Ain Shams University
Faculty of Science
Biochemistry Department

Antitumor Efficacy of Gallium Nanoparticles and Ellagic acid on Mammary Gland Carcinoma in Rats

A thesis Submitted to Faculty of Science, Ain Shams University for Partial Fulfillment of Master degree of Science in Biochemistry

By

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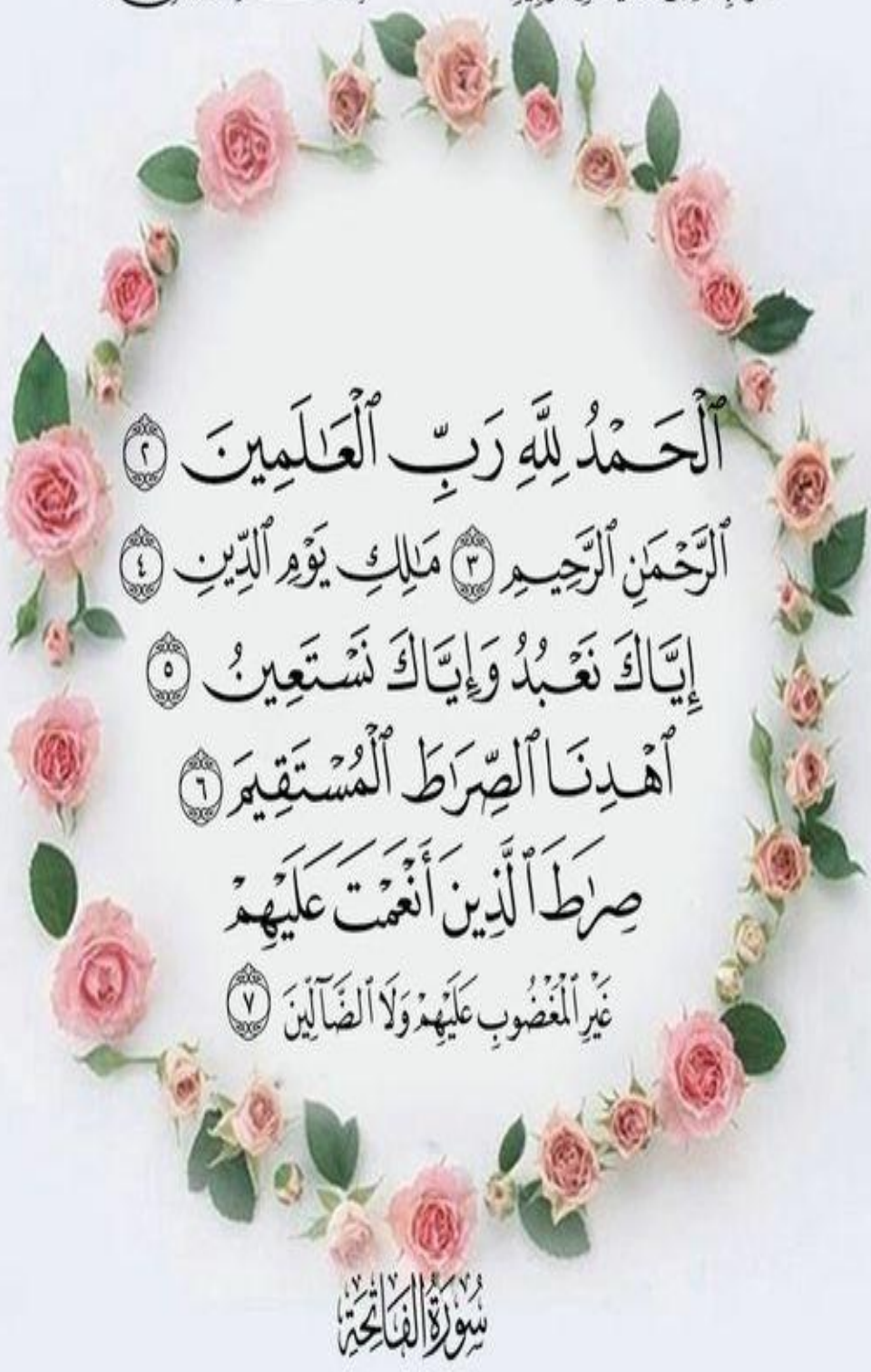
أَعُوذُ بِاللَّهِ مِنَ الشَّيْطَانِ الرَّجِيمِ

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ



ٱلْحَمْدُ لِلَّهِ رَبِّ ٱلْعَٰلَمِينَ ﴿٢﴾

ٱلرَّحْمَٰنِ ٱلرَّحِيمِ ﴿٣﴾ مَٰلِكِ يَوْمِ ٱلدِّينِ ﴿٤﴾

إِيَّاكَ نَعْبُدُ وَإِيَّاكَ نَسْتَعِينُ ﴿٥﴾

ٱهْدِنَا ٱلصِّرَٰطَ ٱلْمُسْتَقِيمَ ﴿٦﴾

صِرَٰطَ ٱلَّذِينَ أَنْعَمْتَ عَلَيْهِمْ

غَيْرِ ٱلْمَغْضُوبِ عَلَيْهِمْ وَلَا ٱلضَّآلِّينَ ﴿٧﴾

سُورَةُ الفَاتِحَة

Ain Shams University
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Approval Sheet

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Declaration

I declare that this thesis has been composed and the work recorded has been done by myself and it has not been submitted for any other degree at this or any other university.

Amira mamdouh

Dedication

I dedicate this work to my dear grandmother's soul, all members of my dear family, my dear professors and friends for their support, encouragement, guidance and continuous backing.

Acknowledgement

*First, foremost, all thanks to **"Allah"** by whose grace this work had been completed in such comeliness way and May Allah benefit the people with it.*

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Amira mamdouh

Contents


Abstract

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Cancer is an important mortality contributor worldwide and breast cancer is the most common among women. Despite of the numerous breast cancer therapeutic strategies, they either have limitations or sometimes are resisted by the cancer, so new approaches are needed to tackle those restrictions. Nanotechnology offers exciting leaps forward in diagnosis and treatment of cancer, especially breast cancer. The main object of this study was to investigate the effect of the newly synthesized gallium nanoparticles coated by ellagic acid (EA-GaNPs) on the induced mammary gland carcinogenesis in female rats. The antitumor efficacy of EA-GaNPs was conducted both *in vitro* and *in vivo*. *In vitro* study showed that EA-GaNPs inhibited human breast cancer cell line (MCF-7) proliferation with IC_{50} of 2.86 µg/ml. while *In vivo*, the administration of EA-GaNPs to DMBA-treated rats ameliorated the hyperplastic state of mammary gland carcinogenesis induced by DMBA. Additionally, EA-GaNPs administration significantly modulated the activities of ALT and AST, as well as the levels of urea and creatinine in serum. Also EA-GaNPs administration improved the antioxidant state by increasing SOD activity and GSH content, and decreasing MDA content in the mammary tissue, besides enhancing of the apoptotic activity through elevating the levels of caspase-3 and decreasing the protein intensities of AKT & PI3K. Furthermore, a significant decrease in serum TIBC accompanied with significant increase in the level of calcium were noted. Hence, it can be concluded that EA-GaNPs could be a promising potent anticancer compound.

List of Abbreviations

ACS	American Cancer Society
AhR	Aryl hydrocarbon receptor/ transcription factor
ALT	Alanine aminotransferase
ANOVA	Analyzed using one way analysis of variance
AP-1	Activator protein-1
ARNT	Aryl hydrocarbon receptor nuclear translocator
AST	Aspartate aminotransferase
BAD	Bcl-2-associated death promoter
BAX	Bcl-2-associated X protein
BC	Breast cancer
BER	Base excision repair pathway
BTG	Betaine Tetrachloro-Gallate complex
CAT	Catalase
CoA	Coactivator Complexes
CY	Cytokines
DES	Diethylstilbestrol
DLS	Dynamic light scattering
DMBA	7,12-Dimethylbenz(*a*)anthracene
DNA	Deoxy ribonucleic acid
Dndp	Deoxy nucleoside diphosphate
DTNB	5, 5'-Dithio-bis(2-nitrobenzoic acid)
E	Estrogen
EA	Ellagic acid
EA-GaNP4	Gallium nanoparticles coated by Ellagic Acid
EDTA	Ethylene diamine tetra acetic acid

EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
ER	Estrogen receptor
ERT	Estrogen replacement therapy
FAK	Focal adhesion kinase
FbpA	ferric-binding protein
Fe	Iron
Fe^{+3}	Ferric iron
FOXO	One of forkhead family of transcription factors
FTIR	Fourier transforms infrared spectroscopy
Ga	Gallium
$GaNO_3$	Gallium nitrate
GaNPs	Gallium nanoparticles
GFs	Growth factors
GPCR	G protein-coupled receptors
GPx	Glutathione peroxidase
GSH	Reduced glutathione
GSK3	Glycogen synthase kinase 3
GSSG	Glutathione disulfide
H_2O_2	Hydrogen peroxide
HCl	Hydrochloric acid
HER2	Human epidermal growth factor receptor 2
HRP	Horse radish peroxidase
IC_{50}	The half maximal inhibitory concentration
IGF1-R	Insulin-like growth factor receptor
JNK	C-Jun N-terminal kinase

LD_{50}	Median lethal dose
MAPK	Mitogen- activated protein kinase
MCF-7	Michigan cancer foundation-7
MDA	Malondialdehyde
mTOR	mammalian target of rapamycin and is a member of PI3K related family
MTT	3-[4,5-dimethylthiazole-2,5 diphenyltetrazolium bromide
NaCl	Sodium chloride
NaOH	Sodium hydroxide
NCI	National Cancer Institute
NCRRT	National Center for Radiation Research and Technology
NDP	Nucleoside diphosphate
NER	Nucleotide excision repair pathway
NPs	Nanoparticles
O.D	Optical density
$O_2^{\cdot}$	Super oxide anion
$OH^{\cdot}$	Hydroxyl radical
PAH	Polycyclic aromatic hydrocarbon
PALB2	Partner and localizer of BRCA2 gene
PHLPP	PH domain and leucine rich repeat protein phosphatases
PI3K	Phosphatidylinositol 3-kinases
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol 3,4,5-triphosphate
PKB (AKT)	Protein kinase B The "Ak" was a classification name for a mouse that developed spontaneous thymic lymphomas. The "t" stands for 'thymoma'
Pt	Platinum

PTEN	Phosphatase and tensin homologue gene
PTEN	Phosphatase and tensin homolog
PUFA	Poly unsaturated fatty acids
PVDF	Poly vinylidene difluoride
R	Reagent
r.p.m	rounds per minute
RE	Response elements
ROS	Reactive oxygen species
RTKs	Receptor tyrosine kinases
S.D	Standard deviation
SDS-PAGE	Sodium dodecyl dulfate -poly acrylamide gel electrophoresis
SEM	Scanning electron microscope
SHIP	SH2-containing inositol phosphatase
SOD	Superoxide dismutase
SPSS	Statistical package for social science
SRC	Steroid receptor coactivator
St.	Standard
TBA	Thiobarbituric acid
TCA	Tri chloroacetic acid
Tf	Transferrin
TFR	Transferrin receptor
TIBC	Total iron binding capacity
TP53	Tumor suppressor gene produces p53 protein
UV	Ultra violet
VIS	Visible
WHO	World Health Organization
ZS	Zetasizer