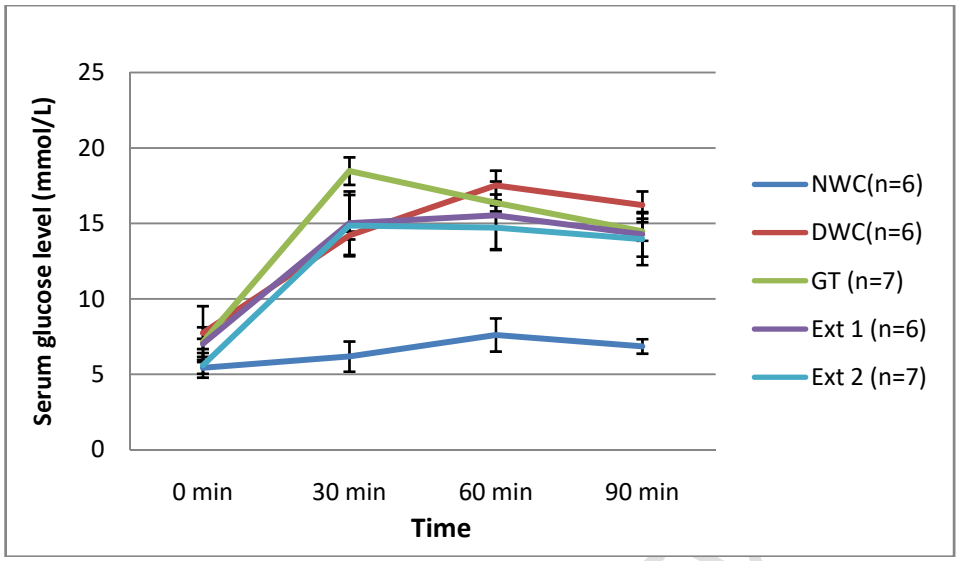

Figure 02: Oral glucose tolerance test on normal and type 2 diabetic model rats at 21 day.
Group NWC, DWC, GT, Ext 1 and Ext 2 represented normal water control rat, diabetic water control rat, Glybenclamide treated diabetic rat, C capsularis treated diabetic rat and C olitorius treated diabetic rat respectively. Data represented as mean ± standard deviation (M ± SD). Statistical comparison between groups was performed using one way ANOVA.

3.4 Effect of *C capsularis*and *C olitorius*extract on lipid profile

Chronic effect of *C capsularis*and *C olitorius*leaf on lipid profile has been presented in Figure 3&4.At the beginning and end of the experiment the triglyceride level of NWC, DWC, GT, Ext-1, Ext-2 treated groups were 59±3 & 59±7, 78±13 & 83±13 (↑6%), 69±11 & 58±13 (↓16%), 73±5 & 83±17 (↑14%), 70±16 & 82± 23 (↑18%) (mg/dl,mean±SD) respectively and the changes were non-significant when comparing with their base line value. The total cholesterol level were 57±5 & 49±10 (↓13%), 64±11 &77±11 (↑21%), 66±9 & 58±9 (↓11%), 69±18 & 66±13 (↓4%), 69±21 &77±17 (↑11%) respectively, HDL level were 45±4& 35±3(↓22%), 43±7& 46±6 (↑7%), 41± 5 & 41±1, 43±9 & 46±5 (↑6%), 43±7&43±6 respectively and finally LDL level were 83±17 & 73±10 (↓12%), 91±15 & 106±16 (↑17%), 93±13 & 88±8 (↓5%), 97±26 & 97±12 , 98±25 & 104±20 (↑5%) respectively. Moreover, no significant changes were observed within the different treated groups compared with their baseline value.

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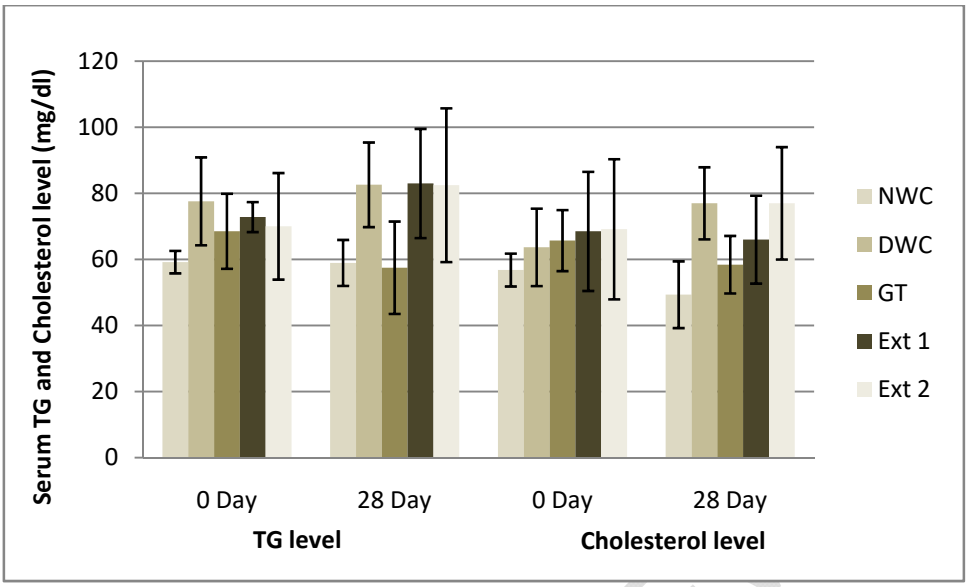

Figure 03: Effects of *C capsularis* and *C olitorius*extracts on serum triglycerides and total cholesterol level.

Group NWC, DWC, GT, Ext 1 and Ext 2 represented normal water control rat, diabetic water control rat, Glybenclamide treated diabetic rat, C capsularis treated diabetic rat and C olitorius treated diabetic rat respectively. Data represented as mean ± standard deviation (M ± SD). Statistical comparison between groups was performed using one way ANOVA and pair sample t test.

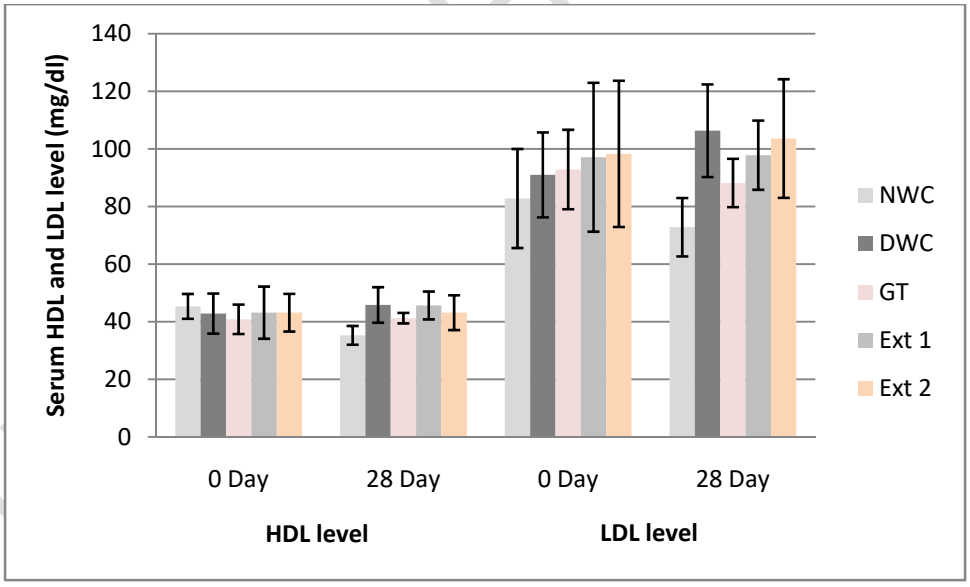

Figure 04: Effects of *C capsularis* and *C olitorius*extracts on serum HDL and LDL level.

NWC, DWC, GT, Ext 1 and Ext 2 represented normal water control rat, diabetic water control rat, Glybenclamide treated diabetic rat, C capsularis treated diabetic rat and C olitorius treated diabetic rat respectively. Data represented as mean ± standard deviation (M ± SD). Statistical comparison between groups was performed using one way ANOVA and pair sample t test.

Table 2 demonstrates the ratio of total cholesterol/HDL cholesterol level as well as the ratio of triglycerides/HDL cholesterol level. At the beginning of the experiment both ratio lied between 1.25±0.1 to 1.87±0.53 (mean±SD) and end of the experiment it was 1.4±0.36 to 1.95±0.69 respectively. At the end day GT and Ext 1 treated groups showed reduction of TC/HDL-C ratio (up to 9-13%) and increment of TC/HDL-C ratio (up to 11-14%) for NWC, DWC and Ext-2 treated groups where NWC and Ext-2 increased TG/HDL-C ratio (up to 16-27%) and rest of the treated groups (DWC,GT, Ext-1) decreased up to 2-18%. However, all changes were non-significant compared with their baseline value.

Table 2: Effects of *C capsularis*and *C olitorius*extract on total cholesterol to HDL-C and triglyceride to HDL-C ratio

Groups	TC/HDL-C		TG/HDL-C	
	0 Day	**28 Day**	**0 Day**	**28 Day**
NWC	1.25±0.10(100%)	1.41±0.34 (112.8%)	1.31±0.13 (100%)	1.67±0.16 (127.5%)
DWC	1.52±0.37(100%)	1.69±0.25 (111.2%)	1.87±0.53 (100%)	1.84±0.45 (98.4%)
GT	1.61±0.13(100%)	1.41±0.22 (87.6%)	1.70±0.38 (100%)	1.40±0.36 (82.4%)
Ext 1	1.58±0.27(100%)	1.44±0.23 (91.1%)	1.77±0.54 (100%)	1.49±0.78 (84.2%)
Ext 2	1.59±0.42(100%)	1.81±0.51 (114%)	1.67±0.56 (100%)	1.95±0.69 (116.8%)

Group NWC, DWC, GT, Ext 1 and Ext 2 represent normal water control rat, diabetic water control rat, Glybenclamide treated diabetic rat, C capsularis treated diabetic rat and C olitorius treated diabetic rat respectively. TC / HDL-C = Ratio of Total cholesterol and HDL cholesterol level and TG / HDL-C= Ratio of Triglycerides and HDL cholesterol. Data represented as mean ± standard deviation (M ± SD). Statistical comparison between groups was performed using one way ANOVA and paired sample t test.

3.5 Effect of *C capsularis*and *C olitorius*extracton hepatic glycogen level

The effect of ethanolic extract on hepatic glycogen level in type 2 diabetic model rats has been presented in Figure 5. At the end of the experiments the hepatic glycogen content of NWC, DWC, GT, Ext-1 and Ext-2 treated groups were (M±SD g/mg tissue) 4.6±4.8, 13.5±7.1(100%), 17.7±6.5 (131.1%), 5.0±2.5 (37%) and 7.5±6.4 (55.5%) (mean ±SD) respectively. Glibenclamide treated group showed 31% increment of hepatic glycogen level compared with DWC group. However Ext-2 treated group decreased (44.5%) glycogen content in comparison with DWC group where Ext 1 significantly reduced liver glycogen comparison to both DWC and GT groups.

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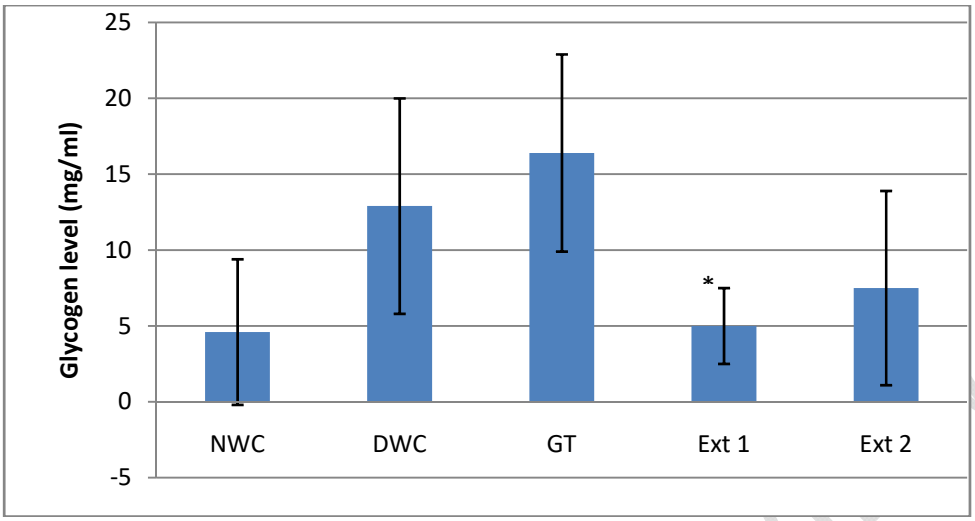

Figure 5: Effects of *C capsularis* and *C olitorius*extracts on liver glycogen level of normal and type-2 diabetic model rats.

Group NWC, DWC, GT, Ext 1 and Ext 2 represent normal water control rat, diabetic water control rat, Glybenclamide treated diabetic rat, C capsularis treated diabetic rat and C olitorius treated diabetic rat respectively. Data represented as mean ± standard deviation (M ± SD).). Statistical comparison between groups was performed by using independent sample t test

Jute leaf is a green leafy vegetable popularly used as food and in traditional medicine for the management of diabetes mellitus where currently dietary control remains one of the most desirable avenues for the prevention and management of chronic degenerative diseases as type 2 diabetes and cardiovascular diseases ([40]. According to our aim to establish the plausible antidiabetic effect of jute leaf, current experimental investigation was done and the obtained results are quite interesting. Present study has explored that the ethanolic extract of *C olitorius*significantly (p=0.001) reduces fasting serum glucose level (27%) and another varieties *Ccapsularis*also reduces serum glucose level by 17%. The hypoglycemic effect by two varieties of jute leaf strongly indicates that both may possess antidiabetic agent(s) which are responsible to control hyperglycemic state. This observation also supported by the earlier reports where the authors claimed that green leafy vegetables of jute (*C olitorius*) possess antihyperglycemic effects [14]. Moreover, after simultaneous glucose load, extract treated groups had shown their inability to occlude glucose absorption from intestine (Figure 02). According to the glycogen estimation (Figure 06), both extract has reduced total amount of liver glycogen those may be due to glycogenolysis [41]. Therefore, the extracts of jute leaf may contain hypoglycemic principle(s) which possibly do not act through enhancing glycogenesis or impeding intestinal ion channel or transporter those are responsible for regulation of intestinal glucose absorption [42]. Present study also assume that jute leaf extract may not stimulate insulin release from pancreatic beta cells and inhibits glucagon release from pancreatic alpha cells, because resulting of high insulin/glucagon ratio stimulates glycogenesis and suppress glycogenolysis; where current investigation indicates the stimulation of glycogenolysis rather than suppression which is characterized by low insulin/glucagon ratio [43]. Thus the possible reason of hypoglycemic effect by jute extract may be due to increment of gut hormone such as glucagon-like peptide-1 (GLP-1) which activates neural circuits that communicate with peripheral organs, especially including the muscle tissue, adipose tissue and coordinate overall energy intake and assimilation [44].

Additionally, current investigation explored the lipidemic status of different experimental groups. No significant changes has been obtained among the different treated groups while analyzing serum triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol

(HDL-C) and low density lipoprotein cholesterol level (LDL-C). There is growing evidence that elevated concentration of serum triglycerides, LDL-C and ratio of TG/HDL-C, TC/HDL-C is a marker of increased cardiovascular (CV) risk whereas high HDL-C is cardioprotechtive [45-46]. Though both extract treated group showed increment of triglycerideup to 14-18% (Figure 3) which might contribute in gaining their body weight (↑24-35%) at the end of the experiment (Figure 1) [47]. HDL-C and LDL-C level remained almost same (↑up to 1-6%) during the 28 days experimental period. Elevated serum triglyceride concentration had seen in both extract treated groups either due to over-production of triglyceride or underutilization [48]. It is well established that serum Insulin also has a key role on lipid metabolism. Although serum insulin was not measured in this study, it may be the assumed that low insulin secretion from pancreatic β-cell by both extracts treatment might be also another cause of elevated triglyceride and LDL-C level by this study [48]. However, the ratio of TG/HDL and TC/HDL laid between1-2 and it was reported that TG/HDL ratio >4 and TC/HDL-C ratio >5 are the most powerful independent predictor of coronary artery disease development [49-51]. Since people of Bangladesh and neighboring countries consume these two varities of jute leaf as vegetables, this investigation strongly sought that both varieties of jute leaf are devoid of cardiovascular risk.

4. CONCLUSION

Ethanol extract of jute leaf (*C capsularis and Colitorius*) showed antidiabetic properties in type 2 diabetic model rat, which may be, partly, due to the presence of huge number of beneficial phytochemicals (specially, phytol and monogalactosyldiacylglycerol) in jute leaves. Further in-depth studies are recommended to explore the exact mechanism(s) of hypoglycemic effect.

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CONSENT (WHEREEVER APPLICABLE)

N/A

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

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