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ISSN: 2151-1918 (Print), 2151-1926 (Online)
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Chinese Medicine (CM)

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Inter-Organ Relationships among Gut, Lung and Skin beyond the Pathogenesis of Allergies: Relevance to the Zang-Fu Theory in Chinese Medicine

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Abstract

Research on allergy has recently uncovered an apparent co-occurrence of allergies in skin and the lungs, a phenomenon that has been coined “atopic march”. A positive correlation has been found between gut microbiota at birth and the development of asthma and skin eczema later in life. Chinese medicine has long described a functional relationship between the large intestine and the lungs, and between the lungs and skin. In this short article, we examined the evidence in support of these inter-organ physiological/pathological relationships. In addition to the clinical observation of the relationship between the composition of gut microbiota at birth and the development of asthma later in childhood, gut microorganisms have also been shown to exert a protective effect on bacteria-induced pneumonia in experimental animals. Genetic predisposition was also found to play an important role in the co-existence of certain diseases of lung and skin. Despite the fact that the mechanism(s) underlying the connection of immune systems between two organs (such as the large intestine and the lungs) is still not clearly understood, it is the first time to correlate the relationship among gut, lung and skin based on recent clinical studies in relation to the Zang-Fu Theory in Chinese medicine. Future investigation of the gut-lung and lung-skin axes in terms of physiological/pathological relationships may help to provide a greater understanding of the pathogenesis of allergies, possibly establishing relevance to the Zang-Fu Theory in Chinese medicine.

Keywords

Gut, Lung, Skin, Zang-Fu Theory
1. Introduction

The development of a comprehensive theory of how the functions of organs are inter-connected and influence each other has become an area of increasing research interest in modern medicine; whereas a large body of evidence from observations and numerous clinical applications were accumulated over the thousands of years where Chinese medicine was practiced. Among the inter-organ functional networks recognized in the Zang-Fu Theory in Chinese medicine, two such physiological/pathological relationships are that involving the large intestine and the lungs, and that of the lungs and the skin. Based on research findings in modern medicine, mention has been made of the possibility of a gut-lung connection and, to a lesser extent, a lung and skin relationship in terms of physiological function and pathological conditions. This article seeks to examine the evidence in support of these inter-organ physiological/pathological relationships.

Atopic March

Recent research has uncovered an apparent co-occurrence of skin and lung allergies, in that atopic dermatitis in infancy tends to be followed by allergic rhinitis and asthma later in childhood [1]. This phenomenon was coined “atopic march” [1], which is currently an area of considerable research interest. In addition, a positive correlation between gut microbiota at birth (which is associated with the development of asthma) and skin eczema later in life has also been found [2] [3]. All these suggest possible functional interactions among gut, lungs and skin. The existence of such inter-organ relationships could be instrumental in leading to an understanding of the pathogenesis of allergies, and other diseases in relation to these organ systems.

2. Functional Similarities between Gut, Lung and Skin

Inner surfaces of the gut, lung and the outer surface of skin are all covered by epithelial cells, which have direct contact with exogenous substances, particularly pathogens and bacteria. Despite being the body’s first line of defense against such pathogens, a well-defined microbial environment, or microbiota, is also essential for the optimal functioning of these organs. If the microbiota is altered or disrupted, health problems can arise [4].

The microbiota in the gut, which is the most densely populated with microorganisms among all surfaces of the human body, has been extensively studied. It has been noted that the taxonomic gene composition of gut microbes is highly variable between individuals, implying that a healthy gut microbiota is found in terms of function and not certain microbial species [5]. The upper part of the respiratory tract is easily colonized by pathogen and bacteria, whereas the lower part of the lungs is less populated by microorganisms, possibly due to the relatively unfavorable environment [6].

2.1. Gut-Lung Functional Interrelationship

According to Chinese medicine theory, visceral organs can be divided into 2
categories, namely, Zang and Fu, wherein each Zang organ has its corresponding Fu organ(s). The Lung is such a Zang organ, and its Fu organ is the Large Intestine. The Zang-Fu Theory states that the Lung can be infiltrated by “evil” (i.e., pathogens) entering from the Large Intestine [7].

In modern medicine, it has been observed that some lung diseases are pathologically related to the gut. Chronic lung disorders such as asthma and cystic fibrosis have been shown to exhibit manifestations in the gastrointestinal tract, namely, shifts in the gut microbiota composition [6]. A strong correlation was found between childhood asthma and low diversity of gut microbiota during infancy. It should be noted that the microbiota diversity is restored as early as 12 months after birth, long before asthmatic symptoms arise, suggesting the existence of a time-frame window for the pathogenesis of asthma [3]. A similar correlation was observed experimentally in mice; following a reduction in the number and diversity of gut microorganisms by the administration of antibiotics at 3 weeks of age, adult mice showed exacerbated experimental allergic airway inflammation upon aero-allergen exposure [8]. Similarly, for children with cystic fibrosis, which is a genetic disorder that mainly affects the lungs, there is a large difference between their gut microbiota as compared to healthy children of the same age, with diminished levels of certain bacteria in affected children [9].

The connection between gut microbiota and lung health is further emphasized in a study by Schuijt et al. [10], in which mice were depleted of gut microbiota, and then infected with Streptococcus pneumoniae. A group of mice were then given a fecal microbiota transplant and compared with control mice in terms of parameters of inflammation and alveolar macrophage whole-genome responses. Results showed that fecal microbiota transplantation protected microbiota-depleted mice against pneumonia, as assessed by parameters relating to bacterial dissemination, inflammation, organ damage and mortality. Metabolic pathways within alveolar macrophages were significantly affected by the absence of gut microbiota, with reduced cellular responses to certain metabolites, such as lipoteichoic acid and lipopoly saccharide. Macrophages from microbiota-depleted mice also showed a reduced ability to kill bacteria (Streptococcus pneumoniae) by phagocytosis.

Taken together, these experimental results suggest a pathological inter-relationship between gut microbiota and lung diseases. It is thought that the gut affects the lung’s immune system, but the mechanism is not well understood. A paper by Trompette et al. [11] found that the fatty acid moiety produced in the metabolism of dietary fibre, by gut microbiota, influences the severity of allergic inflammation in the airways. More research is still needed to further explore the mechanism underlying the effect of gut microbiota on pulmonary function and susceptibility to respiratory diseases.

2.2. Lung-Skin Relationship

The Zang-Fu Theory proposes that skin is functionally linked to the Lung, with the Lung playing a role in controlling the “gaps” or pores on the skin, thereby
regulating sweating and body temperature, as well as the skin’s immune system. According to Chinese medicine theory, if a patient manifests symptoms reflecting poor respiratory function, or insufficient Lung Qi (which refers to the physiological functioning of the Lung), foreign “evil” can easily invade the body by passing through its outer surface. If Lung Qi is at an optimal level, then the skin is glossy and the complexion shiny. In this connection, *Houttuynia cordata* Thunb is a commonly used herb for treating both pneumonia and skin eczema [12].

In modern medicine, an association between allergic diseases of the lungs and airways with those of the skin has been observed (see “atopic march”). However, this pathological inter-relationship can extend beyond allergies, i.e., including non-allergic diseases of these two organs.

However, it is important to first note that many pulmonary diseases, although sometimes exhibiting dermatological manifestations [13] [14], many of them also show symptoms elsewhere in the body. For example, lung cancer has a 1% to 12% likelihood of developing skin metastases, but the neoplasia may also invade other organs in the body [13]. Similarly, *Mycobacterium tuberculosis* can infect organs other than the lungs, including the skin, and cause lesions [14], displaying the possibility of relation between skin and lungs. But again, the tuberculosis bacterium can also invade other organs. Using only dermatological manifestations of non-allergic pulmonary diseases which have no high co-occurrence, especially in the case where it is not an exclusive manifestation, is not enough to form a convincing argument for a unique connection between skin and lungs.

One example of strong co-occurrence of lung and skin problems is high levels of airborne pollutants and lower skin health. Smoking and air pollution have long been known to affect the condition of the skin—for example, causing premature wrinkles, as evidenced by epidemiological studies. Huls et al. reported an association between nitrogen dioxide (NO₂) levels in the environment and the geometric mean number of cheek lentigines, or pigmented spots, commonly known as liver spots [15]. This association was observed in two different populations (Germany and China) in regions with similar UV exposures, and with individuals over 50 years of age [15]. In this regard, NO₂ exposure has been known to impair lung function and increase the risk of lung cancer [16]. However, it should be noted that the increase in the incidence of cheek lentigines was fairly small when estimated on the basis of a per unit increase in NO₂. Further studies are required to confirm these findings [17].

In another study, Vierkotter et al. (2010) showed that cigarette smoking and ambient soot levels promoted prominently visible signs of skin aging, including pigment spots and wrinkles [18]. With this finding, they demonstrated, for the first time, that airborne particulate matter was a factor in causing extrinsic skin aging [18].

### 2.3. Co-Occurrence of Skin and Lung Issues in Certain Genotypes

In the foregoing discussion, it has been shown that extrinsic factors, such as air
pollutants and cigarette smoke, are associated with both skin wrinkling and a decline in lung function [18]. In this regard, a study from Vierkotter et al. showed that elderly women carrying certain matrix metalloproteinase (MMP) promotor variants exhibited a higher susceptibility to skin wrinkling and decreased lung function (as assessed by the ratio of forced expiratory volume to forced volume capacity) [19]. As such, not only did they demonstrate an association between skin wrinkling and obstruction of lung function, but also a common genetic predisposition to skin and lung disorders. MMP are a group of extracellular matrix (ECM) degrading enzymes. It has been suggested that the association of smoking with lung dysfunction and skin aging is due to such MMP-induced structural changes in ECM [19]. The specific MMP promotor variants identified are designated MMP-1 and MMP-3. Interestingly, MMP-1 promotor polymorphism also appear to increase susceptibility to colorectal cancer, according to two other studies, again implicating a possible linkage between lung and gut health [20] [21].

In research of allergic diseases, genetic and environmental factors have both been noted to strongly influence the development of atopic march [1]. The common genetic predisposition to lung and skin aging above suggests an association between lung and skin function that extends beyond those of allergic diseases. One study followed a group of infants who had acute severe bronchiolitis, and found that 50% of them developed dry skin or eczema within 12 months post-recovery from the bronchiolitis. [22]. Another study found that babies suffering from atop dermatitis in their first 2 years of life had an increased risk of not only asthma, but other respiratory system-related diseases, as assessed by the incidence of acute otitis media (a middle ear infection), pneumonia and the use of antibiotics [23]. The association between atop dermatitis and respiratory infections prevailed even after stratification for asthma.

### 2.4. Gut-Skin Relationship

The gut-skin relationship, which is not the main scope in this review, has been reported recently. In brief, O’Neill et al. have proposed a gut-skin relationship in regulating the physiological functions [24]. It has been suggested that the metabolites, hormones or neurotransmitters arising from gut microbiota may circulate in the blood and hence affect the physiological functions of the skin. Various diseases, such as inflammatory bowel disease, coeliac disease, rosacea, cutaneous paraneoplasia and Peutz-Jeghers syndrome, have shown manifestations in gut and skin, suggesting a possible pathological relationship between gut and skin. In support of this, the diversity of gut microbiota in the early life seems to possess an inverse relationship to the development of atop eczema in the later life [25].

### 3. Conclusions and Perspective

In summary, there is a growing body of evidence supporting the presence of a gut-lung axis and a lung-skin axis, wherein one organ of the axis is functionally
related to the other (Table 1). For the gut-lung axis, experimental evidence supports a relationship between gut microbiota composition and lung function (Figure 1). It has been suggested that the microbiota of the two organs communicate and somehow influence each other. As regards investigation, it is difficult to analyze microorganisms in the lower respiratory tract, and the techniques for growing “difficult-to-culture” gut bacteria remain to be optimized. It appears that gut microbiota can undergo changes during infancy, but becomes less sensitive to change in later stages of life [6].

For the lung-skin axis, the pathological relationship between the two organs is particularly prominent in regard to allergic diseases, as exemplified by the phenomenon of “atopic march” (Figure 1). Existing evidence indicates that a genetic factor may be involved in such an association of organ function. The presence of certain alleles is linked to a phenotype that is susceptible to allergic reactions in both the lungs and the skin.

Furthermore, evidence shows that it is possible that the functional relationship involving the lung-skin axis can go beyond allergies to include infectious diseases and aging. Allergic responses occurring in one organ can increase the risk of the other in developing non-allergic diseases, suggesting that a functional deficiency in one organ can impair that of another. This linkage may also be a result of a genetic predisposition, wherein an individual of a certain genotype would have diminished function in both the lungs and skin.

The mechanism determining the functional connection between organs is yet to be identified. Conceivably, it may be related to the connectivity of the immune system by cross-talk between mucosal epithelial cell layers in different

Table 1. Summary of gut-skin and skin-lung relationships.

<table>
<thead>
<tr>
<th>Recent findings on Gut-skin and Skin-lung relationships</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>Gut-lung relationship</strong></td>
<td></td>
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<tr>
<td>The degree of diversity in gut microbiota at birth negatively correlated the tendency to develop to asthma in children in human</td>
<td>[3]</td>
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<tr>
<td>The disturbance of gut microbiota in mice at 3 weeks of age was found to increase the occurrence of allergic airway inflammation in adult mice</td>
<td>[8]</td>
</tr>
<tr>
<td>The transplantation of fecal microbiota can protect against the pneumonia in microbiota-depleted mice</td>
<td>[10]</td>
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<tr>
<td>The metabolism of dietary fiber afforded by gut microbiota can influence the extent of allergic inflammation in the airway in mice</td>
<td>[11]</td>
</tr>
<tr>
<td><strong>Lung-skin relationship</strong></td>
<td></td>
</tr>
<tr>
<td>The number and/or diversity of gut microbiota at birth is likely to be positively associated with the pathogenesis of skin eczema in human</td>
<td>[2] [3]</td>
</tr>
<tr>
<td>About 1% - 2% patients with lung cancer may develop skin metastases</td>
<td>[13]</td>
</tr>
<tr>
<td>Elderly women with certain matrix metalloproteinase promotor variants demonstrated a higher susceptibility to skin wrinkling and lung dysfunctions</td>
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</tr>
<tr>
<td>About 50% infants who had acute severe bronchiolitis developed dry skin or eczema within 12 months thereafter</td>
<td>[22]</td>
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Figure 1. Summary of inter-organ relationships among gut, lung and skin.

Organ systems communicate through the intermediacy of signalling molecules. Certain questions arise: 1) to what extent can mucosal membranes communicate (given that there are many such epithelial cell layers inside the body in addition to those of the gut and the lungs)? 2) which organs are more susceptible to be influenced by others? and 3) what kinds of diseases have a stronger influence among different mucosal membranes.

The human body is comprised of multiple-organ systems. The organ axes, as discussed here, are likely to play a role, at least in part, in determining the function of the respective organs under normal and pathological conditions. Even in the practice of Chinese medicine, such inter-organ relationships are not used as the main guide for prescribing treatments. However, such understanding can arouse interest in investigating the etiology/pathogenesis of diseases beyond the organ of concern in modern medicine. Given the co-occurrence of certain diseases, therapeutic interventions should be targeted to organs that are functionally connected. This holistic approach in the prevention and/or treatment of diseases has long been adopted in Chinese medicine, but it is yet to be exploited in modern medicine.

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Markers of Heart, Lung and Dorsal Aorta Damage of Mother Rats and Their Neonates Post Therapeutic Treatment with Doxorubicin, Cisplatin and 5-Flurouracil

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Abstract

Aim: Recently, there is an increased average of developing cancers. Though, the chemotherapeutic-treatment is unfavorable during pregnancy due to its harmful effects on developing fetuses, physicians have two ways to minimize these effects either by termination of the pregnancy or minimizing its side effects. The present work aimed to illustrate the susceptibility of cardiac, lung and dorsal aorta function to the widely applicable drugs doxorubicin and cisplatin as well as 5-flurouracil. Materials and Methods: Mother albino rats were arranged into four-groups (control, doxorubicin, cisplatin and 5-flurouracil-treated groups). Each pregnant rat received intraperitoneal administration of 0.2 mg/kg body weight at 10th and 14th day of gestation and sacrificed at parturition (two doses). At parturition, serum of mother rats used to assess troponin I, heat shock protein 70, 8-hydroxydeoxyguanosine, vascular endothelial growth factor and adhesion molecules (ICAM-1 & VCAM-1). Isoenzyme electrophoresis of alkaline and acid phosphatases, glucose-6-phosphate dehydrogenase and lactic dehydrogenase were estimated in serum, myocardium and dorsal aorta of mother rats. The myocardium and lung were processed for histopathological investigations for both mothers and their offspring. Single strand (comet assay) and double strand DNA damage were carried out in heart and dorsal aorta of mother rats. Results: The present finding revealed that there are detected alterations of myocardial markers and lung amino acid metabolism as well as disruption of myocardial isoenzymes.
DNA damage of myocardium and dorsal aorta were observed. **Conclusions:** The authors concluded that the metabolic activity of heart and lung is highly susceptible to doxorubicin and cisplatin treatment compared to 5-flourouracil and the therapeutic doses must be degraded.

**Keywords**

Anticancer Drugs, Heart, Lung, Dorsal Aorta, Isoenzyme Electrophoresis, Biochemical Markers, Amino Acids, DNA Damage

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**1. Introduction**

Chemotherapeutic-treatment is unfavorable during pregnancy due to its unusual effects on the developing fetus. Termination of pregnancy is the most protocol of treating mother to improve maternal prognosis. However, under the emergency of diagnosed cancer in pregnant women, approximately one in every 1000 births is from women having or being treated from breast cancer, cervical cancer, malignant lymphoma and malignant melanoma [1] [2].

Renal cell carcinoma in horseshoe kidney was diagnosed during the second trimester of gestation [3]. Boudy et al. [4] reported 108 pregnant patients developed breast cancer and undergoing chemotherapeutic-treatment with trastuzumab. The diagnosis of lymphoma in pregnant women gives a therapeutic challenge needed of the developing fetus without compromise of therapeutic potential for the mother. The decision of therapy during gestation is hardly influenced by mother and fetuses [5].

Gwyn [6] reported treatment of 98 breast cancer pregnant at the University of Texas M.D. Anderson Cancer Center, and observed normal growth of fetuses exposed maternally to the chemotherapy in the second and third trimesters.

The chemotherapeutic drugs 5-fluorouracil (F), doxorubicin (A) or epirubicin (E) and cyclophosphamide (C), or the combination doxorubicin and cyclophosphamide (AC) are considered safe when undertaken after the first trimester of pregnancy [7].

Cardiotoxicity induced by the anticancer drugs is a public health problem. Heart needs large demands of energy to maintain its contractility via depolarization of the sarcolemma surface membrane [8]. There is a large requirement of heart to increase demand of fatty acids, glucose, ketone bodies, pyruvate, lactate, amino acids and other protein constituents. The energy liberated from these nutrients supports mechanical contraction, transmembrane pumps, ionic homeostasis, electrical activity, metabolism and catabolism [9].

The development of adult lung disease starts as a result of stress and injury during perinatal development, the critical period of organogenesis [10]. Although most studies have postulated that adult respiratory disorders, may have developmental origins in the perinatal period [11]. However, its mechanism and
onset of disease later in life are unclear. The mechanism of doxorubicin and cisplatin and 5-fluorouracil on cardio-and lung toxicity are still under investigations.

Taking into consideration that the chemotherapeutic treatment is unfavourable during pregnancy but under critical emergency and drug application, it is needed to follow up the health status of offspring to overcome any side effects. The present work designed to outline the role of the used anticancer drugs on cardiac and lung function of mother and their offspring. These organs give the mother and their neonates the creation of life through pumping the blood, nutrients and oxygen to all body organs. Different tools are employed such as histopathology, isoenzyme electrophoresis, biochemical and amino acid analysis and single and double strand DNA damage.

2. Materials and Methods

2.1. Applied Drugs-Treatment

The used chemotherapeutic drugs (Doxorubicin, cisplatin and 5-fluorouracil) were intraperitoneal administered at doses of 0.2 mg/kg body weight at 10th and 14th day of gestation and sacrificed at 19th days of gestation (two doses). Cisplatin (CS, cis-diamminedichloroplatinum), obtained from Sigma Chemical Co (St. Louis, MO, USA). Doxorubicin (DOX, adriamycin) obtained from adriablastina, Farmitalia Carlo Erba, Milan, Italy, meanwhile fluorouracil (5-Fu, pyrimidine antagonist) was supplied by Saladax Biomedical company.

2.2. Experimental Design

Twenty-four virgin albino rats weighing approximately 160 - 180 g body weight (4 month old) were obtained from Hellwan Breeding Farm (Ministry of Health, Egypt) and kept in aerated room with 12 hour light and dark cycle at 22˚C - 25˚C. Free access of standard diet and water were allowed ad-libitum. Mating was carried out with healthy fertile male (2 female/1 male) for overnight and onset of gestation was determined in the next morning after observing sperm in vaginal smear. Pregnant rats were divided into four groups (n = 6). Control (saline-treated), DOX, Cs, and 5-FU-treated groups. Each pregnant mother received intraperitoneal administration of 0.2 mg/kg body weight at 10th and 14th day of gestation and sacrificed at parturition (two doses). At parturition, the animals were anesthetized and sacrificed according to the guidelines of the Egyptian Bioethics Committee. Blood was obtained from sacrificed mother groups (n = 6) and their serum was separated. The heart, dorsal aorta and lung were separated from mothers, meanwhile only heart and lung from their newly born (n = 5). For biochemical assessments and enzyme electrophoresis, the maternal tissues were homogenized in phosphate buffer (pH 7.4), centrifuged and their supernatants were stored at −10˚C. Extra whole specimens were kept in refrigerator for determination of comet assay and DNA fragmentation.

2.3. Biochemical Investigations

The tissue homogenates of heart and dorsal aorta were subjected for estimating
the followings:

Troponin I: This was carried out by using ELISA kit of My Bio Source company (San Diego, CA 92195-3308, USA). The tissue samples were incubated with horse reddish peroxidase containing the antibody of TNI and the product reaction forms a blue colored complex by using 3,3',5,5'-tetramethylbenzidine and measured spectrophotometrically at 450 nm.

Heat shock protein 70 (HSP-70): It was measured by ELISA Kit (Nunc Immunoplate Maxisorp; Life Technologies, UK). The specimens were coated with 10 ng of recombinant Hsp 70 in phosphate-buffered solution, followed by treating with its antibodies (Sigma-Aldrich, Inc, USA) and o-phenylenediamine for coloring development and measured at 492 nm [12].

8-hydroxy-2-deoxy guanosine (8-OHdG): Its amount was determined by the Bioxytech-ELISA Kit (OXIS Health Products, Portland, OR, USA, Catalog No. KOG-200S/E). The tissue samples were incubated with horse reddish peroxidase in wells containing the antibodies of 8-OH-dG and incubated at 37˚C for 1 h, followed by addition of tetramethylbenzidine for color production and measurement at 450 nm [13].

Vascular endothelial growth factor (VEGF): It was determined by ELISA kit (R&D System, Minneapolis, MN, USA) via combination of avidin with horseradish peroxidase and TMB substrate in wells containing tissue samples and VEGF antibodies. The color reaction was assayed spectrophotometrically at 450 nm.

Intracellular adhesion molecule (ICAM)-1 and vascular adhesion molecule (VCAM)-1: These were assayed using ELISA kit (R & D Systems; Minneapolis, MN) after conjugation of rat ICAM-1 and VCAM-1 to horseradish peroxidase and development of the color by the addition of 100 μL of tetra-methylbenzidine at wavelengths of 450 & 620 nm.

2.4. Isoenzyme Electrophoresis

Fresh serum and homogenized heart and dorsal aorta were used. The homogenized specimens were centrifuge and their supernatants were assayed for their protein content [14] and electrophoresis was carried out [15]. The protein bands were stained with Coomassie blue R-250 (60 mg/l) in an acidic medium [16]. For visualization of alkaline and acid phosphatase, glucose-6-phosphate dehydrogenase (G6PD) and lactic dehydrogenase, the electrophoretic tissue samples were incubated in the selected medium for each kind of the assessed enzyme. Alkaline phosphatase (ALP) was determined by incubating the gel in a alkaline tris-borate buffer, pH 9.5 containing α-naphthyl phosphate and Fast Blue BB at 37˚C [17].

For acid phosphatase (AP), electrophoresis was carried out of the serum and tissue samples and incubated in 0.09 M citrate buffer at pH 4.8 containing p-nitrophenyl phosphate disodium salt at 37 Å [18].

Glucose-6-phosphate dehydrogenase gel electrophoresis was performed at 4˚C according to Gaal et al. [19]. The electrophoretic buffer is composed of 5 mM Tris, 80 mm aspartate, and 20 μM NADP + at pH 7.4. Staining of the gel was
carried out by a solution composed of 20 ml 1.2 mmol Tris-Pi (pH 8.5), 25% (v/v) glycerol, 30 µmol glucose-6-phosphate, 4 µmol NADP+, 6 mg p-nitroblue tetrazolium, and 0.5 mg phenazine methosulfate. For lactic dehydrogenase, after electrophoresis, the gel was incubated in buffer medium containing tetrazolium-blue, phenazine methosulphate, Na-lactate and NAD to develop colour reaction after 20 min [20].

2.5. Lung Amino Acid Content

Known weights of lung samples of mother rats were hydrolyzed by 6 M hydrochloric acid, followed by hot dilute detergent solution at neutral pH and distilled water. The protein samples was squeezed out in the column and extracted with petroleum ether and 95% ethyl alcohol and allowed to dry under vacuum. These was followed by dissolving in a known volume of 0.2 M sodium citrate buffer (pH 2.0) and loaded on the amino acid analyzer equipped with a cation exchange column (Amersham Pharmacia Biotech). Elution of the amino acids were carried out and determined calorimetrically at 440 nm for proline and hydroxyproline and at 570 nm for all other ones [21].

2.6. Histological Investigation

Fresh heart and lung of mother rats and their newly born were fixed in 10% phosphate buffered formalin (pH 7.4), dehydrated in an ascending grades of ethyl alcohol, cleared in xylene, and mounted in molten paraplast at 58˚C - 62˚C. 5 µm-thick sections were cut, stained with hematoxylin and eosin, and investigated under a Olympus bright field microscope.

2.7. Single Cell Gel Electrophoresis (Comet Assay)

The heart and dorsal aorta of both control and experimental mother rats were homogenized in chilled homogenizer buffer and a 10% tissue solution was obtained. Six µL of the homogenate was placed on 0.5% low melting agarose and sandwiched between 0.6% normal and low melting agarose on frosted slides. After solidification, the slides were mounted in a lysis solution to allow unwind of the DNA. Neutralization was carried out by Tris-HCl buffer (pH 7.5) as well as staining with a fluorescent DNA-specific stain; ethidium bromide or propidium iodide. Each slide was analyzed using a Leitz Orthoplan epifluorescence microscope (Wetzlar, Germany). Fifty cells were investigated on each slide using the Comet Assay II Automatic Digital Analysis System. The head is composed of intact DNA, while the tail consists of damaged ones. The tail length (mm), tail moment and DNA concentration were measured automatically by the image analysis software [22].

2.8. DNA Fragmentation Assay

Freshly dissected maternal heart and dorsal aorta were washed in ice-cold phosphate-buffered saline and suspended in 100 mL lysis buffer (10 mM Tris-HCl/10
mM EDTA/0.5% Triton X-100, pH 8.0), vortexed, sonicated, and incubated on ice. Centrifugation were carried out for 20 min at 4°C (14,000 × g) and the supernatants containing DNA were treated with RNase A and followed by protease K (0.4 mg/mL; Sigma) at 37°C. DNA concentrations were determined and their electrophoretic mobility was carried out on 1.5% agarose gel against the standard [23].

2.9. Biostatistics

Data are presented as means ± standard error of six replicates. Statistical differences were estimated by analysis of variance; comparisons was carried between the control and treated group using multivariance one way anova. Statistical significance was recorded at P < 0.05.

3. Results

3.1. Biochemical Observations

From Table 1, there was a marked increase of TN I, 8-OHdG, HSP-70 and decrease of VEGF and adhesion molecules (VCAM-1 & ICAM-1).

3.2. Amino Acid Analysis

From Table 2, there was a detected depletion of the amino acids contents in lung of mother rats post—the anticancer drug-treatment. A marked depletion was reported for arginine (arg), cysteine (cys), glutamine (glu), histidine (his), leucine (leu), methionine (met), phenylalanine (phe), proline (pro) and lysine (Lys) in all the treated groups. Only significant decrease for alanine (ala), glycine (gly) and lysine (lys) in 5-Fu-treated mother rats. Isoleucine (Ile) is non-significantly changed.

3.3. Isoenzyme Electrophoresis

From Figure 1, the expression of alkaline phosphatase isoenzyme in serum, heart and dorsal aorta of mother intoxicated with the applied anticancer drugs

<table>
<thead>
<tr>
<th></th>
<th>TNI (pg/100 mg)</th>
<th>8-OHdG (ng/100 mg)</th>
<th>VEGF (pg/100 mg)</th>
<th>HSP-70 (ng/100 mg)</th>
<th>VCAM-1 (ng/100 mg)</th>
<th>ICAM-1 (ng/100 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>1.52 ± 0.16</td>
<td>2.06 ± 0.09</td>
<td>57.73 ± 2.55</td>
<td>54.78 ± 1.38</td>
<td>6.76 ± 0.12</td>
<td>5.57 ± 0.19</td>
</tr>
<tr>
<td>DOX</td>
<td>2.91 ± 0.19*</td>
<td>4.22 ± 0.12*</td>
<td>45.63 ± 2.57*</td>
<td>58.86 ± 1.86*</td>
<td>4.36 ± 0.19*</td>
<td>3.21 ± 0.11*</td>
</tr>
<tr>
<td>Cs</td>
<td>3.87 ± 0.13*</td>
<td>5.52 ± 0.11*</td>
<td>41.38 ± 1.18*</td>
<td>65.36 ± 1.52*</td>
<td>4.11 ± 0.14*</td>
<td>3.09 ± 0.08*</td>
</tr>
<tr>
<td>5-FU</td>
<td>3.64 ± 0.13*</td>
<td>5.28 ± 0.09*</td>
<td>46.85 ± 1.89*</td>
<td>61.52 ± 3.39*</td>
<td>4.96 ± 0.17*</td>
<td>3.13 ± 0.09*</td>
</tr>
</tbody>
</table>

Each result represent mean ± SE (n = 6). *significant at P < 0.05. Abbreviations; TNI, troponin I; 8-OHdG, 8-hydroxydeoxyguanosine; VEGF, vascular endothelial growth factor; HSP-70, heat shock protein 70; VCAM-1, vascular adhesion molecule; ICAM-1, Intracellular adhesion molecule.
Table 2. Lung amino acid contents of mother rats intoxication with doxorubicin, cisplatin and 5-fluorouracil.

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>C</th>
<th>DOX</th>
<th>Cs</th>
<th>5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µmol/100 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential amino acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>His</td>
<td>0.041 ± 0.024</td>
<td>0.014 ± 0.001*</td>
<td>0.018 ± 0.048*</td>
<td>0.013 ± 0.001*</td>
</tr>
<tr>
<td>Ile</td>
<td>0.156 ± 0.002</td>
<td>0.138 ± 0.014</td>
<td>0.149 ± 0.002</td>
<td>0.133 ± 0.002</td>
</tr>
<tr>
<td>Leu</td>
<td>0.597 ± 0.047</td>
<td>0.326 ± 0.022*</td>
<td>0.494 ± 0.008*</td>
<td>0.427 ± 0.007*</td>
</tr>
<tr>
<td>Lys</td>
<td>0.047 ± 0.006</td>
<td>0.035 ± 0.003*</td>
<td>0.038 ± 0.001*</td>
<td>0.028 ± 0.001*</td>
</tr>
<tr>
<td>Met</td>
<td>0.641 ± 0.021</td>
<td>0.452 ± 0.005*</td>
<td>0.416 ± 0.014*</td>
<td>0.439 ± 0.037*</td>
</tr>
<tr>
<td>Phe</td>
<td>0.177 ± 0.012</td>
<td>0.146 ± 0.012*</td>
<td>0.143 ± 0.006*</td>
<td>0.142 ± 0.011*</td>
</tr>
<tr>
<td>Non-essential amino acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ala</td>
<td>0.034 ± 0.01</td>
<td>0.025 ± 0.002</td>
<td>0.021 ± 0.001</td>
<td>0.018 ± 0.001*</td>
</tr>
<tr>
<td>Arg</td>
<td>0.198 ± 0.012</td>
<td>0.158 ± 0.006*</td>
<td>0.168 ± 0.012*</td>
<td>0.136 ± 0.012*</td>
</tr>
<tr>
<td>Asp</td>
<td>0.554 ± 0.030</td>
<td>0.316 ± 0.014*</td>
<td>0.337 ± 0.016*</td>
<td>0.378 ± 0.019*</td>
</tr>
<tr>
<td>Cys</td>
<td>0.949 ± 0.093</td>
<td>0.742 ± 0.010*</td>
<td>0.755 ± 0.025*</td>
<td>0.513 ± 0.018*</td>
</tr>
<tr>
<td>Glu</td>
<td>0.459 ± 0.025</td>
<td>0.281 ± 0.014*</td>
<td>0.337 ± 0.019*</td>
<td>0.275 ± 0.013*</td>
</tr>
<tr>
<td>Gly</td>
<td>0.151 ± 0.015</td>
<td>0.134 ± 0.019</td>
<td>0.122 ± 0.008</td>
<td>0.093 ± 0.004*</td>
</tr>
<tr>
<td>Pro</td>
<td>0.194 ± 0.011</td>
<td>0.157 ± 0.007*</td>
<td>0.1682 ± 0.008*</td>
<td>0.166 ± 0.007*</td>
</tr>
</tbody>
</table>

Each result represent mean ± SE (n = 6). *significant at P < 0.05. Abbreviations; Ala, alanine; Arg, arginine; Asp, aspartic acid; Cys, cysteine; Glu, glutamic acid; Gly, glycine; His, histidine; Ile, isoleucine; Leu, leucine; Lys, lysine; Met, methionine; Phe, phenylalanine.

exhibited decreased expression of the isoenzyme fractions 2 and 3 compared with increased intensity of fraction I. Also, the diffusion rates were altered. Increased intensities of double bands of isoenzyme fraction one was observed in dorsal aorta of 5-Fu-treated mother. For AP, 3 isoenzyme fractions are detected. There is no change in isoenzyme expressions post-drug treatment.

In G6-PD, 5 isoenzyme fractions are observed in serum, heart and dorsal aorta. DOX-treated mother showed faint expression of the serum isoenzyme fractions VI & V comparing with control and other Cs and 5-Fu. In heart tissue, there was a detected missing of the isoenzyme fraction V in DOX- and Cs-treated group meanwhile fraction II weakly expressed in 5-Fu. In dorsal aorta, the isoenzyme fractions I and V were altered (Figure 2).

Lactic dehydrogenase expressed 5 isoenzyme fractions in the investigated tissues. Anticancer-drug treatment decreased the enzyme expression and increased their rate of diffusion.

3.4. Histopathological Observations:

3.4.1. Heart

In control mother, the myocardial muscle fibers are binucleated and regularly oriented (Figure 3(a)). Myocardial muscle intoxicated with the applied
Figure 1. Isoenzymes electrophoresis of alkaline and acid phosphatase, glucose-6-phosphate dehydrogenase and lactic-dehydrogenase of heart and dorsal aorta of mother rats treated with doxorubicin, cisplatin and 5-flururacil. Abbreviations; ALP, Alkaline phosphatase; AP, Acid phosphatase; DA, Dorsal aorta; G6PD, Glucose-6-phosphatase dehydrogenase; H, Heart; LDH, Lactic dehydrogenase; S, Serum. *Means decreased or missing expression of the isoenzyme.

anticancer drugs showed eosinophilic disorganized muscle fibers having numerous necrotic zones (Figures 3(a1)-(a3)).

The control myocardium of offspring is composed of regularly oriented binucleated muscle fibrils aligned in contact with each other (Figure 3(b)). However, offspring maternally-treated with the used anticancer drugs exhibited
Figure 2. Photomicrographs of histological sections of myocardial tissues of both mother rats (a)-(a3) and their offspring (b)-(b3) and lung tissues of mother rats (c)-(c3) and offspring (d)-(d3) of both control (a)-(d) and anticancer-drug-treatment (a1)-(a3), (b1)-(b3), (c1)-(c3) and (d1)-(d3). (a1) Mother rats intoxicated with doxorubicin. (a2) Mother rats intoxicated with cisplatin. (a3) Mother rats intoxicated with 5-Fu. (b1) Offspring maternally treated with doxorubicin. (a2) Offspring maternally treated with cisplatin. (b3) Offspring maternally treated with flurouracil. (c) Control mother lung. (d) Control offspring lung. a1. Mother rats intoxicated with doxorubicin. (c2) Mother rats intoxicated with cisplatin. (c3) Mother rats intoxicated with 5-Fu. Note focal collection of inflammatory cells forming granulomatous lesions. (d1) Offspring maternally treated with doxorubicin. (d2) Offspring maternally treated with cisplatin. (d3) Offspring maternally treated with flurouracil. Note hyperplasia and necrosis of alveolar lining epithelium. HX-E.

Disorganization of the muscle fibers with leukocytic infiltration and widespread of necrotic patches (Figures 3(b1)-(b3)).

3.4.2. Lung

The lung of control mother rats are composed of numerous alveoli outlined with a very thin layer of connective tissue and fine blood capillaries. The alveoli are lined by a single layer of squamous epithelium (Figure 3(c)). Treatment with the used anticancer drugs including DOX, Cs and 5-Fu revealed damage and hyperplasia of alveolar lining cells. The leukocytes densely aggregated within the alveolar tissues missing their lumina and disorganized their structures. DOX
exhibited massive lung damage compared to the other applied drugs (Figures 3(c1)-(c3)).

On the other hands, offspring maternally-treated with the used anticancer drugs developed hyperplasia of the alveolar lining cells and widespread of necrotic patches leading to obstructive losing of the alveolar lumina compared to the control (Figures 3(d)-(d3)).

3.4.3. Single and Double Strand DNA Damage
The genomic degree of laddering (total DNA fragmented) increased in heart and dorsal aorta post-treatment with the used anticancer drugs. Dorsal aorta showed the highest degree of damage (Figure 4). Applying single strand DNA (Comet assay); there was a marked increase of detaching, tail length and tail mobility in heart and dorsal aorta of the chemotherapeutic drug-treatment (Figure 5).

4. Discussion
Although the chemotherapeutic treatment is unfavorable during pregnancy, under critical emergency and drug application, it is needed to follow up the health status of offspring to overcome any side effects. The present work is designed to illustrate the role of anticancer drugs on cardiac and lung function of mother and their offspring. These organs give the mother and their neonates the creation of life through pumping the blood, nutrients and oxygen to all body organs.

The observed myocardium of mother rats received one of the following drugs: doxorubicin, cisplatin and 5-fluorouracil exhibited widespread necrotic patches and disorganized muscle fibers. There was little pathological alternations detected in maternally-treated neonates due to their metabolic detoxication and placental barriers.

The present findings agree with Lipshultz [24] whom reported 11.8-fold of cardiotoxicity in children receiving a cumulative dose of anthracyclines more
than 300 mg/m² compared to the less dose-treatment. Assessment of dose and follow up is of critical importance during chemotherapeutic treatment.

The disrupted cardiac function was confirmed by altering of the electrophoresis of alkaline phosphatase, glucose-6-phosphate dehydrogenase and lactic dehydrogenase.

There are similar findings of altered myocardial enzymes in relation to anticancer drug-therapy. Serum lactic dehydrogenase increased during either Cs or DOX-treatment [25] [26] [27].
Figure 5. Genomic DNA fragmentation showing degree of laddering of DNA expressing DNA fragmentation in heart and dorsal aorta of DOX,Cs and 5-Fu-treated mother rats. Abbreviations; C, control; DOX, doxorubicin; Cs, cisplatin; 5-Fu, flurouracil.

The observed altered glucose-6 phosphate dehydrogenase isoenzyme fractions I, VI and V in serum, heart and dorsal aorta may reflect the disruption of pentose phosphate pathway, retarding the synthesis of NADPH from NADP [28].

Glucose-6-phosphate dehydrogenase X-linked mice were found to impaired myocardial relaxation [29] through increased liberation of reactive oxygen species and reduction of glutathione levels [30].

The observed high level of serum troponin I, heat shock protein 70 and 8-hydroxy-deoxyguanosine reflected the damage of cardiomyocytes in mother rats and their newborn.

Myocardial troponin I is a sensitive biomarker of cardiotoxicity. DOX-treatment induced high level of troponin I in dogs receiving five doses every three weeks of 30 mg/m² body surface area [31]. The present findings supported the work of El-Awady et al. [32] who reported elevated activities of lactate dehydrogenase, plasma cardiac troponin, depletion of the glutathione S transferase content, superoxide dismutase activity and increased of malondialdehyde in rats administered intraperitoneally a single dose of 10 mg cisplatin/kg body weight.

The alterations of the assayed isoenzyme fractions are correlated with the decreased metabolic activity of heart and dorsal aorta and these reflected on declining the metabolic activity of amino acids of lung tissue.

The present findings agree with Kroese and Scheffer [33] whom observed increased level of 8-OHdG in atherosclerotic patients with cardiovascular diseases. The increased level of 8-OHdG predicted the cardiotoxicity of the applied treatment of the anticancer drugs.

It is known that heat shock protein 70 is important for cell growth, protein synthesis [34], transport and degradation of protein components [35]. Increased HSP70 predicted the damage of cardiomyocytes.

On the other hand, treating mother rats with used anticancer drugs exhibited depletion of serum VEGF and adhesion molecules (ICAM-1 & VCAM-1).

Also, vascular endothelial growth factor is known to regulate the proliferation,
sprouting, and migration of the endothelial cells and overexpressed in cardiomyocytes [36]. Exogenous VEGF is a potent arteriogenic growth factor that can induce cardiac hypertrophy and counteract metabolic problems of obesity [37] [38].

Similar findings of decreased level of ICAM-1 were reported in cardiac tissue of rats administered single dose of 20 mg/kg I.P. as well as in in vitro studies of Abou-El Hassan et al. [39].

The pathological changes in lung tissues were assessed by decreased lung metabolism via depletion of argenine, cysteine, glutamine, histidine, leucine, methionine, phenyl alanine, proline and lysine in all the treated groups. The decrease amino acids reflect the hypoxic stress affected the lung tissues as detected by increased fibrosis of maternal lung and hyperplasia and necrotic foci in newborn rats [40].

Kim et al. [40] reported a decrease of threonine, citrulline, histidine and tryptophan and increase in proline, isoleucine, phenylalanine and ornithine in lung of Korean cancer patients with advanced pulmonary disease showed inverse correlation with alanine, phenylalanine and tyrosine, however citrulline and tryptophane were markedly changed in relation to energy intake [41].

L-leucine represents important signal molecule for promoting cell growth by activating the mechanistic/mammalian target of rapamycin [42] that enhanced phosphorylates translational regulators, p70 ribosomal kinase 1 (p70S6K) and the initiation factor 4 E binding protein [43].

The observed findings of the chemotherapeutic drugs predicted pulmonary fibrosis in mother rats and hyperplastic alveolar with missing of their alveolar lumina in their newborn. Although mother rats showed moderate degree of lung fibrosis, their neonates showed less degree of lung damage due to the high capacity of maternal tissues for biodegradation and clearance of the applied drug.

As we know that the lung is rich in blood capillaries and the endothelium is the first physiological barrier between blood and tissues. This impairs oxygen and carbon dioxide exchange and elevated hypoxic stress interfered with cardiomyocytes function in mother and their neonate.

The present findings agree with authors studies other classes of the anticancer drugs such as methotrexate, procarbazine and bleomycin [44] and azathioprine [45] [46].

The hypoxic stress in lung tissues and disorganized pulmonary vascular anastomoses reproduced myocardial damage [47]. The lung dysfunction may lead to decrease respiratory mechanics, impaired gas exchange and cardiovascular abnormalities [48], increased arterial stiffness, the marker of heart failure [49].

Also, the altered biomarkers characteristic of lung and heart function coincides with the marked single and double strand DNA damage in cardiomyocytes and aorta.

The present findings agree with the work of Ray et al. [50] who reported increased average of apoptosis and DNA fragmentation of cardiac and lung tissues of mice subjected to doxorubicin-treatment.
The observed abnormal cardiac and dorsal aorta isoenzyme electrophoresis, biochemical alterations, single and double strand DNA damage may contribute to decrease its elasticity and contraction minimizing the oxygen and nutrients to the body organs.

Similar findings of damaged endothelial cells were achieved through in vitro and in vivo studies post-cytosine arabinoside or daunorubicin [51], paclitaxel [52] and 5-FU-treatment [53] [54].

Both cardiac and lung diseases may be attributed to the increased oxidative stress, inflammation and DNA damage in the vascular cells [55] leading to apoptosis [56].

Finally, the author concluded that under critical emergency of treating mother with a chemotherapeutic drug, the dose must be justified to minimize the cytotoxicity on cardiac and lung tissues of mothers and their neonates.

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