Iraqi Journal of Veterinary Sciences

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Protective effect of quercetin against corneal toxicities induced by cisplatin in male mice

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Article information

Article history:
Received May 16, 2021
Accepted July 11, 2021
Available online March 10, 2022

Keywords:
Cisplatin
Cornea
Histopathology
Quercetin

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Abstract

The Aim of study was conducted to evaluate the potential protective role of quercetin against the corneal toxicity which caused by administration of cisplatin in male mice. Thirty-six adult male albino mice were divided into three equal groups; Group I control, Group II cisplatin mice injected as single dose I.P of cisplatin 10 mg/kg, and Group III mice received Q 75 mg/ kg with cisplatin 10 mg/ kg. The treatment continues for eight days then the tissues were collected for histopathological study. The histopathological changes in the cornea of eye were demonstrated in groups of mice received cisplatin. The changes represented by damages of superficial epithelial layer, vacuolar degeneration, hyperplasia, separation of stromal layer and sever damage of the stromal hemorrhage, and perforation of sclera, edema and inflammatory cells infiltration as well as separation of descement membrane from stroma layer. While these changes were diminished when the mice are treated with Q in the combination of cisplatin in comparison to treated cisplatin alone mice. Cisplatin induced structural and histopathological changes in the cornea of adult albino rat that could be ameliorated by concomitant treatment with quercetin.

DOI: 10.33899/ijvs.2021.130145.1741,

Introduction

Cancer chemotherapy has the potential effect to produce damage in some organs and these damages were varied from organs to others (1,2), the eye is one of important organs which is usually regarded as actuary site, and has a greater degree for sensitivity to different toxic agents (3). The wide uses of anti-cancer drugs have resulted in toxicities in patients. Consequently, the main side effects were recorded in eyes as a secondary effect to these agents which was includes disturbance effecting the physiological, biochemical and histological, changes of the eyes (4). Cisplatin (cis-diamminedichloroplatinum) (Cis) a heavy metal compound, is an alkylating anti-cancer agents which are used in different kinds of tumors including tumor of the gonads, bladder cancer, lung cancer and breast cancer, as well as leukemia such as lymphoma (5). Therefore, their use is very limited due the side effects as toxicity in different organs of the bodies like kidney, eyes and nervous system (6,7). As well as cisplatin causes toxic effect in different healthy tissues by participation of formation of (ROS), such as damage of mitochondria, inhibiting anti-oxidant enzymes, and releasing some of free radicals (8). These products may contribute with anti-oxidant defense mechanisms acquire tissue damage, due to formation by free radicals, as well as mutagenic activity of cisplatin. Furthermore, DNA damage formation of lipid peroxidation (9) also which is one source to the response of cispaltin management was recorded (10,11). The toxicity of eyes induced by chemotherapy in anticancer treatment is not very common, but under estimation. Visual disturbance has been observed to a variety of anti-cancer drugs used in human. Cisplatin is recorded to causes non-specific blurred vision, edema of eyes and inflammation of nerve neuritis with high doses, beside the

cumulative dose regimens (12). While the systemic effect of chemotherapies can induce both chronic and acute damage of organs, in the eye is recorded as one of important organs. In other hand, it has been recorded that the side effects of eyes with anti-cancer drugs was not common. Less compared to other organs, the oculo-visual system has showed a more effective damage to the toxic agents (13). Flavonoids are naturally occurring polyphenolic compounds synthesized by plants and having many pharmacological activities. They act as powerful free radical scavengers protecting the human body through the OH group present in their molecular structure. They include six major classes: flavonols, flavones, flavanones, catechins, anthocyanidins and isoflavones (14). Quercetin (Q) is regarded one of natural flavonoids present in variety vegetables and fruits as Onion, Apples, Red wine, Potatoes, Broccoli, soybeans, and Green tea. Many of experimental studies have showed that many effective qualities, such as anti-infarction, hypolipidemic, cyto-protective, anti-angiogenic, antispasmodic, antimutagenic, antiplatelet, antihypertensive, antioxidant, anti-inflammatory, antithrombotic, anti-cancer, antiproliferative and antiviral (15-19). Many researches showed several cancer toxicity models, therefore, Q is recorded one of important to natural flavonoids against the toxicity and damage of tissues which is caused by these anti-chemotherapeutic substances (20,21).

The aim of our study was to investigate the further ameliorative effect of Q on cisplatin induced corneal changes in mice and protective role.

Materials and methods

Experimental animals

A total number of 36 Male Albino mice weighting 250-300gm were obtained from the animal house of college of Veterinary Medicine, Duhok University. The mice used in this study were housed in a special way at normal condition as temperature of about 24°C as well as all mice was allowed for obtained source of foods and tap water under laboratory experiment until end of experiment (22). The study was approved by Animal Ethics Committee of the College of Veterinary Medicine, University of Duhok.

Experimental design

The mice were randomly divided into 3 groups (twelve Mice for each groups). Group I: Mice administered with equivalent volume of distal water 2ml orally. Group II: Mice given a single dose of cisplatin 10 mg/kg (I.P) intraperitoneally. Group III: Mice given Quercetin 75mg/kg orally once for 7 days before and 7 days after a single dose of cisplatin 10 mg/kg I.P (23, 24).

Histopathological study

After the end of experiments, the mice were scarified at 8th day for all of three groups and specimens from eye were obtained. Then were fixed in neutral buffer formalin10%, for 48 hrs. specimens dehydrated with gradual concentration of ethanol. Then by using of xylene for clearing and finally embedded in pure paraffin wax at a melting point. A serial section about (6,7,25,26) micrometers in thickness were prepared using rotatory microtome (Leica, Germany) and stained with Harris hematoxylin and eosin (H&E). The prepared slides were examined and photographed using a light microscope provided with digital camera (27,28).

Results

Microscopical examination of control mice group appears as normal structure layers of the cornea. Is composed of a single layer of basal columnar cells set on the basement membrane and 4-5 cell layers of non-keratinized, stratified squamous epithelial cells. The corneal epithelium represented continuing on a uniform basement membrane underneath which is called the Bowman's membrane. The corneal stroma formed from orderly organized of collagen fibrils in equal with each other. The keratocytes cells which appears as flattened cells called (fibrocytes) are found within the layers of collagen fibers. The distribution of the collagen fibers is account for the translucence of the cornea. Descemet's membrane appeared under of the stroma and its wrapped by Descemet's endothelium (Figure 1).

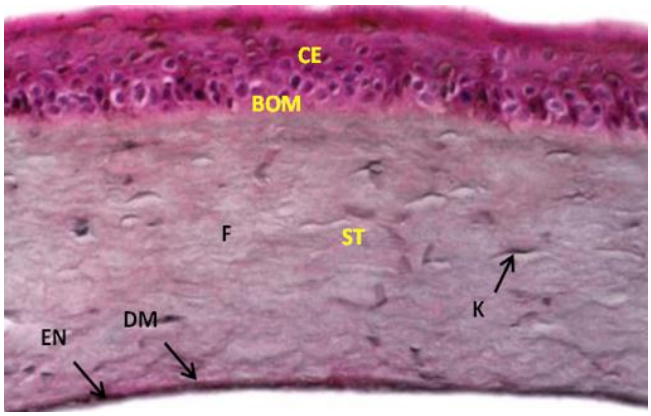

Figure 1: Microphotography of rat cornea of control group showed the normal structures of eye. corneal epithelium (CE), Bowman's membrane (BOM), keratocytes (K), collagen fibers (F), Descemet's membrane (DM) stroma (St), and endothelium (EM). H&E, 200x.

Results of histological examination of eye sections of mice treated with cisplatin 10 mg/kg showed sever histopathological observation in the cornea of eyes, these observation were included changes of superficial epithelial layer, degeneration (vacuolar), increase of number of cells (hyperplasia), separation and damage of stroma layer beside severe changes of the stroma fibers, hemorrhage and congestion, perforation of cornea, edema and infiltration of

inflammatory cells as well as separation Descemet's membrane from stroma layer were seen compared to control group (Figure 2 and 3).

Furthermore, these damages were diminished when the mice received Q with cisplatin comparison with alone, the study also showed there were clear improvement of the corneal structure no changes were observed in stroma which is appears as normal (Figure 4).

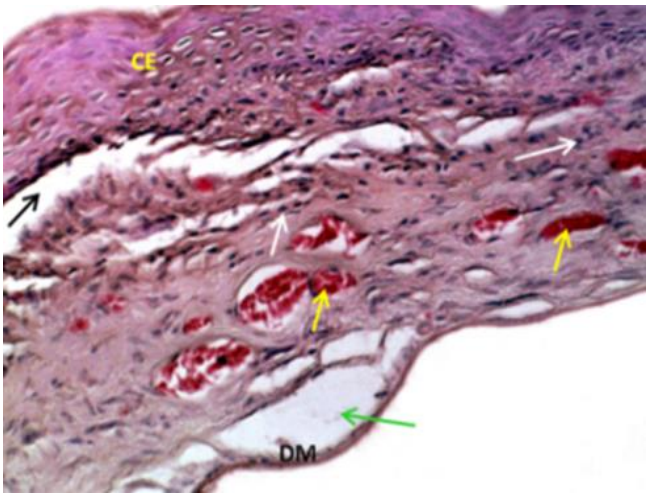

Figure 2: Microphotography of rat cornea of group II (Cisplatin) Cisplatin 10mg showed hyperplasia of superficial epithelial layer (CE) and separation from stroma (black arrow), edema (green arrow), infiltration inflammatory cells (white arrow), hemorrhage of sclera (yellow arrow) and separation Descemet's membrane from stroma (DM). H&E, 200x.

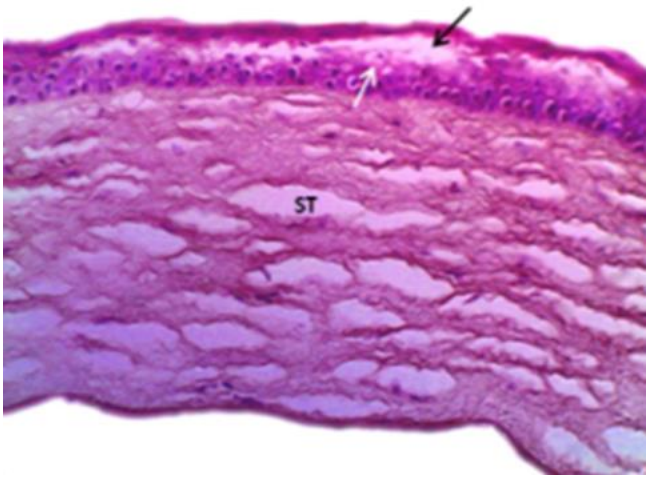

Figure 3: Microphotography of cornea of eye mice with Cisplatin 10mg showed damage of superficial epithelial tissue (black arrow), vacuolar (white arrow) and damage of stroma fibers (ST). H&E 200x.

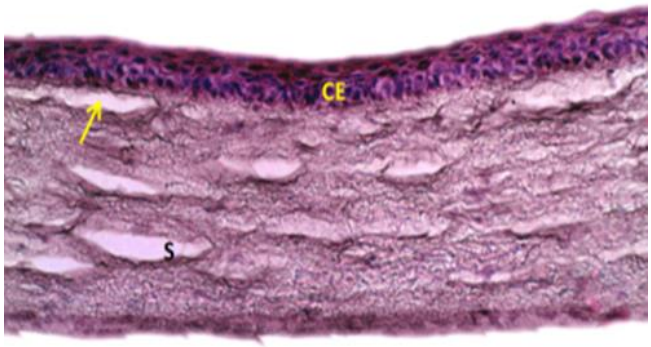

Figure 4: Microphotography of cornea of eye mice with (Cisplatin) 10mg with Q group showed slight normal structure of superficial epithelial tissue (CE) and separation from stroma (yellow arrow), and intrcorneal edema (S). H&E, 200x

Discussion

Anti-cancer which represented general as a chemotherapies and has eventual to induce some alteration in different organs of the body, while the eye is recorded as potential site since the ocular-visual structure has a more resistance for sensitivity to the toxic agents (13,29,30). The general toxic effect of tissues is due to oxidative stress and free radical's formation which have been shown (31-34). While the previous studies shown the ocular damage of the cisplatin has been observed beside sever infiltration of inflammatory cells to the central nervous system (35,36).

In the current study the main side effect which observed after cisplatin treatment was altered the histological structure of the cornea and caused deformations especially in the epithelial layer that appeared desquamated. The remaining epithelium was vacuolar and degenerated having pyknotic nuclei. These results were similar to those observed by N-Ethyl- N-Nitrosourea (ENU) in mice treated with 600 mg/ kg group for 7 days (37) as well as to those induced by cisplatin treatment (38). In addition, these results were consistent with the clinical results of Waikhom *et al.* (39) who recorded two cases having decreased vision and ocular irritation, beside corneal deposits associated with drug capecitabine use. Moreover, such corneal structural changes were consistent with the clinical findings in patients receiving other anti-chemotheraputic alkylating agents who complain of photophobia, foreign body sensation and tearing due to corneal epitheliopathy (40).

Wide spaces were observed between the collagen bundles in the stroma, and this indicates corneal edema. This was accompanied by a sign of inflammation in the form of mononuclear cellular infiltration in the anterior region of the stroma. This comes in agreement with the previous work Al-Gebaly (41). The cellular inflammatory infiltration of stroma due to high increase of interleukin-1β (IL-1β) from the

damage epithelial cells. This cytokine is recorded a multi-potent cytokine involved in acute inflammatory response which leading to increase infiltration of inflammatory cells such as macrophages and neutrophils (42).

Flavonoids consider potent anti-oxidant effects due to their capacity to act as blocking of free radical formation. Inside of the flavonoid family, the quercetin is the recorded the important powerful blocker of ROS, including superoxide, peroxyl, alkoxyl and hydroxyl radicalos, peroxynirrite and reactive nitrogen species (RNS) such as nitric oxide (NO) (43-55).

At the protective level, quercetin was introduced to examine its probable role in alleviating the cisplatin induced corneal toxicity. Results from this study clearly observed that quercetin has an evident improvement in the corneal structural changes. This could be due to the effect of antioxidant capacity of flavonoids. Many studies recorded that quercetin accelerated the antioxidant defense mechanisms and diminished the oxidative stress effect. In addition, other studies proved that quercetin is a hydrogen-donor and a free-radical scavenger (56-60).

The study showed pretreatment with quercetin caused decreased the inflammatory cellular infiltration. This anti-inflammatory effect of quercetin has been contributed to its effect on the prostaglandin synthesis with the cyclo-oxygenase-2(COX-2) pathway which is reported by many in vitro and in vivo studies (43,61).

Based on the previous results, the current study suggests that quercetin beneficial in minimizing the cisplatin-induced corneal structural changes in mice. Therefore, quercetin a useful therapeutic agent for the patient undergoing chemotherapeutic treatments with cisplatin drug to decrease its corneal complications.

Conclusion

A recent study showed the corneal cellular injury that can appear in the eye when using the anti-cancer drug cisplatin, which was represented by several different pathological lesions, particularly necrosis and haemorrhage. Quercetin's protective role in reducing the percentage of pathological lesions in the eye cornea of male mice treated with cisplatin was also indicated and observed. As a result, quercetin can be considered a therapeutic substance to reduce the risk of pathological changes caused by anti-cancer drugs, especially cisplatin. As a matter of fact, quercetin acts as both a hydrogen donor and a reactive oxygen species scavenger.

Acknowledgment

The authors are grateful to the University of Mosul, and the Deanship of the College of Veterinary Medicine at the University of Dohuk, Iraq for improving the facilities that aided in the improvement of this research.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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التأثير الوقائي للكيورستين ضد التسمم القرني الناجم عن استخدام عقار السيسبلاتين في ذكور الفئران

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الخلاصة

هدف الدراسة هو معرفة الدور الوقائي المحتمل للكيورستين ضد التسمم القرني الناجم عن معاملة ذكور الفئران بالسيسبلاتين. قسمت ستة وثلاثون من ذكور الفئران البيض البالغة إلى ثلاثة مجاميع متساوية. المجموعة الأولى (السيطرة)، المجموعة الثانية (سيسبلاتين) حقنت الفئران في الخلب بجرعة مفردة من السيسبلاتين بتركيز ١٠ ملغم/كغم. والمجموعة الثانية جرعت الفئران مادة الكيورستين بتركيز ٧٥ ملغم/كغم مع السيسبلاتين ١٠ ملغم/ كغم. استمر العلاج حتى اليوم الثامن، بعد ذلك جمع النسيج لغرض الدراسة المرضية النسيجية. ظهرت تغيرات مرضية نسجية في قرنية عيون الفئران المعالجة بالسيسبلاتين. التغيرات المسجلة هي أضرار في الطبقة الظهارية السطحية، تنكس فجوي، تضخم، تلف طبقة السداده وانفصالها. فضلاً عن ذلك ظهرت نتيجة بدرجة أكبر منها تلف شديد في الياف السداة، نزف وثقب القرنية، وذمة وارتشاح الخلايا الالتهابية وكذلك انفصال غشاء دسمنت عن طبقة السداة، بينما انخفضت هذه التغيرات عند معاملة الفئران بالكيورستين بالمشاركة مع السيسبلاتين مقارنة مع الفئران المعالجة بالسيسبلاتين لوحده. أحدث السيسبلاتين تغيرات مرضية نسجية وتركيبية في قرنية فئران البيض البالغة ومن الممكن تحسين هذه التغيرات عن طريق مرافقة العلاج بالكيورستين.

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