Evaluation of chemotherapeutic efficacy of the novel compound Of Zinc oxide nps modified with basic nanocurcumin and sodium ascorbate on nicotine induced-lung cancer of Swiss Albino Mice

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A B S T R A C T

The present study was designed to evaluate the potential protective and therapeutic efficacy of the novel prepared compound of Zinc oxide nps modified with basic nanocurcumin and ascorbate on nicotine induced-lung cancer in mice. The chemopreventive efficacy of such treatment was evaluated through determenation of p53gene experession, tumor necrosis factor-alpha (TNF-α) and caspase-3 activity in addition to the activities of the antioxidant defense system in lung tissues homogenate including: glutathione reductase (GR), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase(CAT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP)activities also determened in nicotine induced-lung cancer in mice.The obtained result revealed that novel nano compound was able to mitigate lung tissues damage induced nicotine through increasing of GRx, GPx, SOD and CAT activities. In addition to decreasing p53 gene expression, TNF-α and caspase3 in lung tissue as well as LDH and ALP activities in the serm of mice. These results suggest that noval nano compound may be effective in enhances the protection of lung cancer by its radical scavenging and anti-carcenogenic effect and regenerating endogenous antioxidant mechanisms.

KEYWORDS: Nicotine, Lung cancer, Novel nano compound, Antioxidant enzymes, p53, Caspase3, TNF-α.

(http://www.bvmj.bu.edu.eg) **(BVMJ-27(2):354-362 , 2014)**

1. INTRODUCTION

Nicotine is a naturally occurring alkaloid found in the nightshade family plants (solanaceae), predominantly in tobacco plant (nicotianatabacum) (Wu et al., 2002 and Hellermann et al. 2002). Nicotine has many effects such as on heart rate, brain excitation, and blood pressure (Shivij et al., 2006). Wu et al. 2002 reported that nicotine induced a wide range of biological effects and is a major risk factor in the development of chronic obstructive lung diseases, cardio-vascular disorders and lung cancer. Morever nicotine through smoking, induced an inflammatory response in the lung and plays a role in pathogenesis of obstructive pulmonary diseases (Carpagnano et al., 2003 and Hackett et al., 2003). Apoptosis is strongly induced in alveolar epithelium exposed to smoking (Piipari et al., 2000). The application of nanotechnology for cancer therapy has received considerable attention in recent years; cancer nanotechnology can interdisciplinary area of research in science, engineering and medicine is an upcoming field with extensive applications. It provides a unique approach and comprehensive technology against cancer through early diagnosis, prediction, prevention, personalized therapy and medicine. Target –specific drug therapy and method for early diagnosis of pathologies are the priority research areas in which nanotechnology would play a vital part (Misra et al. 2010). Accordingly, the purpose of the present study was to

investigate the effect of novel nano compound in a mice model of nicotine induced lung cancer. In addition to determine whether Novel nano compound when administered to lung cancer induced-mice would attenuate the oxidative stress in lung tissue, beneficial for protection and treatment of lung cancer complications.

2. MATERIAL AND METHODS

2.1. Experimental animals

Experimental animals were obtained from the breeding unit of National Cancer Institute (NCI), Cairo University; Cairo, Egypt. One handered and twenty virgin male Swiss albino mice (8-10) weekes old weighted (20-25 gm body weight). Mices were used in this study housed in separated wire mesh cages and kept at constant environmental and nutritional conditions throughout the period of experiment. The mices were fed on constant ration and fresh, clean drinking water was supplied ad-libitum .

2.2. Induction of lung cancer

To induce lung cancer, mices were injected nicotine at a dose level of 2.5 mg/kg b.wt intrapretoneally (i/p) three times weekly for 4 weeks according to Hecht, 2003 .Nicotine purchased from (Sigma, USA), 99% pure nicotine dissolved in 0.9% saline, Molecular formula (C10H14N2) Mol.mass 162.23g/mol, Density 1.01 g/cm³, Melt. point -79 °C (-110 °F), Boiling point 247 °C (477 °F (

2.3. Preparations of novel nano compound (nanoparticeles zinc oxide with basic nan curcumin and ascorbate (Curcumin was purchased from (Sigma, USA).

2.3.1. Curcumin

has a melting point of 180°C; its molecular formula is (C21H20O6) and molecular weight 368.39 (Aggarwal et al., 2003) Zinc oxide nanoparticeles purchased from (Sigma, USA), Molecular formula ZnO Molar mass 81.408 g/mol, Density 5.606 g/cm3 Melting point 1975 °C Boiling point 1975 °C Solubility in water is Insoluble (Takahashi, et al. 200.).Sodium bicarbonate purchased from Indian company.

2.3.2. Basic Nanocurcumin

Basic nanocurcumin is prepared by mixing the pure curcumin and sodium bicarbonate by ratio (1:4) and grinding the mixture in the ball mail at 3500r.p.m for 8 hrs that allow the solid reaction between the curcumin and bicarbonate and the formation of the disodium salt of curcumin

2.3.3. Zinc Oxide nps Modified with Basic Nanocurcumin

Modified ZnO nps was achieved by sooking ZnO nps for 24 h in basic nanocurcumin 0.05g in 50ml distilled water and stirred overnight to allow complete complexation. The resulting solids were dried in an evacuated desicator to give Zinc oxide nps modified with basic nanocurcumin.

2.3.4. Sodium Ascorbate Mixing to Zinc Oxide nps modified with Basic Nanocurcumin

About 0.5 gm powder of sodium ascorbate was add to nano compound and mixed well to *produce* noval nano compound which used dirctely in experimental study

2.3.5. Sodium Bicarbonate (Na HCO3) add to noval compound

Approximatly 0.5 gm powder of sodium bicarbonate (Na HCO3) was added to adjuste pH till alkaline pH 8.5 The extracellular pH of malignant solid tumors is acidic, in the range of 6.5 to 6.9, whereas the pH of normal tissues is significantly more alkaline, 7.2 to 7.5 Griffiths JR., 1991. Acid pH was inhibited using oral NaHCO3, which has previously been shown to effectively reverse pH gradients in

tumors and not affect the pH of normal tissues Raghunand N et al.,1999.

Novel nano compound dissolved in 0.9% saline solution and administered to mice orally by stomach tube (70 mg/kg body weight for 28 days

2.4. Experimental design

The present study was carried out on 120 male swiss albino Mices were randomly divided into four main equal groups, each group placed in individual cages and classified as follow-:

Group 1: Control Normal group:

Received no drugs, served as control non-treated for all experimental groups

Group 2: Novel nano compound group:

Consistes of thirty mice treated only with novel nano compound administered orally by stomach tube at a dose of 70 mg/kg b.wt. three times a week for 4 weeks

Group 3: Nicotine group :

Comprised thirty mice injected intraperitonelly (i.p) with nicotine at dose of 2.5 mg/kg body weight three times per a week for 4 weeks

Group 4: novel nano compound + Nicotine) group :

Included thirty mice treated with novel nano compound administered orally by stomach tube at a dose of 70 mg/kg b.wt. three times per a week for 4 weeks as in group II, Two hours before nicotine injected as in the group III. until the end of experiment.

2.5. Sampling

Blood samples and tissue specimens (lung tissues) were collected at the end of experiment on 28th day for all groups (control and experimental groups).

2.5.1. Blood samples

Blood samples for serum separation were collected from the heart at the end of experimental period in dry, clean, and screw capped tubes and serum were separated by centrifugation at 2500 r.p.m for 15 minutes .The clean, clear serum was separated by automatic pipette and received in dry sterile samples tube and kept in a deep freeze at -200c until used for subsequent biochemical analysis .All sera were analyzed for determenation the of lactate dehydrogenase(LDH) and alkaline phosphatase(ALP) activities .

2.5.2. Tissue specimen (lung tissue)

At the end of the experiment, mices of each group were sacrificed by cervical decapitation. The abdomen and chest were opened and the lung specimen was quickly removed and opened gently using a scrapper, cleaned by rinsing with ice-cold isotonic saline to remove any blood cells, clots, then blotted between 2 filter papers and quickly stored in a deep freezer at (-20°C) for subsequent biochemical analysis.Briefly, lung tissues were divided into appropriate portions, homogenized with a glass homogenizer in 9 volume of ice-cold 0.05 mM potassium phosphate buffer (pH7.4) to make 10% homogenates. The homogenates were centrifuged at 6000 r.p.mfor 15 minutes at 4°C then the resultant supernatant were used for the determination of the following parameters:GPx, CAT, SOD, GR, p53 gene, caspase 3 and TNF- α .

2.6. Biochemical analysis

Serm ALP, LDH activities and lung tissues, GPx, CAT, SOD, GR ,TNF, Caspase3, and p53gene were determined according to the method discrebed by King, 1998., Dito, 1979. Gross et al.,1967, and Necheles et al.,

1968. Sinha, 1972. Kakkar, 1984. Beutler et al., 1963. Beyaertand fiers,1998. Tribukait, 1984. respectevily

2.7. Statistical analysis

The obtained data were statistically analyzed and using the statistical package for social science (SPSS, 13.0 software, 2009), for obtaining mean and standard deviation and error. The data were analyzed using one-way ANOVA to determine the statistical significance of differences among groups. Duncan's test was used for making a multiple comparisons among the groups for testing the inter-grouping homogeneity.

3. RESULTS

Effects of treatment with noval nano compound, on some serm and lung tissues parmeters of nicotine-induced lung cancer (LC).The obtained results in table (1) revealed that, a significant decrease in lung tissue GR, CAT, SOD and GPx, caspase 3 activities and p53 gene, were observed in nicotine induced LC in mice.Meanwhile, a significant increase in tissue TNF-α level and serm LDH and ALP were observed in nicotine-induced lung cancer (LC) in mice when compared with control group . Treatment groups with novel nano compound in nicotine-induced LC in mices resulted in significant increase in lung tissue GRx, CAT, SOD and GPx activities p53,and caspase 3 gene with decreasing lung tissue TNF- α, and serm ALP,and LDH activities. when compared with nicotine group. After dosing of nicotine supplementation of noval nano compound and show that highly significant increase in activities of SOD, GSH, GPx and CAT compared to nicotine induction group at $p < 0.05$, while showed slightly significant increase compared to Nano composite supplement group and highly significant decrease compared to nicotine induction group the at $p < 0.05$, and showed slightly increase in Caspase -3 &p53 compared to control group and very highly significant decrease compared to Nano supplement group and very highly significant increase compared to nicotine induction group at $p < 0.05$ as in table (1).

Table 1: Effect of noval nano compound treatment on some serum and lung tissue parameters of nicotine-induced lung cancer in mices.

ExperimentGps Parameters	Control Gp	Nano gp	Nicotine gp	Nano+ Nicotine gp
TNF- α (pg/ml)	12.8 ± 2.5	12.6±1.3	15.9± 3.2^{abd}	9± 0.9^{abc}
Ca spase3(Unit/g.tissue)	44.1±1.4	45.8±2.02	34.08±2^{abd}	40.8±2.8^{abc}
P53 gene(Unit/g.tissue)	13.6 ± 1.7	13.8±1.9	6.7 ± 1.2^{abd}	11.6 ± 0.8^{abc}
GPx (ng/ g.tissue)	26.1 ± 2.5	25±1.6	17.3 ± 1.7^{abd}	20.6 ± 1.6^{abd}
GRx (ng/g.tissue)	6.1 ± 0.5	6.6±0.6	4.1 ± 0.5^{abd}	5.2 ± 0.6^{abc}
SOD (U/g.tissue)	38.06 ± 1.2	38.4±2.9	27.2 ± 1.4^{abd}	35.3 ± 2.1^{abc}
CAT(mmol/g.tissue)	73.5 ± 2.8	75.5±3.1	62.7 ± 2.2^{abd}	73.4 ± 1.1^{c}
ALP (U/L)	181.4 ± 2.7	181.6±1.1	214.6 ± 4.1^{abd}	184.5 ± 2.5^{c}
LDH (U/L)	112.4 ± 2.5	112±3.8	175.6 ± 1.8^{abd}	119.8 ± 1.9^{abc}

Data are presented as (Mean ± S.E).S.E = Standard error.Mean values with different superscript letters in the same row are significantly different at (P<0.05).

4. DISCUSSION

Nicotine the major component of cigarette smoke plays an important role in the development of lung complications. Early-stage disease can be treated with curative intent although the risk for relapse is notoriously high. Unfortunately, the majority of lung cancer patients present at an advanced stage. Despite an initial response to treatment, most of these late stage patients will eventually progress on standard therapy and die from their disease. Despite the complex nature of lung cancer biology, its molecular underpinnings are becoming increasingly clear (Salgia *et al*., 2011). Nicotine is considered a prototype polycyclic aromatic hydrocarbon (PAH), classic DNA damaging agent and carcinogen.

Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications (Boisseau and Loubaton, 2011). Antioxidants are the first source of protection of the body against free radicals and other oxidants, being the compounds that the attack and the formation of radical species within cells. The group of antioxidants inside the organism is known as the total antioxidantstate (TAS)(Teixeira *et al*., 2013).

The antioxidant protection of human cells includes enzyme mediated and non-enzymatic defense mechanisms. Superoxide dismutase (SOD), catalase (CAT) and glutathione-peroxidase (Gpx) are the most important antioxidant enzymes. SOD catalyses' the reaction of superoxide anion to hydrogen peroxide (H_2O_2); in turn, CAT converts H_2O_2 into water and oxygen. The affinity of CAT for H_2O_2 is relatively low, therefore, some H_2O_2 remains in the cell. GSH-px is capable of detoxifying the remaining H_2O_2 (Arrigoni O and De Tullio MC, 2002).

Curcumin is a potent "scavenger" of the superoxide radical, a free radical that initiates potentially harmful oxidative processes such as lipid peroxidation (Sreejayan and Rao, 1996). Through in Curcumin also increases survival of cells exposed in vitro to the enzyme hypoxanthine/xanthine oxidase, which stimulates superoxide and hydrogen peroxide production.Also curcumin demonstrates several other in vitro effects linked to free radical scavenging.Morever, curcumin has also been shown to quench reactive oxygen species and scavenge superoxide anion radicals and hydroxyl radicals and strongly inhibits nitric oxide (NO) production by down-regulating inducible nitric oxide synthase gene expression (Ghoneim, 2009 and Wang *et al*., 2008). Decrease in tumorigenesis caused by turmeric is also associated with inhibition of DNA adduct formation. Curcumin inhibits of phase I enzymes systems consist of cytochrome P450 isoforms, the P450 reductase, the cytochrome b5 and the epoxide hydrolase and protect from the toxic effects of chemicals and carcinogens (Jee *et al*. 1998). On the other hand, curcumin induces phase II enzymes (glutathione S-transferases and epoxide hydrolase), which play a protective role by eliminating toxic substances and oxidants and conferring benefit in the prevention of the early stages of carcinogenesis (Liao *et al*.2 008)

Furthermore curcumin induces apoptosis in p53-null lung cancer cells (Singh, 2009) curcumin can block cell cycle progression or even apoptosis in a p53-independent manner as well, especially in the cells that lack functional p53 (Shankar and Srivastava, 2007). Addetionally curcumin exhibits pleiotropic properties that involve the modulation of nuclear factor-kappaB (NF-κB), transcription factor activator protein-1 (AP-1), mitogen-activated protein kinase (MAPK), tumor protein 53 (p53), nuclear β-catenin signaling, and serine/threonine protein kinase (AKT) signaling pathways (Hatcher *et al.* 2008). Curcumin has been shown to suppress the expression of epidermal growth receptor and estrogen

receptors, which are cancer-associated growth factors (Kunnumakkara *et al*. 2008).

Zinc is one of the structural component of wide variety proteins and dependent enzymes like superoxide dismutase (SOD) that act as essential component of antioxidant defense system (Bao and choct, 2009).

Nano ZnO is able to protect cell membrane integrity against oxidative stress damage, increase antioxidant enzyme levels and decrease MDA level (Dawei *et al.* 2009). Consequently, ZnONPs were shown to selectively induce apoptosis in cancer cells, ZnO NPs show much promise as new anticancer agents, given the specific apoptotic response of cancer cells.

Ascorbate has been examined in various epidemiologic studies as a potential chemopreventive agent for cancer (Lee *et al.* 2003). Many referances have described that millimolar concentrations of ascorbate have a deep inhibitory effect on the growth of several cancer cell lines in vitro (Chen Q *et al.* 2005). Ascorbic acid is a good scavenger of free radicals and it protect cellular membranes their by preventing degenerative disease like cancer (Gutteridge *et al*. 2000 and Vijayavel *et al*. 2006). Caspase-3 was activated on sodium ascorbate treatment, sodium ascorbate induced apoptosis via the mitochondria-dependent pathway in melanoma cells (Shuw-Yuan Lin. 2006).

5. CONCLUSION

From the obtained results it could be concluded that novel nano compound was an effective in protection against lung cancer induced by nicotine in mices since novel nano compound was able to ameliorate serum biochemical parameters, suppression of p53 gene, TNF- α concentration, and caspases -3 activity, enzymatic and non-enzymatic antioxidant defense system in lung tissue. Therefore, We recommend that these findings suggest that novel synthetic compound derivatives may potentially presents new hope for the development of lung cancer therapeutics, which should attract further scientific and pharmaceutical interest.

Acknowledgements

The authors are particularly grateful to the central lab, faculty of veterinary medicine, Benha University, Egypt, for assistance in laboratory tests.

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تقييم التأثير العلاجى لجزيئات نانو أوكسيد الزنك مضافا اليه نانو الكركمين الاساسى و الاسكوربيت على سرطان الرئه المحدث تجريبيا بالنيكوتين في الفئران السوسيريه البيضاء

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الملخص العربي

وأوضحت الدراسة أن استخدام مركب النانو المبتكر (جزيئات نانو اوكسيد الزنك مضافا اليها نانو الكركمين وسكوربيت الصوديوم) كماده واقية مضادة للأكسدة ومضادة للألتهابات كان لها دور فعال في حماية ووقاية الرئه من السرطان المحدث تجريبيا فى الفئران باستخدام مادة النيكوتين و أدى استخدامه كذلك الى الحفاظ على نسب القياسات البيوكيميائية فى الدم والأنسجة لما يقارب النسب الطبيعية.لذلك توصى الدراسة بضرورة استغلال تلك المزايا الهائلة لمركب النانو المبتكر كماده وقائية وعلاجية ومضادة للأكسدة والألتهابات و إدخاله كماده فعالة فى صناعة العقاقير الطبية المستخدمة فى الوقاية و العلاج من الالتهابات الرئويه و سرطان الرئه.

(مجلة بنها للعلوم الطبية البيطرية: عدد 27(2):254-362, ديسمبر 2014)