

# Evaluating the Anticancer and Antioxidant Potentials of Star Anise (*Illicium verum*) Extract Against Ehrlich Solid Tumor Induced Kidney Toxicity, Oxidative Stress and Inflammation

Fadi Sawaqed<sup>1</sup>, Afaf El-Atrash<sup>2</sup>, Maha Elkholy<sup>2</sup>, Ehab Tousson<sup>2</sup>, Youssef Hussein<sup>3,\*</sup>

<sup>1</sup> Department of Special Surgery Faculty of Medicine, Mutah University, Karak, Jordan; <sup>2</sup>Zoology Department, Faculty of Science, Tanta University, Tanta 31527, Egypt; <sup>3</sup>Department of Anatomy and Histology, Faculty of Medicine, Mutah University, Karak, Jordan

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## Abstract

Cancer, a cellular malignancy that results in the breakdown of normal cell-cycle regulation, such as uncontrolled growth and a lack of differentiation, can arise in any tissue of any organ at any time. Therapeutic effectiveness of existing medications is low, and they do not inhibit the development of cancer. Ehrlich solid tumour (EST) is a mimicked breast cancer and a spontaneous mouse mammary adenocarcinoma; therefore, the current work aims to define the ameliorating and therapeutic role of star anise extract (SAE) against EST- induced renal oxidative stress, toxicity, and inflammation in mice. Sixty mice were randomly and similarly separated into six groups (Gp1, control; Gp2, SAE (orally at doses 50 mg/kg for two weeks); Gp3, EST (2.5-3×10<sup>6</sup> EAC cells); Gp4, SAE+EST; Gp5, EST+SAE; Gp6, Self t. EST). Current results showed: EST induced significant elevation in urea, creatinine, chloride, potassium, tissue damage, renal MDA, and conversely, a significant reduction in sodium, calcium, renal SOD, GSH, and catalase as associated to control. The treatments of EST with star anise extract (EST+SAE) enhanced kidney functions, electrolytes, oxidative stress, renal tissue and protected against EST with best improvement for post treatment than co-treatments. This indicates the potential benefits of star anise extract (SAE) as a natural chemotherapy and cure of kidney toxicity may inhibit cancer cells through apoptosis.

**Keywords:** Star anise; Ehrlich solid tumor; mice; nephrotoxicity; oxidative stress; DNA damage.

## 1. Introduction

Both rich and developing nations are threatened by the shared public health issue of cancer because of both external and internal reasons (Arbyn *et al.*, 2020). Estimates indicate that the number of new cases of cancer would increase from 11.8 million in 2008 - 15.9 million in 2030, partly as a result of the world's population aging and expanding (Siegel *et al.*, 2021). DNA changes in the damaged cells cause cancer, which creates a tumor an extra mass of tissue from the damaged cells (Zeeneldin *et al.*, 2013; Tousson *et al.*, 2014; Nofal *et al.*, 2023). Numerous cancer treatments degrade DNA chemically or physically, which indirectly triggers apoptosis (DeSantis *et al.*, 2015; Tousson *et al.*, 2016; Tousson *et al.*, 2018).

The Ehrlich tumor is one of several in-vivo experimental models that are derived from experimental animals (Oshiba *et al.*, 2021). Ehrlich tumor (EST & EAC) has been employed as a model for transplantable tumors to facilitate easy investigation into the anti-cancer characteristics of several chemical substances (Tousson *et al.*, 2020; Abd Eldaim *et al.*, 2021; Alotaibi *et al.*, 2021). Ehrlich solid tumour is a mimicked breast cancer and a spontaneous mouse mammary adenocarcinoma (El-Masry *et al.*, 2020; El-Masry *et al.*, 2019; Abd Eldaim *et al.*, 2019; Abd Eldaim *et al.*, 2021).

Numerous studies have looked at finding complimentary medicines to address a variety of human conditions (Moustafa *et al.*, 2014; Oyouni *et al.*, 2018). It has been demonstrated that several phytochemicals are safe and may have therapeutic benefits (Essawy *et al.*, 2022; Radwan *et al.*, 2023).

Star anise (*Illicium verum*) is traditionally used to cure nausea, vomiting, inflammation, and rheumatic pain, and it is a sweet-smelling evergreen tree that thrives in China and Vietnam (Al-Ameri *et al.*, 2017; Shahrajabian *et al.*, 2019). The crude of star anise is regarded being the primary foundation of shikimic acid, that is a key component of the Tamiflu medication (Wang *et al.*, 2011). These features include antioxidants that prevent the formation of free radicals and lipid peroxidation as well as antibacterial capabilities (Elmasry *et al.*, 2018; Singh *et al.*, 2020). Hence, the goal of this investigation was to define the ameliorating and therapeutic role of star anise extract against EST- induced renal oxidative stress, toxicity and inflammation, in mice.

## 2. Materials and Methods

### 2.1. Plant Material

Star anise was bought at a neighbourhood store and mechanically dried at 65°C. After Elmasry *et al.* (2018), and the dried materials were first heated to between (21

\* Corresponding author. e-mail: Dr\_youssefhussein@mutah.edu.jo.

and 27°C), kept in the dark in airtight plastic bags, and then transformed into a fine powder.

## 2.2. Induction of EST

The mice that had EAC were donated by the Egyptian National Cancer Institute. According to Elgharabawy *et al.* (2021), viable cells ( $2.5-31^{06}$  cells/mouse) each recipient mouse's left thigh with hypodermically injections to maintain the tumour line and evaluate EST.

## 2.3. Experimental Animals

### 2.4. Experimental Design and mice groups

Mice were similarly separated into 6 Gps.

Gp1: Control, mice in the control group did not obtain any therapy.

Gp2: SAE in which mice obtain SAE orally at doses 50 mg/kg for two weeks (Elmasry *et al.*, 2018).

Gp3: EST, counting mice, each inoculated hypodermically with  $2.5-3 \times 10^6$  EAC cells (Elgharabawy *et al.*, 2021).

Gp4: SAE+EST in which mice obtain SAE and inoculated hypodermically with EAC cells for 14 days.

Gp5: EST+SAE including mice, each first inoculated hypodermically with EAC cells for 14 days before orally treated with SAE for another 2 weeks.

Gp6: Self t. EST in which mice were inoculated with EAC. The study involved 60 Swiss albino mice from the Egypt Vaccine Company's animal house colony in Egypt. The mice were housed under ambient conditions, with a commercial diet and water supply, following the animal ethics committee under ID: IACUC-SCI-TU-0223.

cells for 14 days and kept for another 14 days without treatments.

### 2.5. Blood Sampling

Mice were slaughtered at the conclusion of the experiment by administering sodium pentobarbital intraperitoneally, and they underwent a full necropsy. Blood sample was collected from each mouse in plain *vacutainers* tubes to investigate the electrolytes and renal function levels.

### 2.6. Kidney functions and Electrolyte estimation

Creatinine and urea were assessed after Patton and Crouch (1977). After El-Masry *et al.* (2020) conducted their study, a technique was developed to evaluate the concentrations of electrolytes using Sensa-core kits.

### 2.7. Enzymatic and non-enzymatic antioxidant assays

#### Malondialdehyde (MDA)

According to Mesbah *et al.* (2004), malondialdehyde (MDA) concentration in kidney tissue homogenate were measured.

#### Reduced glutathione (GSH)

After receiving therapy with 5.5'- dithiobis-(2-nitrobenzoic acid), the Tipple and Rogers technique was

used to measure the GSH content in kidney homogenates (Beutler, 1963).

#### Catalase (CAT)

By observing the breakdown of a 19 mM hydrogen peroxide solution made in potassium phosphate buffer, CAT activity was determined at 20°C. Over the course of five minutes, the loss of H<sub>2</sub>O<sub>2</sub> was observed at 240 nm per minute. Saggu *et al.* (2014) mentioned the enzyme's specific activity was measured in micromoles per milligramme of protein.

#### Superoxide Dismutase (SOD)

After Misra and Fridovich (1972), SOD activity was measured. The primary tactic is to prevent the auto-oxidation of adrenaline to adrenochrome in an alkaline media, that significantly impeded by the presence of SOD.

### 2.8. Histological processing

Following Tousson (2016), kidney specimens from different groups were extracted, fixed in 10% neutral buffered formalin, and stained with hematoxylin and eosin, and the results were seen under a light microscope.

### 2.9. Immunohistochemical detection for tumor necrosis factor alpha (TNF- $\alpha$ )

Altwaijry *et al.* (2020) used the Avidin Biotin Peroxidase immunohistochemistry approach (Elite-ABC, Vector Laboratories, CA, USA) to assess the expression of TNF- in deparaffinized sections of the mouse kidney (5 m).

### 2.10. Statistical Analysis

Data were reported as the one-way ANOVA was used to examine the significance of difference. Values are shown as means SE. \* and # signify a significant departure from the control group and, correspondingly, the EST group at p 0.05.

## 3. Results

### 3.1. EST induced kidney toxicity

When comparing EST and self-treated EST to control, there was a notable decrease in electrolytes (calcium and sodium) and a notable increase in blood levels of renal functions (urea and creatinine) and electrolytes (potassium and chloride) (Table 1). However, treatments of mice with SAE in Co-treated (SAE+EST) and in post-treated (EST+SAE) showed a significant depletion in urea, creatinine, chloride and potassium while a significant elevation in calcium and sodium when compared to EST and self-treated EST group, the ameliorated group was more marked in the post-treated (Table 1).

**Table 1:** Variation in kidney functions and electrolytes levels

	Control	SAE	EST	SAE+EST	EST+SAE	Self.T EST
Creatinine (mg/dl)	0.82 <sup>#</sup> ±0.10	0.78 <sup>#</sup> ±0.12	1.66*±0.05,	1.36* <sup>#</sup> ±0.09	0.96 <sup>#</sup> ±0.10	1.44* <sup>#</sup> ±0.08
Urea (mg/dl)	28.0 <sup>#</sup> ±2.07	26.1 <sup>#</sup> ±2.55	47.9*±1.18	41.1* <sup>#</sup> ±0.86	26.8 <sup>#</sup> ±1.59	39.6* <sup>#</sup> ±0.69
Na <sup>+</sup> (mmol/l)	135.7 <sup>#</sup> ±0.58	136.3 <sup>#</sup> ±0.36	121*±0.91	134.5 <sup>#</sup> ±1.90	136.7 <sup>#</sup> ±0.31	126.5* <sup>#</sup> ±1.45
K <sup>+</sup> (mmol/l)	5.3 <sup>#</sup> ±0.08	5.4 <sup>#</sup> ±0.09	7.12*±0.18	6.49* <sup>#</sup> ±0.19	5.98* <sup>#</sup> ±0.05	6.68* <sup>#</sup> ±0.06
Cl <sup>-</sup> (mmol/l)	102.2 <sup>#</sup> ±0.64	101.6 <sup>#</sup> ±0.65	113.2*±1.42	108.7* <sup>#</sup> ±0.63	104.6 <sup>#</sup> ±0.62	109.8* <sup>#</sup> ±0.66
Ca <sup>++</sup> (mmol/l)	0.95 <sup>#</sup> ±0.011	0.95 <sup>#</sup> ±0.013	0.68*±0.018	0.88* <sup>#</sup> ±0.024	0.95 <sup>#</sup> ±0.012	0.81* <sup>#</sup> ±0.013

Values are articulated as means SE. \* and # signify a significant departure from the control group and from the EST group, respectively, at p 0.05.

### 3.2. Antioxidant enzyme activities

A significant elevation in MDA while a significant reduction in the activities of GSH, SOD and CAT in was observed in kidney homogenate of EST and self-treated EST as compared with control mice (Table 2). However, treated mice with SAE in Co-treated (SAE+EST) and in

post-treated (EST+SAE) groups showed a significant reduction in MDA while a significant elevation in GSH, SOD, and CAT when compared to EST and self-treated EST group, the ameliorated group was more pronounced in the post-treated group (Table 2).

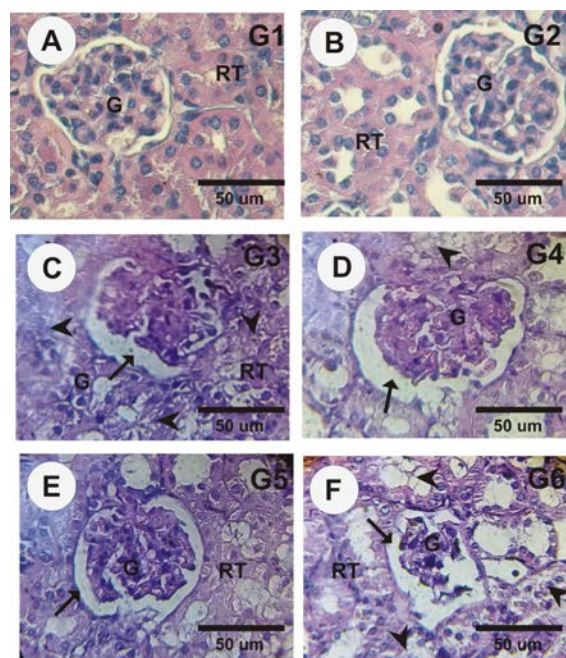
**Table 2:** Effect of star anise extract upon markers of oxidative stress in kidney

	Control	SAE	EST	SAE+EST	EST+SAE	Self.T EST
MDA (nmole/g tissue)	0.36 <sup>#</sup> ±0.02	0.32 <sup>#</sup> ±0.04	1.92*±0.12	0.86* <sup>#</sup> ±0.043	0.41 <sup>#</sup> ±0.022	1.70*±0.06
SOD(U/g tissue)	2.73 <sup>#</sup> ±0.20	2.77 <sup>#</sup> ±0.15	1.13*±0.12	2.13* <sup>#</sup> ±0.18	2.23* <sup>#</sup> ±0.12	1.28*±0.12
CAT(μmole/min/g tissue)	2.97 <sup>#</sup> ±0.15	3.15 <sup>#</sup> ±0.15	0.77*±0.18	2.27* <sup>#</sup> ±0.09	2.50 <sup>#</sup> ±0.12	1.03*±0.13
GSH (mmole/g tissue)	1.81 <sup>#</sup> ±0.05	1.88 <sup>#</sup> ±0.08	0.39*±0.07	1.19* <sup>#</sup> ±0.11	1.65 <sup>#</sup> ±0.04	0.52*±0.11

Values are articulated as means SE. \* and # signify a significant departure from the control group and from the EST group, respectively, at p 0.05.

### 3.3. Kidney histopathology

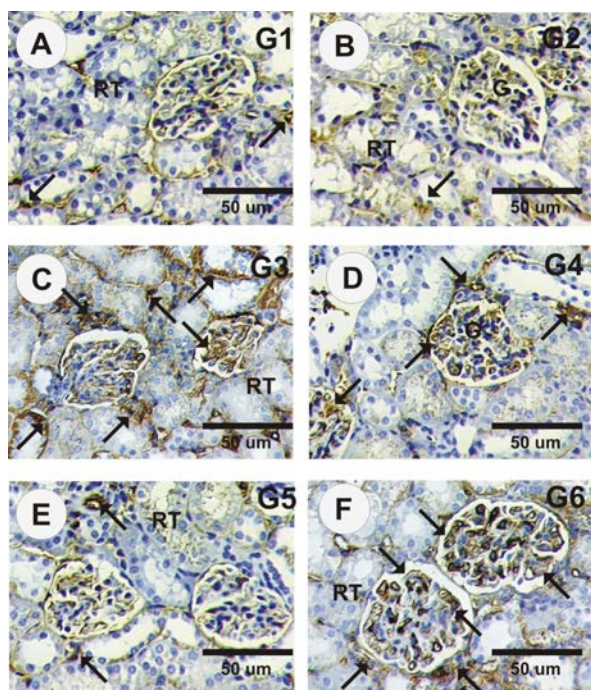
Kidney histological evaluation of cortical and medullary part in control and SAE gps of mice show typical glomeruli and renal tubules structures (Figure 1A and 1B). Conversely, kidney in EST and self-treated EST exposed severe atrophy in glomeruli and, necrotic tubular cells with mild inflammatory cellular infiltration (Figure 1C and 1F). Kidney sections co-treated of EST mice with SAE (EST+SAE) revealed moderate atrophy in glomeruli and renal tubular cells (Figure 1D), while mild atrophy in glomeruli were observed in kidney sections in SAE+EST (Figure 1E).



**Figure 1.** Photomicrographs of H&E -stained kidney sections. A and B: Control and SAE groups; the structure of glomeruli (G) and renal tubules (RT) appear normal. C and F: EST-bearing mice and self-treated EST with SAE revealed severe atrophy in glomeruli (arrows) and, necrotic tubular cells (arrowheads). D and E: Moderate and mild atrophy in glomeruli and renal tubular cells in kidney sections in EST+SAE and SAE+EST respectively.

### 3.4. Changes of TNF $\alpha$ expression in kidney

Regarding TNF $\alpha$  expressions in the sections of control and SAE kidney, fine positive reactions (Figure 2A and 2B), while, our results showed that; TNF- $\alpha$  level was significantly enlarged in EST and self t. EST when compared with the control and SAE (Figure 2C and 2F). Levels of TNF $\alpha$  were significantly decreased in treated EST+SAE and slightly decreased in SAE+EST as compared to their increased in EST (Figure 2D and 2E). These results indicate that star anise extract acts to reduce EST induced nephrotoxicity through its anti-inflammatory effects.



**Figure 2.** Photomicrographs of TNF $\alpha$  stained in kidney sections (arrows). Stained glomeruli and renal tubules show faint expression of TNF $\alpha$  in (A) the control and (B) the SAE groups. Expression was strong in mice with EST and self-treated EST with SAE (C and F), while moderate and mild TNF $\alpha$  in SAE+EST and EST+SAE respectively (D and E).

## 4. Discussion

One of the main causes of death in the globe is cancer (Tousson *et al.*, 2014). Investigating the potential of star anise extract as a therapy for renal damage caused by EST was the aim of the current investigation. As demonstrated by increased blood levels of creatinine, urea, potassium, and chloride and lower levels of sodium, our results suggest that EST induction changed renal function. Renal tissue damage caused by EST may be linked to this alteration in kidney function. Abd Eldaim *et al.* (2019) and Aldubayan *et al.* (2019) found that EST caused renal damage in female mice, and these findings supported their findings. These findings also supported those of Mutar *et al.* (2020) and Abd Eldaim *et al.* (2021), who discovered that; EAC increased renal functioning. According to recent findings, renal functions were enhanced when EST was treated with star anise extract. This outcome is consistent with the findings of Al-Ameri *et al.* (2017), who found that treatments with SAE decreased renal toxicity, electrolyte imbalance, and damage caused by etoposide.

The development of cancer is linked to ROS damaging DNA, which leads to mutations and abnormal chromosomes; these manifest as disruption of tissue structure and tumours. According to research by Jones and Thompson (2009), cancer cells benefit from enhanced antioxidant defense mechanisms that help them adjust to the redox imbalances caused by fast growth. Due to the imbalance between pro oxidants and antioxidants, ROS and oxidative stress are hypothesised to have an influence on the growth and progression of breast cancer (Calaf *et al.*, 2018). According to the current findings, kidney homogenates showed a considerable increase in MDA content in response to EST, whereas GSH, catalase, and SOD levels decreased. These effects were modulated by treating EST with star anise extract.

Therefore, these antioxidant enzymes can reduce the harmful effects of ROS (Mansour and Mossa, 2009). By reducing the amount of MDA and raising the levels of catalase, SOD, and GSH, the current study showed that star anise extract was efficient in regulating antioxidant enzyme activities, indicating that star anise had free-radical scavenging and antioxidant characteristics. These results concurred with those of Hemdan and Abdulmaguid (2020) who reported that EAC induced oxidative stress and the mixture of kiwifruit juice and star anise enhanced these changes. Star anise contains a variety of bioactive substances, including phenolic compounds known as flavonoids, which have been shown to have the ability to control the proliferation and cell death pathways that lead to cancer through a variety of mechanisms, including the inhibition of cell growth and the induction of apoptosis.

Our findings show that the suppression of TNF-dependent intracellular signalling caused the expression of TNF to enhance in kidney sections treated with star anise. According to the aforementioned findings, star anise treatment of the EST enhances renal function, serious destruction to improve TNF- expression, and promotes antioxidant parameters to diminish oxidative stress. El-Masry *et al.* (2020) found that EST caused DNA breakage and an increase in TNF- $\alpha$ , which this data supported.

## 5. Conclusion

Our investigation has demonstrated that star anise administration in EST-bearing mice boosted kidney function and may inhibit cancer cells through apoptosis, hence controlling cancer cell proliferation and preventing the spread of cancer to other organs. Thus, star anise has the potential to perform as a natural chemotherapy and may be applied as a therapeutic that has been modified to support human metabolic homeostasis.

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## Authors' contributions

Maha Elkholy: Contributed materials, reagents, and analytical tools; conducted experiments; and produced the original paper. The original manuscript was written by Ehab Tousson, Fadi Sawaqed, Youssef Hussein and Afaf El-Atrash, who also conceptualized and planned the

experiments, read paper drafts, and approved the final version.

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### Data availability

All the information and resources are accessible from this manuscript. The article itself contains the data for this article.

### Ethical approval and consent to participate

This article is original and contains unpublished material. The corresponding author confirms that we have read and approved the manuscript, and mice were raised and taken care of during the study period in compliance with the Institutional Animal Care Committee-approved animal care handbook for Tanta University's Faculty of Science and use IACUC-SCI-TU-0223.

### Conflict of interests:

All authors declare no conflict of interests.

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