Original Article

A STUDY OF POTENTIAL PROTECTIVE EFFECT OF NARINGENIN ON LUNG TOXICITY INDUCED BY PARABENS IN ADULT MALE ALBINO RATS

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ABSTRACT

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Background: Parabens induced toxic effects on different body organs via induction of oxidative stress. Naringenin is considered as potent free radicals scavenger. Aim of the work: to investigate antioxidant effect of naringenin on the lungs toxicity induced from parabens in adult male albino rats. Materials and Methods: The research study have been conducted on 30 healthy adult male albino rats divided into five groups each of 6 rats: Group I a (negative control group): No intervention was done. Group I b (positive control group): Rats received 0.2 ml pea nut oil orally for 8weeks. Group II (naringenin group): Rats received naringenin (50 mg/kg body weight) dissolved in water orally. Group III (parabens treated group): Rats were administrated 1/10 of the lethal dose of the butyl parabens which equal to (4.6 mg/rat/day) dissolved in pea nut oil orally for 8 weeks. Group IV (parabens and naringenin treated group): Rats were administered parabens and naringenin orally once daily for 8 weeks. Twenty- four hours after the end of experiment, the rats were subjected to sampling of blood for estimating oxidative markers and interlukin-6. Lung tissues were examined by light microscope. Results: This study revealed impairment in oxidative markers and interlukin-6 with histopathological changes in lung tissues in parabens treated group and these effects were ameliorated by intake of naringenin. Conclusion: Parabens oxidative stress damage can be ameliorated by naringenin supplementation.

Key words: Parabens, Naringenin, Oxidative markers, Interlukin-6

I.INTRODUCTION:

Parabens are alkyl esters of p-hydroxybenzoic acid which are considered as antimicrobial preservatives for many years in different personal care products, many pharmaceuticals, lots of cosmetics and manufactured foods (Nowak et al., 2020).

Cosmetic products are one of the reasons of dermal absorption of parabens in human (Giulivo et al., 2016). This is in addition to oral exposure to them via consumption of many manufactured foods as jams, beverages, jellies and canned foods (Boberg et al., 2016).

Furthermore, the toxic effects of parabens on different body organs like liver, brain, lungs, testes and kidney, they also proved as potential carcinogens in skin cancer, breast cancer, and uterine cancer (Watkins et al., 2015).

The toxic effects parabens were attributed to its estrogen-like activities and oxidative stress induction (Padmanabhan et al., 2021).

Flavonoids are a polyphenolic constituents of human diet exist in lots of foods (Ross and Kasum, 2002). They have a wide biological activity range as antibacterial, antiviral, anti-inflammatory and anti-ischemic (Muhammad et al., 2015; Trimech et al., 2015).

Naringenin is a predominant flavanone, found in plants as grapefruit Citrus and other citrus species. Several biological actions have been owed to its antioxidant, anti-inflammatory, antibacterial, antiviral, anticarcinogen, antiadipogenic and cardioprotective effects (Tutunchi et al., 2020).

Naringenin is considered as potent free radicals scavenger and proved to have the ability to chelate many heavy metals (Jagetia and Reddy, 2011). Also, it can protect against both lipid peroxidation and mutagenesis (Hernández-Aquino and Muriel , 2018). So the aim of this work was to investigate antioxidant effect of naringenin on the toxicity of lung tissues induced from parabens in adult male albino rats.

II.MATERIALS AND METHODS:

II.1 Ethical approval:

The experimental work was performed according to the basic instructions advised through the Institutional Research Board for the use and care of experimental animals. The protocol of the study was approved by Ethical Committee Board of Zagazige University with acceptance number: ZU-IACUC/3/F/262/2022.

II.2 Experimental Animals:

The research study have been conducted on 30 healthy adult male albino rats weighing 150- 200g. Rats were obtained from the animal house of Zagazig Faculty of Medicine. Rats were given balanced food consisting of milk, barley and bread which is considered as rich diet with all necessary substances needed to preserve their health before and during the experiment. Water was given in a different clean utensils.

II.3 Chemical Substances:

1-N-butyl parabens (Butyl 4-hydroxybenzoate):

N-butyl parabens (n-ButP, purity ≥ 99%, white crystalline powder) of analytical grade was purchased from Sigma Aldrich co. USA, product number: W220302**.**

2-Naringenin was purchased from Sigma Aldrich Co. USA, product number: N1376.

3-ELISA kits supplied by Cytimmune sciences INC, 8075 Green mead Drive. College park Mary Land 20740.

II.4 Experimental design:

Rats were randomly divided into five groups of 6 rats each:

Group I a (negative control group): No interventions were done to rats in this group for adjusting the basic parameters, and allowed drinking water ad libitum.

Group I b (positive control group): Rats administered 0.2 ml pea nut oil orally for 8 weeks.

Group II (naringenin group): Rats received naringenin (50 mg/kg body weight) dissolved in water and administered orally using an intra-gastric tube (Renugadevi and Prabu, 2010) for 8 weeks.

Group III (parabens treated group): The experimental animals were administrated 10 % of the lethal dose of the butyl parabens which equal to (4.6 mg/rat/day), according to Masten and Tice (1999) dissolved in pea nut oil and was given by stomach tube for 8 weeks.

Group IV (Parabens and naringenin treated group): The group was administered parabens and naringenin at the previously mentioned doses for 8 weeks.

II.5. Parameters:

Twenty- four hours after the end of experimental study, the rats were subjected to sampling of blood and lung tissues as the follows: -

II.5.A Biochemical parameters:

Venous blood samples were obtained from animals by means of capillary glass tubes from the retro orbital plexus under light ether anesthesia (Semler, 1992) and used to measure the following parameters:

- **Oxidative markers:**

1- Malondialdehyde (MDA) (nmol/ ml) that was assayed colorimetrically according to Ohkawa and colleagues (1979).

2- Glutathione (GSH) (ng/ml) that was assayed colorimetrically according to Beutler and colleagues (1963).

3-Catalase activity (U/ml) that was assayed colorimetrically according to Aebi, (1983).

- Measurement of serum interleukin-6 (IL-6) by ELISA technique.

II.5.B Tissue parameters:

Lungs were immediately dissected out and grossly inspected to determine any apparent gross changes then washed with cold normal saline and used for histopathological study and were fixed in 10% formalin solution. After that, lung tissues were embedded in paraffin blocks and processed into 5 u. thickness sections. They were stained by Hematoxyin and Eosin (Horobin and Bancroft, 1998) and examined by light microscope.

II.6 Statistical analysis:

Data were analyzed by Statistical Package of Social Science (SPSS), software version 22.0 using one way ANOVA and least significant difference tests (SPSS Inc., 2013).

III. RESULTS:

Regarding oxidative markers and IL-6, There was no significant difference between group Ia (negative control group) Ib (positive control group) (Table 1). So, group 1a was used for comparison with other treated groups.

There was a highly significant ($p<0.01$) increase in MDA, and highly significant ($p<0.01$) decrease in both GSH and catalase in parabens treated group when compared with control group. While rats receiving parabens and naringenin showed a significant ($p<0.05$) decrease in MDA with a highly significant ($p<0.01$) increase in GSH and catalase activity when compared with parabens treated group (Table 2).

As regard inflammatory marker (IL6) a significant ($p<0.05$) increase in IL-6 was observed in parabens treated group when compared with control group. Naringenin administration modify the inflammatory

markers, as there was a significant ($p<0.05$) decrease in IL-6 in parabens and naringenin treated group when compared with parabens treated group (Table 2).

As regarding light microscopic examination of lung tissues with H&E among Ia, Ib and II groups, they showed normal histological features of lung tissues as patent alveoli and thin inter alveolar septa in alveolar sacs. Alveoli were lined by type I pneumocytes, few type II pneumocytes with some macrophages. Patent bronchioles lumen surrounded by regular smooth muscle layer lined by ciliated simple columnar epithelial (Figure 1A). However, lungs of parabens treated group showed extensive manifestations of pulmonary inflammation and inflammatory cell infiltration leading to subsequent destruction of the bronchiolar structure (Figures 1B, 1C). Parabens and Naringenin treated groups showed mild inflammation with mild inflammatory cell infiltration (Figure 1D).

Table (1): Comparison among negative (Ia), positive (Ib) control groups and Naringenin group (II) as regard mean values oxidative stress markers and IL- 6 using one-way ANOVA test.

Groups / **Parameters**	**Ia**	**Ib**	**II**	**P**
MDA (nmol/ ml)	158.25 ± 1.23	159.55± 2.33	159.25 ± 1.25	0.398 >0.05
GSH (ng/ml)	0.93 ± 0.85	0.88 ± 0.33	0.89 ± 0.34	0.987 >0.05
Catalase activity (U/ml)	5.42 ± 0.25	5.25 ± 0.45	5.45 ± 0.28	0.556 >0.05
interleukin-6 (IL-6) (pg/Ml)	1.88±0.80	1.87±0.75	1.86±0.85	0.999 >0.05

NB: All values are expressed as Mean±+ SD; N: Number of rats in each group=6 rats; SD: standard deviation; P: >0.05 non-significant; MDA: Malondialdehyde; GSH: Glutathione; IL-6; interleukin-6.

Table (2): Comparison among different group of the study as regard mean values oxidative stress markers and IL- 6 using one-way ANOVA test, and difference between groups by (LSD)

Groups / Parameters	Ia	III	IV	P
(MDA)(nmol/ ml)	158.25 ± 1.23	314.95±95.35[a]**	189.35±55.45[b]*	0.002 <0.05*
(GSH) (ng/ml)	0.93 ± 0.15	0.22±0.12 [a]**	0.89± 0.15 [b]**	0.000 <0.01**
activity (U/ml)	5.42 ± 0.25	2.25±0.73 [a]**	4.35 ± 0.85 [a]*, [b]**	0.000 <0.01**
(IL-6) (pg/Ml)	1.88±0.80	2.95±0.70 [a]*	1.99±0.35 [a]*, [b]*	0.022 <0.05*

N: Number of rats in each group=6 rats; SD: standard deviation; P: >0.05 non-significant;*: significant (p<0.05); **: highly significant (p<0.01); a=versus control; b=versus parabens treated group; (LSD): least significant difference; MDA: Malondialdehyde; GSH: Glutathione; IL-6; interleukin-6.

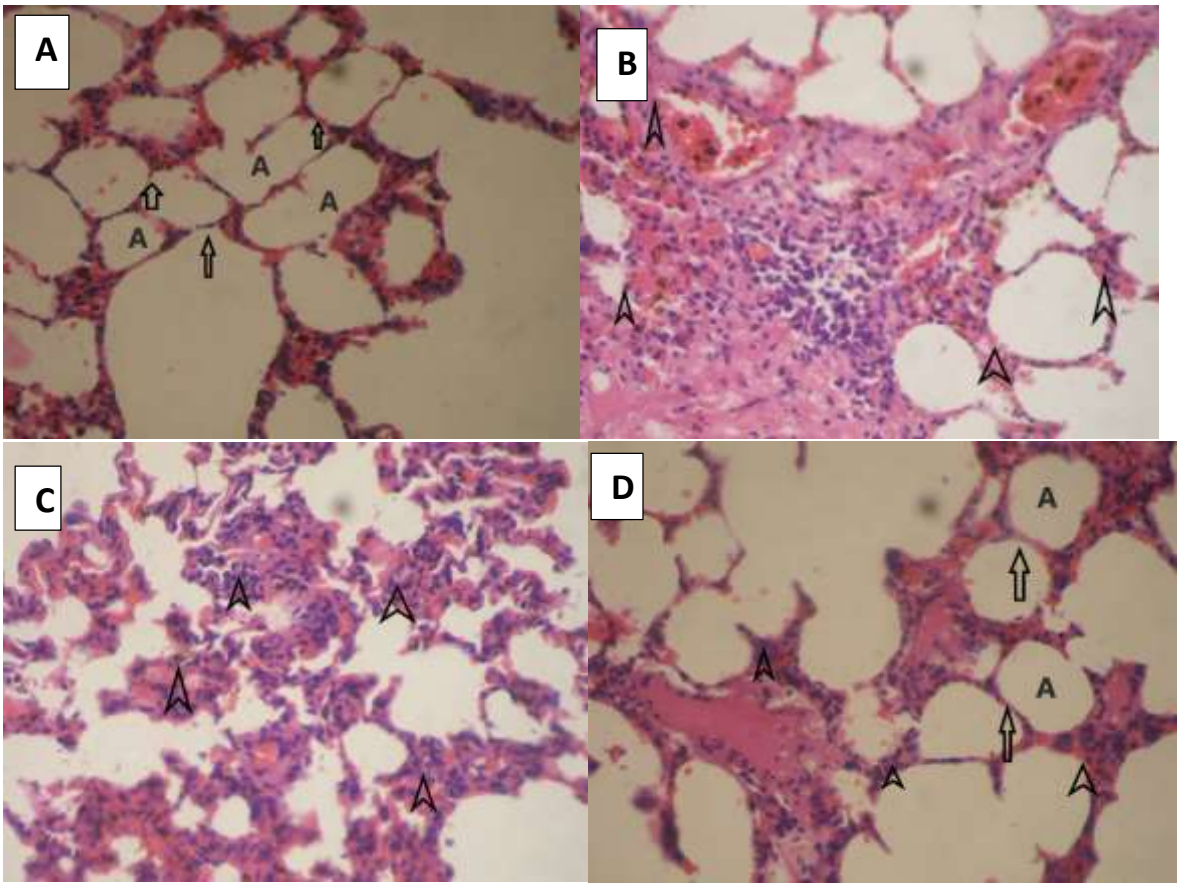

Figure 1: Hematoxylin and Eosin staining Lung sections; A): control group (Ia): showed patent alveoli (A) and thin inter alveolar septa (arrow) (x200). B): Parabens treated group (III): showed extensive pulmonary inflammation (arrow head) (x200).C): Parabens treated group: showed extensive pulmonary inflammation with most of the bronchiolar lumen and the wall is infiltrated by neutrophils and pus cells (arrow head) (x200). D): Parabens and naringenin treated group (IV): showed patent alveoli (A) and thin inter alveolar septa in alveolar sacs (arrow) with mild inflammatory cellular infiltrate (arrow head) (x200).

IV. DISCUSSION:

Parabens belong chemically to parahydroxybenzoates or the esters of parahydroxybenzoic acid (Cashman and Warshaw, 2005). They exist in natural food as blueberries, cloudberry, and yellow passion fruit with very low concentrations (Kirchhof and de Gannes, 2013).

parabens are preservatives materials in many cosmetic products (e.g. shampoos, hair conditioners, body lotions, shower gels, scrubs, deodorants and sunscreen), pharmaceutical preparations and processed foods as beverages, frozen dairy products, jams, jellies, pickles, sauces, desserts, processed fish, processed vegetables and flavoring syrups from the 1930s. They have been consumed from long times due to low cost with effective preservative and antimicrobial action (Tade et al., 2018).

Although parabens were considered as safe component, many studies have raised regarding its safety (Tavares et al., 2009; Xue and Kannan, 2016). The harmful effects of parabens occur either through ingestion, inhalation, or dermal absorption. The cytotoxicity of parabens may be attributed to mitochondrial failure from induction of membrane permeability transition associated with mitochondrial depolarization and depletion of Adenosine triphosphate (ATP) through uncoupling of oxidative phosphorylation process. In addition, parabens were reported to modulate the endocrine system and to induce oxidative stress tissue damage (Kang et al., 2013).

Naringenin (4, 5, 7-trihydroxyflavanone) is one of flavonoid present in citrus fruits, honey, and bee pollen. It has many pharmacological properties as antioxidant, anti-inflammatory, antimicrobial, anti-diabetic, and anticancer (Den Hartogh and Tsiani, 2019). Beside its protective role to different body organs as lung, liver and kidney, it has been considered as protective agent against oxidative neurodegenerative changes in central nervous system and other disorders like depression. These effects are attributed to inhibiton of monoamine oxidase enzyme (Olsen et al., 2008) and neuroprotective action which are attributed to free radical scavenging activities through free radical production modulation by phagocyte (Uckun et al., 2020; Rivoira et al., 2021).

In current study, there is a highly significant change in oxidative markers (MDA, GSH and Catalase) and a significant change in inflammatory marker (IL6) in parabens treated group when compared with control

group. However, rats receiving parabens and naringenin showed a significant ameliorative changes in MDA and IL6 with a highly significant ameliorative changes in GSH and catalase activity when compared with parabens treated group.

These results were in lined with Asnani and Verma (2009); Ulusu et al. (2019); Oliveira et al. (2020) who declared that parabens cause oxidative balance impairment which is the leading cause of different organs damage.

Watkins et al. (2015) stated that parabens were considered as harmful to many organs as uterus, ovary, and mammary gland as they increase the free radicals production and lowering glutathione, superoxide dismutase, and ascorbic acid.

In addition to Daniele et al. (2018) who demonstrated that parabens exposure induced alterations in the antioxidant enzymatic capacity and the non-enzymatic antioxidant content in both gills and liver of Nile tilapia.

Jayaraman et al. (2012); Nishimura et al.(2013); Jagetia and Lalnuntluangi (2016); Rashmi et al. (2018); Akamo et al.(2021) declared that naringenin revealed potent free radical scavenging activities as it neutralized hydroxyl radicals, superoxide, hydrogen peroxide, and nitric oxide radical effectively with increase of antioxidant levels.

The scavenging of free radicals and ROS of naringenin is come back to the two hydroxyl groups of the A ring at positions 5 and 7 and a carbonyl group of the C ring at position 4, which interact with iron and copper, Which considered as potential enhancer to oxidative stress process (Alam et al., 2014) . In addition to, the ability of naringenin to oxidize superoxide and hydroxyl radicals by hydrogen atom donation (Rahman, 2007).

As regard light microscopic examination of lung tissues the present experimental study showed extensive pulmonary inflammation and lymphoid follicles formation destroying the bronchiolar structure in parabens treated group which ameliorated in Parabens and Naringenin treated group.

Two cross-sectional studies in the 2005–2006 National Health and Nutrition Examination Survey (NHANES) conducted on children from the United States, declared that exposure to parabens is important risk factor for development of asthma and allergic diseases due to aeroallergen sensitization (Savage et al., 2012; Spanier et al., 2014).

These results were matched with Chin et al. (2021) who suggested that naringenin played a main role either in prevention or treatment of airway inflammatory diseases.

Chronic airway inflammatory lung diseases caused by pathogens, smoke, and dust particles, result in increased the production of inflammatory cells, mucous, and inflammatory mediators causing impairment of lung function. It is mediated by cytokines, interleukins, glucocorticoid receptors, tumor necrosis factors, and nuclear factor kappa B which result from oxidative stress with subsequent stimulation of immune response resulting in hyper-responsiveness of the bronchi, and increases the secretion of mucin (Chin et al., 2021).

Many studies reported that naringenin played a role in inhibition of the inflammatory pathway involved in chronic airway inflammatory lung diseases by inhibiting nuclear factor kappa B transcription activity (Amelimojarad et al., 2022). Further, it ameliorated the oxidative stress through inhibition of inflammatory response mediated by cytokines, interleukins, glucocorticoid receptors, tumor necrosis factors, and nuclear factor kappa B (Kim et al., 2020).

V. CONCLUSION:

Parabens induced oxidative stress damage, with subsequent harmful effects which can be ameliorated by naringenin due to its potent antioxidant effects and free radical scavenging property.

VI. RECOMMENDATION:

Future experiments are required to evaluate the possible toxic effect of parabens on different organs and to study the protective effect of other antioxidant on these effects.

VII. CONFLICT OF INTEREST:

Authors declared no conflict of interest.

VIII. FUNDING:

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الملخص العربى

دراسة التأثير الوقائي المحتمل للنارينجينين على تسمم الرئة المستحث بواسطة البارابين في ذكور الجرذان البيضاء البالغة

يسبب البارابين الإجهاد التأكسدي بالإضافة إلى تأثيراته السامة على الكبد والكلى والخصيتين والرئتين والدماغ. يعتبر النارينجينين مضاد للأكسدة و مضاد للتسمم بالمعادن الثقيلة.و لذا تم إجراء هذه الدراسة لدراسة التأثير النارينجينين كمضاد للأكسدة على سمية الرئتين الناتجة عن البارابين في ذكور الجرذان البيضاء البالغة.و قد أجريت الدراسة على ٣٠ من ذكور الجرذان البيضاء السليمة مقسمة إلى خمس مجموعات: المجموعة الأولى أ (المجموعة الضابطة السلبية): لم يتم إجراء أي تدخل للجرذان في هذه المجموعة و تم استخدامها لقياس المؤشرات الاولية. المجموعة الأولى ب (المجموعة الضابطة الإيجابية): تم إعطاء الجرذان٢، مل من زيت الفول السودانى عن طريق الفم لمدة ٨ أسابيع. المجموعة الثانية (مجموعة النارينجينين): تم إعطاء النارينجينين للجرذان بهذه المجموعة بجرعة (٥٠مجم / كجم من وزن الجسم) مذابة في الماء ويتم تناولها عن طريق الفم باستخدام أنبوب داخل المعدة. المجموعة الثالثة (المجموعة المعالجة بالبارابين): تم إعطاء البارابين بنسبة ١٠\١ من الجرعة المميتة والتي تساوي (4.6 مجم / جرذ / يوم) ، مذاب في زيت الفول السودانى وأعطي بواسطة أنبوب المعدة لمدة ٨ أسابيع. المجموعة الرابعة (المجموعة المعالجة بالبارابين والنارينجينين): تم إعطاء المجموعة البارابين و النارينجينين عن طريق الفم مرة واحدة يوميًا لمدة ٨ أسابيع بالجرعات السابقة . بعد أربع وعشرين ساعة من انتهاء التجربة ، تم إخضاع الجرذان لأخذ عينات من الدم لقياس علامات التأكسد وقياس الإنترلوكين 6 وتم فحص أنسجة الرئة بواسطة المجهري الضوئي.و قد أظهرت النتائج تغير واضح في العلامات التأكسدية و تغيرات مرضية في أنسجة الرئة في المجموعة المعالجة بالبارابين بالمقارنة مع المجموعة الضابطة وتم تخفيف هذه التأثيرات بواسطة اعطاء النارينجينين. الخلاصة: يسبب البارابين أضرار بسبب الإجهاد التأكسدي و التى يمكن أن تتحسن مع اعطاء النارينجينين بسبب تأثيره المضادة للأكسدة.