



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

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

أَعُوذُ بِاللَّهِ مِنَ الشَّيْطَانِ الرَّجِيمِ

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سُورَةُ الْفَاتِحَةِ



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## **Antitumor efficacy of Gallium Nanoparticles and Ellagic acid on Mammary Gland Carcinoma in Rats**

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*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.*

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**Amira mamdouh**

## ***Contents***

<b>Items</b>	<b>Page</b>
<b>Abstract</b>	<b><i>i</i></b>
<b>List of Abbreviations</b>	<b><i>ii</i></b>
<b>List of Figures</b>	<b><i>vi</i></b>
<b>List of Tables</b>	<b><i>ix</i></b>
<b>Introduction</b>	<b>1</b>
<b>Aim of the work</b>	<b>5</b>
<b>I. Review of literature</b>	<b>6</b>
I.1.Cancer	<b>6</b>
I.2. Breast cancer	<b>6</b>
I.2.1. Etiology of breast cancer	<b>7</b>
I.2.2. Pathophysiology of breast cancer	<b>13</b>
I.2.3. Oxidative stress and breast cancer	<b>18</b>
I.2.4. Management of breast cancer	<b>21</b>
I.3. Nanotechnology	<b>23</b>
I.3.1. Nanotechnology and cancer	<b>23</b>
I.3.1.1. Therapeutic approaches of nanotechnology	<b>23</b>
I.3.1.2. Metal nanoparticles in cancer therapy	<b>24</b>
I.4. Gallium	<b>25</b>
I.4.1. Gallium's applications	<b>26</b>
I.4.2. Mimicry of Gallium to Iron	<b>28</b>
I.4.3. Therapeutic applications of Gallium	<b>31</b>
I.4.4. Diagnostic application of Ga isotopes (Ga- scanning)	<b>36</b>
I.5. Synthesis of nanoparticles	<b>37</b>
I.5.1. Green nanotechnology	<b>37</b>

1.6. Ellagic acid	38
I.6.1. Therapeutic and biological health benefits	38
<b>II-Materials and methods</b>	<b>45</b>
II.1. Materials	45
II.1.1. Chemicals	45
II.1.2. Cell line	46
II.1.3. Experimental animals	46
II.2. Chemical studies	47
II.2.1. Biosynthesis of GaNPs coated by EA (EA-GaNPs)	47
II.2.2. Preparation of DMBA.	47
II.2.3. Characterization of the EA-GaNPs	48
II.2.3.1. Dynamic light scattering (DLS)	48
II.2.3.2. Ultraviolet-visible absorption (UV/VIS) Spectroscopy.	48
II.2.3.3. Scanning Electron Microscope (SEM) analysis	48
II.2.3.4. Fourier transforms infrared spectroscopy (FT-IR) spectroscopy	48
II.3. Evaluation of the antitumor efficacy EA-GaNPs	49
II.3.1. <i>In vitro</i> study	49
II.3.2. <i>In vivo</i> study	51
II.3.2.1. Determination of the median lethal dose (LD <sub>50</sub> )	51
II.3.2.2. Experimental design	51
II.4. Samples collection	52
II.4.1. Blood sampling	52
II.4.2. Tissue sampling	53
II.5. Biochemical parameters	53
II.5.1. Evaluation of liver biomarkers in serum	53
II.5.2. Evaluation of kidney biomarkers in serum	58



## Contents

---

II.5.3. Evaluation of oxidative stress and antioxidant markers in mammary gland tissue	65
II.5.4. Determination of serum total iron binding capacity (TIBC)	72
II.5.5. Determination of serum calcium concentration	75
II.5.6. Assessment of caspase-3 concentration in mammary gland tissue	76
II.5.7. Immunoblotting of phosphatidyl inositide 3- kinases (PI3K) and protein kinase B (PKB) (AKT)	80
II.5.8. Histopathological studies	83
II.5.9. Statistical analyses	84
<b>III- Results</b>	<b>85</b>
<b>IV- Discussion</b>	<b>125</b>
<b>V- Summary and Conclusion</b>	<b>144</b>
<b>VI- References</b>	<b>150</b>
الملخص العربى	١
المستخلص العربى	



## *Abstract*

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  $\mu\text{g/ml}$ . 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***

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

## *List of abbreviations*

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

## *List of abbreviations*

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

## *List of abbreviations*

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