شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

HANAA ALY

شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

HANAA ALY

Cairo University
Faculty of Veterinary Medicine

Alterations in some genetic expression in relation to gold nanoparticles application

A thesis submitted by

Ghada Ali Abdallah

(BVSc, Cairo University, 2010; MVSc, Cairo University, 2014)

For the PhD. degree of the

(**Biochemistry and Chemistry of Nutrition**)

Under Supervision of

Said Z. M. Moussa
Prof. of Biochemistry and Chemistry of Nutrition,
Faculty of Veterinary Medicine,
Cairo University.

Hassan A. Amer
Prof. of Biochemistry and Chemistry of Nutrition,
Faculty of Veterinary Medicine,
Cairo University.

Marwa I. Abdel-Hamid
Prof. of Biochemistry and Chemistry of Nutrition,
Faculty of Veterinary Medicine,
Cairo University.

Ayman H. M. El-Deeb
Assist. Prof. of Virology,
Faculty of Veterinary Medicine,
Cairo University.

2020

Cairo University
Faculty of Veterinary Medicine
Biochemistry and Chemistry of Nutrition

Supervision Sheet

Supervisors

Prof. Dr. Said Zaki M. Moussa

Professor of Biochemistry and Chemistry of Nutrition
Faculty of Veterinary Medicine
Cairo University

Prof. Dr. Hassan Abdel-Halim Amer

Professor of Biochemistry and Chemistry of Nutrition
Faculty of Veterinary Medicine
Cairo University

Prof. Dr. Marwa Ibrahim Abdel-Hamid

Professor of Biochemistry and Chemistry of Nutrition
Faculty of Veterinary Medicine
Cairo University

Dr. Ayman H. M. El-Deeb

Assistant Professor of Virology
Faculty of Veterinary Medicine
Cairo University

Cairo University
Faculty of Veterinary Medicine
Biochemistry and Chemistry of Nutrition

Name	**Ghada Ali Abdallah**
Nationality	**Egyptian**
Date of Birth	**12/ 8/ 1988**
Place of Birth	**Cairo**
Department	**Biochemistry and Chemistry of Nutrition**
Thesis Title	**Alterations in some genetic expression in relation to gold nanoparticles application**
Supervisors	**Prof. Dr. Said Z. M. Moussa** **Prof. Dr. Hassan A. Amer** **Prof. Dr. Marwa I. Abdel-Hamid** **Dr. Ayman H. El-Deeb**

Abstract: Gold nanoparticles (AuNPs) have been considered as an ideal candidate in various biomedical applications due to their ease of tailoring into different size, shape, and decorations with different functionalities. The current study was conducted to investigate (both *in vitro* and *in vivo*) some of the genetic and epigenetic alterations in lung cells in response to the exposure to AuNPs. Forty Wister rats were divided into two equal groups, control group and AuNPs-treated group received a single intravenous (IV) injection of citrate-capped spherical AuNPs (25 ± 3 nm) at a final dose of 0.015 mg /kg body wt. Lung samples were then collected from both groups at one day, one week, one month and two months post-injection. The *in vitro* experiment involves the treatment of human lung fibroblast cells (WI-38) with the same AuNPs sphere at a final concentration of 2 nM for 24, 48, 72 and 96 h. Transmission electron microscopy (TEM) and energy-dispersive X-ray (EDX) spectroscopy verified both the *in vivo* and *in vitro* cellular uptake of AuNPs into the cytoplasm at the ultrastructural level. The *in vitro* effect of AuNPs on cell viability was investigated by MTT assay. The molecular modifications caused by AuNPs exposure at level of expression of *microRNA-155 (miR-155*) were analyzed by TaqMan® qRT-PCR. Meanwhile, the molecular alterations of two of miR-155 target genes; *protein S (PROS1)* and *tumor protein 53 inducible nuclear protein 1 (TP53INP1)* were investigated by qRT-PCR with the determination of the *in vivo* protein S (PS) expression by western blotting technique Moreover, the alterations of two of DNA damage response (DDR) genes; *Breast Cancer Susceptibility 1* (*BRCA1*) and *Nibrin* (*NBN*) genes were measured by qRT-PCR. The present study suggests that AuNPs could induce genetic modulations in lung cells both *in vivo* and *in vitro* experimental models which assort further insights into AuNPs molecular mechanisms and their impact on epigenetic processes that can predispose to lung injury.

Keywords: AuNPs; Epigenetic; WI-38; MiR-155; PROS1; TP53INP1; BRCA1; NBN.

DEDICATION

To the soul of:

The man who taught me that life is a message written only by belief in ALLAH and communicated by work and patience my ever loving "Father ".

To her:

The lady with the strength of a warrior, the mercy of an angle, the mind of scientist and the heart of artist my ever loving and caring "Mother".

To him:

My life partner and soul mate who share me the load and gave me the strength to bear any difficulties my ever loving and caring "Husband "

To them:

The partners who support me and give me the love and passion my ever loving and caring "Brothers, Daughters and Son"

Acknowledgments

*First and foremost, I would like to thank **ALLAH.** Praise is always and forever to god.*

*"Whoever does not thank people, does not thank **ALLAH**"*

*So I'd like to express my gratitude and deepest thanks to **Prof. Dr. Said Zaki M. Moussa** Professor of Biochemistry and Chemistry of Nutrition, Faculty of Veterinary Medicine, Cairo University for his scientific supervision ,kind encouragement and valuable guidance who played an important role in completion of this work.*

*Deep gratitude to **Prof .Dr., Hassan A. Amer** Professor of Biochemistry and Chemistry of Nutrition, Faculty of Veterinary Medicine, Cairo University for his support , valuable supervision and encouragement .*

*My sincere thanks to **Prof. Dr. Marwa Ibrahim** Professor of Biochemistry and Chemistry of Nutrition, Faculty of Veterinary Medicine Cairo University for her valuable spiritual and academic advice and for her continuous encouragement and subtle direction of my effort throughout the preparation of this thesis.*

*I would like to express my deepest thanks to **Dr. Ayman H. M. El-Deeb** Assist. Professor of Virology, Faculty of Veterinary Medicine, Cairo University for his patience, steadfast encouragement and guidance to complete this study.*

And lastly, I would like to express my deep thanks to all members and my friends of Biochemistry and Chemistry of Nutrition, Faculty of Veterinary Medicine, Cairo University.

CONTENTS

		Page
1	**Introduction and Aim of work…….**	1
2	**Review of Literature…….**	8
	2.1. Nanomaterials (NMs)…….....	8
	2.2. Gold Nanoparticles (AuNPs)…….	18
	2.3. Safety assessment of NMs…….....	26
	2.4. Epigenetic Toxicity of NPs…….....	26
	2.5. MicroRNAs (miRNAs)……	28
	2.6. MicroRNA-155 (miR-155)……..	39
	2.7. *Protein S (PS) (PROS1)* gene……..	46
	2.8. *Tumor protein 53 inducible nuclear protein 1 (TP53INP1)* gene…….	52
	2.9. DNA Damage Response (DDR) and the potential genotoxic effect of AuNPs…….....	56
	2.10. *Nibrin (NBN)* gene…….	62
	2.11. *Breast Cancer Susceptibility 1* (*BRCA1*) gene….....	69
3	**Published papers…….....**	75
	Pulmonary deregulation of expression of miR 155 and two of its putative target genes; PROS1 and TP53INP1 associated with gold nanoparticles (AuNPs) administration in rat.....	5569-5579
4	**Discussion……...**	86
	4.1. Biological effects of AuNPs in rat lung…….....	87
	4.2. Biological effects of AuNPs in WI-38 lung fibroblasts.....	90
	4.3. The effect of AuNPs on *miR-155* expression…….....	93
	4.4. The effect of AuNPs on miR-155 target genes.....	96
	4.5. The effect of AuNPs on the expression of DNA Damage Response (DDR) genes……	102
6	**Conclusion and Recommendation……**	106
7	**Summary…….....**	108
8	**References…….**	112