UNIVERSITI PUTRA MALAYSIA

ACUTE TOXICITY ASSESSMENT OF NEWLY NANOFORMULATED GALLIC ACID-LOADED GRAPHENE OXIDE USING ZEBRAFISH EMBRYONIC MODEL

AHMAD ASHRAFUL HADI BIN ABDUL GHAFOR

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AHMAD ASHRAFUL HADI BIN ABDUL GHAFOR

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Chairman : Seri Narti Edayu Sarchio, PhD
Faculty : Medicine and Health Sciences

Gallic acid (GA) is a phenolic compound found in almost all plants and has been reported to possess powerful health benefits such as anti-oxidant, anti-inflammatory, anti-cancer, and anti-diabetic properties. However, GA suffers a short half-life when administered *in vivo*. Recent studies have employed graphene oxide (GO), a biocompatible and cost-effective graphene derivative, as a nanocarrier for GA. This newly formulated nano-compound is called gallic acid-loaded graphene oxide (GAGO). However, the toxicity effect of this formulated nano-compound has not been fully studied. Thus, the present study aims to evaluate the toxicity and oxidative stress effects of GAGO nanoformulation, using the zebrafish embryonic model. GAGO was exposed to zebrafish embryos ($n \geq 30$; 24 hours post-fertilization (hpf)) at five different concentrations ranged between 0-500 µg/mL for up to 96 hours of exposure. Pure GO, pure GA and distilled water were used as controls to GAGO. The development of embryos was monitored twice daily throughout the study. Significant high mortality rate, delayed hatching rate, low heartbeat, and high reactive oxygen species (ROS) content were recorded in GO-treated embryos exposed to concentrations ≥ 50 µg/mL, at all-time points ($p < 0.05$). GA also exhibits similar effects in concentration- and time-dependent manners. Interestingly, when compared to GO and GA, significant improvement in the survival rate was observed in GAGO-treated embryos at all concentrations tested and all time points measured. Furthermore, GAGO also exhibits normal ROS level when compared to GA and GO. Noticeable malformations of pericardial and yolk sac edema were observed in embryos treated with GAGO. Altogether, the present data demonstrates that GAGO nanofomulation demonstrates significant improved toxicity profile compared to its pure compounds, GO and GA ($p < 0.05$). Further study is still warranted to correlate the toxicity of GAGO with its effective concentrations at molecular level, in *in vitro* and *in vivo* models.

Keywords: Gallic acid, graphene oxide, nanoparticles, toxicity, zebrafish embryo

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENILAIAN KETOKSIKAN TERHADAP NANOFORMULASI BARU ASID GALIK DIMUAT KE DALAM GRAFIN OKSIDA MENGGUNAKAN MODEL EMBRIO IKAN ZEBRA

Oleh

AHMAD ASHRAFUL HADI BIN ABDUL GHAFOR

Februari 2022

Pengerusi : Seri Narti Edayu Sarchio, PhD
Fakulti : Perubatan dan Sains Kesihatan

Asid galik (GA) adalah sebatian fenol yang terdapat pada hampir kebanyakan tumbuhan dan dilaporkan mempunyai pelbagai manfaat kesihatan seperti antioksidan, antiradang, antibarah, dan antidiabetes. Walau bagaimanapun, GA mempunyai tempoh hayat yang singkat apabila digunakan secara *in vivo*. Kajian terkini menggunakan grafin oksida (GO), iaitu salah satu terbitan grafin yang memiliki bioserasi dan menjimatkan kos, sebagai pembawa nano untuk GA. Formulasi sebatian nano yang baharu ini dikenali sebagai *Gallic Acid-Loaded Graphene Oxide* (GAGO). Walau bagaimanapun, kesan ketoksikan formulasi sebatian nano ini masih belum dikaji sepenuhnya. Oleh itu, kajian ini dijalankan bertujuan untuk menilai kesan ketoksikan dan kesan tekanan oksidatif formulasi nano GAGO, menggunakan model embrio Ikan Zebra. Sampel GAGO didedahkan kepada embrio Ikan Zebra ($n \geq 30$; 24 jam selepas persenyawaan (hpf)) pada lima kepekatan berbeza di antara 0-500 μg/mL sehingga 96 jam pendedahan. GO tulen, GA tulen dan air suling digunakan sebagai perbandingan kepada GAGO. Perkembangan embrio dipantau dua kali sehari sepanjang kajian. Kadar kematian tinggi, kadar penetasan lambat, degupan jantung rendah, dan kandungan spesis oksigen reaktif (ROS) yang tinggi dicatatkan pada embrio yang terdedah kepada GO pada kepekatan ≥ 50 μg/mL, pada semua masa yang diuji ($p < 0.05$). Sampel GA juga menunjukkan kesan serupa berkadar langsung dengan dos dan masa pendedahan. Menariknya, peningkatan yang ketara pada kadar kelangsungan hidup dapat diihat pada embrio yang dirawat dengan GAGO berbanding dengan GO dan GA, pada semua tahap kepekatan dan masa ujian. Selain itu, GAGO menunjukkan tahap ROS normal pada semua kepekatan yang diuji jika dibandingkan dengan GA dan GO. Pembentukan kecacatan edema pada perikardium dan kantung yok adalah ketara pada embrio yang dirawat dengan GAGO. Secara keseluruhan, data ini menunjukkan bahawa nanofomulasi GAGO mempamerkan penambahbaikan yang signifikan pada profil ketoksikan berbanding dengan sebatian tulennya, GO dan GA ($p < 0.05$). Kajian lebih lanjut masih diperlukan untuk mengkaji tahap ketoksikan GAGO dengan kepekatan efektifnya di peringkat molekul, menggunakan model *in vitro* dan *in vivo*

Kata kunci: Asid galik, grafin oksida, nanopartikel, ketoksikan, embrio Ikan Zebra.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Seri Narti Edayu Sarchio, PhD
Department of Biomedical Science
Faculty Medical and Science Health
Universiti Putra Malaysia
(Chairman)

Suhaili Shamsi, PhD
Department of Biochemistry
Faculty Biotechnology and Science Molecule
Universiti Putra Malaysia
(Member)

Faizah Md Yassin, PhD
Department of Chemical and Environmental Engineering
Faculty of Engineering
Universiti Putra Malaysia
(Member)

_____
ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 13 October 2022

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Signature: _____
Name of Chairman of
Supervisory Committee: Seri Narti Edayu Ssarchio

Signature: _____
Name of Member of
Supervisory Committee: Suhaili Shamsi

Signature: _____
Name of Member of
Supervisory Committee: Faizah Md Yassin

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LIST OF ABBREVIATIONS

$AGNO_3$	Silver Nitrate
AIDS	Acquired Immunodeficiency Syndrome
CAT	Catalase
Ca^{2+}	Calcium ion
Cu^{1+}	Copper
DCFH-DA	2′,7′-Dichlorofluorescin Diacetate
DL	Drug Loading
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
dpf	Day Post Fertilization
FESEM	Field Emission Scanning Electron Microscope
Fe^{2+}	Iron
g	Gram
GA	Gallic Acid
GAGO	Gallic Acid Loaded Graphene Oxide
GFN	Graphene Family Nanomaterial
GO	Graphene Oxide
GST	Glutathione S-Transferase
GSH	Glutathione
HCL	Hydrochloric Acid
$HepG_2$ cell	Human Liver Cancer Cell
HIV	Human Immunodeficiency Virus
hpf	Hour Post Fertilization
hr	Hour

H_2O_2	Hydrogen Peroxide
H_3PO_4	Phosphoric Acid
H_2SO_4	Sulphuric Acid
IACUC	Institutional Animal Care and Use Committee
$KMnO_4$	Potassium Permanganate
LDH	Lactate Dehydrogenase
LE	Loading Efficiency
LC_{50}	Lethal Concentration to Kill 50% Of Population
MDA	Malondialdehyde
min	Minute
mL	Millilitre
mM	Millimol
mm	Millimetre
MRSA	Methicillin Resistant *Staphylococcus aureus*
mg/mL	Milligram per millilitre
mg/L	Milligram per Litre
Nm	Nanometre
OH	Hydroxyl radical
O_2^-	Superoxide radical
PBS	Phosphate Buffered Saline
Pb	Lead
PE	Pericardial Edema
PEG	Polyethylene Glycol
pH	A Scale Used to Specify the Acidity or Basicity of an Aqueous Solution
PLGA	Poly Lactic-*Co*-Glycolic Acid
PTFE membrane	Polytetrafluoroethylene Membrane

ppm	Parts Per Million
rGO	Reduce Graphene Oxide
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
Rpm	Revolutions Per Minute
SC	Spinal Curvature
Sec	Seconds
SEM	Standard Error Mean
SOD	Superoxide Dismutase
Tio_2	Titanium Dioxide
Yr	Year
YSE	Yolk Sac Edema
µg/mL	Microgram per millilitre
µL	Microlitre
µm	Micrometre
^oC	Degree Celsius

CHAPTER 1

INTRODUCTION

1.1 Background of Study

In recent years, the advancement and development of nanotechnology have been used in various kinds of areas such as engineering, biotechnology and medicine. Nanomaterial can be defined as a particle or constituent that is produced by nanotechnology at nano-scale dimension. It is characterized by ultra-small size properties that can aid in the study of drug mechanisms to increase the therapeutic efficiency. There is a significant advantage of using nanomaterial in medicine for the diagnosis and treatment of diseases, especially in drug delivery. The ability of nanomaterials is mostly based on their physical properties to carry drug or compound on their surface plane, thus enhancing drug transportability directly into the targeted site. There are many types of potential nanomaterials that can be used for drug delivery such as dextran, albumin, chitosan, alginate, gelatin, hydrogel and graphene oxide (De Jong & Borm, 2008). Among available nanomaterials, graphene oxide (GO) has recently emerged as a new and competitive drug delivery system due to its advantageous properties.

GO is the product of chemical exfoliation of graphite, a carbon compound made up by single or multi-layer sheets of graphene films consisting of single lattice-shaped carbon layer with atomic thickness (Sheshmani & Fashapoyeh, 2013). GO is produced when graphite undergoes an oxidation process, in which oxygenated functionalities are introduced in the graphite structure, thus expanding the layers separation. GO has the presence of high oxygen functional groups such as carboxylates, epoxides, and hydroxyls at the basal planes and edges of graphene (Dreyer et al., 2010). This structure makes the material more hydrophilic on its basal planes and edges which aids the production of a stable aqueous suspension of GO, which is easily exfoliated into monolayer sheets (Sheshmani & Fashapoyeh, 2013). GO has a high surface area and this enables a lot more drugs to be loaded onto its surface compared to other forms of nanoformulation, such as polymeric, alginate and chitosan nanoparticles. In addition, due to its low toxicity, GO has also been investigated for targeted drug delivery in cancer therapy (Chang et al., 2011). Previous studies have reported that GO has anti-microbial activity against gram-negative and gram-positive bacteria (Hu et al., 2010; Santos et al., 2012; Shamsi et al., 2018).

In the present study, we formulated GO as a drug carrier and gallic acid (GA) as a drug model, called “gallic acid-loaded graphene oxide” (GAGO). GA (3,4,5-trihydroxy benzoic acid) is a phenolic acid that commonly occurs in plant kingdoms that is important in human nutrition (Lu et al., 2006). GA has been widely used in pharmaceutical, cosmetic, food, printing, and dyeing industries (Brewer, 2011; Saeed et al., 2012). In the biomedical field, there are numerous reports demonstrating the potential of GA for health benefits, such as anti-oxidant, anti-inflammatory, anti-

bacterial, anti-fungal, anti-carcinogenic, and anti-diabetic properties (Dludla et al., 2019; Dorniani et al., 2016; Hyun et al., 2019; Shao et al., 2015). However, GA suffers a short half-life when administered *in vivo* (Khan et al., 2019). GA has a specific conformation with three adjacent aromatic phenoxyl groups involved in intra- and inter-molecular hydrogen bonding, which is exhibited in binding and it also exhibits strong chelating abilities with numerous inorganic ligands and proteins (Masoud et al., 2012; Rawel et al., 2006). These unique characteristics allow GA to be modified and loaded onto the drug carrier, such as GO.

The combination of GO and GA, has proven to produce beneficial synergistic effects in anti-cancer and anti-microbial studies. According to Shamsi et al. (2018), GAGO formulation has increased the capability of anti-microbial activity of GA as compared to when it was treated with GA alone. Similarly, GA-reduced GO (rGO) formulation also showed high anti-cancer activity with up to 72% inhibition recorded against A498 renal cancer cells (Jiang et al., 2018). Although GO and functionalized GO demonstrate high biocompatibility towards mammalian cells (Sun et al., 2008), the toxicity status of GO as a drug carrier is still unclear. Studies in human fibroblast cells reported that GO caused apoptosis and DNA damage to the cells (Wang et al., 2013) and posed obvious toxicity at concentration higher than 50 μg/mL (Wang et al., 2011). Thus, this study was conducted to assess the toxicity effects of the newly formulated GAGO using zebrafish embryos.

Zebrafish has emerged as a powerful *in vivo* model system for small molecule screening which has been utilized as the alternative model organism for rodents, especially in toxicology and drug discovery studies (Shamsi et al., 2020). It is considered as a good model for its unique characteristics which are small, transparent and fast developing eggs that aid high throughput chemical screening and short generation times (Gerlai et al., 2009). Furthermore, 70% of genes in the zebrafish embryo are homolog to human genes and it also mimics human physiological response during the development of chronic disease (Howe et al., 2013). These numerous advantages make zebrafish an ideal toxicological model in view to understand the toxicity mechanism of newly formulated drugs, including oxidative stress indices and antioxidant parameters.

1.2 Problem Statement

GO is one of the ideal nanomaterials that earns its popularity in the biomedical field as a drug carrier, due to the high surface-to-volume ratio that enables adsorption and loading of a myriad of substances. However, the toxicity status of this potential nanocarrier remains elusive. Several studies reported that GO caused high cytotoxicity in *in vivo* and *in vitro* studies (Wang et al., 2013; Zhang et al., 2011(b)). In human fibroblast cells, GO exerts toxicity at concentration greater than 50 μg/mL, which is then followed by a decrease in cell adhesion and promotion of cell apoptosis (Wang et al., 2011). In addition, it was also reported that intravenous administration of GO or amine-derived GO (GO-NH2) in mice (250 μg/kg body weight) leads to extensive pulmonary embolism, with GO-NH2 was found to be less toxic compared to its non-functionalized counterpart (Singh et al., 2012).

In the present study, GA has been chosen as a drug model to be loaded onto GO. GA was known for its low bioavailability and suffer a short half-life when it is administered *in vivo*, thus limiting its potential (Khan et al., 2019). Combination of GA and GO in nanoformulation is hoped to improve the toxicity and stability issues of both, as compared to their native forms. This newly nano-formulated drug is called gallic acid-loaded graphene oxide (GAGO). However, the underlining toxic effects of GAGO are still largely unknown. At the same time, to whether or not the toxicity status of GO as a drug carrier can be improved when it is functionalized with drugs, it remains a question and concern among researchers (Dorniani et al., 2016; Jiang et al., 2018).

1.3 Significance of Study

The combination of GA and GO compound, GAGO, shows a good potential as a drug candidate. Currently, researcher has reported that GAGO has posed anti-cancer activity against human HepG2 liver cancer cell (Dorniani et al., 2016) and significantly increased anti-microbial activity of GA against methicillin-resistant *Staphylococcus aureus* (MRSA) (Shamsi et al., 2018). Despite the promising anti-cancer and anti-microbial activities of GAGO, it is imperative to establish a proactive approach for these materials by evaluating their potential toxicity, which is unknown. Thus, the present study intended to evaluate the toxicity and teratogenicity effects of a newly formulated nanocomposite compound (GAGO), as well as its pure forms, GA and GO, using a zebrafish model.

1.4 Hypothesis

Previous study has reported that GAGO nanoformulation is biocompatible with normal fibroblast cells and did not pose any cytotoxic effect for up to 50 µg/mL of concentration (Dorniani et al., 2016). Similarly, a study on formulated GA biofabricated rGO reported to exhibit no significant toxicity on normal HK-2 human kidney cells (Jiang et al., 2018). Thus, it is hypothesised that the GAGO nanoformulation would improve the toxicity effects of its native compounds, pure GA and pure GO. It is also hypothesised that GAGO nanoformulation would reduce the oxidative stress development at the same concentration as compared to its pure GA and pure GO.

1.5 Objective

1.5.1 General Objective

To assess the toxicity effects and oxidative stress of a newly formulated GAGO nanoformulation on zebrafish embryogenesis.

1.5.2 Specific Objective

a) To synthesize and characterize GAGO nanoformulation.

b) To evaluate the survival rate, hatching rate and heartbeat rate of zebrafish embryos treated with GAGO nanoformulation.

c) To assess the teratogenicity effect of GAGO through morphology observation on the early development of zebrafish embryogenesis.

d) To measure the levels of oxidative stress in zebrafish embryo-treated with GAGO nanoformulation.

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