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Original Research Article

Mitigation of Diabetic Hepato-Renal Toxicity by Green Tea Leaf Extracts

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Abstract: ***Background***: Hepato-renal toxicity is a common complication of diabetic hyperlipidemia due to disease and its therapeutic drugs. Excessive utilization of tea (Camellia sinensis L.) is linked with a reduced risk of hyperlipidemia and its associated disorders. Purpose of current study was to assess hepato-renal therapeutic effects of intraperitoneally induced 25 mg/mL/kg b.w. of n-Hexane, ethyl acetate, methanolic and water extracts of green tea (C. sinensis L.) leaves against streptozotocin-induced (55 mg/mL/kg b.w.) diabetic hyperlipidemia in albino Wistar rats (equally genders, 300- 400 g), by keeping metformin (250 mg/mL/kg b.w.) as positive control and high fed diet as negative control. Statistically analyzed results (at p≤ 0.05) showed that C. sinensis (L.) extracts significantly improved ALT (52.2±4.8 U/L), AST (57.14U/L), ALP (148±25U/L),bilirubin (0.13±0.02 mg/dL), albumin (2.4±0/dL), globulin (1.8±04 mg/dL), A/G ratio (0.8±0.6 mg/dL), proteins (4.9±0 mg/dL), urea (41.1±1.8 mg/dL), creatinine (1.0±0.1 mg/dL) and uric acid (2.16±16 mg/dL), as compared to negative control group [ALT (85±5.8U/L), AST (162.1±10.1U/L), ALP (150.3±41U/L), urea (66 mg/dL), creatinine (1.2±0.2 mg/dL) and uric acid (5.1±4 mg/dL)].Effects of plant extracts were almost similar to positive control group as their ALT (81 U/L), AST (183±3U/L), ALP (338U/L), urea (56.2±25 mg/dL), creatinine (0.81 mg/dL) and uric acid (4.42±9 mg/dL) were nearly equal. Histopathological analysis hepto-renal tissues showed recovery of the glomerular structure of the renal and Hepatic tissues exhibit a decrease in mononuclear cell infiltration and an enhancement in steatosis alterations. Given results can be retrieved for separation of active compounds behind the study through silicon, in vitro and in vivo approaches.

Keywords: Camellia sinensis L., hepto- renal protective, hypolipidemic, Streptozotocin

INTRODUCTION

Medicinal plants have long been used to treat a variety of ailments (Jamshidi-Kia et al. 2018). There are numerous grounds for increasing the use of medicinal plants, including the fact that herbal formulations are highly effective with few or no adverse effects (Rabiei et al. 2016). The World Health Organization (WHO) identified various medicinal plants for treatment due to their low cost, efficacy, and minimal or no negative effects. (Viktorinova et al.2016).

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Hyperlipidemia is one of the most frequent noncommunicable diseases in the world, and the most fatal complication has emerged in recent years: a cardiovascular event that is difficult to control and cannot be reversed. Both, diseases are present in Pakistan and drastically affect the hepatic and nephric systems and their prevalence is very high all over the world. Treatment modalities that are already present cause derangement of biochemical markers of the liver and kidney and drugs have multiple off target effects and extreme monetary expenditure. Polyphenol can lower the risk of these diseases. There is a paucity of information in the literature on the effect of green tea extracts on the hepatorenal systems (Mardeen et al.2018). Cardiovascular diseases affect the people of both developed and developing countries and it's due to abnormalities in carbohydrate and lipid metabolism because of decreased insulin levels, which eventually leads to hyperglycemia. Defects in carbohydrate metabolism force the body's physiological system to work overtime to maintain glucose and electrolyte balance, resulting in overexertion of the endocrine system and, eventually, hyperglycemia (Rahimi-Madisehet al.2017). Diabetic hyperlipidemia affects around 150 million people worldwide, with a projected increase to nearly 300 million by 2025 (Mardee et al. 2018).

Since old-time plants have been the source of medicine and used for various diseases. WHO identified various medicinal plants for therapy based on their reduced cost, efficacy, and little or no side effects.

(Islam et al. 2019). Presence of quelene in aqueous extracts of *C. sinensis* (L.) leaves showed improvement in kidney and liver biomarkers after carbon tetra chloride injury in rats (Caglaret al. 2019).

Liver is the main metabolic organ that plays important role in human body due to its fundamental role while hepatic disorders remain the major health problem in the world therefore discovery of less toxic and most effective treatment for liver diseases gaining more intention and for that many natural products have been used for their strong hepatoprotective role, out of which *C. sinensis* (L.) is the major one (Suhayla et al., 2022). People suffering from diabetes mellitus are at high risk of complications and most lethal is nephropathy because it leads to end stage renal failure and this developed due to excessive development of reactive oxygen species and imbalance between oxidant and antioxidant levels. Uncontrolled hyperglycemia because development of microvascular disorders that includes changes in endothelial renal cells, smooth muscle cells, mesangial cells, podocytes, tubular and ductal cells, and myofibroblasts (Maezawa et al. 2015). Liver is also affected by diabetes mellitus and leads to the development of non-alcoholic fatty changes that start with simple steatosis and ultimately cause liver fibrosis (Lucchesi et al. 2013). The main component of *C. sinensis* L is catechins that have strong antioxidant activity and activate many antioxidant enzymes and remove free radicals from the body (Prasanth et al. 2019). It also has hepatoprotective activity. Many studies showed that regular intake of *C. sinensis* for several weeks has a significant hypoglycaemic effect, it could avoid or lower the incidence of diabetic complications. (Moodley et al. 2015, Betonico et al. 2016, Hirata et al., 2017). It is important to investigate alternative therapy that cures diabetic hepato renal complications. This alternative therapy may include use of *C. sinensis* (L.) extracts as it contains alkaloids, theaflavins, flavonols and catechins, which plays important role in controlling diabetic hepato renal complications. So, objective of current study was to demonstrate the significant protection by *C. sinensis* (L.) by using n-hexane, ethyl acetate, methanolic and distilled water extracts to treatdiabetic hyperlipidemia.

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MATERIAL AND METHODS

Collection, identification and preparation of plant

Partially processed leaves of *C. sinensis* (L.) have been collected from National Tea Research Institute, Shinkiari, and Khyber Pakhtunkhwa, Pakistan, identified by a renowned taxonomist and deposited at university herbarium with botanical number. Leaves were shade dried at room temperature and grinded into 80 mesh powder by mechanical means, followed by the addition of n-hexane (in 1:10 ratio) with shaking for 24 hours in shaker incubator (K-J-201BD), centrifugation for 15 minutes at 5000 rpm (SIGMA 203,43191) and filtration through What man filter paper 1.0. Filtrate had been shade dried at room temperature while next solvent (ethyl acetate, methanol and dist. water respectively) had been added in residue with repetition of previous procedure. Dried filtrate has been re- dissolved in 15 % DMSO to prepare stock solution (100 mg/ ml) (Asma et al.2016).

Animal grouping:

Healthy and disease free albino Wistar rats(300- 400 g)were divided into eight groups (Table 1) (each having half male and half female) in animal house of IMBB, The University of Lahore in standard lab conditions (at 20-26 0C/ 68-78.8 0F, 30%–70% humidity)and fed with standard diet (mixture of 23 % crude protein,3.0% crude fat, 7.0% crude fiber, 8% acid insoluble ash, 1-2.5 % calcium, 0.9% Phosphorus, 0.5-1% sodium and 12% moisture) has been given during the period of whole experiment.

RESULTS AND DISCUSSION

Table 1 Animal groups

Animal groups		Treatments
Control groups	Vehicle	Only normal saline
	Negative/ High fed diet treated	High fed diet treated
	Negative/ Hyperlipidemic	Only 55mg/Kg/b.w. STZ induced
	Positive/ Hypolipidemic	250 mg/Kg/b.w. metformin induced*
Experimental groups (Treated with *C.sinensis* L. leaves extracts @25mg/mL/kg b.w.).	n-HE	n-hexane extract treated*
	EAE	Ethyl acetate extract treated*
	ME	Methanolic extract treated*
	Dwe	Distil. water extract treated*

* Drug and extracts induced after the induction of diabetic hyperlipidemia through 55 mg/Kg/b.w. STZ after STZ induction.

Induction of diabetic hyperlipidemia, plant extracts and Hypolipidemic drug

Before inducing diabetic hyperlipidemia and determining which animals can become diabetic quickly, an OGTT was performed in 8-10 hour fasted rats by administering a 10% glucose solution and measuring blood glucose levels after 0, 30, 60, 90, and 120 minutes. Animals with blood glucose levels greater than 200 mg/dL were considered to develop diabetes (Asma et al., 2016). Rats were produced hyperlipidemic by administering 55mg/kg body weight streptozotocin (STZ) intraperitoneally, followed by oral administration of a 10% glucose solution to minimize STZ's severe hypoglycemia impact (Brian et al., 2021). After STZ induction, rats were given an intraperitoneal injection of 25mg/mL/kg b.w. of n-hexane, ethyl acetate, methanolic, and distilled water extract of C. sinensis L. Leaves (in experimental groups) and 250 mg/mL/kg b.w. metformin (in positive control group) (Zaabi et al., 2021).

25mg/mL/kg b.w. of n-hexane, ethyl acetate, methanolic and Distilled water extract of *C. sinensis* L. leaves (in experimental groups) and 250 mg/mL/kg b.w. metformin (in positive control group) had been injected intraperitoneally in rats

Effect of drugs and plant extracts on hormonal, biochemical and histological profile

Rats were anesthetized using inhalant anesthesia (chloroform and halogenated ether in a closed container for 2 to 3 minutes). After sedation, rats were removed from the container and placed on a slab (pre-cleaned with spirit to avoid skin contamination) before making a small cut in the middle of the abdomen to the snout anteriorly and the genital opening posteriorly by making transverse incisions along the length of the limbs. Blood samples were collected in EDTA and non-EDTA blood vacutainers and centrifuged at 2000 rpm for 5 minutes to separate serum and blood cells for the estimation of urea, creatinine, bilirubin, uric acid, albumin, globulin total protein, A/G ratio, alkaline aminotransferase (ALT), aspartate transferase (AST), and alkaline phosphatase (ALP) using kit methods. Urea, creatinine and uric acid level has been measured by standard method (Bamanikar et al., 2016) Bilirubin level has been examined by using kit method (Jendrassik and Grof, 1938) AST, ALT level has been estimated the by using kit method (Pezeshki et al., 2016), ALP level has been measured by the kit method (Sundaramet al., 2013) and Albumin,

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globulin and A/G ration was measured by the kit method (Yokozawa et al., 2005). Liver and the kidneys were kept in 10% neutral formalin for histological examination at 400 um (Alkiyumi et al. 2012).

Statistical analysis:

The data was analyzed by using Two-Way ANOVA by considering P<0.05 level of significance through GraphPad prism 8.0 while results has been expressed as± SEM.

RESULTS

Plant has been identified by the botanical number of GC.Herb.Bot.3779.

Analysis of biochemical and hormonal profile of animals

Male rats in the negative control group had the same creatinine content (0.7±0.1 mg/dL) as those in the vehicle group (0.63±0.08 and 0.8±0.2 mg/dL), but it decreased when compared to animals in the high-fed group (1.5±0.2 and 2.8±0.1 mg/dL). Male rats in the positive control group had lower creatinine (0.56±0.06 mg/dL), while females had higher levels (2.8±0.1 and 0.7±0.1 mg/dL) compared to vehicle rats,methanolic (45.3±3 and 33.6±3 mg/dL respectively), ethyl acetate (68±0 and 41.6±0.06 mg/dL) and distilled water (48.6±4 and 34±0 mg/dL respectively) extracts of *C.sinensis* (L.) as compared to positive control group (Figure 1a).

Male rats in the negative control group had the same creatinine content (0.7±0.1 mg/dL) as those in the vehicle group (0.63±0.08 and 0.8±0.2 mg/dL), but it decreased when compared to animals in the high-fed group (1.5±0.2 and 2.8±0.1 mg/dL). Male rats in the positive control group had lower creatinine (0.56±0.06 mg/dL), while females had higher levels (2.8±0.1 and 0.7±0.1 mg/dL) compared to vehicle rats. Creatinine levels of both male and female rats treated with n-hexane (0.7±0.1 mg/dL and 2±0 mg/dL respectively), methanolic (1.9±0.06and 0.8±0.2 mg/dL respectively) and distilled water extract (0.63±0.1 and females 0.8±0.2 mg/dL respectively) extracts of *C.sinensis* (L.) leaves has been decreased as compared to the negative control group (Figure 1, b).

Males and females in the vehicle group had lowest urea content (1.6±0.1 and 1.8±0.1 mg/dL, respectively) compared to animals in the negative control group (3.03±0 and 3±0 mg/dL, respectively) and the high fed diet group (2.16±0.1 and 2.83±0.16 mg/dL, respectively), while it was nearly similar to animals in the positive control group (1.5±0.26 and 1.33±0.16 mg/dL, respectively) and n-hexane extract treated group (1.7±0.1 and 1.6±0.4 mg/dL respectively). Least value of uric acid was observed in male and female rats treated with the methanolic (1.8±0.3 and1±0.05 mg/dL respectively) and distilled water extracts (1.26±0.1 and 1.16±0.1 mg/dL) (Figure 1, c).

Statistically analyzed results showed that bilirubin that the negative control group's male and female bilirubin levels increased (2.3±0.1 and 2.6±0.2 mg/dL, respectively) compared to the vehicle (0.2±0 and 1.6±0 mg/dL). Males and females in the positive control group had higher levels (1.6±0 and 1.1±0 mg/dL, respectively), while animals on a high-fed diet had lower levels (1.83±0.1 and 2.2±0.05 mg/dL, respectively) compared to the vehicle. Bilirubin levels in males and females treated with n-hexane (0.13±0.02 mg/dL and 0.13±0.03 mg/dL, respectively), methanolic (1.33±0.1 and 1.7±1 mg/dL, respectively), ethyl acetate (0.13±0.03 and 0.36±0.1 mg/dL, respectively), and distilled water (0.16±0.03 and 0.53±0.2 mg/dL, respectively) extracts of *C.sinensis* (L.) leaves has been decreased more prominently as compared to a positive control group (Figure 1, d).

Albumin content was same in both males and females of high fed diet treated group (2.66±0.3 and 3.76±0.1 respectively), hyperlipidemic (2.9±0.5 and 3.36±4 g/dL respectively) and hypolipidemic (2.6±0.3 and 3.7±0.2g/dL respectively) control groups and it was also same in animals treated with n-Hexane (2.6±0.1 and 3.06±0.08 g/dL respectively), ethyl acetate (2.3±0.2 and 2.4±0 g/dL respectively), methanolic (2.6±0.2 and 2.7±0.1g/dL respectively) and distilled water (2.4±0.1 and 2.8±0.2g/dL respectively) extracts of *C.sinensis* (L.) leaves (Figure 1, h).

Statistical analysis of globulin content showed that it spiked minutely in both males and females rats treated with high fed diet (2.6±0.1 and 1.8±0.1 g/dL respectively), methanolic (3.3±0 and 2.3±0.1 g/dL respectively) and distilled water (3.2±0.1 and2.7±0.05 g/dL respectively) extracts of *C.sinensis* (L.) leaves and decreased in rats treated with nHexane (2.8±0.06 and 2.7±0.06 g/dL respectively) and ethyl acetate (2.4±0.1 and 2.3±0.2 g/dL respectively) extracts of *C.sinensis* (L.) leaves and these results were significantly similar to that of hyperlipidemic (1.03±0.03 and 2.4±0.2g/dL respectively) and positive (1.8±0.2and1.7±0.1g/dL respectively) control groups as compared to vehicle (2±0.05and2.06±0.2g/dL respectively)(Figure 1, i).

After statistical analysis of total protein content, results showed that protein level of males and females in negative control (6.56±7and 6.46±.2 mg/dL respectively) has been significantly increased as compared to vehicle (6±0 and5.16±0 mg/dL respectively) and it slightly elevated in rats treated with high fed diet (6.16±0.4 and5.23±0.1 mg/dL respectively) and in positive control group

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(6.56±7and 6.46±.2 mg/dL respectively). But it has been decreased significantly in rats treated with n-Hexane (5.53±0.3 and 3.76±0.1 mg/dL respectively), ethyl acetate (4.33±0.3 and 5.83±2 mg/dL respectively), methanolic (5.93±0.3 and 5.96±0.6 mg/dL respectively) and Distilled water (5.63±0.2 and 5.1±0.1 mg/dL respectively) extracts of *C.sinensis* (L.) (Figure 1, j).

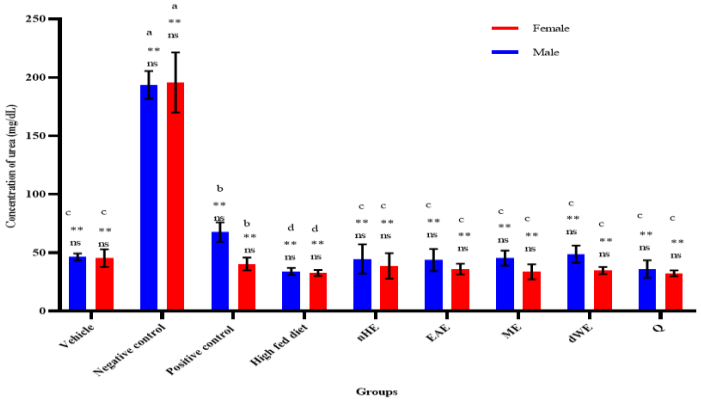
Statistically analyzed results of A/G ratio showed A/G ratio of males and females treated with high fed diet (1.23±0.03 and 1.33±0.03 % respectively) has been increased as compared to vehicle (1.26±0.1 and 1.4±0.2 % respectively), and slightly decreased in hyperlipidemic (1.1±0.1 and 1.1±0.08 % respectively) and positive control(1.1±0.5 and1.1±0.09 % respectively) groups, while it has been decreased significantly in rats treated with n-Hexane(1.1±3 and 1.03±0.03 % respectively), ethyl acetate (1.02±0.01and1.06±0.02 % respectively), methanolic (1.02±0.01and1.06±0.02 % respectively) and distilled water (1.04±0.02 and 1.23±0.6 % respectively) extracts of *C.sinensis* (L.) leaves has as compared to the negative control group(Figure 1, k).

Concentration of enzymes in animals

Statistically observed results showed that AST level in both males and females of high fed diet treated group (63±1 and 73±3 U/L respectively), hyperlipidemic control (72.3±2 and77±2 U/L respectively) and anti-hyperlipidemic control (88.4±1 and 94±2 U/L respectively) has been increased as compared to vehicle (40±0.5 and 43±2 U/L respectively), while its levels in male and females rats treated with n-Hexane (41.3±1 and 33.3±7U/L respectively), ethyl acetate (32.6±1 and 40±0.5U/L respectively), methanolic (28.6±4 and 27±3U/L respectively) and distilled water (44±2 and 35.5±4U/L respectively)extracts of *C.sinensis* (L.) leaves has been decreased as compared to positive control group(Figure 1, e).

ALT content in both males and females animals of high fed diet treated group (63±1 and 73±3 U/L respectively), hyperlipidemic (72.3±2 and 77±2 U/L respectively) and positive control (88.4±1 and 94±2U/L respectively) has been increased as compared to vehicle (40±0.5 and 43±2U/L respectively), while it has been decreased in male and females rats treated with n-Hexane (41.3±1 and 33.3±7U/L respectively), ethyl acetate (32.6±1 and 40±0.5 U/L respectively), methanolic (28.6±4 and 27±3U/L respectively) and distilled water (44±2 and 35.5±4 U/L respectively) extracts of *C.sinensis* (L.) leaves as compared to positive control group(Figure 1, f).

Statistically analyzed results of ALP content showed that in both males and females of rats treated with high fed diet (108.3±1 and 122.3±2U/L respectively) has been decreased as compared to vehicles (111±5 and 128±4U/L respectively) and but still it was more than the animals in negative (95±3 and89±1 U/L respectively) and positive control (95.4±2 and104±3 U/L respectively) groups. n-Hexane extract of *C.sinensis* (L.) leaves has decreased ALP content (98±8 and127±3 U/L respectively) as compared to the negative control group, while rats treated with ethyl acetate (147.3± 4 and118±4 U/L respectively), methanolic (128.6±4 and 27±3 U/L respectively) and distilled water (106.6±4 and119±1 U/L respectively) has elevated levels of ALP as compared to vehicle (Figure 1, g).



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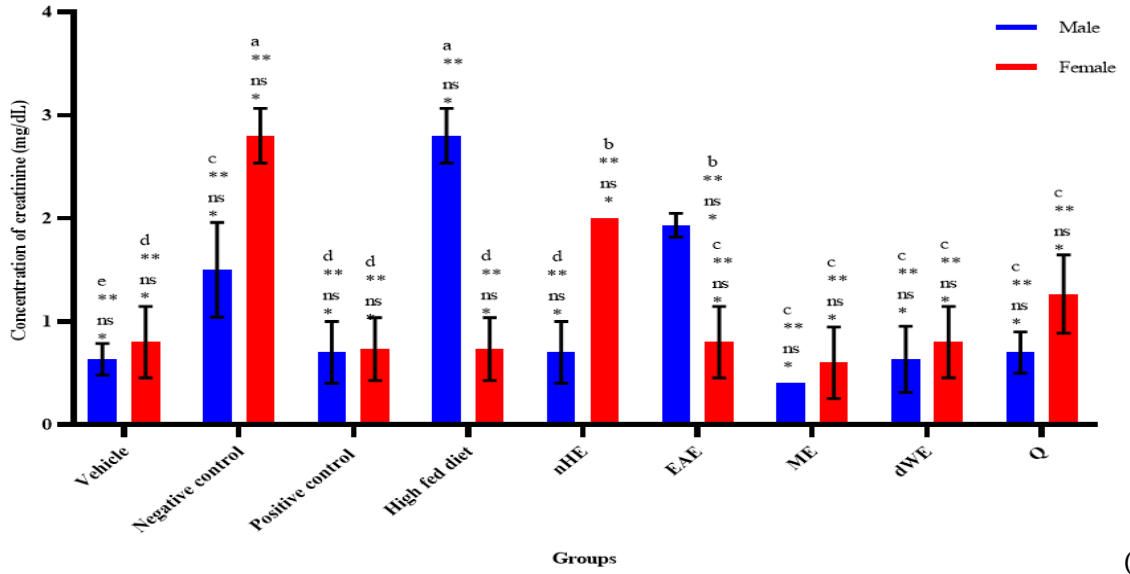

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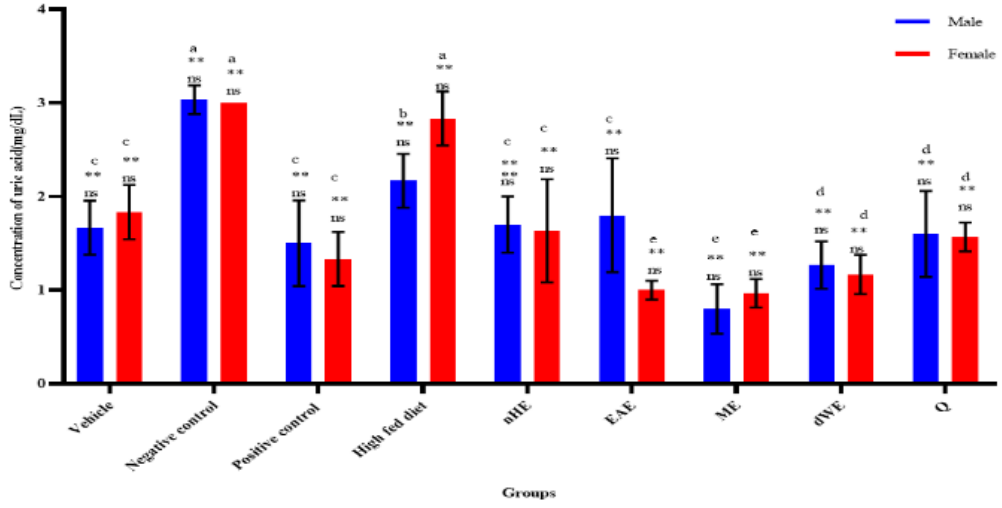

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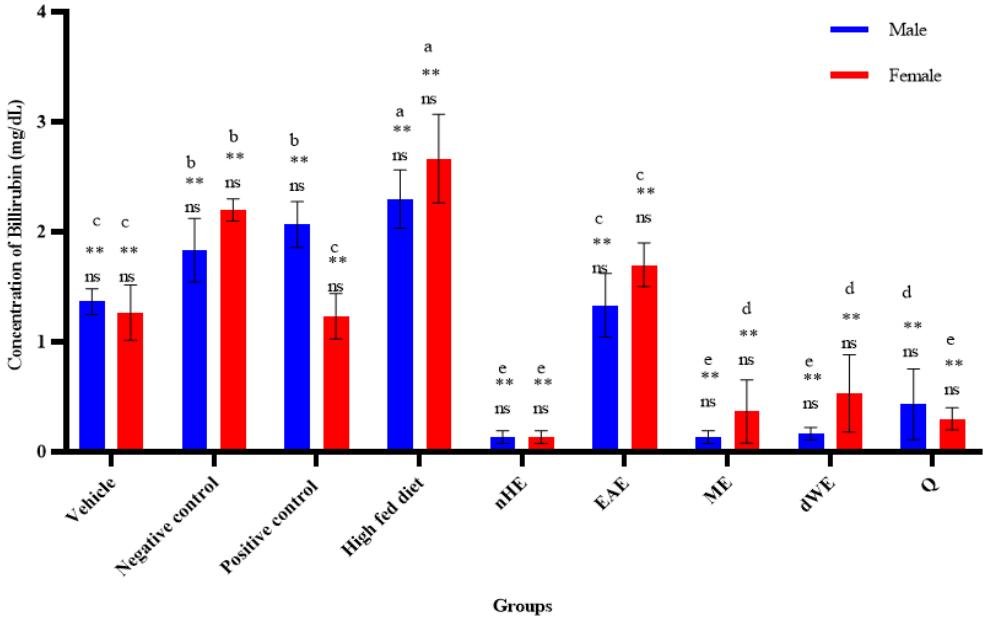

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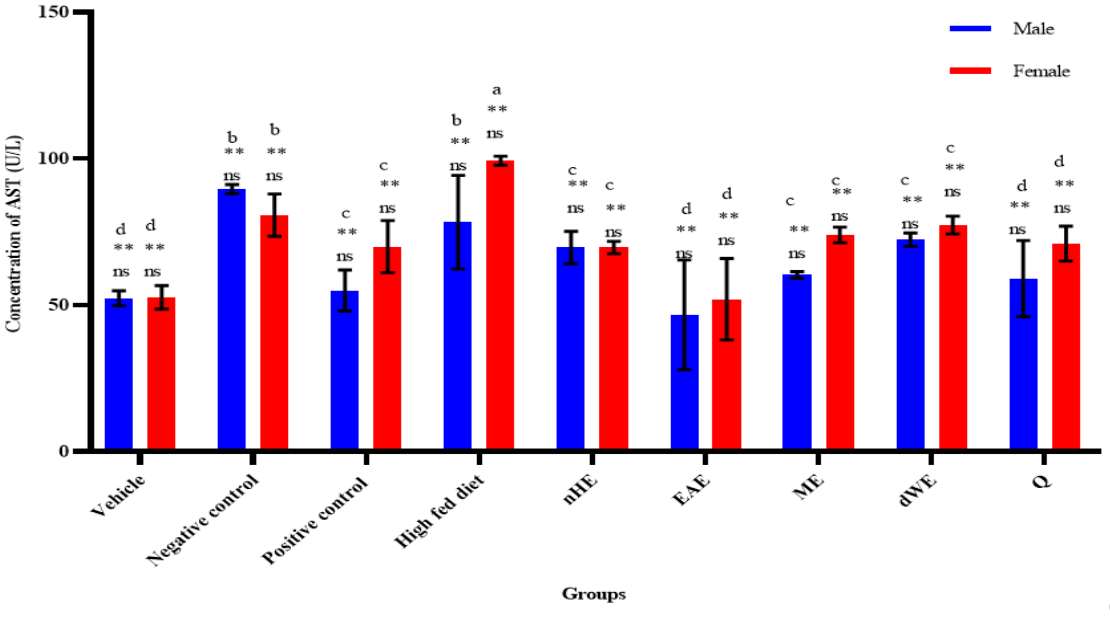

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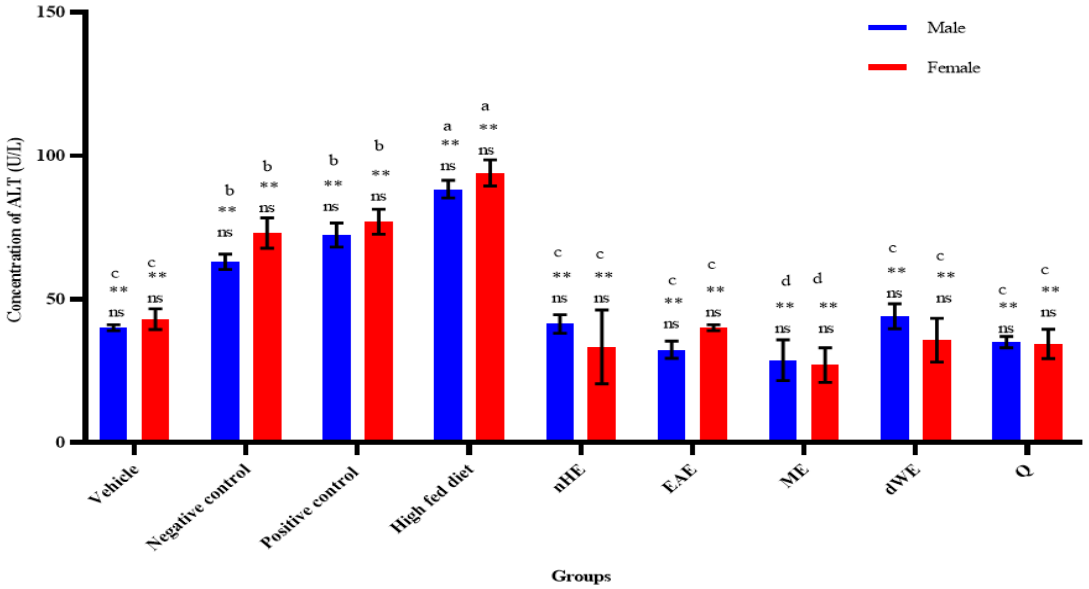

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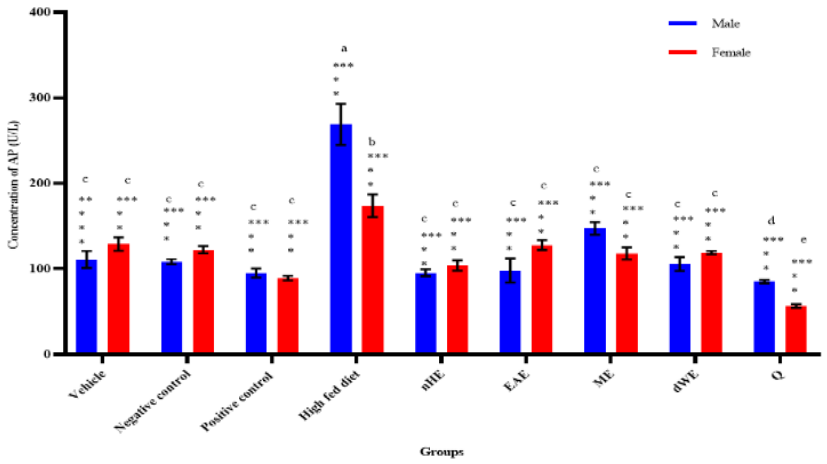

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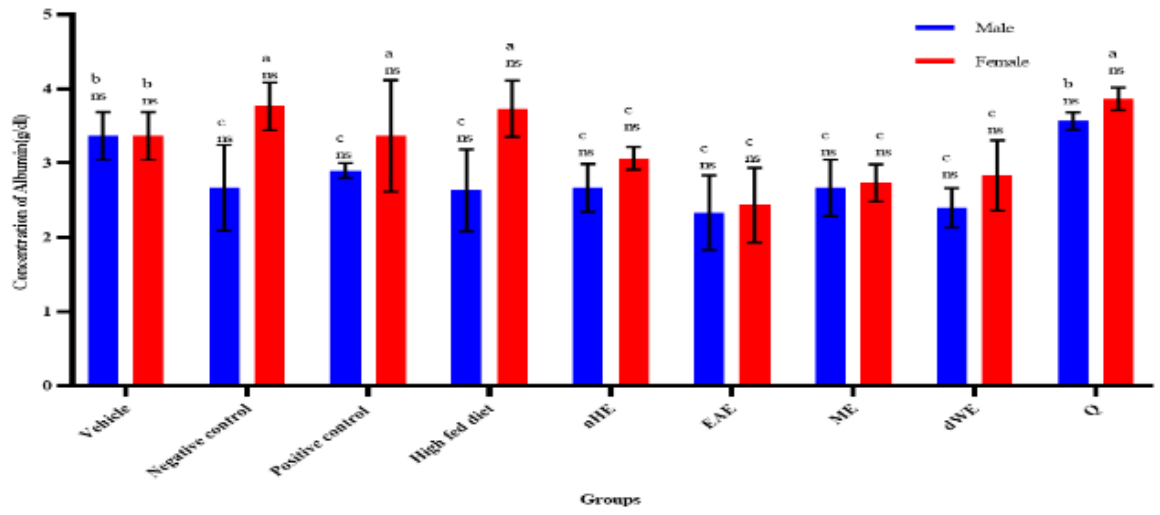

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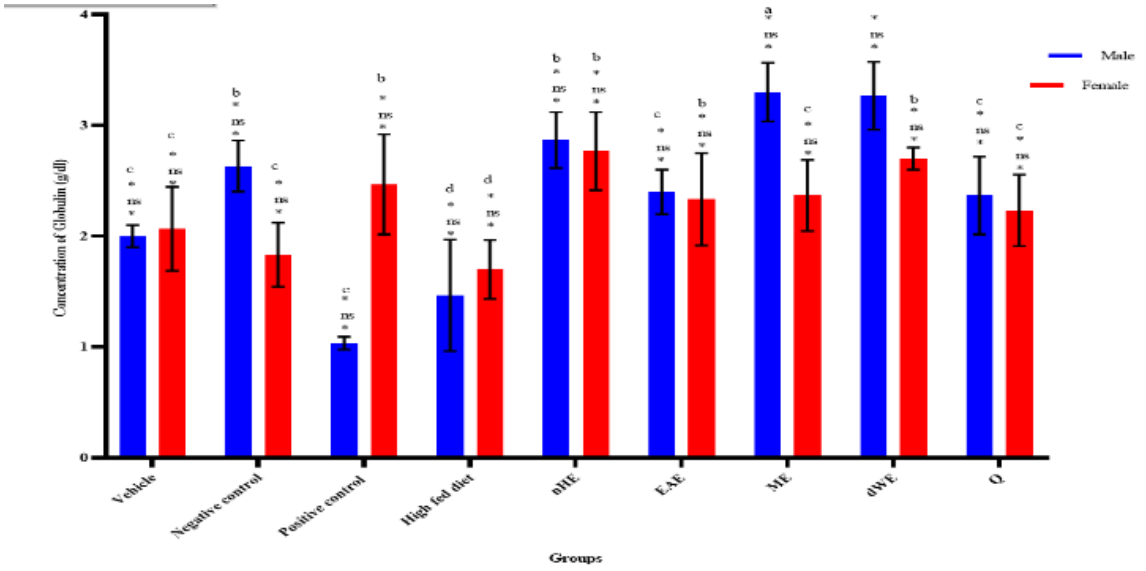

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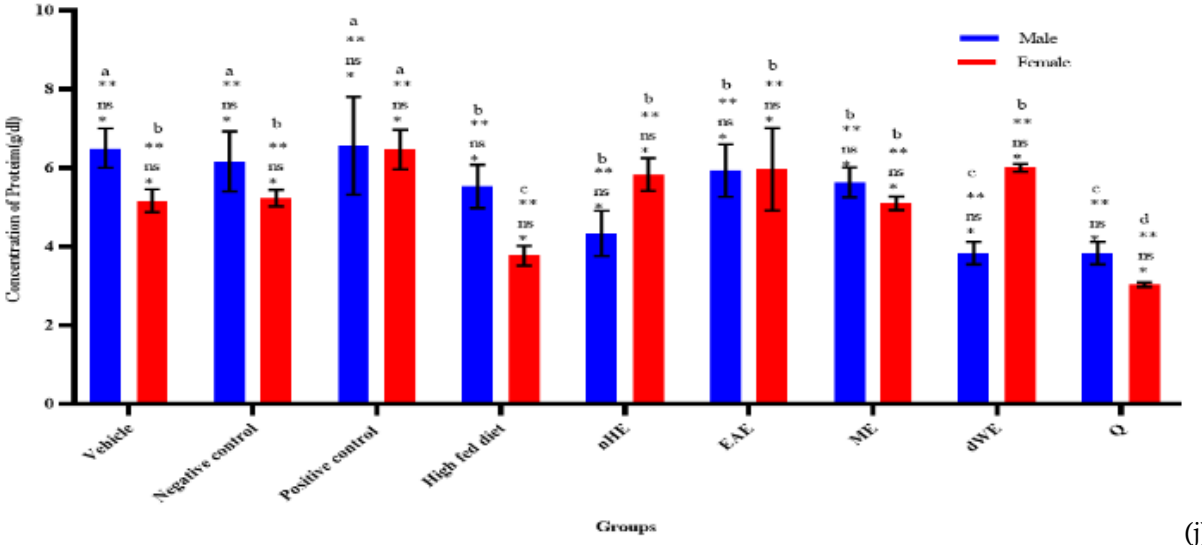

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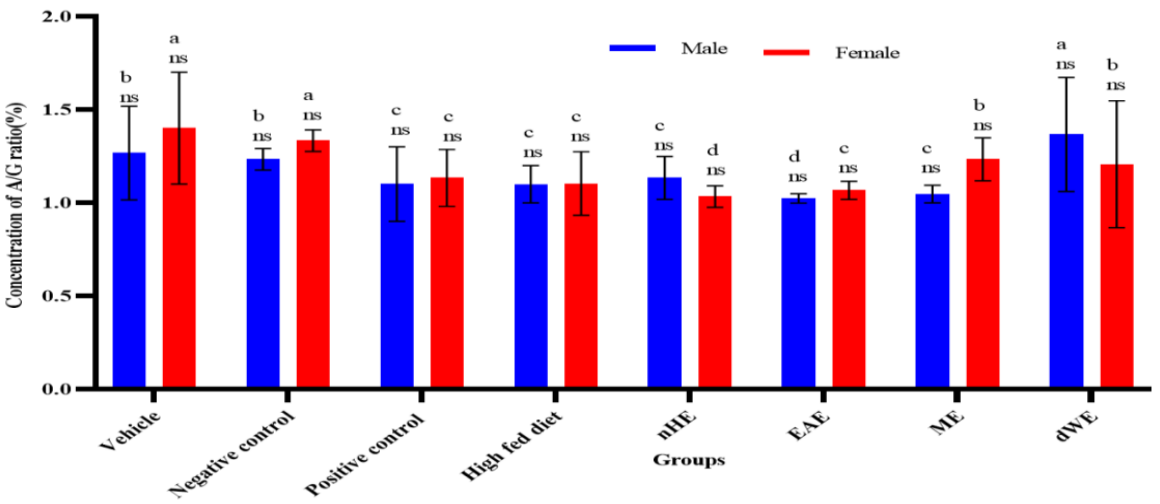

(k)

Figure 1: Concentration of urea (a), creatinine (b),uric acid (c), bilirubin (d), AST (e), ALT (f), ALP (g), albumin (h), globulin (i), total protein (j) and A/G ratio (k) in albino Wistar rats HFD= high fed diet, nHE=-n-Hexane extract, EAE= ethyl acetate extract, ME= Methanolic extract, dWE= distilled water extract. a-e =Comparison of animal groups from most significant results to less significant. Highly significant ***= P- 0.0001, Most significant**= P<0.01(0.0010-0.0092), Significant*= P<0.05(0.0392-0.0471), ns=nonsignificant

Histopathological profile of renal and hepatic tissues

In the vehicle control group, histological characteristics of renal tissue revealed normal glomerular and tubular structure, while vascular bleeding, congestion, hyperplasia, and edema were unremarkable. Renal tissues in the high-fed diet group showed modest blood vessel dilatation and increased space in the Bowman capsule. There was an infiltration of mononuclear cells, as well as enhanced glomerular sclerosis and connective tissue in a small number of segments. The hyperlipidemic control group had aberrant kidney structure in the form of mesangial cell growth with dilated glomerular blood capillaries, but the primary pathology was tubular regeneration. The positive/hypolipidemic group recovered pathological abnormalities in a few portions of renal tissue. The n-hexane extract-treated group exhibited intact renal tissue architecture in all segments. Congestion and severe chronic inflammation was present in all segments, while Glomeruli were unremarkable, and necrosis was also present. No RBCs and no sign of chronic pyelonephritis in any segments have been observed. Ethyl acetate extract treated group showed intact architecture of renal tissues, with congestion and chronic inflammation in all renal segments. Glomeruli were unremarkable and necrosis, RBCs casts and signs of chronic pyelonephritis were absent. Methanolic extract treated kidney cells were found with intact architecture, with the presence of congestion and chronic inflammation in all renal segments. Glomeruli were unremarkable, while necrosis was absent. RBCs casts and sign of chronic pyelonephritis were also present. In rats treated with distilled water extract showed presence of congestion and chronic inflammation, with unremarkable glomeruli and necrosis, while RBCs casts and signs of chronic pyelonephritis were present (Figure 2 A).

In vehicle, histological aspects of hepatic tissue revealed normal lobular structure, whereas fatty alterations, sinusoidal dilatation, chronic venous congestion, and lobule fragments remained unremarkable. Hepatic tissues in the high-fed diet treated group exhibited usual liver steatosis with lipid droplets, however in the negative/hyperlipidemic control group, aberrant disruption in the radiating pattern of hepatocyte cords was detected. Hepatocytes revealed degeneration with loss of architecture and cytoplasmic vacuolation, while nuclei were diverse in form and size, with blood vessel hemorrhages in several hepatic segments. Hepatic tissue from the positive/hypolipidemic group revealed a disruption in the radiating pattern of the hepatocyte cord, but with less cytoplasmic vacuolation and fatty alterations as compared to the solely STZ treated group, which showed modest pathological recovery with no vascular hemorrhage. The n-hexane extract-treated hepatic tissues showed intact liver cell architecture, mild venous congestion, and chronic inflammation.Necrosis was absent while central vein dilation, hemorrhage, and microvascular steatosis were present. Ethyl acetate extract treated hepatic tissue showed intact architecture of liver cells, moderate venous congestion, while chronic inflammation, necrosis, central vein dilation, hemorrhage, and microvascular steatosis were not seen. Methanolic extract treated hepatic tissue showed intact architecture of hepatic tissues, with the presence of central vein dilation, severe hemorrhage, and microvascular steatosis. Distilled water extract treated hepatic tissue showed partly intact architecture of hepatic tissues, with moderate venous congestion, mild chronic inflammation and necrosis, presence of central vein dilation and hemorrhage, while microvascular steatosis was absent (Figure 2 A).

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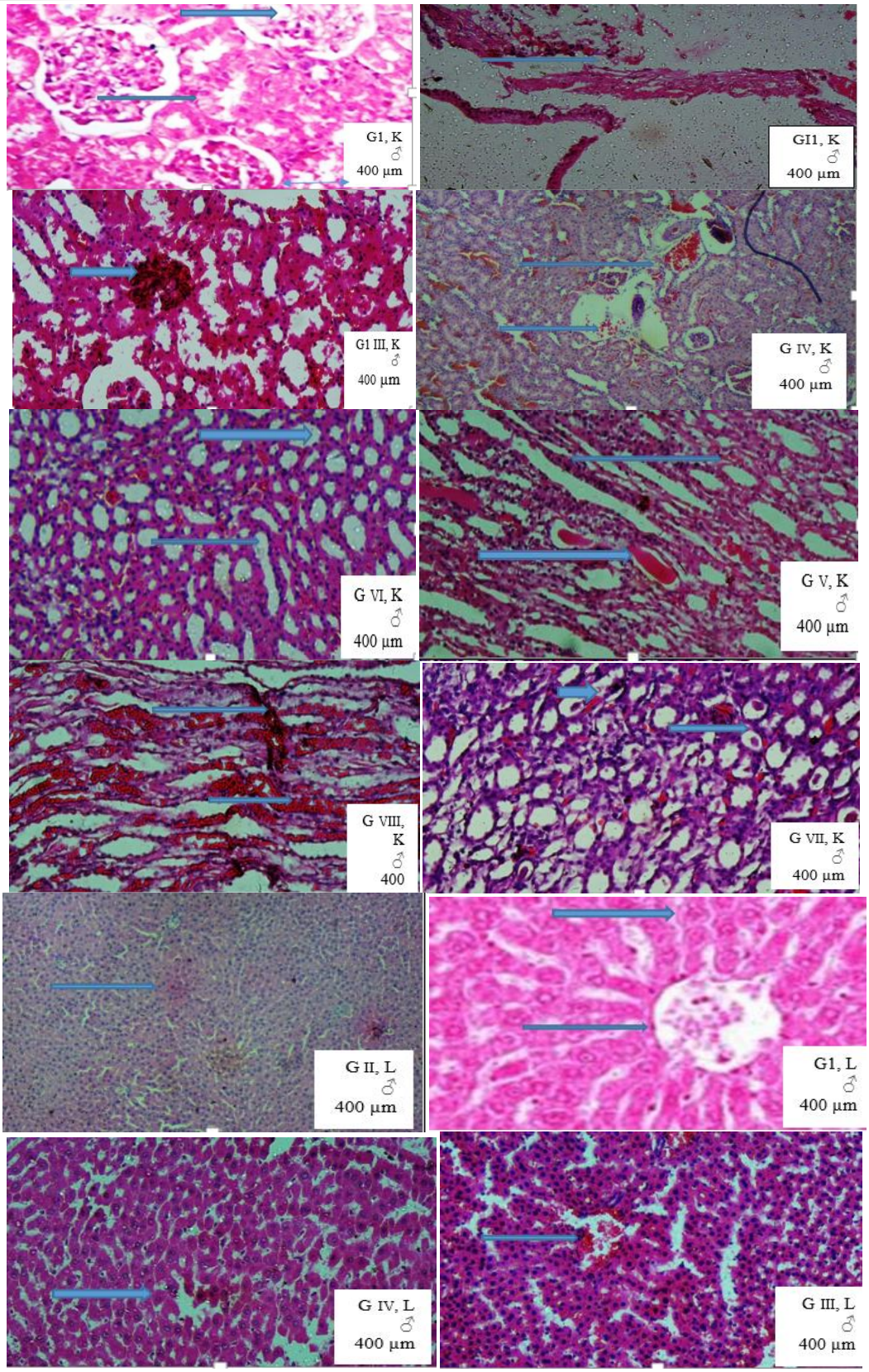

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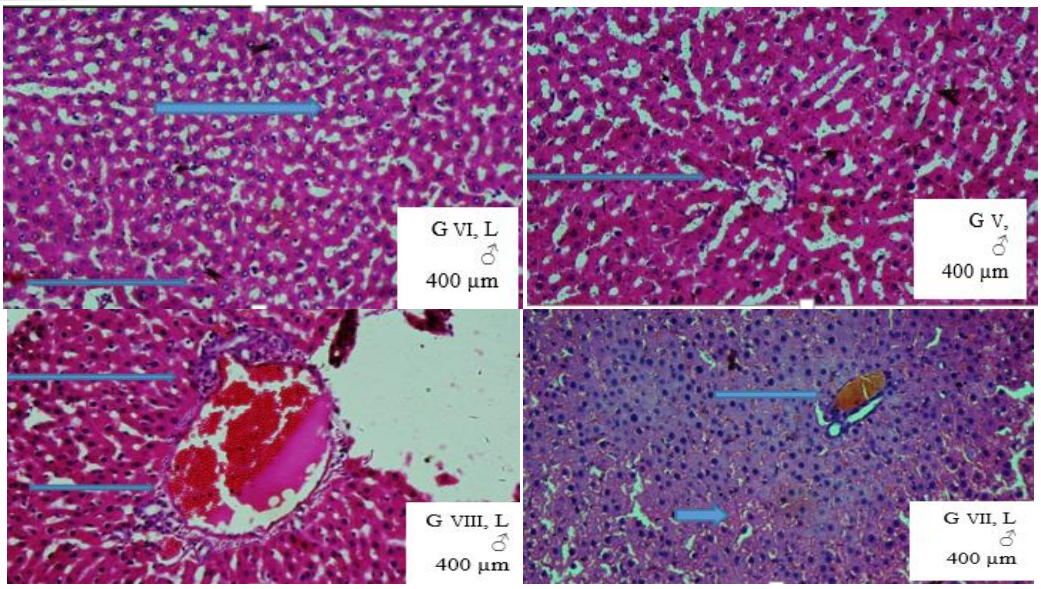

Figure 2: Histological Features Kidney/ Renal (K) and Liver/ Hepatic (L) Tissues of at400 µm. G I= Vehicle, G II= High fed diet group, G III= Negative control group, G IV= Positive control group, G V= Rats treated with n-hexane extract of *C.sinensis* (L.) leaves, G VI= Methanolic extract of *C.sinensis* (L.) leaves, G VII= Ethyl acetate extract of *C.sinensis* (L.) leaves, G VIII= Distilled water extract of *C.sinensis* (L.) leaves. ♂ = Male, ♀= Female

Liver and kidney diseases are most common diseases in world. Currently available medications are not organo-protective as compared to natural products. *C.sinensis* (L.) is most used as a drink as green or black tea and have many health-preserving properties. Extracts of *C. sinensis* (L.) have been used as an herbal medication in the treatment of many diseases. Safety and tolerability of long-term use of *C. sinensis* (L.) extracts have been well defined. Hepato and nephro toxicity due to diabetic hyperlipidemiais considered a good model for the study of effects of synthetic and natural drugs on liver and kidney as streptozotocin (STZ) causes destruction of liver and kidney cells (Rezagholizadehet al.2016).

Nephropathy developed by long-term hyperglycemia, while liver failure develops by long term complications of hyperlipidemia and other metabolic disorders of the liver. STZ induced toxicity of organ lead to many complications over a period of time such as hepatopathy, nephropathy and hyperglycemia, while protective effects of *C. sinensis* (L.) extracts in STZ-induced rats on the liver and kidney are due to its anti-oxidant and anti-inflammatory properties by affecting the genes expressions of CAT, GPX1, MT-I, MT-II, SOD-I, SOD-II, and SOD-III genes (Al-Awaida et al,2019). Moreover, polarity-based *C. sinensis* (L.) extracts reduced the levels of serum creatinine and ALT, without affecting other parameters due to MDA(Malondialdehyde), SOD (superoxide dismutase, and GSH (glutathione hydrogenase) (Opuwari ET AL. 2020). *C. sinensis* (L.) leaves contain anti-oxidant and anti-inflammatory properties and it by affecting the genes expressions of CAT(catalase), GPX1(glutathione peroxidase 1), MT-I and II (mitochondrial encoded gene 1 and II) (Ziamajidi et al. 2017).Therefore *C.sinensis* leaves is probably an effective agent for treatment of liver and kidney diseases, which are attributed to phytocompounds identified in *C.sinensis* .(L.) (Figure 3).

Compounds					
IUPAC names	Methylxanthines	Bempedoic acid	Theobromine	Theophylline	Kampherol
Molecular formula	$C_{19}H_{36}O_5$	$C_7H_8O_4$	$C_7H_8N_4O_2$	$C_7H_8N_4O_2$	$C_{15}H_{10}O_6$
Molecular Weight	152	349.51	180.16	180.17	286
Pubchem ID	70639	150503445	5429	2153	5280863
Compounds					
IUPAC names	Protocatechuic acid	Ferulic acid	Diabasic acid	Vanillic acid	Quercetin
Molecular formula	$C_7H_6O_4$	$C_{10}H_{10}O_4$	$C_{28}H_{31}ClN_2O_3$	$C_8H_8O_4$	$C_{15}H_{10}O_7$
Molecular Weight	154	194	479	168	302
Pubchem ID	72	445858	6694	8468	5280343

Figure 3: Phytocompounds of *C.sinensis* (L.) with their physiochemical properties

Therapeutic potential of *C.sinensis* (L.) is attributed to active chemical constituents such as glycosides, terpenoids and steroids, flavonoids, reducing sugars, tannins 3-4% of alkaloids ormethylxanthines (caffeine, theobromine, and theophylline), phenolic acids (gallic acid and chlorogenic acids), characteristic/ essential amino acids (glycine,

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serine, valine, leucine, threonine, andtheanine), polyphenols (flavanols, flavandiols), flavonoids(quercetin, kaempferol, myricetin), proanthocyanidins (prodelphinidin), polysaccharides, vitamins (B, C, E), minerals and trace elements (calcium, magnesium, manganese, copper, zinc, selenium, potassium)(Rishi et al., 2018). Thea Flavin plays an important role in the expression of pancreatic lipase which is the main enzyme involved in obesity and deranged lipid metabolism by regulating AMPK–FoxO3A– Mn-SOD pathway in 3 T3-L1 adipocytes (Lijun et al.,2016).Phenolic compounds constitute 30% of total dry weight, which includes Epigallocatechin (EGC) (19%), Epicatechin–3–gallate (ECG) (13.6%), Epicatechin (EC) (6.4%) (Waheed et al., 2020) (Figure 4).

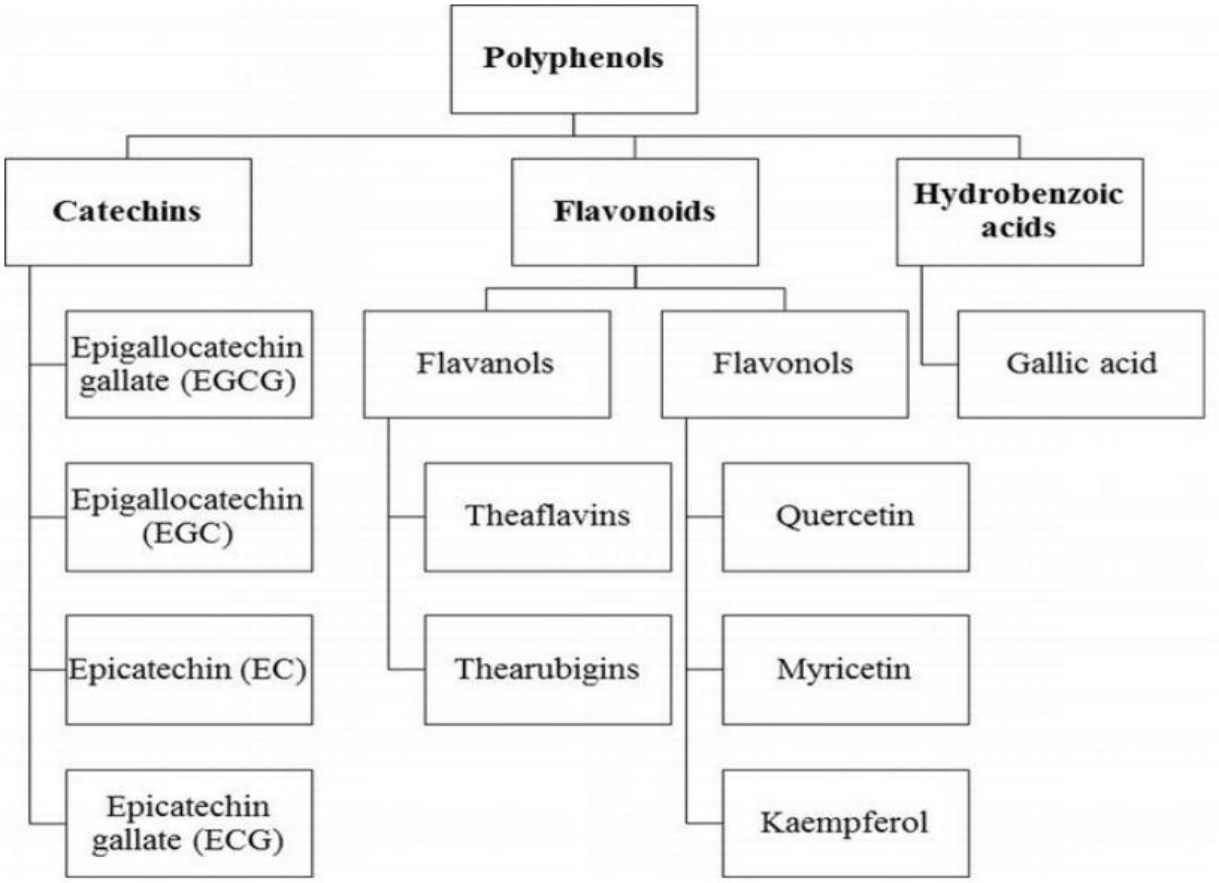

Figure 4: The main hypolipidemic, hypoglycemic hepato and nephro protective components of *C. sinensis* (L.) (Ali I., 2017)

Streptozotocin induces diabetes and has toxic effects on beta cells of pancreas, thus it decreases insulin levels and causes hyperglycemia and chronic hyperglycemia, with impaired function of kidney and liver (Giri et al. 2018). In current study diabetic control rats showed significant effects on urea, uric acid, creatinine, bilirubin, AST, ALT, ALP and globulin and strongly effected alkaline phosphate, but doesn't showed any effects on albumin and A/G ratio and similar results have been reported in previous studies (Chawla et al. 2016, Duwaerts and Maher 2019, Meng et al. 2019).Metformin can decrease glucose production from hepatocytes (Proks et al. 2018) and also stimulates beta cells to bind to the sulfonylurea receptor-1 and block the ATP-sensitive channels that stimulates the release of insulin from pancreatic b-cells (Pandarekandy et al. 2017).Alcoholic green tea extracts significantly improved hepatorenal syndrome in rats, as all biochemical parameters of HRS (hepatorenal syndrome) were controlled except for ACE1(angiotensin converting enzyme inhibitor-1) and creatinine clearance, which showed significant reduction (Youssef et al 2019).Flavonoids of green tea extracts inhibit glucose absorption by inhibiting glucosidase activity and by stimulating glucose transporter 4 (GLUT4) which stimulate glucose uptake in muscle and cause hypoglycemic effects (Ueda-Wakagi et al. 2019). Epigallo catechingallate (EGCG) effects by inhibiting inflammatory factors and reducing ROS in vitro (Pastoriza et al. 2017). Another study showed that combined treatment of *C.sinensis* (L.) extracts and metformin had a potent synergitic effects on hepato renal complication of diabetes (Duwaerts and Maher 2019) (Figure 5).

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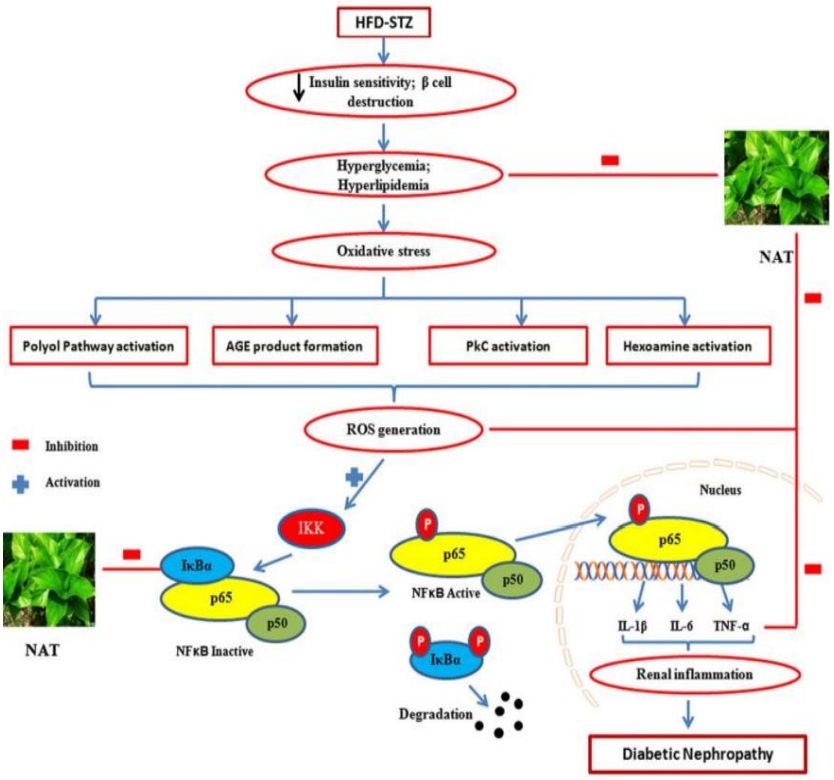

Figure 5: Mechanism of action of STZ and HFD in the development of ROS generation (Mousum et al., 2018)

In this study urea in blood and serum creatinine failed to indicate substantial improvement with metformin therapy , nevertheless they showed a greater decrease after treatment with plant extracts as several hepato-renal pathological changes were seen in the diabetic control group. These extracts decreased diabetic complications by hindering advanced glycation end product (AGE) formation and cutting (Zhu et al. 2014). EGCG and epicatechin gallate in the extracts may be responsible for improving the thickness of the basement membrane by easing the damage caused by matrix metalloproteinase, which could breakdown extracellular matrix and fibrosis(Sarkar et al. 2016; Yazdi et al. 2019). In histopathological examination of diabetic control group, disruption in the radiating pattern of hepatocyte cords, fatty degeneration of hepatocytes with heterogeneous nuclei were detected, which have already been reported in the identical manner (Asokan et al. 2019), and these changes were incompletely improved in all extracts treated groups , which might be due to the improvement of liver inflammation and decrease in oxidative stress due to levels of malondialdehyde and glutathione (Caro-Ordieres et al. 2020).

CONCLUSION

Streptozotocin caused organ toxicity of kidney and liver and led them to work abnormally. AST, ALT, ALP serum creatinine, urea and uric acid contents showed that n-Hexane, ethyl acetate, methanolic and distilled water extracts of C. sinensis (L.) leaves had averystrong organo-protective effects, which might be due to their antioxidant properties, thus may lead to improvement in hepato-renal protection.

COMPETING INTREST

Authors have declared that no competing interest exists.

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