THE POSSIBLE PROTECTIVE EFFECTS OF ACETYLSALICYLIC ACID (ASA) AGAINST CISPLATIN-INDUCED NEPHROTOXICITY IN ADULT ALBINO RATS

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ABSTRACT

Cisplatin-induced nephrotoxicity is related to an increase in lipid peroxidation and oxygen free radicals in kidney. Acetylsalicylic acid (ASA) has been suggested to be an antioxidant besides its well known therapeutic effects and is also known to improve lipid profile via acting as a free radical scavenger. This study aimed to investigate the possible protective effects of ASA on the extent of renal damage in cisplatin-induced nephrotoxicity. A total of 40 rats were divided into four equal groups. The first group was served as vehicle control, the second group (ASA group) was treated with 100 mg/ kg bw, orally, for 5 days, the third group (cisplatin group) was received cisplatin only 7mg/kg bw, i.p., single dose, while the fourth group (ASA + cisplatin group) was administered ASA 100 mg/kg bw, orally for 5 days and cisplatin 7mg/kg bw, i.p., single dose on day 2 of the experiment. Cisplatin administration induced a marked nephrotoxicity as evidenced by a significant decrease in creatinine clearance with severe reduction of renal blood flow and a significant increase in blood urea, serum creatinine and urine volume compared with the control rats. In addition, histopathological assessment revealed marked tubular necrosis, degeneration, tubular dilatation and luminal cast formation. Cisplatin also induced oxidative stress as indicated by significant increase in kidney tissue concentrations of malondialdehyde (MDA) and significant decrease in glutathione (GSH) content of renal tissues. ASA supplementation produced significant increase in creatinine clearance and renal blood flow with significant decrease in blood urea, serum creatinine and urine volume. ASA treatment caused a significant reduction of the elevated renal MDA level and a significant increase in the GSH content of kidney tissues. Furthermore, ASA ameliorated cisplatin-induced pathological changes in kidneys when compared to cisplatin group alone. In conclusion, ASA significantly protected against cisplatin-induced nephrotoxicity and oxidative stress in rat through its antioxidant properties but not enough to inhibit renal dysfunction completely.
INTRODUCTION

Cisplatin [cis-diamminechloroplatinum (II) [CDDP] is a potent antineoplastic agent used for the treatment of a wide range of cancers (Wang et al., 2004).

Cisplatin has a broad spectrum of activity against many different solid tumours such as lung, ovary, testis, bladder and head and neck cancers and is also an effective agent in treatment of some haematological malignancies such as refractory lymphomas (Links and Lewis, 1999), but its severe side effects can limit its usage. These side effects include nephrotoxicity (Arany and Safirstein, 2003), neurotoxicity, ototoxicity (loss of hearing or balance or both), gastrointestinal toxicity and myelosuppression (Blakley et al., 1994). However, its dose-limiting nephrotoxicity is a major clinical problem seen in about 20 % of patients despite the use of saline hydration and diuretics. It's characterized by decreased glomerular filtration and tubular injury (Shimeda et al., 2005). Primary targets of cisplatin in kidneys are proximal straight and distal convoluted tubules, where it accumulates and promotes cellular damage by involving multiple mechanisms including oxidative stress, DNA damage, apoptosis and inflammation (Mohan et al., 2006). Many in vivo and in vitro studies indicate an important role of reactive oxygen species (ROS) in the pathogenesis of nephrotoxicity (Baliga et al., 1998).

Cisplatin induces free radical production causing oxidative renal damage, possibly due to depletion of non-enzymatic and enzymatic antioxidant systems. (Rybak et al., 1995)

Salicylates are among the most commonly used medicines for their anti-inflammatory, analgesic, antipyretic, and antithrombotic properties mostly in the form of acetylsalicylic acid (ASA), which is metabolized to salicylate in serum within 15 to 30 minutes. Although its anti-inflammatory actions are primarily based on an inhibition of the enzyme
cyclooxygenase and possibly on suppression of cylooxygenase-2-transcription (Xu et al., 1999), salicylate has several other properties that may contribute to its therapeutic activity, it can affect the activation of transcription factors, thereby intervening in apoptotic pathways (Yin et al., 1998).

There is very limited data about the effects of ASA on cellular antioxidant system and oxidant status of the body. In a study, it has been reported that ASA in vivo slightly affect lipid peroxidaion and antioxidant enzyme activity in erythrocytes and liver (Kirkova et al., 1995). Similarly, it was suggested that the direct effects of ASA on the integrity of vascular wall has been reported via free radical scavenging properties and its capacity to protect the endothelial cells from the deleterious effects of hydrogen peroxide (Podhaisky et al., 1997). In another, ASA is proposed to be an anti-ischemic substance since it enhances nitric oxide production (Lopez-farre et al., 1996). In a previous study, it's even suggested that ASA treatment increases plasma antioxidant activity (McGahan, 1990).

Therefore, the goal of the current study was to determine the possible nephroprotective role of ASA against cisplatin-induced nephrotoxicity in male adult albino rats.

MATERIAL AND METHODS

Drugs

- **Cisplatin** (10 mg /10 ml), product of Aventis Pharma, in the form of solution. It was injected intraperitoneally in a single dose of 7 mg/kg bw. The dose of cisplatin was selected according to previous work that demonstrated significant damage in renal parameters of rats (Atessahin et al., 2006).

- **Acetylsalicylic acid** (aspirin, ASA), product of Chemical Industries Development (CID), in the form of tablet. It was dissolved in 5% aqueous solution of gum acacia to form a uniform suspension. ASA
was given in a daily oral dose of 100 mg/kg bw for 5 days via an appropriate sized tube specific for gastric intubation of rats (Tauseef et al., 2007).

**Animals:**

Forty male albino rats of a uniform strain, weighting 150-200 gm were used in the present study. They were divided into 4 equal groups and housed under constant environmental conditions, and were kept for a 7 days acclimatization before use, food and water were freely allowed.

The rats were randomly divided into 4 groups (n = 10 each):

- **Group 1:** Control group, was received 1 ml of aqueous solution of gum acacia via gastric tube for 5 days and a single i.p. dose of 0.9 % saline on day 2.
- **Group 2:** ASA-treated group, was received ASA in the form of uniform suspension in aqueous solution of gum acacia via gastric tube in a daily oral dose of 100 mg/kg bw for 5 days and a single i.p. dose of 0.9 % saline on day 2.
- **Group 3:** Cisplatin group, was received 1 ml of aqueous solution of gum acacia via gastric tube for 5 days and treated with cisplatin i.p. in a single dose of 7 mg/kg bw on day 2.
- **Group 4:** ASA and cisplatin treated group was administered ASA orally in a dose of 100 mg/kg bw for 5 days and a single i.p. dose of 7 mg/kg bw of cisplatin on day 2 of the experiment.

The experiment was conducted for 5 days. At the end of the experimental period, the animals were placed in individual metabolic cages for 24 hours; urine was collected for measurement of urine volume. Then the rats were anaesthetized with thiopentone 40 mg/kg. The abdominal cavity was opened through a midline incision, the kidneys and the renal arteries were exposed. A transonic flow probe (Hadeco 10 MH) was placed on top of the right renal artery for the measurement of renal blood flow by a flowmeter (Hadeco ES 1000 SPM, Japan). Blood
samples were collected from the descending aorta. The kidneys from each rat were excised and washed with cold normal saline and divided into two parts, one part for biochemical analysis and the other part for histopathological examination.

Each sample of blood was centrifuged at 3500 r.p.m. for 10 minutes and the serum was separated for spectrophotometric determination of blood urea and serum creatinine levels.

**Biochemical analysis:**

1. **Spectrophotometric determination of serum urea and creatinine levels:**
   - Blood urea was measured in mg/dl according to *Patton and Crouch* (1977).
   - Serum creatinine was measured in mg/dl according to the method of *Fabiny and Ertingshausen* (1971).

2. **Determination of creatinine clearance:**
   - Creatinine clearance was estimated in ml/min. according to the following equation:
     \[
     \text{Creatinine clearance} = \frac{\text{mg creatinine} \times \text{urine} \times \text{ml urine} / \text{24 hrs}}{\text{mg creatinine} \times \text{urine} \times \text{ml serum} \times 1440} \text{ ml/min.}
     \]

3. **Determination of renal MDA and GSH:**
   One gram of each kidney was homogenized in ice cold phosphate buffer (0.1 M, pH 7.4) at a concentration 30% and centrifuged at 3000 r.p.m. for 15 minutes. The supernatant obtained was used for estimation of MDA and GSH (*Wills, 1966*). MDA was measured in renal tissues in nmol/mg wet weight by the method described by *Zdenek* (1966). Glutathione was determined in µmol/g protein in renal tissues according to *Ellman* (1959).
Histopathological Examination:

Kidneys for light microscopy were fixed in 10 % formalin, embedded in paraffin and sectioned at 5 μm in thickness. Sections were stained with haematoxylin and Eosin (Hx. & E.) according to Drury and Wallington (1980).

Statistical Analysis:

The experimental data are expressed as mean ± S.D. The data were analyzed by the student t-test. The differences were considered to be statistically significant when P < 0.05.

RESULTS

Table (1) shows insignificant difference (P > 0.05) in the mean values of renal blood flow, urine volume, blood urea, serum creatinine and finally creatinine clearance between the control group (group 1) and the ASA-treated rats (group 2). Cisplatin administration (group 3) produced, significant decrease (P < 0.05) in renal blood flow and creatinine clearance. At the same time, there was a significant (P < 0.05) increase in mean values of blood urea, serum creatinine and urine volume compared with control group (group 1).

Regarding the protective effects of ASA (group 4), there was a significant (P < 0.05) increase in the renal blood flow and creatinine clearance. At the same time, the level of blood urea, serum creatinine and urine volume showed a significant (P < 0.05) decrease when compared with cisplatin group (group 3). However, these parameters showed a significant (P < 0.05) decrease in renal blood flow and creatinine clearance while the level of blood urea, serum creatinine and urine volume showed a significant (P < 0.05) increase when compared with control group (group 1) (Figs. 1-5).
Table (1): Effect of cisplatin administration on renal and urinary functional and biochemical parameters and the protective effect of ASA.

<table>
<thead>
<tr>
<th></th>
<th>Renal blood flow (cm/s)</th>
<th>Urine volume (ml/24 hrs)</th>
<th>Blood urea (mg/dl)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Creatinine clearance (ml/min.)</th>
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<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
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<tr>
<td>Group (1) n = 10</td>
<td>4.03 ± 0.47</td>
<td>13.45 ± 2.35</td>
<td>26.8 ± 6.43</td>
<td>0.85 ± 0.25</td>
<td>1.2 ± 0.16</td>
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<tr>
<td>ASA-treated group</td>
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</tr>
<tr>
<td>Group (2) n = 10</td>
<td>3.91 ± 0.44</td>
<td>14.55 ± 2.51</td>
<td>25.8 ± 5.86</td>
<td>0.91 ± 0.24</td>
<td>1.3 ± 0.16</td>
</tr>
<tr>
<td>Cisplatin group</td>
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<tr>
<td>Group (3) n = 10</td>
<td>1.96 ± 0.27*</td>
<td>26.2 ± 4.9*</td>
<td>83.1 ± 13.64*</td>
<td>3.14 ± 0.84*</td>
<td>0.66 ± 0.18*</td>
</tr>
<tr>
<td>Cisplatin + ASA-treated</td>
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<tr>
<td>Group (4) n = 10</td>
<td>2.71 ± 0.28* #</td>
<td>19.55 ± 2.78* #</td>
<td>38.1 ± 8.37* #</td>
<td>1.27 ± 0.421* #</td>
<td>0.8 ± 0.118* #</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± S.D.

* P < 0.05 significant difference when compared to control group.
# P < 0.05 significant difference when compared to cisplatin group.
Table (2) shows non-significant difference in the mean values of renal MDA and renal GSH content in ASA-treated group (group 2) when compared with control group (group 1).

Cisplatin administration (group 3) resulted in oxidative stress which was manifested by a significant (P < 0.05) increase in the mean value of renal MDA and a significant (P < 0.05) decrease in renal GSH content when compared with control group (group 1).

ASA supplementation (group 4) resulted in modulation of cisplatin induced oxidative stress which was manifested by a significant (P < 0.05) decrease in the level of MDA and a significant increase in renal GSH in the rats which treated with cisplatin and ASA (group 4) when compared with rats treated with cisplatin only (group 3). At the same time, renal MDA showed a significant (P < 0.05) increase and renal GSH content showed a significant (P < 0.05) decrease in rats treated with ASA and cisplatin (group 4) when compared with control group (group 1) (Figs. 6, 7).

Table (2): Effect of cisplatin administration on renal malondialdehyde (MDA) and renal glutathione (GSH) content and the protective effect of ASA.

<table>
<thead>
<tr>
<th></th>
<th>Renal MDA (nmol/mg)</th>
<th>Renal GSH content (µmol/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group (1) n = 10</td>
<td>1.41 ± 0.19</td>
<td>20.6 ± 3.4</td>
</tr>
<tr>
<td>ASA treated group</td>
<td></td>
<td></td>
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<tr>
<td>Group (2) n = 10</td>
<td>1.45 ± 0.32</td>
<td>19.04 ± 1.7</td>
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<tr>
<td>Cisplatin group</td>
<td></td>
<td></td>
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<tr>
<td>Group (3) n = 10</td>
<td>3.14 ± 0.37*</td>
<td>9.03 ± 1.2*</td>
</tr>
<tr>
<td>Cisplatin + ASA treated group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group (4) n = 10</td>
<td>2.46 ± 0.31* #</td>
<td>11.64 ± 2.02* #</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± S.D.
* P < 0.05 significant difference when compared to control group.
# P < 0.05 significant difference when compared to cisplatin group.
**Histopathological results:**

The impaired renal function induced by cisplatin was further confirmed by histological examination of kidney under light microscopy.

As shown in (Figs. 8, 9), the kidney from control group (group 1) or ASA-treated rats (group 2), showed no abnormality whereas the kidney in cisplatin-treated rats (group 3) revealed a marked and severe acute tubular necrosis, the tubules devoid of tubular epithelial cells, leaving a denuded basement membrane, with intraluminal collections of necrotic cells (epithelial cast) (Fig. 10).

The tubular epithelial changes were less severe with regeneration of tubular epithelial cells in group treated with cisplatin and ASA (group 4) when compared with cisplatin-treated rats (group 3) (Fig. 11).
**Fig. (1):** Effect of cisplatin administration on renal blood flow and the protective effect of ASA.

**Fig. (2):** Effect of cisplatin administration on blood urea and the protective effect of ASA.

**Fig. (3):** Effect of cisplatin administration on urine volume and the protective effect of ASA.

**Fig. (4):** Effect of cisplatin administration on serum creatinine and the protective effect of ASA.
Fig. (5): Effect of cisplatin administration on creatinine clearance and the protective effect of ASA.

Fig. (6): Effect of cisplatin administration on renal MDA and the protective effect of ASA.

Fig. (7): Effect of cisplatin administration on renal GSH content and the protective effect of ASA.
Trace recording of renal blood flow in the four experimental groups.
**Fig. (8):** A photomicrograph of a kidney section of the control group (group 1) showing normal tubules and glomeruli (Hx. & E. x 400).

**Fig. (9):** A photomicrograph of a kidney section of ASA-treated rats (group 2) showing normal tubules and glomeruli (Hx. & E. x 400).
**Fig. (10):** A photomicrograph of a kidney section of cisplatin-treated rats (group 3) showing severe tubular necrosis (Hx. & E. x 400).

**Fig. (11):** A photomicrograph of a kidney section of ASA + cisplatin-treated rats (group 4) showing mild tubular necrosis with regenerated tubular cells (Hx. & E. x 400).
DISCUSSION

Cisplatin is an effective chemotherapeutic agent for a wide variety of tumours. Nevertheless, nephrotoxicity is the major complication of this antineoplastic treatment (Chirino et al., 2004). The alterations in renal function observed in rat models correlate well with the nephrotoxic effects of cisplatin in patients treated with this antitumor agents (Daugaard et al., 1988).

In the present study, a single dose of cisplatin (7 mg/kg bw) in rats resulted in the deterioration of renal function manifested by significant reduction of the renal blood flow (RBF) and creatinine clearance and significant increase in urine volume, blood urea and serum creatinine in a comparison with the control group. Acute nephrotoxicity was confirmed by histopathological changes including severe acute tubular necrosis, degeneration, luminal cast formation and tubular dilatation. The results of several studies (Bagnis et al., 2001; Mora et al., 2003; Atessahin et al., 2005) are in accordance with our previous findings.

A decreased glomerular filtration rate (GFR), evidenced by decreased creatinine clearance and increased plasma creatinine levels, has been observed following cisplatin administration (Arany and Safirstein, 2003). It has been previously shown that the reduced glomerular filtration rate (GFR) in the early cisplatin induced renal failure is due, in part to reversible decrease in renal blood flow which is mainly due to increase renal vascular resistance (Winston and Safirstein, 1985).

In addition, Barros et al. (1989) concluded that cisplatin administration induced non-oliguric acute renal failure by decreasing GFR and by increasing urinary volume.

The kidneys accumulate and retain platinum complexes to a greater extent than other organs, perhaps via mediated transport, and it's the main excretory outlet for either intravenous or intraperitoneal cisplatin (Arany
and Safirstein, 2003). In this study, cisplatin-induced renal impairment included an increase in urinary volume. This is in agreement with Antunes et al. (2000). The polyuria observed 5 days following cisplatin administration may be due to impairments in the proximal tubules and thick ascending limb of Henle without changing the response of the papillary collecting duct to antidiuretic hormone (Seguro et al., 1989). This effect has previously been linked to an altered release of antidiuretic hormone (Gordon et al., 1982).

Induction of nephrotoxicity by cisplatin is assumed to be a rapid process involving reaction with proteins in the renal tubules (Montine and Borch, 1990). Because this renal damage occurs within one hour after administration (Rao and Rao, 1998), it is important that the protective agent is present in renal tissue before damage occurs, so ASA was administered one day before cisplatin. Maximum toxic effects of cisplatin were observed 5 days after its injection, while it started after day 1 in the biochemical parameters, such as glutathione depletion in the kidney tissue with concomitant increases in lipid peroxides and platinum content (Al-Majed et al., 2003).

In this work, acetylsalicylic acid (ASA) administered in daily oral dose of (100 mg/kg) for 5 days significantly reduced the development of cisplatin-induced nephrotoxicity as evidenced by significant decrease in urine volume, serum urea and creatinine level and significant increased in renal blood flow and creatinine clearance compared with the cisplatin group. The protective effect of ASA was confirmed by histopathological evaluation of kidney preparation in the group treated with ASA and cisplatin which showed a decrease in tubular necrosis and other pathological changes compared with cisplatin group indicating that the functional changes may have a morphological correlate.

The mechanisms by which cisplatin causes renal damage is unclear, however, it has been suggested that lipid peroxidation is the
major mechanism linked to cisplatin induced nephrotoxicity (Yang et al., 2002). Results obtained from our study indicate that cisplatin increases lipid peroxidation. Renal tissue malondialdehyde (MDA), a lipid peroxidation product, was significantly increased compared with the control group. In addition, glutathione level was significantly decreased after cisplatin therapy.

These data are in a good agreement with previous studies (Shimeda et al., 2005; Mohan et al., 2006). However, the results of other studies showed that GSH level was not changed. This status was explained by the positive regulation in the glutathione biosynthesis which occur under oxidative stress conditions resulting in the increased level of GSH contents (Tian et al., 1997; Yilmaz et al., 2006).

The increase of MDA level and the decrease of GSH content in renal tissue may be a secondary event following the cisplatin-induced increase in free radical generation and decrease in lipid peroxidation protecting enzymes. Cisplatin can cause the generation of oxygen free radicals such as hydrogen peroxide, superoxide anions and hydroxyl radicals. The hydroxyl radical is capable of abstracting a hydrogen atom from polyunsaturated fatty acids in membrane lipids to initiate lipid peroxidation. These radicals can evoke extensive tissue damage, reacting with macromolecules, such as membrane lipids, proteins and nucleic acids (Antunes et al., 2000; Emerit et al., 2001). Moreover, depletion of glutathione, a potent free radical scavenger, may contribute to cisplatin-induced lipid peroxidation (Antunes et al., 2000).

It has been reported that administration of cisplatin to normal rats resulted in depletion of glutathione and subsequent potential of lipid peroxidation in kidney cortical slices (Nakano and Gemba, 1989) and there was a relation between the cisplatin-induced nephrotoxicity and depletion of glutathione content of kidney tissue (Zhong et al., 1990). The reduced glutathione was reported to protect cells from cytotoxic damage by
many compounds (Ketterer et al., 1983) and it is generally known as a potent factor in the control of lipid peroxidation (Younes and Siegers, 1980). The role of GSH depletion with the consequent lipid peroxidation in cisplatin-induced nephrotoxicity is confirmed by the data presented by Anderson et al. (1989), who has demonstrated that administration of reduced glutathione protects against cisplatin-induced nephrotoxicity.

It is known that inhibiting the prostaglandin generating system is the mechanism of ASA. Since free radicals are generated through the prostaglandin synthesis reaction, aspirin has been accepted to inhibit this sequence and to prevent peroxidation (Kukreja et al., 1986).

In the current study, administration of ASA for 5 days significantly attenuated cisplatin-induced increase in lipid peroxidation. MDA level was significantly decreased compared with the cisplatin group. In addition, glutathione level was significantly increased in ASA and cisplatin-treated group compared with the cisplatin group. The protective action of ASA is associated with its antioxidant properties, as it possibly acts as a free radical scavenger (Ghiselli et al., 1992, Powell, 1994) and an inhibitor of lipid peroxidation (McGahan, 1990).

Shi et al. (1999) reported that ASA exhibited a protective effect against silica-induced lipid peroxidation through its antioxidant property and its ability to scavenge hydroxyl (OH) radicals.

O'Connell and Webster, (1990) reported that salicylate is a hydroxyl radical scavenger in both experimental animals and humans who are experiencing oxidative stress. In addition ASA and salicylate protect against 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) induced dopamine depletion, a reaction involving free radicals (Aubin et al., 1998). A similar scavenging role may be played by salicylate in the prevention of aminoglycoside-induced hearing loss (Sha and Schacht, 1999). Recently, Tauseef et al. (2007) concluded that ASA treatment induced significant decrease in lipid peroxidation and significant increase
in reduced glutathione content in serum in hypercholesterolemic rats. Furthermore, ASA may have antineoplastic properties (Thun et al., 1993), making this drug even more attractive as a supplemental therapy in cancer treatment.

In conclusion, the present study suggest that ASA provides partial but significant protection against cisplatin-induced nephrotoxicity through inhibition of lipid peroxidation by scavenging free radicals and increasing intracellular concentration of glutathione. Maintenance of renal blood flow may also play a role. Thus, ASA may be considered as a potentially useful candidate in the combination chemotherapy with cisplatin but further clinical studies are required to evaluate its protective effects and to determine the exact mechanism of ASA.

REFERENCES:


الملخص العربي

التأثير الواقى المحتمل لحامض الأسيتيل ساليسيليك ضد تسمم الكلى المشتت بالسيسبلاتين في الفئران البيضاء البالغة

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تضم الكلى المستحث بالسيسبلاتين برتبطه بقدرته على زيادة كميات الدهون وزيادة انتاج الشوارد الحرة في الكلى. كما أنه قد ثبت في عدة دراسات سابقة أن حامض الأسيتيل ساليسيليك له نشاط مضاد للأكسدة.

الهدف من البحث هو تقييم التأثير الواقى لحامض الأسيتيل ساليسيليك ضد التأثير

السامي المستحث بالسيسبلاتين على الكلى في فئران التجرب البالغة.

وقد أظهرت النتائج أن إعطاء السيسبلاتين جرعة واحدة 7 ملليجرام لكل كيلو جرام في التجويف البرينوني يسبب في إحداث اختلال بوظائف الكلى مما أدى لحدوث انخفاض ذو دلالة إحصائية في معدل استخلاص الكرياتينين ومستوي السمن الدم بالمراجع الكلوية والارتفاع ذو دلالة إحصائية في مستوى البروريا والكرياتينين وتذوق البول مقترنة بالمجموعة الضابطة. هذا بالإضافة لتغيرات هستوپاثولوجية مرضية. كما أن إعطاء السيسبلاتين للفئران أحدث خللًا في أكسدة الدهون مما أدى إلى ارتفاع ذو دلالة إحصائية في مستوى المالونيالدهيد في الكلى وانخفاض ذو دلالة إحصائية في مجموعة الجلوتاتين في الكلى.

إعطاء حامض الأسيتيل ساليسيليك بجرعة 100 ملليجرام لكل كيلو جرام بالفم لمدة خمسة أيام مع إعطاء السيسبلاتين بنفس الجرعة السابقة في اليوم الثاني أدى إلى ارتفاع ذو دلالة إحصائية في معدل استخلاص الكرياتينين ومستوى السمن الكلوي وانخفاض ذو دلالة إحصائية في مستوى البروريا والكرياتينين وتذوق البول. كذلك أدى إلى انخفاض ذو دلالة إحصائية في مستوى المالونيالدهيد في الكلى وارتفاع ذو دلالة إحصائية في المجموعة في كلي فئران المجموعة المعززة. كما حدث تحسن ملحوظ في التغيرات الهستوپاثولوجية للكلى مقترنة بالمجموعة التي حققت بالسيسبلاتين فقط.

خلاصة ما سبق يتضح أن إعطاء حامض الأسيتيل ساليسيليك أدى إلى وقاية الكلى من التسمم المستحث بالسيسبلاتين في فئران التجرب البالغة وهذا يرجع إلى نشاطه كمضاد للأكسدة ولكن هذا بدرجة غير كافية لمنع هذا التسمم الكلى نهائياً.