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Therapeutic Potential of Oleuropein and Taurine in Alleviating Tamoxifen-Related Kidney Injury

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ABSTRACT : ***Antioxidant and plant derived poly-phenolic are used as chemopreventive drugs to alleviate negative effects correlated with drug- generated injuries. Tamoxifen (TAM), chemotherapy hormonal medication, is utilized throughout whole stage of breast carcinoma (BC). Nevertheless, TAM usage for a long time caused side effects such as renal toxicity. The current study supposed to investigate the implication of oleuropein (OLE) and taurine (TAU) administration upon TAM induced renal dysfunction in male albino rats. 50 male albino rats were randomly divided into 5 groups (10 rats in each group) as follows; group 1 [control rats], group 2; rats were received TAM (20mg /kg), group 3; rats administrated with TAU (100mg /kg) and TAM, group 4; rats received OLE (16mg/kg) and TAM and final group 5; rats treated with TAU and OLE in combination with TAM, all treatments were by oral administration for 30 days. In all groups, serum urea and creatinine were estimated. Histopathological investigations of renal tissue were done.***

Results: TAM treated group revealed significant increases in serum urea and creatinine. In contrast, OLE or TAU treated group showed significant reduction in theses parameters, but OLE and TAU treated groups had highly improved compared with other groups and amelioration of kidney histoarchitecture.
Conclusion: Oleuropein and taurine combination mitigated the reverse effects of TAM induced renal damages that may be due to their potential antioxidant.
KEYWORDS: tamoxifen, renal toxicity, taurine, antioxidant.

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I. INTRODUCTION

Cancer, in all its forms, accounts for around 12% of all fatalities worldwide, according to the Indian Council of Medical Research- Population Based Cancer Registries (ICMR-PBCR) data, breast tumor is the second most widespread cancer in humans and the major reason of cancer death in females (**Siegel *et al.*, 2012; Guerrero *et al.*, 2017).** Obesity, being female, sedentary life, hormonal replacement medication, the menopause, ionizing radiation, early onset of menstruation, and aging are all risk factors for developing breast cancer (**Kyu *et al.*, 2016**).

Tamoxifen (TAM) has been the first choice for the treating of all steps of breast carcinoma with positive estrogen-receptor that it was the first chemo-preventive strategy for cancer (**Panchal *et al.*, 2014**). TAM has mixed antagonist-agonist activity, in which it reacts on the target tissue and physiological context that competitively inhibits estrogen receptors. It has an anti-estrogenic effect on the breasts while acting as estrogen in the bones, liver, and uterus (**Ahmed *et al.*, 2021).**

TAM usage to long time may result in a variety of negative side effects, including night sweats, gynecological symptoms (vaginal dryness and vaginal discharge), depression, memory loss, sleep disturbances, and decreased sexual function (**Yeh *et al.*, 2014; Gao *et al.*, 2016**). Also, According with **Ribeiro *et al.* (2014),** taking TAM is linked to a higher risk of ovarian cysts, endometrial polyps, and vaginal bleeding.

TAM's carcinogenicity is caused by its metabolites' covalent DNA binding, which causes DNA adduct formation in the kidney. In addition, anticancer drugs or adjuvant therapies, such as TAM, directly cause a drop in kidney function (**Saleh *et al.*, 2016**). TAM-induced nephrotoxicity caused by the reactive oxygen species

(ROS) created by TAM that produced the free radicals in the renal tissue **(Zuhair, 2011**), TAM generate ROS that exceed its antioxidant capacity, which damages cells and reduces the cell's capability to detoxify ROS. Although many synthetic substances successfully inhibit the growth of cancer cells, many of them also have adverse effects and are extremely risky. One approach to resolving these issues is to use natural substances or their derivatives (**Naso *et al.*, 2016**).

Taurine, 2-amino ethanesulfonic acid is a semi-principal amino acid, found at large quantities into molluscs and plays an important part in animal bile. Also referred to as an antioxidant, that the protective properties of taurine have been verified in repairing for damaged organs resulting from elevated oxidative stress brought on by anticancer medication administration (**Wang *et al.*, 2015; Nagai *et al.*, 2016).** Also, taurine has indirect antioxidants by stabilizing of cellular membrane and preventing alteration of membrane permeability caused by oxidative stresses (**Kim & Cha, 2014).**

There are most individuals utilizing natural antioxidants since they are generally safe and have few adverse effects. Olive leaf extracts have drawn particular attention due to their potential medicinal benefits, which contain phenolic acids, phenolic alcohols, flavonoids, and secoiridoids (oleuropein) **(Badawy *et al.*, 2024).** Oleuropein (OLE), the main phenolic molecule found naturally in Olea europaea, has a wide range of pharmacological properties, including cardiovascular protection, antiviral activity, anticancer, antioxidation, anti-inflammation, skin protection, and antiaging (**Zheng *et al.*, 2022).** OLE may therefore be a useful strategy for avoiding nephrotoxicity. Although OLE has positive effects on both glomerular and tubular cells, there is a notable decrease in renal damage (**Geyikoglu *et al.*, 2017**).

Moreover, OLE remarkably reduced inflammation, apoptosis as well as oxidative stress (**ALHaithloul *et al.*, 2019**). Meanwhile, OLE significantly decreased morphological changes and renal dysfunction. Also, OLE protects against a range of renal damage caused by carbon tetrachloride (**Al-Sowayan and Mousa, 2014**).

OLE-treated rats demonstrated nearly normal renal cortex and medulla histological structure, supporting the potential therapeutic application of OLE as a novel nephroprotective drug against severe renal failure (**Zari and Al-Attar, 2011; Al-Hayaly *et al.*, 2020).**

Therefore, the main aim of this study to explore the efficiency of oleuropein and taurine on renal functions in rats treated with Tamoxifen induced pathophysiological complication.

II.MATERIALS AND METHODS

Reagents and chemicals

Tamoxifen citrate (TAM) was manufactured by Astra Zeneca (Macclesfield, Cheshire, United Kingdom). Taurine powder (TAU) was purchased from BDH Chemicals Ltd (Pool, Dorset, United Kingdom). Assay kits for Kidney biomarkers [creatinine and urea] were purchased from Diamond Diagnostic (23 EL-Montzh St., Heliopolise, Cairo, Egypt). Oleuropein was purchased from Sigma-Aldrich, 98% of purity.

Experimental design

All of experimental animals have been conducted according with the guiding concept for the care and use of research animals examined and authorized by ZU-IACUC committee, with ethical approval no. ZU-IACUC /1 /F / 318 /2022. Firstly, the experiment began with 50 normal male albino rats (Sprague Dawley), aged 9 weeks and weighed nearly 150-200gm. Rats have been taken from the animal house of the Veterinary Medicine of Zagazig University that rats were kept in stainless cages in room with artificial lighting and temperature control 20- 25°C and 12 h light / dark cycle. Rats were given tap water and diet for a week before the experiment to adaption and then they were randomly divided to 5 groups.

Group 1 (Control group): Rats were given normal distilled water and base diet.
Group 2 (TAM treated group): Rats were received TAM (20 mg /kg bw) according to **Panchal *et al.* (2014**).
Group 3 (TAU +TAM treated group): Rats were received 100 mg/kg of TAU, was referred from (**Caletti *et al.*, 2012**) as well as TAM (20 mg /kg bw).
Group 4 (OLE+ TAM treated group): Rats were received 16 mg/kg of OLE according to **Jemai *et al.* (2020**) and TAM (20 mg /kg bw).
Group 5 (TAU + OLE+ TAM treated group): Rats of this group are combined treatment with TAU (100 mg/kg)**,** OLE (16 mg/kg) and TAM (20 mg /kg)**.** All treatments were by oral administration for 30 days.

Blood sample collection

Following complete 30 days experiment, during an overnight fasting, blood specimens were obtained by specific micro-tube placed through the inner retro-orbital venous of rat's eye. blood samples were collected in plain centrifuged glass tube, then were centrifuged for 10 minutes, at 3000 r. p. m. after complete coagulation then sera were separated and kept at (-20^{o} C) until used.

Serum biochemical analysis

Serum creatinine and urea were determined enzymatically using kit (Diamond Diagnostic, Cairo, Egypt) according to **Burtis *et al.* (1999)** and **Tietz *et al.* (1995)** respectively.

Tissue collection and histological study

Upon samples collection, all of the rats were sacrificed after slight anesthesia by di-ethyl ether then cervical dislocation. The animals were dissected, where kidney samples were removed immediately and cleaned using saline solution (0.9%), and preserved in 10% formal saline and neutral buffered formalin until histopathological processing. Then, impregnation in paraffin after dehydration in ascending levels of ethanol cleared in benzene. Serial section was cut to thin section at 4-5 µm thickness and then stained by Hematoxylin-Eosin (H&E), then examined under the microscope.

Statistical analysis

All data were used in software SPSS for Windows, version 26. The parametric analyses were performed on the frequently distributed data, and the normality test was carried out using SPSS. The data were statistical analyzed by using variance analysis (ANOVA). The data were expressed as mean ± standard error, and the significance of the findings was assessed as a P value of ≤ 0.05. GraphPad Prism 9 was used for the graphs.

III. RESULTS

Creatinine and Urea level

The present data revealed that TAM treated rats group exhibited significant increase in serum kidney parameter (creatinine and urea level) compared to control group. Meanwhile, daily intake of TAU+TAM treated group and OLE+TAM treated group afforded significant decrease in level of creatinine and urea comparing with TAM treated group but also afforded significant elevation in creatinine and urea level compared to normal control group.

Also, TAU and OLE as well as TAM combination treated group elucidated significant decrease in serum creatinine and urea level as compared with TAM treated group and non-significant change as compared with control group and this was the best effect treatment as shown in **Table 1** and **Figure 1**.

Table (1): Serum creatinine and urea in the studied groups:

Groups / Parameter	Control mean± SE	TAM group mean± SE	TAU+TAM group mean± SE	OLE+TAM group mean± SE	TAU+OLE+ TAM group mean± SE
Creatinine (mg/dl)	0.44±0.02	0.78± 0.04****	0.63±0.05*	0.59±0.018**	0.50±0.02****
Urea (mg/dl)	55.2± 1.36	90.1± 1.3****	72.2± 2.6****	67.6± 2.9****	59.5± 3.06****

Values represent as mean ± SE (n=10).
Significance of TAM group compared with control, other groups were significant compared with TAM.

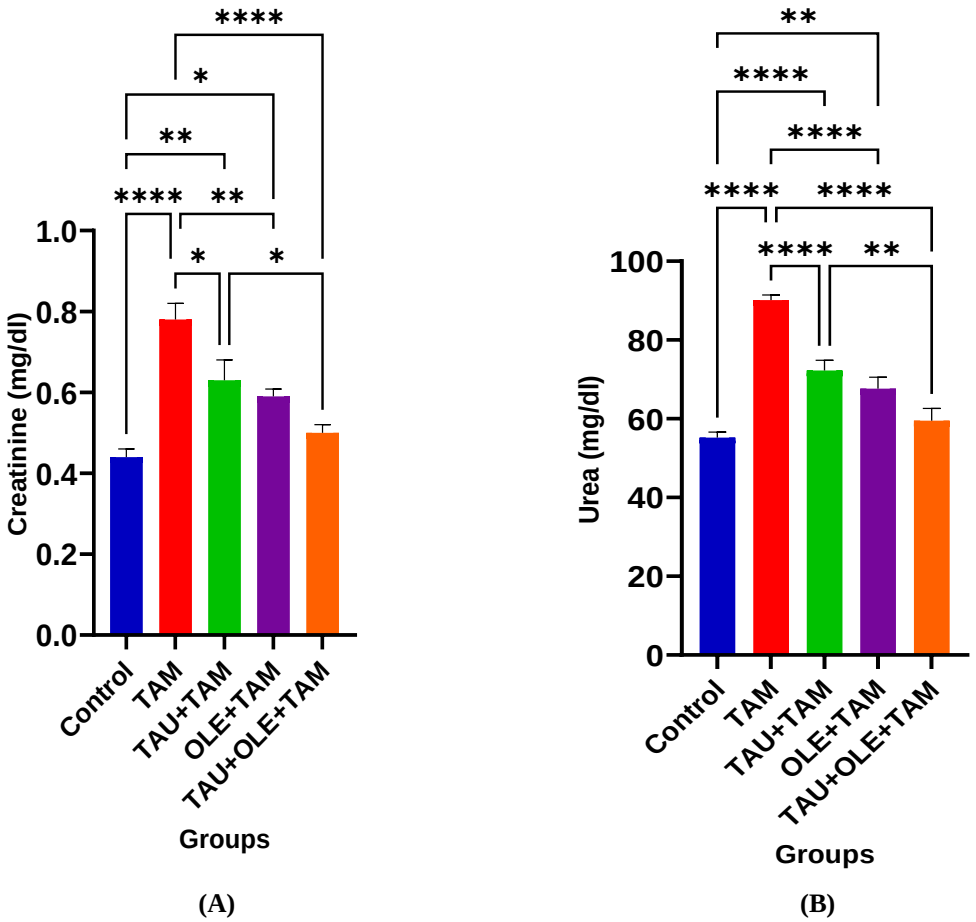
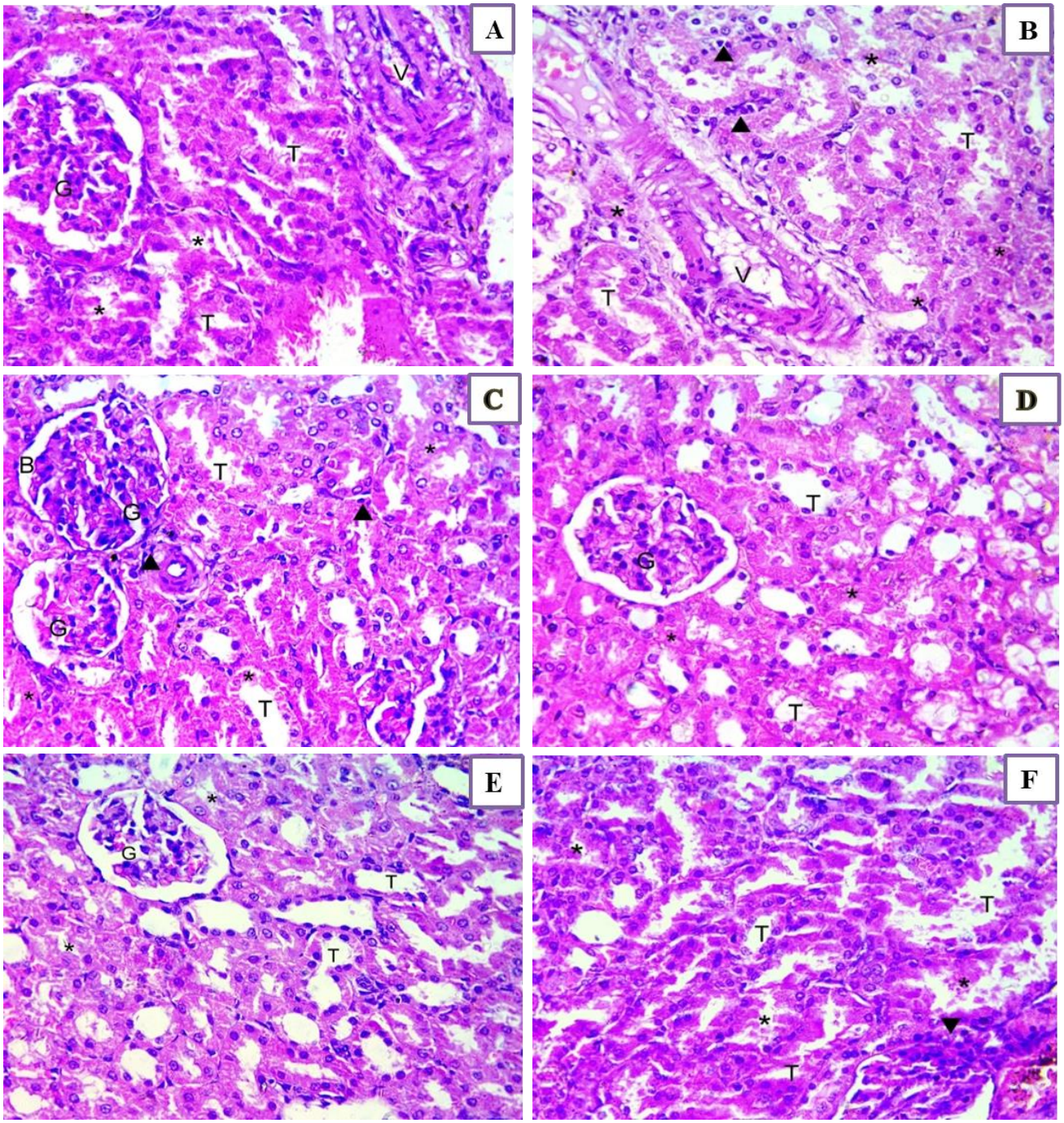


Figure 1 Measurement of kidney parameters: Control and experimental groups show serum creatinine (A) and urea (B). This data represent as mean ± SE (n=10). TAM: Tamoxifen; TAU: Taurine; OLE: Oleuropein
*and ** indicate significant differences at $P < 0.05$
*** indicate significant differences at $P < 0.01$
**** indicate significant differences at $P < 0.001$

Histopathological observations

Histopathology of kidney sections: in the control group, the kidney tissue showed normal glomeruli and normal tubules **Figure 2A**. The TAM treated rats group showed severe kidney injury: Most tubules show fragmentation and necrotic changes of the lining epithelial cells with casts filling the lumen (asterisks) with ill-defined borders. Focal inflammatory infiltrate (arrowhead) and thick-walled blood vessels could be seen in **Figure 2B, C and D**. Conversely, TAM treated rats that received TAU exhibited moderate hypercellularity (glomerular endotheliosis) leaving minimal Bowman's space. Some tubules demonstrated loss of nuclei (asterisks) in the lining epithelial cells. Minimal inflammatory infiltrate (arrowheads) is found in the interstitial tissue as shown in **Figure 2E**; meanwhile the OLE combination demonstrated the same effect with focal necrosis (asterisks) of the lining epithelium **Figure 2F**. Simultaneously, the co-administration of TAU and OLE to TAM intoxicant rats showed evident improvement that glomeruli show intact Bowman's space, mild fragmentation (asterisks) of the lining epithelium of tubules **Figure 2G.**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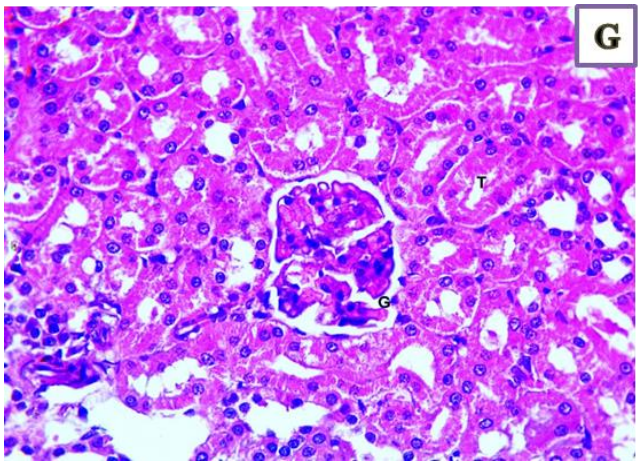

Figure 2 Investigation of histopathological alterations in rats renal sections using staining of Hematoxylin and eosin (H&E, x 400): Photomicrograph of kidney tissue of control group (A), Tamoxifen (TAM) treated group (B, C and D), taurine (TAU) + TAM- treated group (E), oleuropein (OLE) + TAM- treated group (F), and TAU + OLE + TAM- treated group (G). G glomeruli, T tubules, B Bowman's space, V blood vessels, * asterisks, ▲ arrowheads.

IV. DISCUSSION

Chemotherapy involves the use of chemicals to damage cancer cells by preventing them from growing and dividing. Cancer cells are more vulnerable to the effects of these medications because they grow and divide more rapidly than normal cells. Damage to healthy cells, on the other hand, is unavoidable, and this damage accounts for the side effects associated with these drugs (**Lancet, 2017**). Tamoxifen is one of the major chemotherapeutic drugs which used for whole hormone-dependent neoplastic levels and reduced from reversal of breast cancer and death **(Moerkens *et al.*, 2014; Bekele *et al.*, 2016)**. Despite its negative effects such as depression, reduced sexual function and endometrial polyps **Ribeiro *et al.*, 2014; Gao *et al.*, 2016)**. The usage of TAM in the treatment of breast cancer for long time caused toxicity to target organs such as kidney (**Owumi *et al.*, 2021)**. So, recent studies display that medicinal plants and natural antioxidants are chemopreventive agents against the toxicity of anticancer drugs. These chemoprotective have been shown to have powerful antioxidant effects.

Taurine is produced by the body from the metabolism of methionine and cysteine, which is found in a variety of common foods and dietary supplements. It had anti-oxidant and immunomodulatory properties, it is involved in many of physiological processes, such as conjugation of bile salt, calcium homeostasis, osmoregulation, and stabilization of membrane **(Murakami, 2015).** TAU lowers the chance of acquiring metabolic illnesses like diabetes, obesity, dyslipidemia, and hypertension (**Abd Elwahab *et al.*, 2017**). Also, it had the ability to be cytoprotective (**Al-Asmari *et al.*, 2016**). Also, extracts from olive leaves had been the focus of several investigations. The leaf extracts of Olea- europaea have demonstrated impressive anti-inflammatory, antiviral, anti-tumor, antithrombotic, antimicrobial, hypocholesterolemic, and anti-apoptotic characteristics (**Benot-Dominguez *et al.*, 2021; Badawy *et al.*, 2024)**. Oleuropein is a major polyphenol of olive leaves which act as antioxidants and scavengers of free radicals (**Ruzzolini *et al.*, 2018)**, cardiovascular protective, and renal protective **(Zheng *et al.*, 2022 and Badawy *et al.*, 2024**). Our study particularly designed to explore their collaborative effects in improving TAM side effects.

The current investigation showed the protective effects of TAU and OLE on renal toxicity produced by TAM in rats treated groups for 30 days.

The kidneys have a vital role in maintaining fluids physiological levels, minerals, electrolytes as well as eliminating toxic waste products from the body. It has since been proven that the kidneys were among the initial targets of TAM toxicity, which results in both functional and histological alterations (**Petejova *et al.*, 2019; Mitra *et al.*, 2019).** Any significant increase in kidney function markers, which are crucial for correctly identifying nephrotoxicity, is associated with renal injury. Creatinine and urea are results of the cellular destruction of creatine phosphate in the myocytes, and protein metabolism is utilized to determine the same integrity and functionality of the kidney (**Owumi *et al.*, 2021)**. The high level of creatinine and urea is symptomatic of the development of nephrotoxicity. Since creatinine gives an accurate measurement of glomerular filtration rate, it is a more reliable indicator of renal impairment than urea (**van Veldhuisen *et al.*, 2016 and Owumi *et al.*, 2020).**

Insights of the present study revealed that administration of TAM showed significant increases in serum creatinine and urea compared with normal control group. Renal dysfunction could be the cause of this.

The primary cause of TAM-associated nephrotoxicity is thought to be the inhibition of the hexose monophosphate shunt pathway and an increase in the frequency of reaction oxidation species (ROS) in cells, these conditions caused tissue damage and disrupt the kidney's glutathione redox balance, which, in turn, causes the production of free radicals in renal tissue (**Saleh *et al.*, 2016).** These observations agree with **Shahani *et al.* (2017)** and **Owumi *et al.* (2021).** They showed that TAM treatment which increased creatinine and urea levels may refer to kidney damage. In contrast, the administration of OLE alone or TAU alone or combination of OLE and TAU to TAM intoxicated male rats caused an improvement in serum urea and creatinine level compared with TAM treated group. These results were in line with **Geyikoglu *et al.* (2017).** They investigated the important role of OLE in renal damage, illustrated that OLE caused obvious decreasing in serum creatinine and urea level. These observations are indicative to OLE properties that scavenged ROS to reduce the generation of free radicals in renal tissue, are essentially due to antioxidant capacity of OLE. Additionally, TAU administration mitigated serum markers of renal injury creatinine and urea. These outcomes agreed with **Aziz et al. (2020).** The combination therapy TAU + OLE+ TAM demonstrated the best improvement in kidney biomarker.

It would be clinically invalid to assess the biochemical alterations in kidney tissues after TAM-induced renal damage without incorporating the histological changes. Additional evidence for these findings is provided by histological examination of kidney tissues. The effect of TAM on morphology of renal tissues that showed severe renal injury such as fragmentation and necrotic changes of the lining epithelial cells of tubules, Focal inflammatory infiltrate and thick-walled blood vessels. These investigations were in line with **Mourad *et al.* (2020); Owumi *et al.* (2021).** Also, **Saleh *et al.* (2016)** reported that oral administration of TAM is linked to deterioration of the kidneys' vasculature or architecture, resulting in damage to renal function tests. This might be because there are more oxygen radicals such as O^{2-}, OH, and H_2O_2, which can harm the cells in this organ by forming protein crosslinks, lipid peroxidation, and DNA double strand breaks (**Bekele *et al.*, 2016**). Whereas, oleuropein and taurine administrated with TAM demonstrated improvement in cyto- architecture of kidney that show mild fragmentation of the lining epithelium of tubules. This is in line with **(Jemai *et al.*, 2019; Abdoli *et al.*, 2021).**

V. Conclusion

The current investigation concludes that TAM administration seriously impacts the integrity and functioning of kidney tissues. As a result of increasing the serum levels of biomarkers associated with kidney failure.
TAU and OLE were more successful in reducing apoptosis and reversing the histological and biochemical alterations produced by TAM. Through the use of supplements, these parameters were successfully restored to normal. The results of the current investigation highlight the significance of a synergistic treatment strategy for treating tissue damage induced by TAM.

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