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HEALTH SCIENCES

Effect of Rutin on Cytarabine-Associated Pulmonary Oedema and Oxidative Stress in Rats

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Abstract: Cytarabine is effectively used in the treatment of adult acute leukemia, but it has a dose-limiting side effect of fatal pulmonary oedema because it increases the vascular permeability of the alveolar capillaries. The aim of the present study was to conduct a radiological, biochemical and histopathological investigation of the effect of rutin on cytarabine-associated pulmonary oedema in rats. Rats were treated with a combination of rutin+cytarabine by administering oral rutin at a dose of 50 mg/kg; other rat groups were orally administered the same volume of physiological saline. One hour after administration of rutin or saline, the rutin+cytarabine and cytarabine groups received an intraperitoneal injection of cytarabine (200 mg/kg). This administration procedure was repeated once a day for 14 days. Radiologically, 50% of the animals given cytarabine alone showed lung oedema, but the rutin+cytarabine group showed no oedema. The inclusion of rutin decreased the amounts of cytarabine-associated malondialdehyde, tumour necrosis factor-α, and nuclear factor-κB in the lung tissue. Rutin also inhibited the reduction of total glutathione by nitric oxide. These findings suggest that rutin may be a beneficial adjunct that can minimise the development of cytarabine-associated pulmonary oedema.

Key words: Cytarabine, oxidative stress, pulmonary oedema, rutin.

INTRODUCTION

Cytarabine, a pyrimidine nucleoside analogue, has been in use in acute leukaemia treatment since 1964 (Barrios et al. 1987, Patel et al. 2012); however, it has many serious side effects, including neurotoxicity, myelosuppression, gastrointestinal mucosal damage and keratoconjunctivitis that can necessitate treatment cessation (Barrios et al. 1987, Stentoft 1990). In addition, severe or fatal pulmonary toxicity occurs in 12–20% of leukaemia patients given medium and high doses of cytarabine (Forghieri et al. 2007).

Cytarabine is reported to cause a form of pulmonary oedema that is unrelated to heart disease and cancer (Haupt et al. 1981, Briasoulis & Pavlidis 2001), and its effects are dose related (Stentoft 1990). Some researchers have attributed cytarabine-associated pulmonary oedema to increased vascular permeability of alveolar capillaries (Haupt et al. 1981), while others have implicated inflammation induced by tumour necrosis factor-alpha (TNF-α) in the alveolar damage and increased vascular permeability observed following cytarabine treatment (Chiche et al. 1993). Free radical formation also appears to play a role in the mechanism of this alveolar damage (Klausner et al. 1991).

Cytarabine-induced pulmonary oedema, regardless of its mechanism, is characterised by increased capillary permeability and filling of the alveolar spaces with protein and fluid (Flick & Matthay 2000). Therefore, drugs that reduce vascular permeability may be useful in the treatment of cytarabine-associated pulmonary oedema. One compound with known effectiveness in reducing capillary permeability and fragility is the flavonoid rutin (3,3,4,5,7-pentahydroxyflavone-3-rhamnoglucoside) also known as vitamin P1 (Frericks et al. 1950; Harborne 1986). Previous research has demonstrated the effectiveness of rutin in combating increases in capillary permeability and oedema caused by infiltration of fluid from the plasma into the tissue (Chen et al. 2002). Rutin also suppressed the production of TNF-α and pro-inflammatory nuclear factor-κB (NF-κB), while inhibiting leukocyte adhesion and migration, maintaining vascular barrier integrity and reducing hyperpermeability (Lee et al. 2012).

The available literature therefore suggests that rutin may be useful in preventing the development of cytarabine-associated pulmonary oedema, but no actual studies have confirmed this possibility. The aim of this study was to conduct radiological, biochemical and histopathological analyses to investigate the effect of rutin on cytarabine-associated pulmonary oedema in rats.

MATERIALS AND METHODS

Animals

In total, 24 male albino Wistar rats weighing 260–280 g were used in the experiment. The animals were housed under appropriate conditions in a suitable laboratory environment at normal room temperature (22°C). The study was approved by the local animal experimentation ethics committee (Date: 26.10.2017, meeting no: 129).

Chemicals

Cytarabine was obtained from EBV Health Products Co., Inc. (Turkey), thiopental sodium was obtained from I.E. Ulagay (Turkey) and rutin was obtained from Solgar (USA).

The NF-κB and TNF-α levels in tissue homogenates were measured using rat-specific sandwich enzyme-linked immunosorbent immunoassay kits (Rat NF-κB ELISA, Cat. No: 201-11-0288; SunRed) and Rat TNF-α ELISA kits (Cat no: YHB1098Ra; Shanghai LZ), respectively.

The total oxidant status (TOS) and total antioxidant status (TAS) of tissue homogenates were determined using commercial kits (Reel Assay Diagnostics, Turkey).

Experimental groups

The animals used in the experiment were divided into three groups: a cytarabine group, a rutin+cytarabine group and a healthy control group.

Experimental procedure

The rutin+cytarabine group (n=6) was administered rutin by oral gavage at a dose of 50 mg/kg in physiological saline. The cytarabine group (n=6) and the control group (n=6) received the same volume of physiological saline (0.9% NaCl) by oral gavage. One hour after rutin and or saline administration, the rutin+cytarabine and cytarabine groups received an intraperitoneal injection of cytarabine (200 mg/kg). These treatments were repeated once a day for two weeks.

Computed tomography

After the 14 days of drug administration, the lungs of all animals were examined radiologically by computed tomography. The lungs of the animals

were subjected to multidetector computed tomography (MDCT) using a 16-MDCT scanner (Siemens Medical Systems, Erlangen, Germany). A high-resolution computed tomography (HRCT) protocol was used to scan the lungs automatically in the caudocranial direction, as determined by the topogram. The HRCT screening protocol settings were as follows: lung window, 0.5 s scan time, 1.5 mm collimation, 768 × 768 matrix size, 120 kV, 160 mA, 4 cm field of view and 1 mm slice thickness.

Biochemical analyses

After the CT procedures, all animals were sacrificed using high-dose anaesthesia (thiopental sodium: 50 mg/kg) and the lung tissues were removed. Prior to dissection, all tissues were rinsed with a phosphate-buffered saline solution. The tissues were homogenised in ice-cold phosphate buffer (50 mM, pH 7.4). The tissue homogenates were centrifuged at 5,000 rpm for 20 min at 4°C, and the supernatants were used for analysis of NF-κB, TNF-α, total glutathione (tGSH), malondialdehyde (MDA), TAS, TOS and protein. Biochemical results were expressed on a per g protein basis. Histopathological examinations of these tissues were also performed.

MDA analysis

MDA measurements were based on the method of Ohkawa et al. (1979), which involves spectrophotometric absorbance measurements of the pink-coloured complex formed between thiobarbituric acid and MDA The tissue homogenate sample (25 µL) was added to a solution containing 25 µL of 80 g/L sodium dodecyl sulphate and 1 mL of a reaction mixture (200 g/L acetic acid plus 1.5 mL 8 g/L 2-thiobarbiturate). The mixture was incubated at 95°C for 1 h. Upon cooling, 1 mL of n-butanol: pyridine (15:1) was added. The mixture was vortexed for 1 min and centrifuged for 10 min at 4000 rpm. The absorbance of the supernatant was measured at 532 nm. A standard curve was generated using 1,1,3,3-tetramethoxypropane.

tGSH analysis

The method of Sedlak & Lindsay (1968) was used for tGSH analysis. The chromogen 5,5'-dithiobis(2-nitrobenzoic acid) disulphide (DTNB) is reduced by sulfhydryl groups to produce a yellow colour that can be measured by spectrophotometry at 412 nm. For the measurement of tGSH, a cocktail solution (5.85 mL 100 mM sodium phosphate buffer, 2.8 mL 1 mM DTNB, 3.75 mL 1 mM NADPH and 80 µL 625 U/L of glutathione reductase) was prepared. Prior to the measurement, 0.1 mL of tissue homogenate was deproteinised by adding 0.1 mL of meta-phosphoric acid and centrifuging for 2 min at 2000 rpm. A 0.15 mL volume of cocktail solution was then added to 50 µL of the supernatant. A standard curve was obtained using glutathione disulphide (GSSG).

TNF-α and NF-κB analysis

All TNF-α and NF-κB analyses were performed using kits according to the manufacturers' instructions. Briefly, a monoclonal antibody specific for rat NF-κB and TNF-α was coated onto microplate wells. The tissue homogenate, standards, biotinylated specific monoclonal antibody and streptavidin horseradish peroxidase were pipetted into the wells and incubated at 37°C for 60 min. After washing, chromogen reagent A and chromogen reagent B were added, which were acted upon by the bound enzyme to produce a coloured product. The microplates were incubated at 37°C for 10 min and then a stop solution was added. The intensity of the coloured product was directly proportional to the concentration of rat NF-κB and TNF-α present in the original specimen. At the end of the reaction, the well plates were read

at 450 nm and the absorbance of the samples was calculated using formulas and standard graphics.

Measurements of TOS and TAS

The TAS method is based on bleaching of the characteristic colour of 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), a stable radical cation, by antioxidants in the sample. The TAS measurements are performed at 660 nm and the results are expressed as mmol Troxol equivalent/mg protein. The TOS method is based on oxidation of the ferrous ion–o-dianisidine complex to ferric ion by oxidants in the sample. The oxidation reaction is enhanced by glycerol molecules, which are abundant in the reaction medium. The ferric ion produces a coloured complex with xylenol orange in an acidic medium. The colour intensity, which is measured at 530 nm spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The results are expressed as μmol H_2O_2 equivalent/ mg protein

Histopathological examination

The harvested lung tissue was fixed in 10% formalin solution for 24 h, embedded in paraffin blocks and sectioned at 4 μm thickness. After routine tissue preparation, the sections were stained with haematoxylin and eosin and examined by light microscopy (Olympus BX 52, Tokyo, Japan).

Statistical analysis

The data were analysed by Microsoft Excel and MedCal (Ostend, Belgium). The results were given as "mean±Standard error of mean" (x ± SEM). Differences between groups were compared using analysis of variance (ANOVA). Outlier analysis was performed using the Turkey test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Computed tomography findings

The MDCT of the rat lungs using the HRCT protocol revealed diffuse pulmonary oedema in (upper section, Fig. 1a), as well as bilateral pleural effusions in the lungs of the cytarabine group (upper section, Fig. 2a). By contrast, no oedema or pleural effusions were observed in the lungs of the rutin+cytarabine group (upper section, Figs. 1b and 2b) or in the control group (lower section, Figures 1c and 2c).

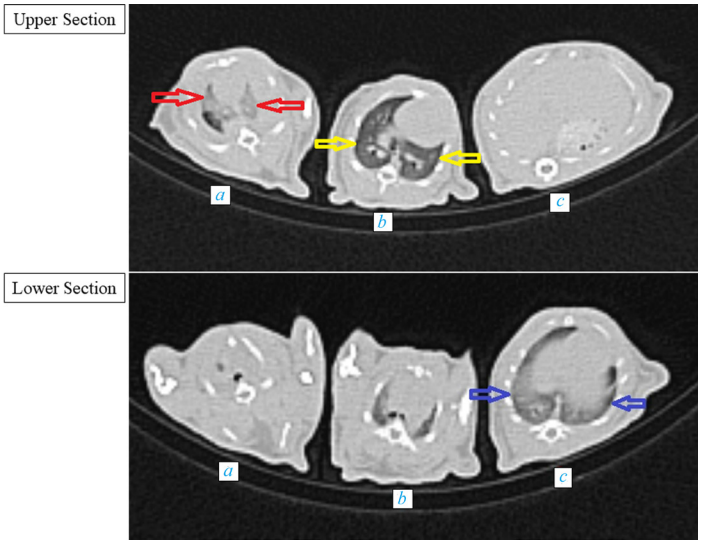

Figure 1. (a) Radiological examination with multidetector computed tomography (MDCT) revealed diffuse pulmonary oedema in the lungs of the rats in the cytarabine (CYT)group (upper section). (b) No oedema was seen in lungs of the rutin+cytarabine (R+CYT) group (upper section). (c) The lungs of the control (HG) animals had a normal appearance (lower section).

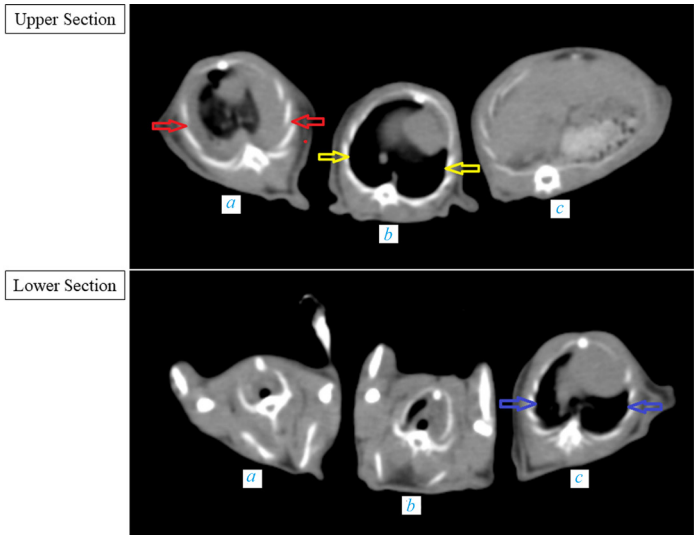

Figure 2. (a) Radiological examination with multidetector computed tomography (MDCT) shows bilateral pleural effusion in the lungs of the rats in the cytarabine (CYT) group (upper section). (b) In the rutin+cytarabine (R+CYT) group (upper section), the lungs are normal. (c) Normal lungs of the healthy control (HG) group (lower section).

Biochemical findings

Tissue MDA, tGSH, TOS and TAS analysis

The amount of MDA was significantly higher in the lung tissue of the cytarabine group (26.8 ± 1.2 µmol/g protein) than in the control group (6.3 ± 0.2 µmol/g protein) ($p < 0.0001$). The addition of rutin decreased the MDA amount in the rutin+cytarabine group (9.7±0.3 µmol/g protein) when compared to the cytarabine group ($p < 0.0001$), but the difference in the MDA level between the rutin+cytarabine group and control group was not statistically significant ($p > 0.05$)

The amount of tGSH in the lung tissue was lower in the cytarabine group (7.5 ± 0.1 nmol/g protein) than in the control group (21.3 ± 0.9 nmol/g protein)($p < 0.0001$). The addition of rutin prevented the decrease in the tGSH level in the rutin+cytarabine group (17.7 ± 0.9 nmol/g protein) ($p < 0.0001$) (Fig. 3).

The addition of rutin also significantly decreased the TOS level in lung tissue of rutin+cytarabine group (18.5 ± 0.8 µmol H_2O_2 equivalent/ mg protein) compared to the cytarabine group ($p < 0.0001$). The TAS level was significantly lower in the cytarabine group (4.4 ± 0.1 mmol Troxol equivalent/mg protein) than in the control group (10.8±0.4 mmol Troxol equivalent/ mg protein) ($p < 0.0001$). Rutin increased the TAS level in the rutin+cytarabine group (8.1±1.4 mmol Troxol equivalent/ mg protein) compared to the cytarabine group ($p < 0.0001$) (Fig. 4).

Tissue TNF-α and NF-κB analysis findings

The cytarabine group showed significantly increased amounts of TNF-α (5.8 ± 0.2 pg/mL) and NF-κB (4.5 ± 0.1 pg/mL) when compared to the control group (1.7 ± 0.2 pg/mL and 1.2 ± 0.2 pg/mL, respectively) ($p < 0.0001$). Rutin reduced the cytarabine-associated increase in TNF-α to 2.6 ± 0.1 pg/mL and NF-κB to 2.4 ± 0.1 pg/mL when compared to the cytarabine group ($p < 0.0001$) (Fig. 5).

Histopathological findings

As shown in Figure 6a, the structure of visceral pleura, alveoli, pulmonary arteries and bronchioles appeared normal in the lungs of the control group. By contrast, the lungs of the cytarabine group showed diffuse oedema, dilated and congested blood vessels, diffuse chronic inflammatory cell infiltration and bronchial damage (Fig. 6b). The lungs of the rutin+cytarabine group showed no unusual

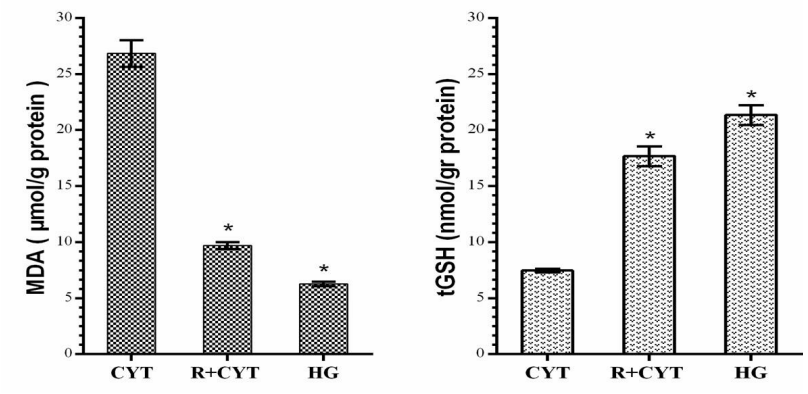

Figure 3. Malondialdehyde (MDA) and total glutathione (tGSH) levels in the lung tissues of the rats in the control (HG), cytarabine (CYT) and rutin+cytarabine (R+CYT) groups. *p<0.0001 according to control (HG) group, **p<0.0001 according to cytarabine (CYT).

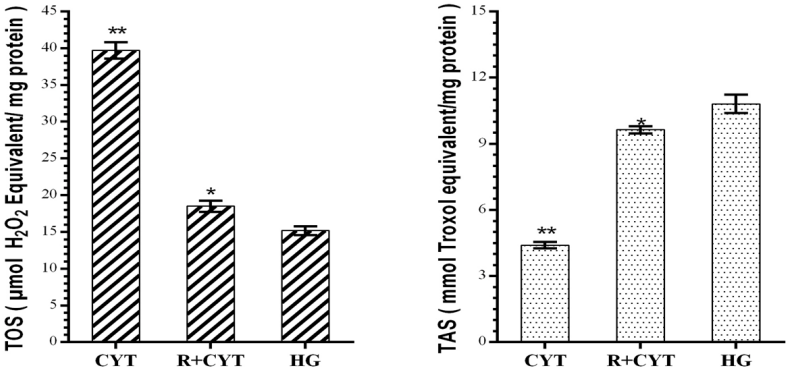

Figure 4. Total oxidant status (TOS) and total antioxidant status (TAS) in the lung tissues of the rats in the control (HG), cytarabine (CYT) and rutin+cytarabine (R+CYT) groups. *p<0.0001 according to control (HG) group, **p<0.0001 according to cytarabine (CYT).

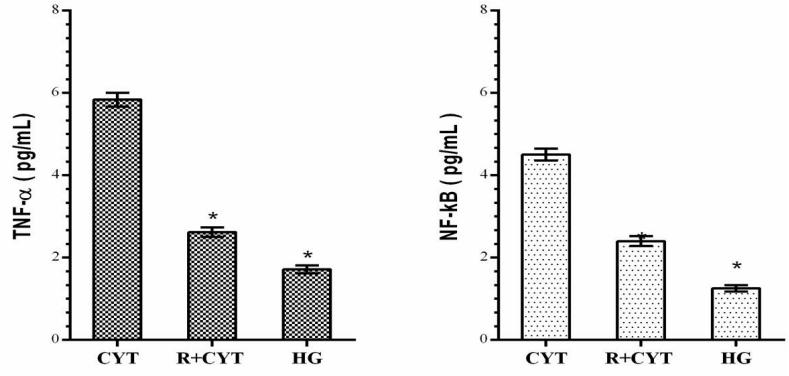

Figure 5. TNF-α and NF-κB content in the lung tissues of the rats in the control (HG), cytarabine (CYT) and rutin+cytarabine (R+CYT) groups. *p<0.0001 according to control (HG) group, **p<0.0001 according to cytarabine (CYT).

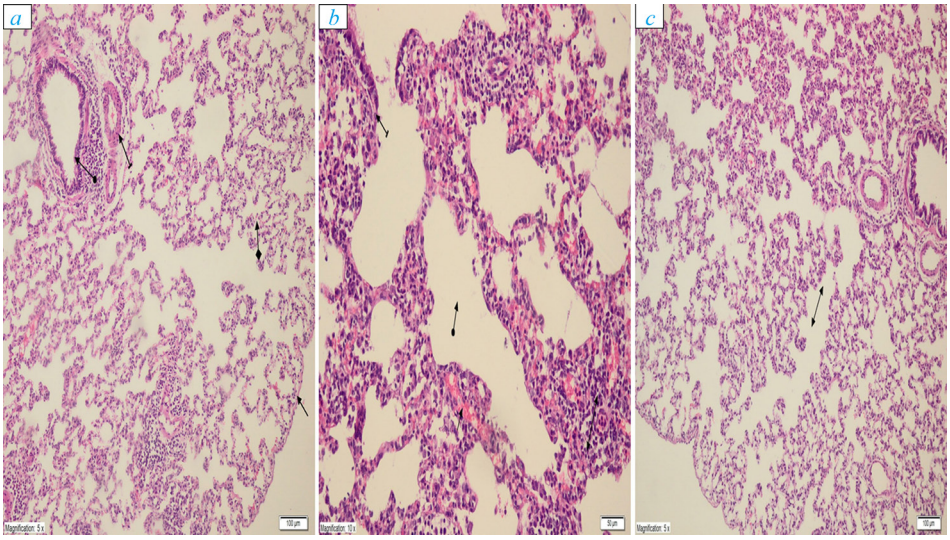

Figure 6. (a) Healthy visceral pleura (plain arrow), alveoli (square arrow), pulmonary artery (striated arrow) and bronchial (round-end arrow) structures in the lung tissue of the rats in the healthy control (HG) group (H&E, 100×). (b) The lungs of the rats in the cytarabine (CYT) group show diffuse oedema (round-end arrow), dilated and congested blood vessels (straight arrow), diffuse chronic inflammatory cell infiltration (double-sided arrow) and bronchial damage (striated arrow) (H&E, 200×). (c) Except for mild oedema (double-sided arrow), the pulmonary tissues of the rats in the rutin+cytarabine (R+CYT) group show a healthy appearance (H&E, 100×).

histopathological findings, except for mild oedema (Fig. 6c).

DISCUSSION

In this study, the effect of rutin on cytarabine-associated pulmonary oedema was investigated radiologically, biochemically and histopathologically in a rat model. The radiological findings showed that pulmonary oedema developed in the rats administered cytarabine. A previous study reported that patients treated with high doses of cytarabine died 1–2 weeks after initiation of pulmonary oedema (Forghieri et al. 2007). In the present study, 50% of the animals treated with cytarabine for 14 days developed pulmonary oedema, as shown by the MDCT findings. A previous thoracic radiographic study on dogs also reported that cytarabine produced pulmonary oedema and diffuse bilateral infiltrates (Hart & Waddell 2016).

In the present study, the results of biochemical tests showed that cytarabine significantly increased MDA and TOS levels in rat lungs. MDA is an end product of lipid peroxidation that is known to further aggravate cell damage (Droge 2002). Esfahani et al. (2012) reported that cytarabine increased the amount of plasma MDA in patients with acute myeloid leukaemia. Patel et al. (2012) also reported that cytarabine administered at a dose of 200 mg/kg increased the amount of MDA when compared with lower doses of 50 and 100 mg/kg. Taylan et al. (2016) stated that lungs subjected to experimentally induced damage elevated TOS levels. In the current study, the tGSH and TAS levels decreased in lung tissues of the cytarabine group, which had high MDA levels. Similarly, Patel et al. (2012) reported that cytarabine reduced tGSH at doses that increased the amount of MDA. Esfahani et al. (2012) showed that patients treated with cytarabine had reduced plasma levels of total antioxidants. Increases in oxidant levels and

decreases in antioxidant levels are considered indicative of oxidative stress (Kisaoglu et al. 2013). The current literature and the findings of the present study would indicate that cytarabine causes oxidative stress in lung tissue.

In the present study, the TNF-α levels, which are associated with oxidative stress, were increased in the lung tissue of cytarabine group. Huang et al. (2010) demonstrated that endogenous antioxidants decreased as TNF-α and oxidant parameters increased in damaged lung tissue. Dinarello (2000) emphasised that TNF-α induced an oxidative burst of neutrophils and the release of free radicals. TNF-α-induced inflammation has been implicated in the alveolar damage caused by cytarabine (Chiche et al. 1993), whereas another study found that increases in free radicals were responsible for alveolar damage (Klausner et al. 1991). In the present study, the cytarabine group showed an increase in TNF-α, as well as NF-κB, in lung tissue. Van der Poll & van Deventer (1999) suggested that increases in plasma levels of NF-κB were indicative of an inflammatory reaction. Similarly, Rashid et al. (2017) reported that oxidative stress increased NF-κB levels. In addition, NF-κB, which increases in response to infection in the lung, was inhibited by antioxidant administration (Pan et al. 2003). Therefore, the findings in the literature support the results presented here for cytarabine-induced lung damage.

We found no radiographic evidence of pulmonary oedema in the rutin+cytarabine group. This group also had significantly lower oxidant and cytokine levels and higher antioxidant levels when compared with the cytarabine group. Rutin has known biological properties, such as antioxidant, anti-inflammatory and anti-cytokine activities, and it inhibits bronchoalveolar infiltration by polymorphonuclear granulocytes (Ganeshpurkar & Saluja 2017, Yeh et al. 2014). These biological properties of rutin suggest that it may preserve vascular barrier integrity and reduce hyperpermeability, thereby suppressing oedema.

Although a number of studies have provided strong evidence for a role for various cytokines in the pathogenesis of pulmonary oedema, no consensus has yet been reached on the underlying mechanism (Guida et al. 1995, Vial & Descotes 1992). Previous research has also failed to detect inflammation in tissue in which massive alveolar oedema, intra-alveolar infiltrates and diffuse alveolar damage were detected radiologically (Andersson et al. 1990). These findings point to the existence of mechanisms other than oxidative damage and inflammation in the pathogenesis of cytarabine-associated pulmonary oedema. As noted earlier, cytarabine-associated pulmonary oedema may possibly be the result of vascular infiltration and breakdown of vascular permeability of alveolar capillaries (Haupt et al. 1981, Briasoulis & Pavlidis 2001). This breakdown would allow plasma protein infiltration into the alveolar space, thereby leading to pulmonary oedema (Grommes & Soehnlein 2011). A previous study reported that rutin may be effective in combatting increases in capillary permeability and oedema resulting from infiltration of fluid from plasma into the tissue (Chen et al. 2014). For this reason, Lee et al. (2012) suggested that rutin may be useful as a therapeutic agent for vascular diseases.

In the present study, severe diffuse oedema, dilated congested blood vessels, diffuse chronic inflammatory cell infiltration and bronchiolar damage were detected histopathologically in the lungs of the cytarabine group. Conversely, the rutin+cytarabine group showed only mild oedema. No information is available in the current literature regarding the effect of rutin on cytarabine-associated lung damage; however, rutin has been reported to reduce the pulmonary

oedema and inflammatory damage induced by bacterial lipopolysaccharide by inhibition of cytokines and inflammatory leukocytes (Feng et al. 2014). A study published by Hart & Waddell (2016) showed that cytarabine-associated pulmonary oedema responded to steroid administration but did not respond to oxygen and furosemide treatment.

In the clinical setting, long-term use of steroids (e.g. dexamethasone) has been reported to cause many undesirable effects, such as suppression of the immune system and induction of Cushing's disease (Feng et al. 2014). However, no evidence exists to date of any side effects of the long-term use of rutin. Therefore, a reasonable speculation is that cytarabine was responsible for the oedema in the lung tissue of the cytarabine group animals and that rutin alleviated cytarabine-associated lung oedema. This effect of rutin may be due to its inhibitory effect on oxidant and cytokine levels, which increase in lung tissue in response to cytarabine treatment.

The current literature and the findings of our experimental study indicate that cytarabine may give rise to oedema by increasing alveolar permeability. Rutin may reduce this increased permeability and thereby exert an anti-inflammatory effect. Therefore, the administration of rutin in clinical practice may help to minimise the development of cytarabine-associated lung oedema.

REFERENCES

ANDERSSON BS, YEE C, KEATING MJ, MCCREDIE KB, LUNA MA & HUI KK. 1990. Fatal pulmonary failure complicating high-dose cytosine arabinoside therapy in acute leukemia. Cancer 65: 1079-1084.

BARRIOS NJ, TEBBI CK, FREEMAN AI & BRECHER ML. 1987. Toxicity of high dose Ara-C in children and adolescents. Cancer 60: 165-169.

BRIASOULIS E & PAVLIDIS N. 2001. Noncardiogenic pulmonary edema: an unusual and serious complication of anticancer therapy. The Oncologist 6: 153-161.

CHEN W-Y, HUANG Y-C, YANG M-L, LEE C-Y, CHEN C-J, YEH C-H, PAN P-H, HORNG C-T, KUO W-H & KUAN Y-H. 2014. Protective effect of rutin on LPS-induced acute lung injury via down-regulation of MIP-2 expression and MMP-9 activation through inhibition of Akt phosphorylation. Int Immunopharmacol 22: 409-413.

CHEN W, JIN M & WU W. 2002. Experimental study on inhibitory effect of rutin against platelet activation induced by platelet activating factor in rabbits. Zhongguo Zhong Xi Yi Jie He Za Zhi 22: 283-285.

CHICHE D, PICO J, BERNAUDIN J, CHOUAIB S, WOLLMAN E, ARNOUX A, DENIZOT Y & NITENBERG G. 1993. Pulmonary edema and shock after high-dose aracytine-C for lymphoma; possible role of TNF-alpha and PAF. Eur Cytokine Netw 4: 147-151.

DINARELLO CA. 2000. Proinflammatory cytokines. Chest 118: 503-508.

DROGE W. 2002. Free radicals in the physiological control of cell function. Physiol Reviews 82: 47-95.

ESFAHANI A, GHOREISHI Z, NIKANFAR A, SANAAT Z & GHORBANIHAGHJO A. 2012. Influence of chemotherapy on the lipid peroxidation and antioxidant status in patients with acute myeloid leukemia. Acta Med Iran 50: 454.

FENG L, WANG D, HE J & QI D. 2014. Protective effect of rutin against lipopolysaccharide-induced acute lung injury in mice. Nan Fang Yi Ke Da Xue Xue Bao 34: 1282-1285.

FLICK M & MATTHAY M 2000. Pulmonary edema and acute lung injury. Textbook of respiratory medicine, 3rd ed., Philadelphia: W.B. Saunders Company.

FORGHIERI F, LUPPI M, MORSELLI M, POTENZA L, VOLZONE F, RIVA G, IMOVILLI A, RIVOLTI E & TORELLI G. 2007. Cytarabine-related lung infiltrates on high resolution computerized tomography: a possible complication with benign outcome in leukemic patients. Haematologica 92: e85-e90.

FRERICKS C, TILLOTSON I & HAYMAN J. 1950. The effect of rutin on capillary fragility and permeability. J Lab Clin Med 36: 933-939.

GANESHPURKAR A & SALUJA AK. 2017. The pharmacological potential of rutin. Saudi Pharm J 25: 149-164.

GROMMES J & SOEHNLEIN O. 2011. Contribution of neutrophils to acute lung injury. Mol Med 17: 293.

GUIDA M, ABBATE I, CASAMASSIMA A, MUSCI M, LATORRE A, LORUSSO V, CORREALE M & DE LENA M. 1995. Long-term

subcutaneous recombinant interleukin-2 as maintenance therapy: biological effects and clinical implications. Cancer Biother Radio 10: 195-203.

HARBORNE JB. 1986. Nature, distribution, and function of plant flavonoids. Prog Clin Biol Res 213: 15-24.

HART SK & WADDELL L. 2016. Suspected drug-induced infiltrative lung disease culminating in acute respiratory failure in a dog treated with cytarabine and prednisone. J Vet Emerg Crit Care 26: 844-850.

HAUPT HM, HUTCHINS GM & MOORE GW. 1981. Ara-C lung: noncardiogenic pulmonary edema complicating cytosine arabinoside therapy of leukemia. American J Med 70: 256-261.

HUANG SH, CAO XJ, LIU W, SHI XY & WEI W. 2010. Inhibitory effect of melatonin on lung oxidative stress induced by respiratory syncytial virus infection in mice. J Pineal Res 48: 109-116.

KISAOGLU A, BOREKCI B, YAPCA OE, BILEN H & SULEYMAN H. 2013. Tissue damage and oxidant/antioxidant balance. Eurasian J Med 45: 47.

KLAUSNER J, PATERSON I, GOLDMAN G, KOBZIK L, LELCUK S, SKORNICK Y, EBERLEIN T, VALERI C, SHEPRO D & HECHTMAN H. 1991. Interleukin-2-induced lung injury is mediated by oxygen free radicals. Surgery 109: 169-175.

LEE W, KU S-K & BAE J-S. 2012. Barrier protective effects of rutin in LPS-induced inflammation in vitro and in vivo. Food Chem Toxicol 50: 3048-3055.

OHKAWA H, OHISHI N & YAGI K. 1979. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Analyt Biochem 95: 351-358.

PAN F, SHI Y, LI H, ZHAO J, TANG S & YAO Z. 2003. Activation of nuclear factor kappa B in newborn rats sepsis. Zhonghua Er Ke Za Zhi 41: 582-585.

PATEL RS, RACHAMALLA M, CHARY NR, SHERA FY, TIKOO K & JENA G. 2012. Cytarabine induced cerebellar neuronal damage in juvenile rat: correlating neurobehavioral performance with cellular and genetic alterations. Toxicology 293: 41-52.

RASHID K, CHOWDHURY S, GHOSH S & SIL PC. 2017. Curcumin attenuates oxidative stress induced NFκB mediated inflammation and endoplasmic reticulum dependent apoptosis of splenocytes in diabetes. Biochem Pharmacol 143: 140-155.

SEDLAK J & LINDSAY RH. 1968. Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Anal Biochem 25: 192-205.

STENTOFT J. 1990. The toxicity of cytarabine. Drug Saf 5: 7-27.

TAYLAN M, KAYA H, DEMIR M, EVLIYAOĞLU O, SEN HS, FIRAT U, KELES A, YILMAZ S & SEZGI C. 2016. The Protective Effects of Caffeic Acid Phenethyl Ester on Acetylsalicylic Acid-induced Lung Injury in Rats. J Invest Surg 29: 328-334.

VAN DER POLL T & VAN DEVENTER SJ. 1999. Cytokines and anticytokines in the pathogenesis of sepsis. Infect Dis Clin North Am 13: 413-426.

VIAL T & DESCOTES J. 1992. Clinical toxicity of interleukin-2. Drug Saf 7: 417-433.

YEH C-H, YANG J-J, YANG M-L, LI Y-C & KUAN Y-H. 2014. Rutin decreases lipopolysaccharide-induced acute lung injury via inhibition of oxidative stress and the MAPK–NF-κB pathway. Free Radic Biol Med 69: 249-257.

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