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IN VIVO EVALUATION OF THE ANTICANCER ACTIVITY OF A WATER-IN-GARLIC OIL NANOEMULSION LOADED WITH DOCETAXEL

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ABSTRACT: Docetaxel (Doc) is an antitumor drug used to treat various types of cancers. However, it has certain limitations in clinical use due to its side effects. The major objective of this study was to assess the antitumor activity and cardiotoxicity of the Doc loaded in a nanoemulsion formulated with the garlic oil (Doc-NEGO) in Ehrlich ascites carcinoma (EAC)-bearing mice. One hundred mice were split into five groups (n = 20). Groups I and II served as untreated mice and untreated EAC-bearing mice, respectively. Groups III-V represented the EAC-bearing mice administered orally by Doc-NEGO, NEGO and Doc dissolved in distilled water, respectively. The antitumor activity included the measurement of the mean survival time (MST) and the lactate dehydrogenase (LDH) activity in the tumor ascetic fluid. The cardiotoxicity was identified by determining the serum enzymes and analyzing the oxidative stress in the heart tissue. It has been found that the z-average diameters of the nanoparticles of NEGO and Doc-NEGO, determined by the zetasizer, were 63.19 ± 1.85 nm and 110.43 ± 14.37 nm, respectively. The administration of NEGO in the EAC-bearing mice has enhanced the LDH activity in the ascetic fluid and ameliorated the heart enzymes when compared to the other groups. Treating the EAC-bearing mice with the Doc-NEGO has improved the MST of the mice (27.7 ± 11.63 days) relative to the MST of EAC-bearing mice treated with Doc-water (23.1 ± 1.52 days). In conclusion, NEGO holds a great potential as a nanocarrier for the Doc in improving its efficacy and eliminating its cardiotoxicity.

INTRODUCTION: Cancer, which is the abnormal growth of the cells, is considered one of the most fatal diseases in the world [1]. Up-to-date, cancer therapy is facing challenges with the adverse side effects generated by the chemotherapeutic agents. In fact, it has been suggested to formulate the anticancer drugs in nanocarriers consisting of essential oils which have protective properties, *i.e.* cardioprotective, hepatoprotective *etc*, and thereby would help in eliminating the toxic effect of the antitumor drugs on the healthy cells.

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Nanoemulsions (NEs) are heterogeneous systems that consist of the combination of two liquids, which largely differ in their surface tensions, by the aid of surfactants and/or co-surfactants and input of energy [2]. Depending on the fractions of the NE components, the oil would solubilize in the water (oil-in-water NE) if the water fraction is larger than the oil, whereas the water would solubilize in the oil (water-in-oil NE) if the oil fraction is more dominant. According to the composition of the NE, a wide range of hydrophobic and hydrophilic drugs would disperse in the NE formula.

There have many recent attempts to improve the garlic oil (GO) bioavailability by loading it in NE in order to be used clinically and to benefit from its great potential as an antitumor, anti-hypertension, antilipidemic, antithrombotic and antiplatelet aggregation [3, 4]. Docetaxel (Doc) is an effective antineoplastic agent that is used to treat numerous kinds of cancers, such as breast, ovarian, gastric, non-small and small cell lung cancers. Doc treatment is usually associated with serious side effects, including intolerance, myelotoxicity, hair loss, inflammation of the mouth and lips, ulcers, and hydropsy [5, 6]. In the present study, the GO was formulated in NE to be loaded with Doc with the aim to assess the antitumor activity of the resulted formula in the mice inoculated with the Ehrlich ascites carcinoma (EAC).

MATERIAL AND METHODS:

Materials: GO was purchased from Sokar nabat for natural oils (Jeddah, KSA). Sorbitan laurate (span 20), sorbitan monooleate (span 80) and distilled water were purchased from Al-rowad modern establishment for the supply of medical equipment (Jeddah, KSA). Doc was obtained from Elezaby Pharmacy (Cairo, Egypt). The Quanti Chrome thiobarbituric acid reactive substances (TBARS) assay kit and Enzy Chrom assay kits of superoxide dismutase, catalase kit, and glutathione peroxidase kit were supplied by Bioassays for diagnostic and research reagents (Hayward, USA). Serum analysis kits were obtained from Crescent diagnostics Company (Jeddah, KSA) and Human Biochemical and Diagnostic (Wiesbaden, Germany). Commercial pelleted mice food, was obtained from Saudi Grains Organization **(**Jeddah, KSA).

Animals: One hundred female Swiss Albino mice (mean weight 22 - 30 g) were acclimatized as recommended by King Abdulaziz University's policy. The ethical approval was obtained from the research ethics committee in the Faculty of Medicine at King Abdulaziz University.

Methods:

Preparation of NEGO Formulations: The drug-free NE formulation (NEGO) was produced by mixing 9.4% (v/v) of surfactant mixture of span 20 and span 80 at ratio of 1:2, respectively, 89.7% (v/v) of GO and 3.6% (v/v) of distilled water. Then, the mixture was vortexed with continuous heating in a water bath for one week at 120 °C. The Doc-loaded-NE (Doc-NEGO) was prepared by dissolving directly a 24 mg of Doc/ kg of mouse body weight in 0.2 ml of NEGO [7]. Another formula of Doc solution (WDoc) was produced by dissolving 24 mg/kg of mouse in 0.2 ml of distilled water.

Characterization of the Prepared NE Formulation by the Zetasizer: The z-average diameters and zeta potentials of the NE formulations were measured by using Zetasizer Nano ZS (version no MAN0487-2-0, Malvern Instruments, UK).

***In vivo* Assessment of the Antineoplastic Activity:** The transplantation of the EAC cells in the mice was implemented according to a method adopted by Alkreathy *et al*., [8] The mice were split into five groups at which each group has 20 mice as illustrated in **Table 1**. Following weighing the mice, all of the mice in each group, excluding group I, were injected intraperitoneally with 2.5×10^6 EAC cells/mouse for forty-eight-hour incubation. Groups III-V were administered with the produced formulas at three doses every two days.

TABLE 1: THE TESTED ANIMAL GROUPS WITH THEIR ADMINISTERED TREATMENT

Group no.	Group name	Administered treatment	Doses
I	G(-)	-	
II	G(+)	-	
III	G(NDoc)	Doc-NEGO	24mg/kg of mouse dissolved in 0.2 ml NEGO
IV	G(NE)	NEGO	0.2ml NGO
V	G(WDoc)	WDoc	24 mg/kg of mouse dissolved in 0.2 ml distilled water

On the 14th day, ten mice from each group were set aside fasting for 12 h and the body weight of each mouse was taken on a digital scale. Also, the ascetic fluid was collected for investigation of the cancer cell death. Finally, these animals were sacrificed in order to collect their hearts and blood for the cardiotoxicity examination. For the antioxidant assays, a small part of each lobe of the

excised heart was removed and rinsed in ice-cold normal saline followed by deep freezing at - 80 °C in a freezer (Revco™ CxF Series Ultra-Low Temperature Chest Freezers) in order to be stored for utmost 3 months before performing the experiment. The rest of the animals in each group were kept for the survival study.

Food Appetite: In each cage, one hundred grams of food were added daily. The amount of food consumed by the mice was calculated by subtracting the amount of the remaining food from the initial amount of the served food. The amount of food consumption was measured every day for around two weeks.

Lactate Dehydrogenase Activity in the Ascetic Fluid: The ascetic fluid from the experimental mice was collected to detect the lactate dehydrogenase (LDH) activity, if any. The supernatant of the fluid was prepared as described by Ghosh *et al*., [9] In brief, the ascetic fluid was centrifuged for 5 min at 800 rpm at 4 °C and the supernatant was taken. The assessment of LDH activity was performed according to the protocol of LDH LR (SCE MOD, Cat. No. CZ 908 L) kit which is based on the enzymatic reaction of reducing nicotinamide adenine dinucleotide hydride (NADH) with pyruvate under the effect of LDH as shown in the following equation:

$$\text{Pyruvate} + \text{NADH} + \text{H} \xrightarrow{\text{LDH}} \text{Lactate} + \text{NAD}^+$$

Survival Study: The mean survival time (MST) and the increase life span percentage (% ILS) of each group containing ten mice were inspected by reporting the daily death for 30 days. The MST is the amount of time after which 50% of the mice have died and 50% have survived. The % ILS was determined as described by Raju *et al*., [10]

Evaluation of the drug Formulations Cardiotoxicity:

Relative Organ Weight: Following resection of the hearts of the slaughtered mice, they were weighed. The relative organ weight was calculated by dividing the heart weight by the body weight of each mouse.

Serum Analysis: Following the collection, clotting and a 15 min centrifugation at 3000 RPM of the blood sample, serum was separated for the detection of the LDH, cholesterol (CHO), high density lipoprotein (HDL), triglyceride (TR), creatine phosphokinase (CK) and creatine phosphokinase-MB (CK-MB) measured by the optimized UV-test according to the International Federation of Clinical Chemistry of the Crescent diagnostics Company (Jeddah, KSA). The amount of low density lipoprotein (LDL) was calculated according to the following equation:

LDL = amount of CHO – amount HDL – (amount of TG) /5

Oxidative Stress Analysis: The lobes of the desired heart tissue (10 mg) of each group were homogenized in 200 µl of cold PBS at pH 7.0 per gram tissue. Then, the homogenized tissue was centrifuged at 14000 rpm for 10 min at 4 °C immediately before the assay. The collected supernatant was used immediately for the estimation of superoxide dismutase (SOD), lipid peroxide (Malondialdehyde, MDA), catalase activity and glutathione peroxidase (GPx). All the antioxidant assays were detected by colorimetric methods using the protocol of the bioassays kit.

Statistical Analysis: The discrepancies between the tested samples were identified by the one-way analysis of variance (ANOVA) test through using the MegaStat Excel (version 10.3, Butler University). They were considered significant when $p < 0.05$.

RESULTS:

Physical Characterization of the NEGO Formulations: As illustrated in **Table 2**, the physical characterizations, including the z-average diameters and zeta potentials were determined for both of NEGO and Doc-NEGO formulations. It has been found that loading Doc in the NEGO has considerably enhanced the z-average diameter of NEGO formula (P-value = 0.0048). The droplets sizes of both of NEGO and Doc - NEGO formulations were homogeneously distributed since the % coefficient of variation (CV) of the droplet sizes of both formulas were less than 25%.

In terms of the droplets charges, both formulas have comparable negative zeta potential (P-value = 0.4138).

TABLE 2: PHYSICAL CHARACTERIZATION OF THE NEGO FORMULATIONS USING ZETASIZER MEASUREMENTS

Formulation	Z-Average diameter (nm)	Zeta Potential (mV)	% CV
NEGO	63.19 ± 1.85	-0.180 ± 0.002	2.93
Doc-NEGO	110.43 ± 14.37	-0.131 ± 0.092	13.01

Antineoplastic Activity of NEGO Formulations: As shown in **Table 3**, the antitumor activity of the drug formulations was examined in terms of body weight change, food appetite, tumor volume, LDH activity in the ascetic fluid, MST and % ILS. The percentages increase in body weight were comparable in all of the tested EAC groups, whereas the increase in body weight was considerably less in the untreated group (G (-)). In fact, EAC groups treated with NEGO formulations, G (NE) and G (NDoc), have a greater food appetite than all of the tested groups that have a similar food appetite. In terms of the tumor volume, all of the treated EAC groups have less ascetic fluid than G (+) group. Interestingly, the LDH activity in the ascetic fluid of G (NE) was the highest. The MST of G (NDoc) group was significantly greater than the MST of G (+) group which was comparable to the other treated groups. It should be mentioned that the % ILS of G (NDoc) was 9.10%.

TABLE 3: ANTINEOPLASTIC ACTIVITY OF DRUG FORMULATIONS IN THE TESTED ANIMALS. DATA WERE EXPRESSED AS $\overline{X}$ ± SD

	G (-)	G (+)	G (NDoc)	G (NE)	G (WDoc)
Weight (g) on 0^{th} day	26.92±1.24	27.23±1.27	25.15±0.85	24.03±2.076	26.95±1.48
Weight (g) on 14^{th} day	28.42±2.59	34.66±5.06	32.35±3.67	30.77±4.29	34.72±4.74
% Change in body weight	8.44±3.06	34.45±10.53[a]	31.51±11.79 [a]	31.76±13.07 [a]	32.35±12.10 [a]
Food appetite	57.85±7.66	64.03±14.78	71.20±15.39[a,b,c]	66.29±13.04 [a]	63.07±9.66 [c]
Tumor volume (mL)	-	8.35±2.48	3.95±2.84[b]	2.3±2.85 [b]	3.17±4.07 [b]
LDH activity in the ascetic fluid (U/L)	-	19.49±4.38	23.20±3.10[e]	51.27±6.09[b,d,e]	28.24±11.13[d]
MST	30 ± 1.0	22.1±3.14 [a]	27.7±11.63[b]	22.6±2.80 [a,e]	23.1±1.52 [a]
% ILS	-	-	9.10	2.26	4.52

[a] There is a significant difference between the desired group and the normal group; [b] There is a significant difference between the desired group and the G(+) group; [c] There is a significant difference between the G(NDoc) and G(WDoc) groups; [d] There is a significant difference between the G(WDoc) and the G(NE) groups; [e] There is a significant difference between the G(NDoc) and the G(NE) groups.

Evaluation of the Drug Formulations Cardiotoxicity:

Relative Heart Weight and Serum Analysis: **Table 4** summarizes the effect of drug formulations on heart function in mice. The relative heart weight ratio has increased in all of the EAC groups when compared to G(-) group. The level of Ck-MB of G(NE) was significantly less than the levels of G(-) and G(+) groups which were comparable to the levels of G(NDoc) and G(WDoc) groups. The G(NE) group has the lowest level of CK compared to all tested groups. When compared to G(-) group, the LDH activity has significantly increased in G(WDoc) group, but it has not considerably changed in the other tested groups.

TABLE 4: THE SERUM ANALYSIS OF THE TESTED MICE IN ORDER TO DETECT THEIR HEART FUNCTION. DATA WERE EXPRESSED AS $\overline{X}$ ± SD

	G(-)	G(+)	G(NDoc)	G(NE)	G(WDoc)
Relative heart weight	0.0102±0.015	0.0035±0.00054[a]	0.004±0.001[a]	0.0041±0.0006[a]	0.014±0.010[a]
Ck-MB (U/L)	9.04 ± 0.47	9.34±0.93	8.35±1.12 [e]	4.97±0.99[a,b]	7.023±1.57 [a,b,d]
CK (U/L)	72.45 ± 5.03	81.25±1.15	65.95±6.39[c,e]	31.02±2.19 [a,b,e]	46.08±21.94[a,b,c]
LDH (U/L)	159.96± 0.44	282.49±21.42	256.28±52.16	302.02±66.40	381.02±167.58[a]

[a] There is a significant difference between the desired group and the G(-) group; [b] There is a significant difference between the desired group and the G(+) group; [c] There is a significant difference between the G(NDoc) and G(WDoc) groups; [d] There is a significant difference between the G(WDoc) and the G(NE) groups; [e] There is a significant difference between the G(NDoc) and the G(NE) groups.

Oxidative Stress Analysis: As Exhibited in **Table 5**, the oxidative stress assessment of the tested animal was determined by measuring the amount of MDA and NADPH consumed by GPx and the activities of catalase and SOD. When compared to G(-) and G(+) groups, the catalase activities have

got considerably raised in G(NE) and G(WDoc) groups. In fact, the calatase activity of G(NE) was very highly significantly greater than all of the groups. The G(NDoc) and G(NE) had the greatest amount of NADPH consumed by GPx when compared to G(+), G(-) and G(WDoc) groups. All tested groups had comparable levels of SOD activity. The MDA level of G(NDoc) had dropped compared to all of the other groups. On the other hand, the MDA level of G(WDoc) was elevated relative to the rest of the groups.

TABLE 5: THE OXIDATIVE STRESS ANALYSIS OF THE TESTED GROUPS IN THE HEART TISSUE. DATA WERE EXPRESSED AS $\overline{X}$ ± SD

	G(-)	G(+)	G(NDoc)	G(NE)	G(WDoc)
Catalase activity (U/L)	2.5±1.20	2.00±5.30	3.57±2.10[c,e]	43.94±8.20[a,b,d]	12.86±5.30[a,b,c]
NADPH consumed by GPx (U/L)	585.28±10.20	262.28±9.30[a]	610.67±8.70[a,b,c]	618.74±10.10[a,b,d]	400.05±8.50[b]
SOD activity (U/mL)	2.91±0.05	2.11±0.53	2.49±1.43	1.65±0.14	2.06±0.69
MDA (μM)	13.53±2.83	23.09±3.94	3.94±1.29[b,e]	19.71±8.52	28.34±7.31[a,c]

[a] There is a significant difference between the desired group and the normal group; [b] There is a significant difference between the desired group and the G(+) group; [c] There is a significant difference between the G(NDoc) and G(WDoc) groups; [d] There is a significant difference between the G(WDoc) and the G(NE) groups; [e] There is a significant difference between the G(NDoc) and the G(NE) groups.

Lipid Profile: As illustrated in **Table 6**, the lipid profile of the tested animals was identified. The amount of CHO was significantly lower in G(NE) group when compared to G(+) group. In fact, the amounts of CHO of all of the tested EAC groups were comparable to G(-) group. On the other hand, the amounts of HDL of all of the EAC groups were significantly less than that of G(-) group. In terms of the TR amount, it did not differ in all of the groups when compared to G(-) group except G(NDoc) has got the raised amount. Interestingly, the calculated LDL amount of all of the treated groups and G(-) group were considerably less than that of G(+) group.

TABLE 6: THE LIPID PROFILES OF THE TESTED MICE. DATA WERE EXPRESSED AS $\overline{X}$ ± SD

Amount (mmol/L)	G(-)	G(+)	G(NDoc)	G(NE)	G(WDoc)
CHO	5.00± 1.19	7.07±0.34	6.47±0.19	3.78±2.18[b,e]	4.96±0.72
HDL	2.56±0.75	0.79±0.03[a]	0.84±0.19[a]	0.77±0.12[a]	0.90±0.09[a]
TR	1.55 ± 0.03	3.15±0.07	4.55±2.47[a,e]	2.28±0.54[e]	2.67±0.04
LDL	1.74±0.42	4.88±0.37[a]	3.54±1.11	1.97±2.06[b]	2.58±1.19[b]

[a] There is a significant difference between the desired group and the G(-) group; [b] There is a significant difference between the desired group and the G(+) group; [c] There is a significant difference between the G(NDoc) and G (WDoc) groups; [d] There is a significant difference between the G (WDoc) and the G(NE) groups; [e] There is a significant difference between the G(NDoc) and the G(NE) groups.

DISCUSSION: In spite of all of the advances in our healthy life, 14.1 million people are diagnosed with cancer each year [11]. In fact, cancer treatment is facing challenges with the chemotherapeutic agents due to their lack of specificity in discriminating between the cancer cells and healthy cells [12]. One of the proposed solutions to eliminate the side effects of the antitumor drugs is to deliver them in nanocarriers.

Nanoemulsions have attracted the pharmacuetical industries due to their ability to solubilize a wide range of drugs that would improve the drug efficacy and reduce their adverse side effects [13]. The objective of the current study was to fabricate water-in-garlic oil nanoemulsion in order to encapsulate the anticancer drug, Doc with the attempt to reduce its side effects. Results have exhibited that the MST for the mice treated with NEGO was comparable with G(WDoc) group. Interestingly, NEGO has greatly enhanced the LDH activity in the ascetic fluid of the mice when compared to the G(WDoc) and G(NDoc) groups, which indicates that the NEGO has antitumor activity similar to Doc. It could be due to the presence of GO in the NE formula as it was reported that GO has impeded the skin cancer growth in mice [14]. In addition, the nano-droplet size of the NEGO would facilitate the cellular and permeation uptake of the GO [15].

Regarding the lipid profile, both of the CHO and LDL were reduced in the mice treated with NEGO. Ragavan *et al.*, [3] have found that formulating NE

consisting of GO, tween 80 and water was very effictive in resotring the lipid profile in the mice when compared to the atorvastatin, a cholesterol-lowering agent, and the free GO. Moreover, the heart profile of the EAC-bearing mice treated with NEGO was amended when compared to the other tested groups. The mice have got reduced levels of CK and CK-MB in the serum.

Additionally, the GPx and catalase activities have increased in the mayocytes. In fact, the administration of Doc-NEGO into the mice has increased the GPx and reduced the MDA in myocytes of the heart tissue. In addition, incorporating the Doc into the NEGO has slightly increased the life span of the mice relative to the mice subjected into the G(WDoc). Cheng *et al*., [16] have reported that GO has protected the cardiomyocytes from apoptosis because of its potential in improving the lipid profile in hamsters with hyper cholesterol diet.

CONCLUSION: NEGO was prepared by mixing different fraction of garlic oil, distilled water, span 20 and span 80. It has been found that NEGO has a cardioprotective property and has the ability to stimulate the antioxidant activities in the heart tissue besides having antitumor activity. In addition, loading Doc in the NEGO has ameliorated the oxidative stress in the heart tissue of the mice and improved their mean survival time. It is recommended to make further studies on encapsulating other chemotherapeutic drugs in the NEGO.

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