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ANTI-NEPHROTOXIC AND ANTI-HYPERLIPIDAEMIC POTENTIALS OF AQUEOUS EXTRACTS OF TURMERIC (*CURCUMA LONGA*) IN HYPERCHOLESTEROLAEMIC ALBINO RAT.

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Abstract

We evaluated the nephroprotective and antihyperlipidaemic effects of aqueous extract of *Curcuma longa* (AECL) in hypercholesterolaemic male albino rats. Twenty (20) rats were randomly grouped into four groups: A, B, C and D of five animals per group. Groups A, B and C received high cholesterol diet (2000mg/kg, oral) and carbimazole (60mg/kg, oral) once daily for six weeks. Group A served as toxic (negative) control. Group B (positive control) was treated with a standard lipid lowering drug (Atorvastatin, 20mg/kg). Group C served as treatment group and received daily dose of AECL (200mg/kg). Group D served as normal control and received no treatment. After the six weeks of administration, serum lipid profile and renal biochemical parameters; and MDA level and SOD activity in kidney homogenates were measured. The harvested kidneys of the experimental rats were also used for histopathological studies. Biochemical and histopathological results show that AECL induced hypolipidaemia, stabilized renal biochemical parameters ($p<0.05$ or $p<0.01$); and protected the kidney tissue from oxidative stress injuries. The results of the present study suggest that the extract has nephroprotective and antihyperlipidaemic effects, and can be used to prevent hypercholesterolaemia-induced nephrotoxicity.

Keywords: *ethnopharmacology, Curcuma longa, antihyperlipidaemia, nephroprotection*

Introduction

Hypercholesterolaemia and hyperlipidaemia, are pathologic factors contributing to atherosclerosis (1, 2), and are also emerging as risk factors for progression of renal disease and coronary heart disease (CHD) (3). Hypercholesterolaemia increases oxidative stress and elicit vascular endothelial dysfunction, which may in turn intensify renal cellular injury, apoptosis, and interstitial fibrosis (4).

The high levels of cholesterol particularly LDL cholesterol are mainly responsible for the onset of CHDs. Lowering lipids and cholesterol levels by a drug or dietary interventions could reduce the risk of CHD. Current interest in natural products has stimulated the search for new cholesterol-lowering agents from this source. Many herbal or plant products were reported to have a potential to reduce lipid and cholesterol in the body.

It has been reported that rats with hypercholesterolaemia are prompt to the development of chronic renal complications (5). Thus investigation into the prevention and treatment of abnormal cholesterol levels, heart injury or renal complications, with a simple and common medicinal plant like *Curcuma longa*, is an important step in maintaining optimum health.

Hypothyroidism has widely been established to cause hypercholesterolaemia, which will raise the risk for CHD by many times, with resultant renal complications. Excessive use of the anti-thyroid hormone drug, carbimazole could not only lead to hypercholesterolaemia but also cause oxidative stress on organs and tissues, including the kidney (5).

Therefore there is need to evaluate medicinal plants for possible lipid-lowering activity, since they are less toxic than orthodox drugs and also harmonize with the body system quite well. There is currently no literature on the effects of Turmeric against hypercholesterolaemia-induced nephrotoxicity. The aims of this research were to evaluate the antihyperlipidaemic and renoprotective effects of aqueous extract of *curcuma longa* in hypercholesterolaemic rats.

Materials and Methods

Collection and authentication of Tumeric

Fresh samples of tumeric (*Curcuma longa*) were obtained from Akwatta, a local market in Enugu, Nigeria. The plant material was authenticated by a consultant taxonomist at the herbarium section of the Department of Plant Science and Biotechnology, University of Nigeria, Nsukka, and a voucher specimen was deposited at the herbarium with reference number for future reference.

Preparation of aqueous extract of Tumeric.

Preparation as described by Al-Taee *et al*. (6) was done, with slight modification. Briefly, water extraction of turmeric was prepared by boiling 100gm in 1000ml distilled water over low flame for 15 minutes, using a heat-stable flask. The content of the flask was allowed to cool for 20 minutes. After cooling, the content of the flask was sieved using clean muslin cloth and filtered with Whatman No.1 filter paper. The filtrate was used to prepare the required concentration.

Acute toxicity test (LD50)

This was performed on mice and the Lorke (7) procedure of LD50 determination was used.

Phytochemical Analysis of tumeric

Preliminary phytochemical screening of tumeric (*curcuma longa*) for the presence of glycosides, flavonoids, saponins, steroids, tannins, carbohydrates, proteins and terpenoids was carried out at Department of Pharmacognosy, Faculty of Pharmaceutical Science, University of Nigeria Nsukka. Procedures outlined by Trease and Evans (8) were employed for the analyses.

Reagents and solutions

Preparation of high-cholesterol diet (HCD)

A mixture of 75g of commercially available cholesterol powder and 9g of sodium deoxycholate (bile salt added to increase bioavailability) was dissolved in coconut oil and made up with the same solvent to 300ml to give a stock concentration of 250mg/ml.

Preparation of carbimazole solution

One hundred (100) tablets of 5mg (i.e. 500mg) carbimazole obtained from hovid® Inc., Malaysia were ground to powder, dissolved in distilled water and made up to 250ml in a measuring cylinder to give a stock concentration of 2mg/ml.

Preparation of atorvastatin solution

Ten (10) tablets of 10mg (i.e. 100mg) atorvastatin obtained from *pfizer*® Inc., New York, USA were ground to powder, dissolved in distilled water and made up to 50ml mark in a volumetric flask to give a stock concentration of 2mg/ml.

Induction of hyperlipidaemia and nephrotoxicity

Each experimental rat was co-administered with high cholesterol diet (HCD) at the dose of 2000mg/kg and high dose of 60mg/kg carbimazole solution through an oral gauge every morning for six weeks.

Experimental animals

Twenty (20) apparently healthy adult male albino rats about three (3) months old were used for the research. They were obtained from the animal house of the college of medicine, University of Nigeria Teaching Hospital (UNTH) Enugu. The rats were divided into four (4) groups. Groups: A, B, C and D, of five (5) rats per group according to their body weights (200±30g) and each group housed separately in clean steel gauzed cages. They were housed under standard condition of temperature (28±3°C) and a 12hours light/ 12hours dark cycle at the animal house at Anatomy department, College of medicine, University of Nigeria, Enugu Campus. They were allowed to acclimatize for a period of two (2weeks). The rats were fed with standard pellets (Top feed, Nigeria) and clean water *ad libitum.* The cages were cleaned daily and food and water changed daily. All the animals used in this study were handled according to Institutional guidelines describing the use of rats and in accordance with the American Physiological Society guiding principles for research involving animals and human beings (9). In addition, proper care was taken as per the ethical rule and regulation of the concerned committee of the University of Nigeria, Nsukka, Enugu State, Nigeria.

Experimental design

The rats were divided into four (4) groups:

Group A received 60mg/kg of carbimazole, 2000mg/kg of HCD with neither extract nor drug for 6 weeks. This served as the negative control group.

Group B received carbimazole, HCD and 20mg/kg of Atorvastatin for 6 weeks. This served as positive control group.

Group C received carbimazole, HCD and 200mg/kg of AECL. This served as treatment group.

Group D was given neither HCD nor the extract; therefore no treatment. This group served as the normal control.

Sacrificing of Animal and Sample Collection

At the expiration of six weeks, fasting blood samples were collected from the axillary vein under ether anesthesia. The blood samples collected into plain tubes were centrifuged to obtain serum for estimation of lipid profile (Total Cholesterol, HDL cholesterol and triglyceride), biochemical parameters of kidney function (Urea, creatinine, K and Na). Malondialdehyde (MDA) and superoxide dismutase (SOD) were evaluated in kidney homogenate. The kidneys were harvested for histopathological studies.

Biochemical analysis

Measurement of serum lipid profile

Total cholesterol was estimated using cholesterol oxidase method as described by Fredrickson *et al*. (10), HDL was determined using precipitation method as described by Albers *et al*. (11) and Triglyceride (TG) was estimated using glycerol phosphate oxidase method as described by Fossati and Prencipe (12).

Measurement of renal biochemical parameters.

The levels of Serum Electrolyte, Urea and Creatinine were estimated using the following methods: K^+ and Na^+ determined using Perlong Medical PL1000A Electrolyte Analyser; Serum urea concentration was determined using the diacetylmonoxime method with protein precipitation according to Natelson *et al*. (13), Serum creatinine concentration determined using the Jaffe Reaction according to Fabing and Ertingshausen (14).

Oxidative stress analysis

Rat kidney homogenates were prepared using the method described by Eldi *et al*., (15). Lipid peroxidation (MDA) level in the kidney homogenate was determined according to the method described by Mihara and Uchiyama (16). Superoxide dismutase (SOD) activity in kidney homogenate supernatant was determined spectrophotometrically according to the method by Roth and Gilbert (17).

Histopathological analysis

The excised kidneys were processed using the paraffin wax embedding technique, sectioned at 5 microns and stained using the Haematoxylin and Eosin [H and E] staining procedure (18). The histological sections were examined using an Olympus ™ light microscope.

Statistical analysis

Data analysis was done using GraphPad prism version 6.0 (GraphPad, San Diego, CA, USA). The results of the biochemical assays were reported as mean±SEM (standard error of mean). The level of significance was tested using one way analysis of variance (ANOVA), followed by the Tukey post hoc analysis.. Probability levels of less than 0.05 were considered significant.

Results

Acute toxicity studies

LD50 value of the extract was 7500 mg/kg which indicates that AECL is safe and is not toxic to mice.

Phytochemical results

Phytochemical analysis indicated the presence of alkaloids, flavonoids, tannins, saponins, terpenoids, glycosides, tannins, phenolic compounds, terpenoids and phytosterols in the plant extract (Table 1).

The effect of aqueous extract of turmeric (Curcuma longa) on body weight

The effect of aqueous extract of turmeric (*Curcuma longa*) on body weight of albino rats fed a high cholesterol diet and carbimazole is represented in figure 1. Rat fed with high cholesterol diet and high dose carbimazole, gained weight, looked hyperlipidaemic and swollen than rats in other groups.

Biochemical results

Table 2 shows the results of serum lipid profile parameters: total cholesterol (TC), HDL and Triglyceride (TG) levels in the different experimental. From the results, AECL showed significant antihyperlipidaemic potentials (*P<0.05) in comparison with negative control (HCD+CBM). Furthermore, it was observed that the standard drug (atorvastatin) showed much better antihyperlipidaemic effects in the rats than the extract.

Table 3 shows the results of kidney biochemical parameters: urea, creatinine, K^+ and Na^+ levels in the four (4) groups. From the results, AECL showed significant renal protection (*P<0.05) in comparison with negative control (HCD+CBM). Furthemore, it was observed that AECL showed a much better protective potential on the kidney than the positive control drug (atorvastatin).

In Figure 2, albino Wister rats which received (HCD+CBM) alone (negative control) for 6 weeks showed the highest MDA level and lowest SOD activity (Figure 2A and 2B; respectively). Data show that coadministration of high cholesterol diet and high dose carbimazole for 6 weeks induced a significant increase and decrease in the tissue levels of MDA ($p<0.001$) and SOD activity ($p<0.01$) respectively in the rat kidneys in comparison with normal control group. The positive control, atorvastatin, a standard lipid-lowering drug was shown to induce a significant decrease and increase in level of MDA ($p<0.05$) and SOD activity ($p<0.01$) respectively in the rat kidney compared with (HCD+CBM) alone. Interestingly, AECL also significantly decreased and increased level of MDA and SOD activity respectively when compared with (HCD+CBM) alone ($p<0.01$).

Histopathological results

In figure 3 microscopic examination of the kidneys isolated from the rats at sacrifice revealed no histopathological alteration in the normal control rats (Figure 3D). Presence of significant distortion and erosion of the glomeruli were observed in the kidney of rats treated with oral administration of high cholesterol diet and high dose carbimazole (Figure 3A); however non-significant degenerations were observed in rats administered with atorvastatin (20mg/kg) and AECL (200mg/kg) separately (Figure 3B and 3C respectively). The kidneys of rats in group B and C showed no significant histological alterations when compared with the normal control group.

Discussion

In hypercholesterolaemia-induced organ or tissue model, cholesterol aggravates stress-mediated apoptosis (19). Carbimazole (an anti-thyroid hormone drug) has been extensively reported to have toxic effects on delicate organs, such as the testes and other tissues, as reported by Saber *et al.* (20-22) and Orji *et al*. (22). Furthermore, hypothyroidism has been reported to alter antioxidant defense system in rat (21, 24). Hence, carbimazole has been scientifically proven to cause oxidative stress, at toxic levels, in the system. Based on this scientific evidence, in this present study, an overdose of carbimazole (60mg/kg, oral), over 40 times the dosage Saber *et al.* administered, was administered to the rats for 6 weeks.

The understanding of the impact of thyroid hormones on lipid metabolism has considerably improved. Thyroid hormone plays an important role in the regulation of lipid metabolism. Thyroid hormone deficiency represents a well-known cause of hypercholesterolaemia in hypothyroid patients (25). Thus carbimazole was used in the study to cause a thyroid hormone deficiency which enables rapid onset of hyperchoresterolaemia in the experimental rats.

Aside enhancing the buildup of cholesterol in the blood, the mechanism of kidney injury by carbimazole is not well understood. Although the mechanism of testicular injury by carbimazole has been extensively reported to be due to increase in oxidative stress, possibly the coadministration of high cholesterol diet and the high dose carbimazole to the rats for 6 weeks synergistically induced the chronic kidney side effects, observed in this study. Therefore, the renal changes could be explained on the basis of increased oxidative stress.

In the last few decades, there has been the growing use of herbal medicines because most plants are believed to have medicinal value, turmeric being one of them. The aim of this study was to evaluate the antihyperlipidaemic effect of aqueous extract of *Curcuma longa* in hypercholesterolaemic rats; using atorvastatin as a reference drug. The aqueous extract of *Curcuma longa* (AECL) in this study prevented hyperlipidaemia, and nephrotoxicity after the 6weeks treatment period. Treatment with atorvastatin caused significant antihyperlipidaemic effect and renal protection. The histopathological results showed concomitant association with our biochemical results.

The effects observed in this study could be due to the singular or combined action of the bioactive phytochemicals present in turmeric extracts. Hyperlipidaemia and oxidative stress following the hypercholesterolaemic diet could be prevented by endogenous and exogenous antioxidants (26). The protection by artovastatin as observed in the present study may be probably due to anti-inflammatory and antioxidant properties of atorvastatin which has a potential protective effect on kidney function (27). Also the increased level of sodium in the positive control group (HCD+CBM+ATOR) might be as a result of effect on the kidney by atorvastatin which decreases fractional urinary sodium excretion, thereby leading to its increase in the blood (27).

Recently, the role of diet in human health has received considerable attention. Several epidemiological studies have indicated that a high intake of plant products is associated with a reduced risk of a number of chronic diseases, such as atherosclerosis and cancer (28). The consumption of plant products was shown to reduce hypercholesterolaemia, oxidative stress, homocystienaemia, endothelia dysfunction and blood pressure (29, 30). These beneficial effects have been partly attributed to the compound which possesses antioxidation. Tumeric is rich in both anti-inflammatory and antioxidant phytochemicals.

Conclusion

This study showed that the aqueous extract of *Curcuma longa* (AECL) has effect on the lipid metabolism and prevents nephrotoxicity in albino rats fed a high cholesterol diet and high dose Carbimazole. Therefore, the alterations in the serum lipid by the aqueous extract of *Curcuma longa* (AECL) may not predispose the heart to atherosclerosis or its associated renal diseases.

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Table 1: Phytochemical analysis of aqueous extract of *Curcuma longa*

Constituent	Indication
Carbohydrate	**–**
Reducing Sugar	**–**
Alkaloids	**+**
Glycosides	**+**
Saponins	**+**
Tannins	**+**
Flavonoids	**++**
Resins	**–**
Proteins	**–**
Oils	**–**
Phenolic Compounds	**++**
Terpenoids	**++**
Phytosterols	**+**

Key: ++ = present; + = present (in trace amount); – = absent

Table 2: Comparison of serum lipid profile of treated groups with negative controls.

Groups	Serum TC (mmol/L)	Serum HDL (mmol/L)	Serum TG (mmol/L)
HCD+CBM (Negative Control)	5.384 ± 0.329	1.301 ± 0.091	2.200 ± 0.294
HCD+CBM+ATOR (Positive Control)	4.063 ± 0.075**	2.249 ± 0.108*	1.281±0.052*
HCD+CBM+AECL (Test)	4.428± 0.300*	2.156 ±0.110*	1.549 ± 0.029
Normal Control	4.420 ± 0.126*	2.319 ± 0.082*	1.336 ±0.038*

Values given as Mean ± SEM. **P<0.01 or *P<0.05 is significant when (HCD+CBM) is compared with all other groups.

Table 3: Statistical comparison of kidney biochemical concentrations in different experimental animal groups.

Groups	Urea (mg/dl)	Creatinine (mg/dl)	K^+ (mmol/l)	Na^+ (mmol/l)
HCD+CBM (Negative Control)	38.48 ± 4.91	1.50 ± 0.09	6.97 ± 0.54	123.69 ± 2.08
HCD+CBM+ATOR (Positive Control)	23.34 ± 2.96*	1.10 ± 0.17	5.35 ± 0.47	132.82 ± 1.14*
HCD+CBM+AECL (Test)	22.87 ± 2.33*	0.71 ± 0.18*	5.18 ± 0.55	130.68 ± 1.45*
Normal Control	21.69 ± 1.45*	0.70 ± 0.06*	5.14 ±0.54	133.02 ± 1.82*

Values given as Mean ± SEM. *P<0.05 is significant when HCD+CBM (negative control) is compared with all other groups.

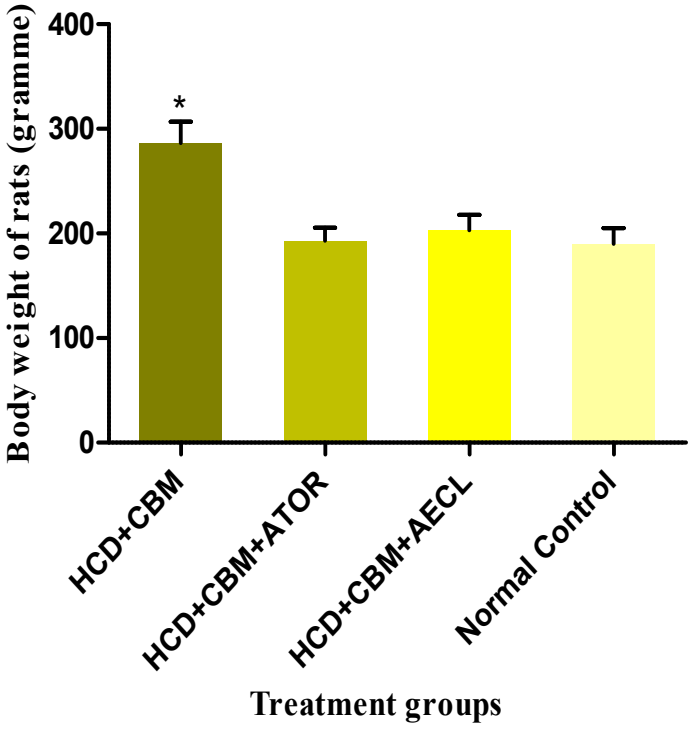

Figure 1: Effects of aqueous extract of *Curcuma longa* on body weight. Histogram show the body weight of rats in the experimental groups. The preliminary data show coadministration of HCD+CBM induced a significant weight gain. However, oral administration of atorvastatin or AECL significantly induced lower body weight when compared with (HCD+CBM) (negative control). Albino whister rats (n=5) were administered with Atorvastatin or AECL once a day for 6 weeks in the presence of HCD+CBM challenge. The data are presented as mean±SEM of body weight (gramme) for individual treatment. See *Materials and Methods* for experimental details. Statistical analyses were performed using ANOVA (* p< 0.05).

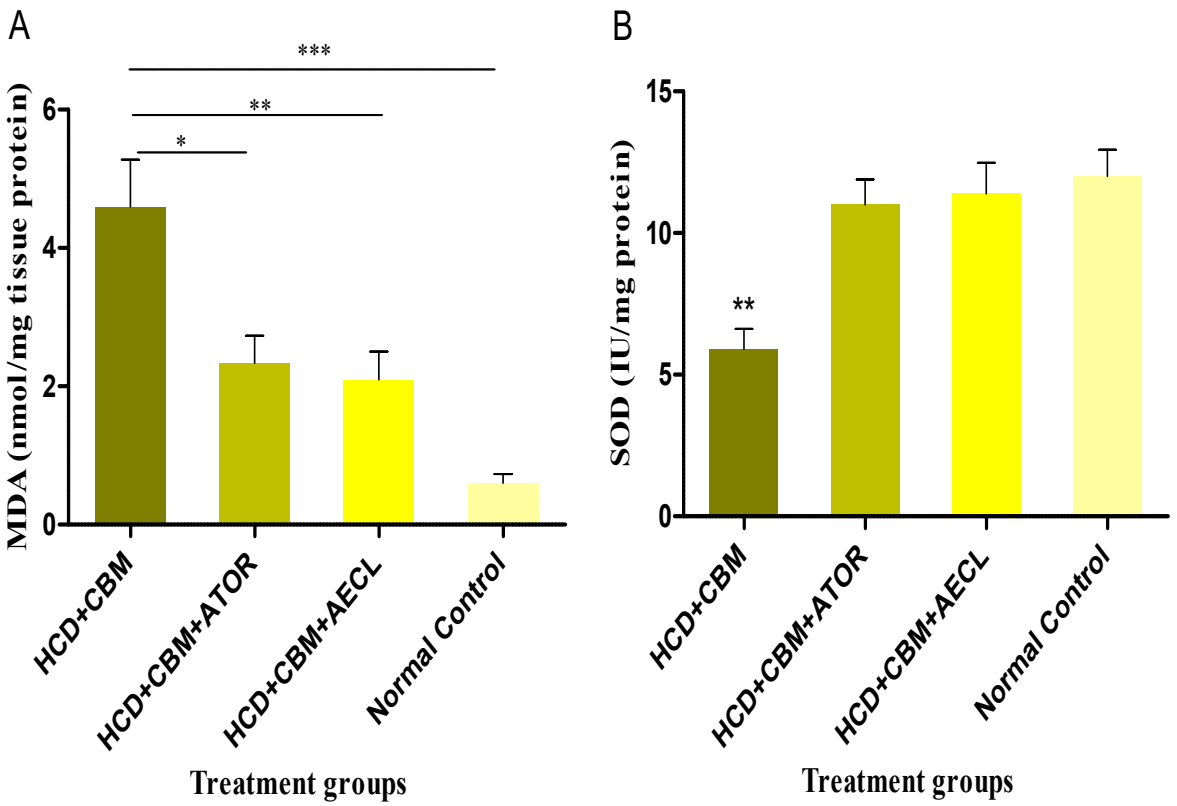

Figure 2. Effect of oral administration of turmeric aqueous extract, AECL at dose (200mg/kg) on MDA levels and SOD activity in the kidney of hypercholesterolaemic rats. The histograms A and B show kidney tissue MDA levels and SOD activity respectively following treatment with (HCD+CBM) alone or in combination with Atorvastatin or AECL. The preliminary data show Atorvastatin or AECL significantly induced lower MDA levels and higher SOD activity when compared with (HCD+CBM) (negative control). Each column represents mean±S.E.M. of data from five rats. Normal control group was administered distilled water as a vehicle. The symbol (***), (**) and (*) represent $p<0.001$, $p<0.01$ and $p<0.05$ respectively when (HCD+CBM) group is compared with other groups. Albino whister rats ($n = 5$) were administered with Atorvastatin or AECL once a day for 6 weeks in the presence of HCD+CBM challenge. See *Materials and Methods* for experimental details. Statistical analyses were performed using ANOVA.

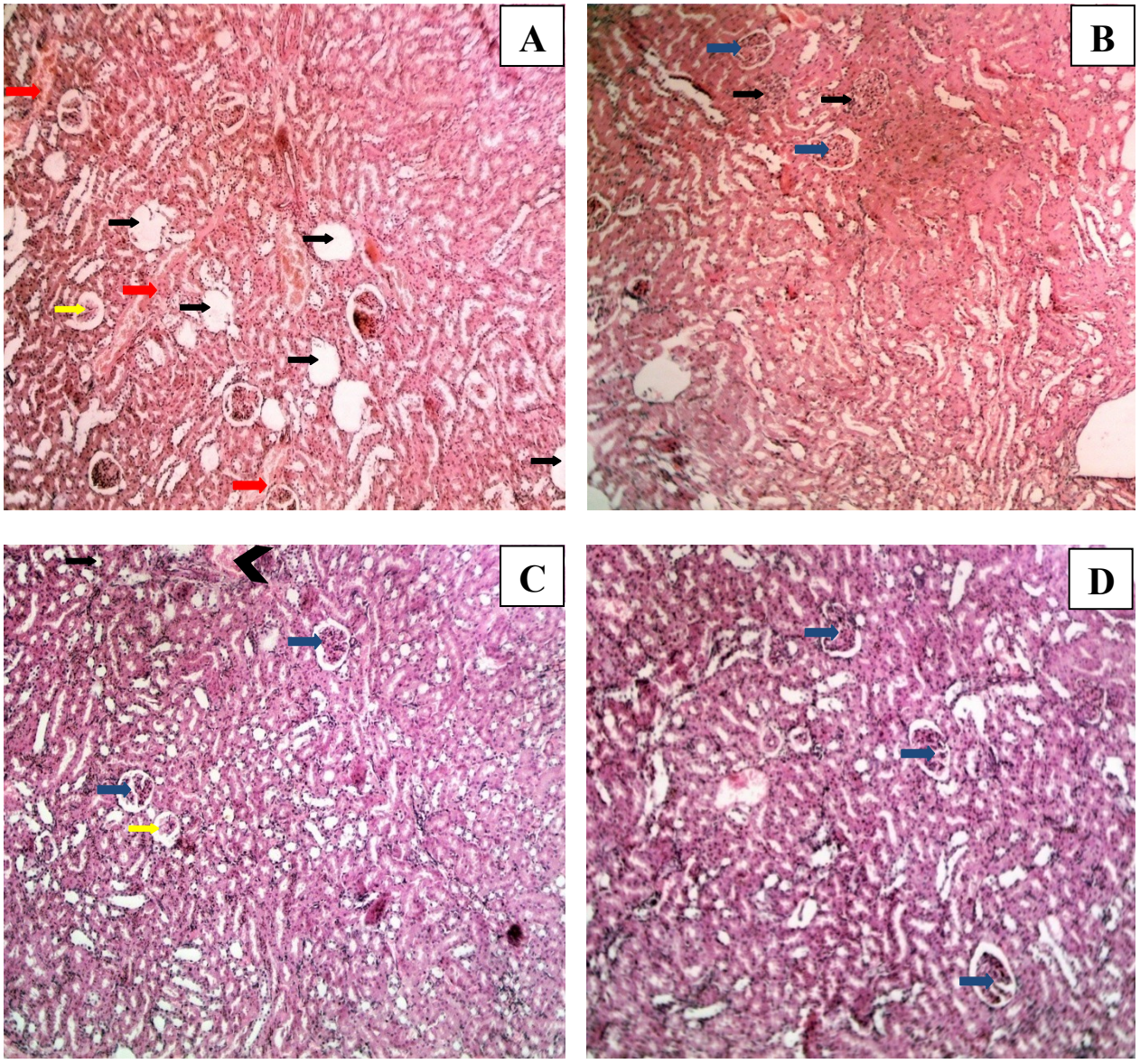

Figure 3: Histopathology and photomicrograph of kidney. **(A)** Co-administration of high cholesterol diet (HCD) and carbimazole (CBM)-treated rats: Most of the glomeruli are eroded (black arrows) while others are constricted (yellow arrow). The tubules appear normal and some areas of congestion are seen (red arrows). **(B)** HCD + CBM + Atorvastatin- treated rats: Some glomeruli (blue arrow) are inflamed with increased cellularity (black arrows). **(C)** HCD + CBM + AECL-treated rats: normal glomeruli seen (blue arrows), the tubules appear normal (black arrow). A hyperaemic portion of the stroma is seen (black arrow head). A constricted glomerulus is also seen (yellow arrow). **(D)** Normal control rats. There is normal appearance of glomeruli (blue arrows) and renal tubules. [Stain: H and E; ×100].