**MENOUFIA JOURNAL OF
FOOD AND DAIRY SCIENCES**

https://mjfds.journals.ekb.eg

RESTORING ANTIOXIDANT LEVELS OF NICOTINE-INJECTED RATS USING SUGGESTED DIETARY FORMULAS

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Received: Oct. 29, 2023 Accepted: Nov. 25, 2023

ABSTRACT: This study was conducted to investigate the effect of tested dietary formulas on restoring antioxidant levels in rats that were injected with nicotine. Fifty male albino adult rats (150±10 g) were used. Rats were fed on basal diet for 7 consecutive days and then divided into two main groups. The first main group (5 rats) fed on a basal diet as a control negative group (-ve) (group 1), while the second main group (45 rats) was injected with nicotine subcutaneously for 7 days. The second main group divided into nine groups (5 rats each). Group (2) (control positive group +ve) fed on basal diet also and eight other rats groups fed on supplemented diet with (prickly pear seeds + sunflower seeds + celery seeds) (1:1:1) (5 & 10%), (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) (1:1:1) (5 & 10%), (cape gooseberry + carob+ doum) (1:1:1) (5 & 10%) & (prickly pear peel + cabbage leaves + celery leaves) (1:1:1) (5 & 10%) respectively for four weeks. At the end of the experiment, biological evaluation (BWG, FI & FER), oxidative stress parameters, CRP, lipids profile & liver enzymes were estimated. The results indicated that nicotine injection caused significant decreases in BWG, FI, FER, SOD, GPx, CAT & HDL. while significant increases were recorded in MDA, CRP, TC, TG, LDL, VLDL, AST, ALT & ALP. Injected rats groups treated with various diets revealed improvement in all previous parameters.
In conclusion, all histopathological examinations of the lungs and biochemical analyses reflect the power of tested dietary formulas as antioxidants and nutraceutical therapeutics for treating inflammation, heart disease, hypercholesterolemic & liver disease in rats, especially diet contain 10% (prickly pear peel, cabbage leaves & celery leaves) (1:1:1) powders. These formulas are highly recommended for helping smokers, however, much more human study is needed.

Key words: Antioxidant Enzymes- Nicotine- Prickly Pear- Celery- Cabbage- Cape Gooseberry – Carob- Doum- Sunflower Seeds.

INTRODUCTION

As a naturally occurring alkaloid, nicotine is mostly present in tobacco plants, which are members of the Solanaceae family (Kumari, 2020). One of the main causes of death worldwide is dual usage, smokeless tobacco use, and cigarette smoking. Tobacco's addictive properties are linked to the alkaloid nicotine, which activates the brain's nicotinic cholinergic receptors and releases a number of neurotransmitters, including dopamine. Dopamine is essential for the reinforcing effects that encourage self-administration of nicotine since it communicates a joyful experience. (Devi *et al.*, 2021).

Not only is nicotine highly addictive, but it also has major systemic negative effects that are widely documented. The heart, reproductive system, lungs, kidneys, and other organs are negatively impacted. Numerous studies have repeatedly shown that it has the potential to cause cancer. (Mishra *et al.*, 2015).

The harmful consequences of nicotine and tobacco use are mediated in part by oxidative stress and weakened antioxidant defenses (Chan *et al.*, 2016). In some mouse brain regions, perinatal nicotine exposure led to decreased cellular defenses and increased lipid peroxidation (LPO) (Ajarem *et al.*, 2017, Al-Basher *et al.*,

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2017). In the same setting, chronic nicotine-administered rats showed a redox imbalance in their blood and tissues, and nicotine-treated peripheral blood cells caused oxidative DNA damage. (Ajarem *et al.*, 2021).

A biological system's capacity to detoxify reactive intermediates either by reducing them with antioxidants or by repairing the damage they cause and its exposure to reactive oxygen species (ROS) throughout the body are out of balance when it comes to oxidative stress. When cells' natural redox balance is disrupted by an excess of reactive oxygen species (ROS) produced by both internal and external sources, it can be hazardous to key cell compartments, cellular signaling homeostatic mechanisms, and macromolecules including protein, lipids, and DNA. Mammalian cells have evolved various defense mechanisms to either repair or tolerate DNA damage. These mechanisms include antioxidant enzymes like catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), free radical scavengers like glutathione (GSH), vitamin C, and E, and complex DNA repair mechanisms. (Andrikopoulos *et al*., 2019).

Prickly pear or cactus pear *(o. ficus-indica)* fruit or juice Consumption may alter the enzymatic levels of SOD, CAT, and GSH or exhibit antioxidant activity through non-enzymatic processes (Cruz-Bravo *et al.*, 2019). (Alimi *et al.*, 2012). Syrup concentrates' polyphenols have been shown to have anti-cancer properties in neuroblastoma and tumorigenic lines of fibroblasts (Dhaouadi *et al.*, 2013), and fermented juice may lessen fibroblasts' exposure to UV-B rays. (Cho *et al*., 2014).

The antioxidant activity of cape gooseberry or golden berry (*P. peruviana*) fruit is due to the high levels of polyphenols found in it, which are responsible for a variety of therapeutic and nutraceutical activities such as anti-cancer activity, anti-hepatotoxic activity, anti-neurotoxic activity, anti-hypercholesteremia activity, anti-hypertensive activity, and hypoglycemic/anti-diabetic activity (Singh *et al*., 2019).

Carob (*Ceratonia siliqua L*.) contains phytochemicals found in all parts of the plant, including phenolic acids, flavonoids, hydrolysable and condensed tannins, and volatile compounds, as well as the useful sugar D-pinitol found in pods, according to recent research. Many in vitro and in vivo pharmacological properties were related with these substances, including antioxidant, gastroprotective, anti-inflammatory, hypoglycemic, hypolipidemic, cardioprotective, anti-proliferative, and cytotoxic activities (Moumou *et al*., 2023).

Hyphaene thebaica, popularly known as doum, is rich in phytochemical substances such as hydroxy cinnamates, flavonoids, essential oils, and saponins. It also has a high concentration of niacin, amino acids, thiamin, and riboflavin (El-Beltagi *et al*. 2018). Many biological actions of *H. thebaica* bioactive substances have been demonstrated, including antibacterial, anticancer, hyperlipidemia, antioxidant, anti-inflammatory, and antidiabetic properties (Abdallah, 2021).

Sunflower (*Helianthus annuus L*.) seeds and oil are high in protein, antioxidants (vitamin E), phytonutrients, minerals including selenium and magnesium, and have a good lipid profile. Thus, sunflower seeds provide a variety of therapeutic effects, including the prevention of some common chronic diseases such as cardiovascular (CVD) and inflammatory diseases (Khurana and Singh, 2021).

Apium graveolens, knowns as "celery" celery organs such seeds, stems, leaves, roots, and stalks contain antioxidant, antibacterial, anti-inflammatory, antifungal, anticancer, and insecticidal substances (Sellami *et al.*, 2012). Celery can help with blood pressure (BP), serum lipids, and diabetes (Triyono and Novianto, 2017). Celery seeds contain more active chemicals than other sections of the plant (Moghadam *et al*., 2012).

Numerous epidemiological and clinical investigations have demonstrated the health benefits of cabbages (*var. capitata L*.). Contributory factors include the presence of vitamins, provitamins (such folic acid), a wide range of phenolic chemicals, and organosulfur

compounds. Numerous studies have found a correlation between phenolic compounds and antioxidant activity, and cabbages have been shown to have stronger antioxidant activity than many other vegetables. (Liang *et al.,* 2019).

One easy, affordable, and ecologically responsible way to produce functional foods derived from plants is through seed germination. The nutritional and therapeutic qualities of seeds alter throughout germination. Protease inhibitors, lectin, and other anti-nutritional and anti-digestible substances can be reduced by germination, which can also cause an increase of secondary metabolites, some of which are classified as antioxidants (Aguilera *et al.,* 2013).

Antioxidants have the ability to inactivate free radicals, which are unstable, highly reactive, and reactive molecules that target proteins, nucleic acids, phospholipids, and other cellular macromolecules, affecting cell function. Various beneficial substances, including as vitamins, -aminobutyric acid, polyphenols, and trace elements, accumulate in seeds and sprouts during germination (Gan *et al.,* 2017).

MATERIALS AND METHODS

1. Materials

- Source of tested materials

Prickly pear (*O. ficus-indica*), cape gooseberry (*Physalis peruviana)*, carob (*Ceratonia siliqua L)*, doum (*Hyphaene thebaica*), cabbage *(var. capitata L*), celery (*Apium graveolens*), sunflower (*Helianthus annuus* L.) seeds & celery seeds obtained from Ministry of Agriculture farms.

- Experimental animals

A total of fifty adult normal male albino rats "Sprague Dawley" strain weighing 150±10g was provided by the Vaccine and Immunity Organization, Ministry of Health, Helwan Farm, Cairo, Egypt.

- The chemicals

(−) - Nicotine obtained from Sigma-Aldrich Chemie GmbH Company, Germany.

2. Methods

- Preparation of germinated seeds

▪ Soaking

Prickly pear seeds, celery seeds, and sunflower seeds were manually cleaned from broken seeds, dust, and other foreign they were immersed in tap water for 12 hours (1:5 w/v). The remaining ingested water was dumped after soaking. After soaking the seeds for two days, they were rinsed twice with regular water and then with distilled water.

▪ Germination

The soaked seeds were allowed to germinate for 72 hours at room temperature in sterile Petri dishes that were lined with damp filter paper, with regular watering. To prevent microbial growth, 0.3% sodium hypochlorite solution was used to rinse the seeds every 12 hours (El-Geddawy *et al.,* 2019). At 40 °C, the seeds were dried. were lastly processed in an air mill to a fine powder, combined with a high-speed mixer, and kept in polyethylene bags at freezing temperatures until needed (El-Kholie *et al.,* 2023).

- Preparation of plant powders

Prickly pear peel, cape gooseberry, carob, doum, cabbage and celery were sun-dried, processed with an electric grinder to a fine powder, and stored in dark, stoppered glass bottles in a cool, dry place until needed, as per Russo (2001), who noted that it is best to store all plant parts in a cool, dry, and dark place to prevent oxidation of their contents.

- Preparation of basal diet

The basal diet in the experiment consisted of casein (12%), corn oil (10%), mineral mixture (4%), vitamin mixture (1%), cellulose (5%), choline chloride (0.2%), methionine (0.3%) and the remained is corn starch (67.5%) according to (AIN, 1993).

- Injection of nicotine

Nicotine (0.25 mg/kg of rat body weight per day) was given subcutaneously into normal healthy male albino rats for 7 days using the method described by (Kim *et al.*, 2022).

Experimental design

The experiment was carried out at Menoufia University's Faculty of Home Economics in Shebin El-Kom. Rats were housed in separate stainless-steel cages under controlled environmental conditions, including normal atmospheric temperature (25 5 °C) and a normal 12-hour light/dark cycle, and were fed a baseline meal for 7 days to adapt. To reduce feed loss or contamination, the diet was given in non-spattering feeding cups, and water was provided to the animals via glass tubes extending through the wire cage from an inverted bottle supported on one side of the cage. Feed and water were checked daily, and rats were weighed once a week. All animal operations were carried out in compliance with the Canadian Committee for the Care and Use of Animals' recommendations (Olfert *et al.*, 1993).

- Rats were divided into 10 groups (5 rats in each group). The groups of rats were as follows:

Group (1) (-ve): Rats fed on a basal diet as a control negative.

Group (2) (+ve): Rats injected with nicotine, fed on basal diet, and used as a control positive group.

Group (3): Rats injected with nicotine fed on a basal diet containing 5% powder of prickly pear seeds, sunflower seeds & celery seeds (1:1:1), (5 rats).

Group (4): Rats injected with nicotine fed on a basal diet containing 10% powder of prickly pear seeds, sunflower seeds & celery seeds (1:1:1), (5 rats).

Group (5): Rats injected with nicotine fed on a basal diet containing 5% powder of prickly pear germinated seeds, sunflower germinated seeds & celery germinated seeds (1:1:1) (5 rats).

Group (6): Rats injected with nicotine fed on a basal diet containing 10% powder of prickly pear germinated seeds, sunflower germinated seeds & celery germinated seeds (1:1:1) (5 rats).

Group (7): Rats injected with nicotine fed on a basal diet containing 5% powder of cape gooseberry fruits, carob fruits & doum fruits (1:1:1) (5 rats).

Group (8): Rats injected with nicotine fed on a basal diet containing 10% powder of cape gooseberry fruits, carob fruits & doum fruits (1:1:1) (5 rats).

Group (9): Rats injected with nicotine fed on a basal diet containing 5% powder of prickly pear peel, celery & cabbage leaves (1:1:1) (5 rats).

Group (10): Rats injected with nicotine fed on a basal diet containing 10% powder of prickly pear peel, celery & cabbage leaves (1:1:1) (5 rats).

Blood sampling and organs

The abdominal aorta was used to obtain blood samples after 18 hours of fasting at the end of the trial. Blood was collected into a dry clean centrifuge tube and allowed to coagulate for 30 minutes in a 37°C water bath at room temperature. To separate the serum, the blood was centrifuged for 10 minutes at 3000 r.p.m. Serum was properly extracted and put into clean, tight-fitting plastic tubes, which were then frozen at (20° C) until analysis (Malhotra, 2003).

According to (Drury and Wallington, 1980), the lungs were removed, washed in saline solution, wiped with filter paper, weighed, and preserved frozen in formalin solution 10% for histological investigation.

-The biological Indices:

During the experimental period (4 weeks) biological evaluation of the different diets was carried out by determination of feed intake (FI) (consumption) daily, body weight gain (BWG) & feed efficiency ratio (FER) according to (Chapman *et al.*, 1959). Using the following formulas:

BWG (g) = Final weight - Initial Weight

$$\text{FER} = \frac{\text{Gain Body Weight (g/day)}}{\text{Feed Intake (g/day)}}$$

-Biochemical analysis

The following techniques were used for the determination of different parameters in serum.

Determination of antioxidant enzymes

SOD activity was determined by the method of (Sun *et al.* 1988). GP_X was assayed according to the method of (Pascual *et al.* 1992). Catalase activity was assayed by the method of (Johansson & Borg, 1988).

Determination of lipid peroxidation marker

MDA was determined by the method of (Draper and Hadley, 1990).

Determination of inflammation marker

The C-reactive protein (CRP) was determined in serum samples using an ELISA Kit by the method of (Padilla *et al.,* 2003).

Determination of serum lipids

Enzymatic colorimetric (TG) was carried out according to (Fossati and Prencipe, 1982), (TC) determination according to (Allain, 1974), and HDL was determined according to (Lopez, 1977). The determination of VLDL (very low-density lipoproteins) and LDL (low-density lipoproteins) were carried out according to the method of (Lee and Nieman, 1996) as calculation follows:

VLDL (mg/dl) = Triglycerides /5

LDL (mg/dl) = Total cholesterol - (HDL + VLDL).

Determination of liver function

Determination of alkaline phosphatase (ALP): Kits were obtained from biosystems S. A. kits, Barcelona (Spain). Serum ALP was determined according to (IFCC, 1983). Determination of GPT was carried out according to the method of (Yound, 1975). Determination of GOT was carried out according to the method of (Henry, 1974) and (Yound, 1975).

Statistical analysis

One-way ANOVA was used to statistically analyses the data using a computerized costate programme. The data is presented as mean SD. Differences between treatments were considered significant at ($P \leq 0.05$) (SAS, 1985).

Histopathological Examination

The histological investigation was performed at Cairo University's Faculty of Veterinary Medicine in Giza, Egypt. Small lungs were obtained from each experimental group and submerged in 10% neutral buffered formalin. The fixed specimens were then trimmed and dehydrated in increasing grades of alcohol, cleaned in xylene, embedded in paraffin, sectioned (4 - 6) m thickness, stained with Hematoxylin and Eosin, and inspected microscopically (Bancroft *et al.,* 1996).

RESULTS AND DISCUSSION

1. Biological evaluation

Data presented in Table (1) show the mean values of body weight gain BWG, FI & FER of rats that injected by nicotine fed on various diets by feeding on (prickly pear seeds + sunflower seeds + celery seeds) (1:1:1) (5 & 10%), (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) (1:1:1) (5 & 10%), (cape gooseberry + carob+ doum) (1:1:1) (5 & 10%) & (prickly pear peel + cabbage + celery leaves) (1:1:1) (5 & 10%) in diets.

It is clear that due to nicotine injection BWG was decreased. Mainly nicotine increases fat metabolism and suppresses weight gain in male rats (Rupprecht *et al.,* 2018). For FI the data revealed that nicotine injection consumed feed decreased, which may be expected, since nicotine decreases appetite (Mineur *et al.,* 2011). Regarding FER it is obvious by nicotine injection FER decreased. This may be expected since FI was decreased and BWG was reduced. Meanwhile, when feeding on diets containing the targeted tested plants, BWG, FI & FER increased. The best group was that by the (prickly pear peel, celery & cabbage leaves) by10%.

The results of this study agreed with those of Mineur *et al.*, (2011), who indicated that stimulation of hypothalamic 34 nicotinic

acetylcholine receptors (nAChRs) stimulate pro-opiomelanocortin (POMC) neurons. The majority of the feed intake reduction in mice caused by nicotinic input was caused via Melanocortin 4 receptors, which are then activated by POMC neurons. This research identifies essential chemical and synaptic pathways involved in nicotine's appetite suppression and illustrates the effect of nicotine on the hypothalamus melanocortin system.

This study's findings agreed with those of (Sheha & El Gezery, 2018), who discovered that prickly pear peels improve FI and increase BWG and FER because they contain essential compounds such as taurine, amino acids, readily absorbable carbohydrates, minerals, vitamin C, flavonoids, tocopherols, and carotenoids. Celery leaves powder increased BWG and FI after 3 weeks feeding of experimental rats (Beltagy *et al.,* 2018).

Golden berries increased BWG, FI & FER by 5% &10% in rats injected once intramuscularly with glycerol (Ali *et al.,* 2019).

El Sayed & El Hawary, (2019) found that the use of sunflower seeds increased FI & FER in obese rats.

Tahoon, (2021) indicated that cabbage extract increased FER in obese rats as compared to the positive control group.

Elmahdy *et al.,* (2022) found that feeding hyperlipidemic and hypertensive rats with an extract of doum increased body weight as compared to the control group.
Carob (*Ceratonia siliqua* L.) pulp powder improved BWG, FI & FER in broiler chicken (Mahmoudi *et al.,* 2022).

Table (1): Effect of suggested dietary formulas on body weight gain (BWG), feed intake (FI), and feed efficiency ratio (FER) of nicotine-injected rats

Parameters / Groups	BWG (g/day) Mean ± SD	FI (g/day) Mean ± SD	FER Mean ± SD
G1: Control –ve	1.43±0.009^{a}	16.83±0.008^{c}	0.085±0.0006^{a}
G2: Control +ve	1.13±0.005^{f}	14.12±0.005^{h}	0.080±0.0003^{b}
G3: (prickly pear seeds + sunflower seeds + celery seeds) powder (5%)	0.9±0.005^{j}	15.8±0.034^{e}	0.057±0.0003^{j}
G4: (prickly pear seeds + sunflower seeds + celery seeds) powder (10%)	1.10±0.007^{g}	16.7±0.14^{d}	0.066±0.0003^{h}
G5: (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) powder (5%)	0.93±0.003^{i}	14.8±0.11^{g}	0.063±0.0008^{i}
G6: (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) powder (10%)	0.98±0.003^{h}	15.17±0.11^{f}	0.067±0.0001^{g}
G7: (Cape gooseberry + carob + doum) powder (5%)	1.20±0.003^{d}	17.1±0.09^{b}	0.070±0.0005^{e}
G8: (Cape gooseberry, carob & doum) powder (10%)	1.27±0.004^{c}	16.71±0.008^{cd}	0.076±0.0002^{d}
G9: (prickly pear peel, cabbage leaves & celery leaves) powder (5%)	1.18±0.002^{e}	17.2±0.02^{ab}	0.069±0.0007^{f}
G10: (prickly pear peel, cabbage leaves & celery leaves) powder (10%)	1.33±0.003^{b}	17.34±0.018^{a}	0.077±0.0004^{c}
LSD	0.0083	0.22	8.02

Values in each column with different letters are significantly different (P≤0.05).

2. Biochemical analysis

- Oxidative stress parameters

Data presented in Table (2) show the mean values of antioxidant enzymes SOD, GPx & CAT and lipid peroxidation marker MDA of rats that were injected with nicotine fed on various diets. It is clear that due to nicotine injection, the activities of serum SOD significantly declined. this loss of antioxidant enzymes may be a consequence of decreased de novo synthesis of enzyme proteins or oxidative inactivation of enzyme proteins. The activities of GPx decreased as compared to the untreated control animals. The reduction in GPx activity could be attributed to its involvement in the nicotine detoxification mechanism. The injection of nicotine significantly decreased CAT activity in the serum. Decreased CAT activity in serum after exposure to nicotine is indicative of an inefficient elimination of toxic H_2O_2 by GPx in tissues (Oyeyipo *et al.,* 2014). Meanwhile, feeding on suggested plants increased the activities of SOD, GPx & CAT of rats. All tested diets raised the enzyme. The best group was that of the (prickly pear peel, cabbage leaves & celery leaves) 10% indicating maximum enzyme rise. Regarding MDA as a lipid peroxidation assay. There was a significant increase in MAD level in positive control as compared to negative control (7.08±0.002 and 0.676±0.0005 nmol/ml, respectively). An increased MDA concentration might be a consequence of decreased production of antioxidants in the nicotine-treated rats' tissues (Oyeyipo *et al.,* 2014), thereby shifting the delicate balance in favor of reactive oxygen species. Treated groups with various diets had a significant decrease in MAD levels. The best result of SOD, GPx & showed in group 10% (prickly pear peel, cabbage leaves & celery leaves). The best MDA level showed in group 3 rats fed on a basal diet containing 5% (prickly pear seeds, sunflower seeds & celery seeds)

Table (2): Effect of suggested dietary formulas on antioxidative stress parameters [superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT)] and malondialdehyde (MDA) of nicotine injected rats

Parameters / Groups	SOD (U/ml) Mean ± SD	GPx (U/ml) Mean ± SD	CAT (ng/ml) Mean ± SD	MDA (nmol/ml) Mean ± SD
G1: Control –ve	213.11±1.98^{a}	189.89±1.52^{b}	12.12±0.007^{a}	0.676±0.0005^{j}
G2: Control +ve	42.20±0.09^{j}	22.34±2^{j}	0.565±0.0004^{j}	7.08±0.002^{b}
G3: (prickly pear seeds + sunflower seeds + celery seeds) powder (5%)	82.28±3.996^{h}	61.15±0.87^{h}	2.11±0.003^{h}	0.959±0.0004^{i}
G4: (prickly pear seeds + sunflower seeds + celery seeds) powder (10%)	63.36±4.22^{i}	35.31±0.01^{i}	0.858±0.0005^{i}	8.58±0.007^{a}
G5: (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) powder (5%)	91.19±0.1712^{g}	77.57±2^{g}	3.75±0.009^{g}	4.11±0.008^{c}
G6: (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) powder (10%)	158.85±6.25^{d}	140.41±1.1^{d}	4.67±0.003^{e}	2.84±0.001^{e}
G7: (Cape gooseberry + carob + doum) powder (5%)	143.34±0.21^{e}	137.44±1^{e}	5.25±0.001^{d}	2.21±0.003^{f}
G8: (Cape gooseberry, carob & doum) powder (10%)	121.42±1.31^{f}	101.25±0.232^{f}	4.27±0.002^{f}	3.28±0.005^{d}
G9: (prickly pear peel, cabbage leaves & celery leaves) powder (5%)	173.37±3.99^{c}	166.36±2.14^{c}	5.82±0.009^{c}	1.85±0.001^{g}
G10: (prickly pear peel, cabbage leaves & celery leaves) powder (10%)	195.58±1^{b}	201.11±1.08^{a}	6.27±0.009^{b}	1.21±0.006^{h}
LSD	5.26	2.35	0.0085	0.0074

Values in each column with different letters are significantly different (P≤0.05).

Our data show that a daily 0.5 mg nicotine injection for two months caused severe oxidative stress, as seen by considerable increases in MDA and GSSG levels, as well as significant decreases in GSH content and GSH/GSSG ratio. Significant suppression of the antioxidant enzymes SOD, CAT, and GPx activities, as well as an increase in GST activity, were also detected. Numerous research have been conducted to evaluate the effect of nicotine on antioxidant levels (Aljohani *et al.*, 2015).

SOD is the initial defense antioxidant enzyme against ROS. SOD catalyzes the dismutation of the highly reactive superoxide anion (O_2 •−) to molecular oxygen (O_2) and hydrogen peroxide (H_2O_2). CAT is an enzyme that catalyzes the decomposition of H_2O_2 into water and oxygen. The attenuation of CAT activity indicated that the oxidative action of nicotine was associated with the overproduction of H_2O_2, which inhibited the enzyme (Elsonbaty & Ismail, 2020).

Opuntia stricta juice extract increase SOD, GPx & CAT and decrease MDA levels significantly ($p < 0.05$) in male albino rat his study revealed that prickly pear juice extract protects against the toxic effects of Cd, possibly through its free radical scavenging and antioxidant activities (Zhu and Athmouni, 2022). Also, these results agree with (Bardaa *et al.*, 2020), (El-Beltagy *et al.*, 2020) & (Elgazar *et al.*, 2023).

- Inflammatory marker

Data presented in Table (3) show the mean value of C-reactive protein (CRP) of rats that were injected with nicotine-fed of various diets. The results indicated that the nicotine injection increased the serum CRP concentration as showed significantly higher serum CRP concentration after nicotine induction (Group 2) compared to without nicotine injection (Group 1). The cause of this increase is nicotine's stimulation of inflammatory mediator production, which includes IL-6, IL-1, and TNF-α, which is the principal regulator of CRP. Furthermore, nicotine activates the transcription factor NF-κB, which causes macrophages to produce CRP. Meanwhile due to feeding on diet containing tested plants, CRP markedly decreased. The best treatment was group (10).

Nicotine can cause the release of CRP via nAChR in macrophages found in atherosclerotic plaques. Synthesized CRP causes a rise in free radicals, a condition known as oxidative stress. Oxidative stress also causes lipid peroxidation, which destroys endothelial cell membranes, as evidenced by an increase in MDA content in the body (Manafe & Agustiningsih, 2016).

Our results are in agreement with (Hassan *et al.,* 2017), (Bardaa *et al.,* 2020) & (Prakoso & Wijayanti, 2022).

Lipids profile

Data of Table (4) show the levels of TC and TG (mg/dl) in serum of rats that injected by nicotine and affected by feeding on (prickly pear seeds + sunflower seeds + celery seeds), (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds), (cape gooseberry + carob+ doum) & (prickly pear peel + celery + cabbage leaves) 5 & 10% levels.

The results indicated that due to nicotine injection TC and TG increased. Therefore, nicotine was damaging to the lipids profile. Meanwhile feeding on a diet containing tested plants reversed such changes. The best group was (prickly pear peel + cabbage leaves+ celery leaves) 10% that recorded the lowest TC & TG. Data from the same table show the HDL, LDL, and VLDL (mg/dl) levels in rats that were injected with nicotine and affected by feeding on various diets. It could be observed that VLDL followed the levels of TG (Table 4), being increased by injection, LDL was also highest for the (C+) group and deserved when nicotine-injected rats fed on tested dietary formulas. Nicotine injection decreases HDL levels. Meanwhile, due to feeding on a diet containing tested plants, HDL markedly increased. The best treatment was (prickly pear peel + celery + cabbage leaves) which recorded the lowest LDL & VLDL, and highest HDL.

Table (3): Effect of suggested dietary formulas on C-reactive protein (CRP) of nicotine injected rats

Parameters / Groups	CRP (ng/ml) Mean ± SD
G1: Control –ve	4.24±0.11^{j}
G2: Control +ve	67.67±1.02^{a}
G3: (prickly pear seeds + sunflower seeds + celery seeds) powder (5%)	55.21±0.18^{b}
G4: (prickly pear seeds + sunflower seeds + celery seeds) powder (10%)	36.58±1.00^{e}
G5: (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) powder (5%)	43.32±0.32^{c}
G6: (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) powder (10%)	31.13±0.99^{f}
G7: (Cape gooseberry + carob + doum) powder (5%)	38.38±2.08^{d}
G8: (Cape gooseberry, carob & doum) powder (10%)	24.15±0.15^{g}
G9: (prickly pear peel, cabbage leaves & celery leaves) powder (5%)	13.37±1.02^{h}
G10: (prickly pear peel, cabbage leaves & celery leaves) powder (10%)	7.20±0.1^{i}
LSD	1.58

Values in each column with different letters are significantly different (P≤0.05).

Table (4): Effect of suggested dietary formulas on TC, TG, HDL, LDL, and VLDL of nicotine-injected rats

Parameters / Groups	TC (mg/dl) Mean ± SD	TG (mg/dl) Mean ± SD	HDL-c (mg/dl) Mean ± SD	LDL-c (mg/dl) Mean ± SD	VLDL-c (mg/dl) Mean ± SD
G1: Control –ve	120.17±0.04^{g}	91.19±1.19^{g}	58.78±1.52^{a}	43.15±0.47^{h}	18.24±0.18^{f}
G2: Control +ve	205.21±0.04^{a}	143.34±2.22^{a}	31.15±0.08^{g}	145.39±1.25^{a}	28.67±0.46^{a}
G3: (prickly pear seeds + sunflower seeds + celery seeds) powder (5%)	150.32±0.99^{b}	115.52±0.29^{e}	48.25±0.75^{f}	78.97±0.72^{b}	23.10±0.05^{d}
G4: (prickly pear seeds + sunflower seeds + celery seeds) powder (10%)	143.56±0.45^{d}	107.75±1.25^{f}	49.30±0.28^{ef}	72.71±0.68^{c}	21.55±0.38^{e}
G5: (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) powder (5%)	146.15±1^{c}	127.75±0.73^{b}	48.11±0.05^{f}	72.45±1.24^{c}	25.55±0.05^{b}
G6: (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) powder (10%)	140.61±1.5^{e}	123.34±2.59^{c}	49.50±0.37^{ef}	66.44±0.52^{d}	24.67±0.33^{bc}
G7: (Cape gooseberry + carob + doum) powder (5%)	124.34±0.011^{f}	119.85±0.7^{d}	50.20±0.9^{de}	50.17±0.08^{e}	23.97±0.88^{c}
G8: (Cape gooseberry, carob & doum) powder (10%)	123.78±0.003^{f}	113.25±0.08^{e}	52.01±0.004^{cd}	49.12±0.11^{ef}	22.65±0.39^{e}
G9: (prickly pear peel, cabbage leaves & celery leaves) powder (5%)	123.68±0.008^{f}	108.16±3.14^{f}	53.36±0.012^{bc}	48.69±0.54^{fg}	21.63±0.62^{e}
G10:(prickly pear peel, cabbage leaves & celery leaves) powder (10%)	119.36±1.29^{g}	90.21±1.24^{g}	54.15±0.008^{b}	47.17±0.21^{gh}	18.04±0.06^{f}
LSD	2.20	3.41	1.89	2.13	1.3

Values in each column with different letters are significantly different (P≤0.05).

Higher triglyceride levels are brought on by nicotine, which also inhibits lipoprotein lipases, which are enzymes that help the extra hepatic tissue absorb circulating triglyceride-rich lipoprotein and VLDL (Sharif *et al.*, 2014).

Fruit from prickly pears lowers TC and LDL and raises HDL in the population under study. Its phytochemical composition, which reduces oxidative stress, together with its fiber content and connections with changed rates of fat absorption are the reasons behind this (Gouws *et al.*, 2020).

These results are the same with (Beltagy *et al.*, 2018) and (El-Gwad *et al.*, 2018).

Liver enzymes

Results of Table (5) indicated the activity of liver enzymes AST, ALT & ALP increased significantly due to nicotine injection. Necrosis or cell membrane damage can cause the release of these enzymes into the blood. Nevertheless, by feeding on all tested plant diets. The best group for ALT level was group 10 (prickly pear peel + celery + cabbage leaves) (10%). The best group for AST & ALP levels was group 4 (prickly pear seeds + sunflower seeds + celery seeds) (10%).

It was observed that the administration of nicotine increased ALT, AST, and ALP levels. Similar results were also reported by Jang *et al.*, (2012).

Treatment with gooseberry extract along with CCl4 significantly reduced the elevated levels of ALT, AST, and ALP compared to the hepatotoxin rats' group. Due to that gooseberry extract exhibit many bioactive features including antioxidant and anti-inflammatory properties as a result of the high concentrations of phenolic chemicals and flavonoids in gooseberry extract, it has several bioactive qualities, including antioxidant and anti-inflammatory capabilities (Elmasry & Moawad, 2021).

Serum transaminases, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were lower in rats treated with Opuntia ficus-indica than in controls. Opuntia's antioxidant activity is of particular importance in the prevention and treatment of fatty liver (Besné-Eseverri *et al.*, 2023).

Table (5): Effect of suggested dietary formulas on AST, ALT, and ALP (U/L) of nicotine-injected rats

Parameters / Groups	AST (U/L) Mean ± SD	ALT (U/L) Mean ± SD	ALP (U/L) Mean ± SD
G1: Control –ve	65.25±0.14^{i}	25.65±0.54^{j}	168.24±1.04^{g}
G2: Control +ve	184.22±0.21^{a}	104.52±0.47^{a}	345.25±2.24^{a}
G3: (prickly pear seeds + sunflower seeds + celery seeds) powder (5%)	102.2±1.2^{d}	44.37±1.23^{h}	182.25±1.04^{f}
G4: (prickly pear seeds + sunflower seeds + celery seeds) powder (10%)	67.94±0.63^{h}	52.26±0.76^{f}	123.75±0.59^{h}
G5: (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) powder (5%)	137.44±2.22^{b}	81.11±1.02^{b}	304.11±4.03^{b}
G6: (prickly pear germinated seeds + sunflower germinated seeds + celery germinated seeds) powder (10%)	128.49±0.48^{c}	55.45±0.55^{e}	168.86±1.01^{g}
G7: (Cape gooseberry + carob + doum) powder (5%)	100.5±0.7^{d}	70.08±2.08^{c}	248.22±1.78^{c}
G8: (Cape gooseberry, carob & doum) powder (10%)	95.2±2.2^{f}	48.58±0.56^{g}	238.58±0.47^{d}
G9: (prickly pear peel, celery & cabbage leaves) powder (5%)	97.75±1.05^{e}	66.96±0.06^{d}	194.45±0.23^{e}
G10: (prickly pear peel, celery & cabbage leaves) powder (10%)	88.48±0.35^{g}	37.74±3.13^{i}	167.54±0.36^{g}
LSD	1.99	2.31	3.84

Values in each column with different letters are significantly different (P≤0.05).

3. Histopathological examination of lungs

Microscopical examination of the lungs of rats from group (1) revealed the normal histological architecture of pulmonary tissue (Normal bronchioles and alveoli) (Photos. 1& 2). On the contrary, the lungs of rats from group 2 showed histopathological alterations characterized by thickening of interstitial septa with inflammatory cells (interstitial pneumonia) and perivasculitis (Photos. 3, 4 & 5). Meanwhile, lungs of rats from group 3 exhibited slight thickening of interstitial septa with inflammatory cells (slight interstitial pneumonia) (Photo. 6) and perivasculitis (Photo. 7). On the other hand, lungs of rats from group 4 described slight thickening of interstitial septa with inflammatory cells (Photos. 8 & 9), congestion of pulmonary blood capillaries (Photo. 8) and perivasculitis (Photos. 9 & 10). Likewise, the lungs of rats from group 5 showed slight thickening of interstitial septa with inflammatory cells and perivasculitis (Photos. 11, 12 & 13). Otherwise, the lungs of rats from group 6 revealed congestion of pulmonary blood vessels and perialveolar blood capillaries (Photos. 14, 15 & 16). Furthermore, lungs of rats from group 7 described slight congestion of perialveolar blood capillaries (Photos. 17 & 18), perivasculitis (Photo. 18) and slight thickening of interstitial septa with inflammatory cells (Photo. 19). Meanwhile, some examined sections from group 8 exhibited no histopathological lesions (Photos. 20 & 21), whereas other sections revealed slight thickening of interstitial septa with inflammatory cells and slight perivasculitis (Photo. 22). Likewise, lungs of rats from group 9 exhibited no histopathological lesions (Photos. 23 & 24) except perivascular inflammatory cells infiltration was noticed in some sections (Photo. 25). Furthermore, examined lungs of rats from group 10 showed no histopathological lesions (Photos. 26 & 27) except focal interstitial pneumonia (Photo. 28) was observed in some examined sections.

The lungs of nicotine-treated rats showed severe congestion of the alveolar lung tissues with scattered congestion per bronchiolar and perivascular cells, as well as inflammatory cells were observed (Hamza & El-Shenawy, 2017).

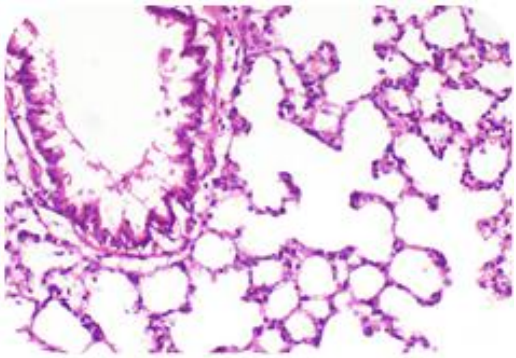

Photo. (1): Photomicrograph of lung of rat from group 1 showing the normal histological architecture of pulmonary tissue (H & E, X 200).

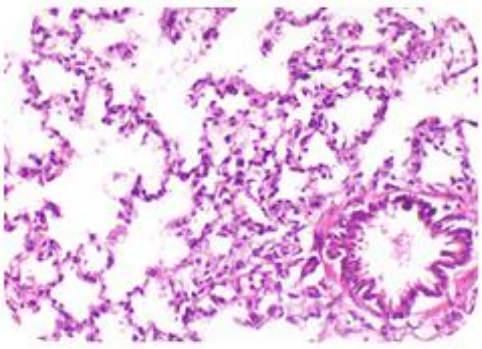

Photo. (2): Photomicrograph of lung of rat from group 1 showing the normal histological architecture of pulmonary tissue (H & E, X 200).

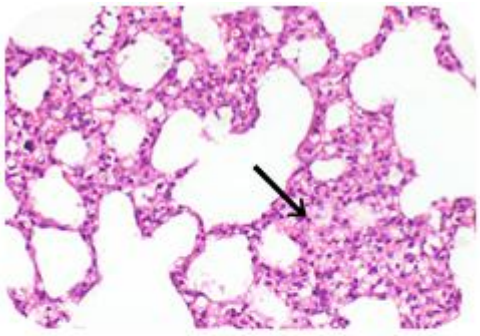

Photo. (3): Photomicrograph of lung of rat from group 2 showing thickening of interstitial septa with inflammatory cells (interstitial pneumonia) (black arrow) (H & E, X 200).

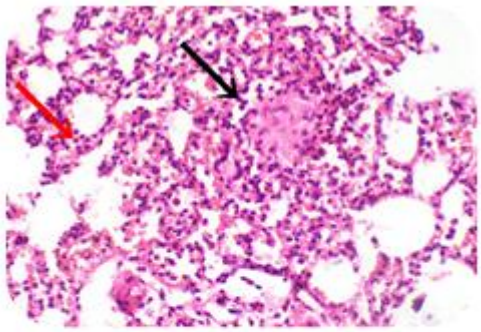

Photo. (4): Photomicrograph of lung of rat from group 2 showing thickening of interstitial septa with inflammatory cells (interstitial pneumonia) (red arrow) and perivasculitis (black arrow) (H & E, X 200).

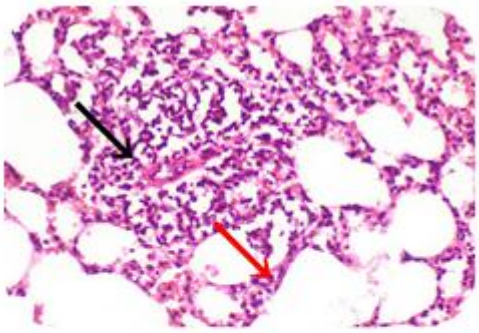

Photo. (5): Photomicrograph of lung of rat from group 2 showing thickening of interstitial septa with inflammatory cells (interstitial pneumonia) (red arrow) and perivasculitis (black arrow) (H & E, X 200).

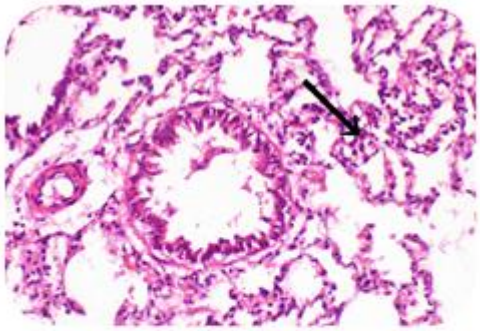

Photo. (6): Photomicrograph of lung of rat from group 3 showing slight thickening of interstitial septa with inflammatory cells (slight interstitial pneumonia) (arrow) (H & E, X 200).

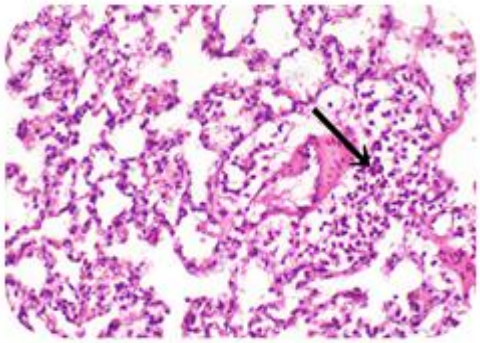

Photo. (7): Photomicrograph of lung of rat from group 3 showing perivasculitis (black arrow) (H & E, X 200).

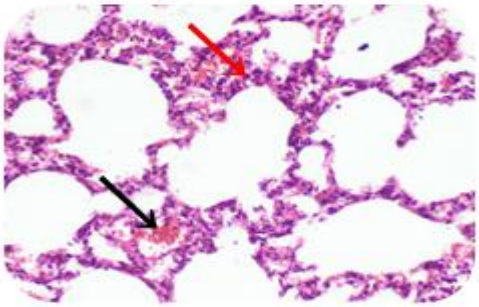

Photo. (8): Photomicrograph of lung of rat from group 4 showing slight thickening of interstitial septa with inflammatory cells (red arrow) and congestion of pulmonary blood capillaries (black arrow) (H & E, X 200).

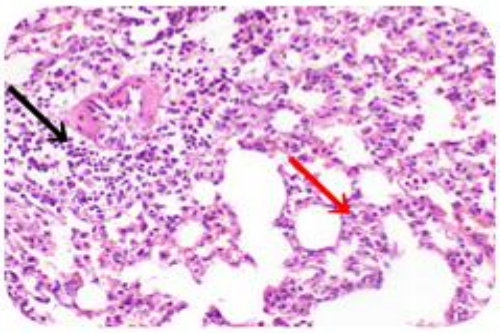

Photo. (9): Photomicrograph of lung of rat from group 4 showing slight thickening of interstitial septa with inflammatory cells (red arrow) and perivasculitis (black arrow) (H & E, X 200).

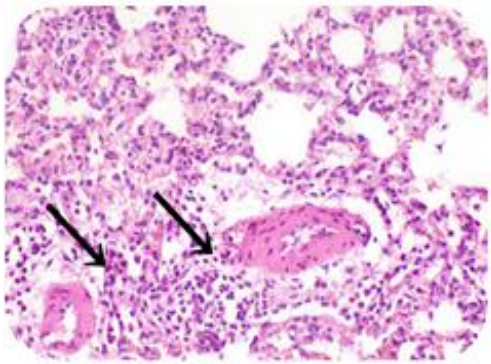

Photo. (10): Photomicrograph of lung of rat from group 4 showing perivasculitis (black arrow) (H & E, X 200).

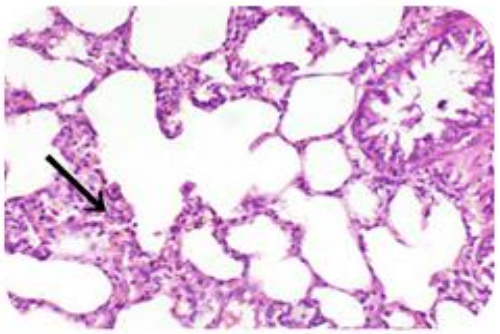

Photo. (11): Photomicrograph of lung of rat from group 5 showing slight thickening of interstitial septa with inflammatory cells (arrow) (H & E, X 200).

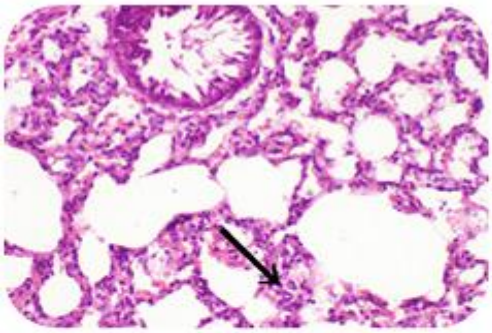

Photo. (12): Photomicrograph of lung of rat from group 5 showing slight thickening of interstitial septa with inflammatory cells (arrow) (H & E, X 200).

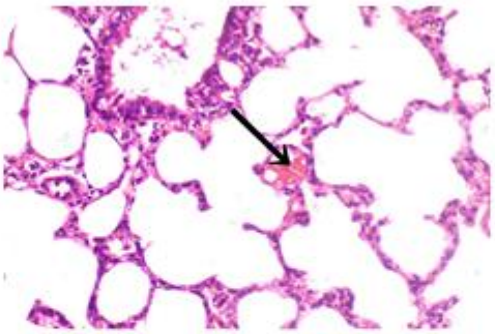

Photo. (13): Photomicrograph of lung of rat from group 5 showing slight thickening of interstitial septa with inflammatory cells (red arrow) and perivasculitis (black arrow) (H & E, X 200).

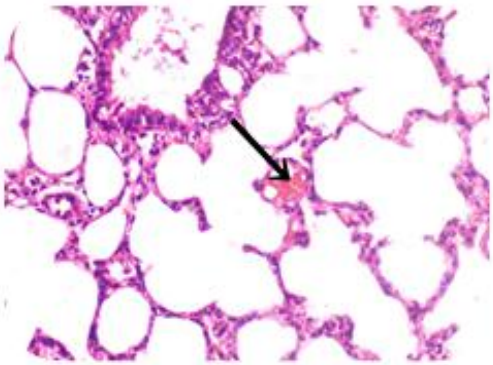

Photo. (14): Photomicrograph of lung of rat from group 6 showing congestion of pulmonary blood vessel (black arrow) (H & E, X 200).

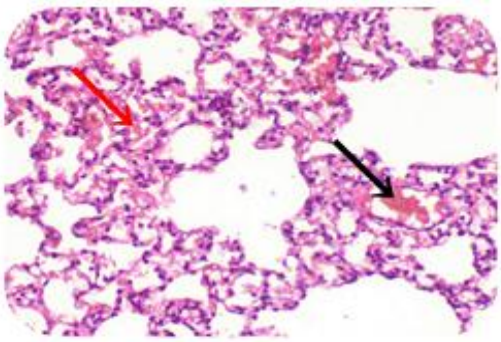

Photo. (15): Photomicrograph of lung of rat from group 6 showing congestion of pulmonary blood vessel (black arrow) and perialveolar blood capillaries (red arrow) (H & E, X 200).

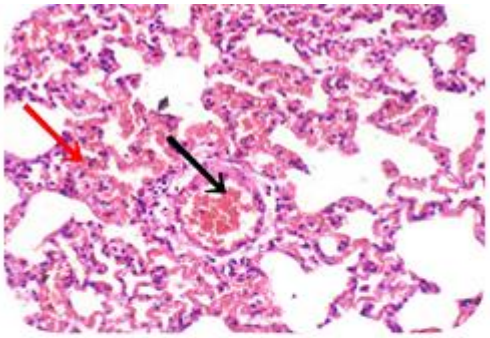

Photo. (16): Photomicrograph of lung of rat from group 6 showing congestion of pulmonary blood vessel (black arrow) and perialveolar blood capillaries (red arrow) (H & E, X 200).

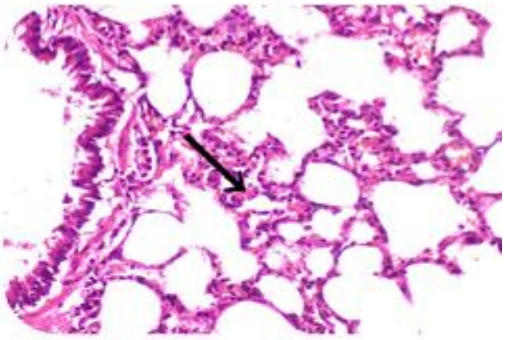

Photo. (17): Photomicrograph of lung of rat from group 7 showing slight congestion of perialveolar blood capillaries (black arrow) (H & E, X 200).

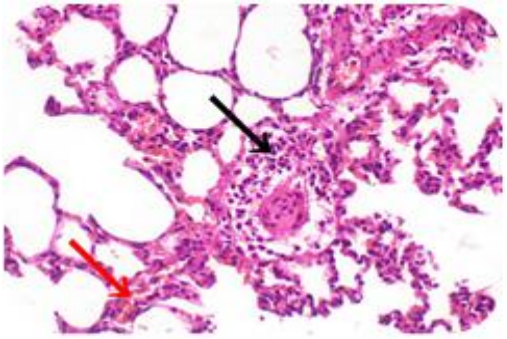

Photo. (18): Photomicrograph of lung of rat from group 7 showing slight congestion of perialveolar blood capillaries (red arrow) and perivasculitis (black arrow) (H & E, X 200).

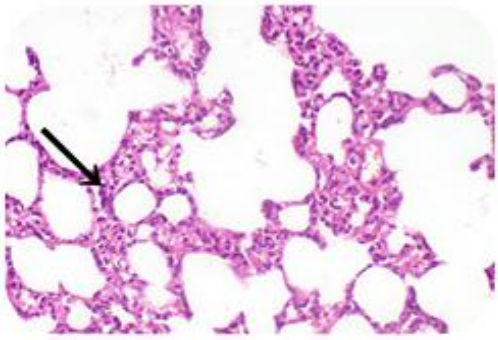

Photo. (19): Photomicrograph of lung of rat from group 7 showing slight thickening of interstitial septa with inflammatory cells (black arrow) (H & E, X 200).

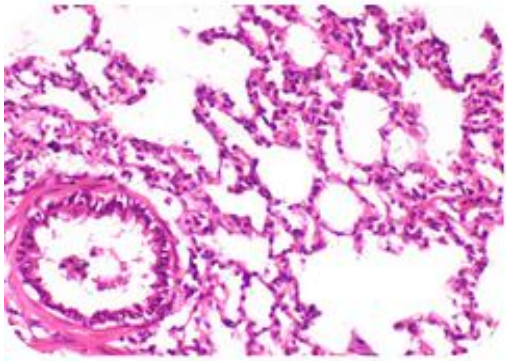

Photo. (20): Photomicrograph of lung of rat from group 8 showing no histopathological lesions (H & E, X 200).

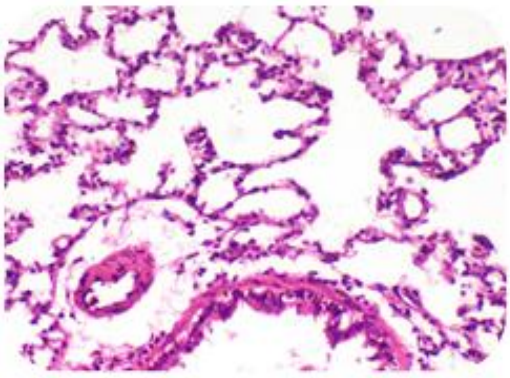

Photo. (21): Photomicrograph of lung of rat from group 8 showing no histopathological lesions (H & E, X 200).

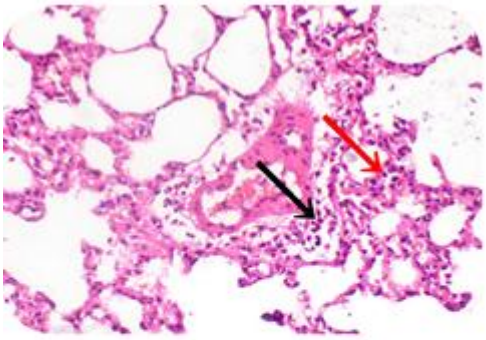

Photo. (22): Photomicrograph of lung of rat from group 8 showing slight thickening of interstitial septa with inflammatory cells (red arrow) and slight perivasculitis (black arrow) (H & E, X 200).

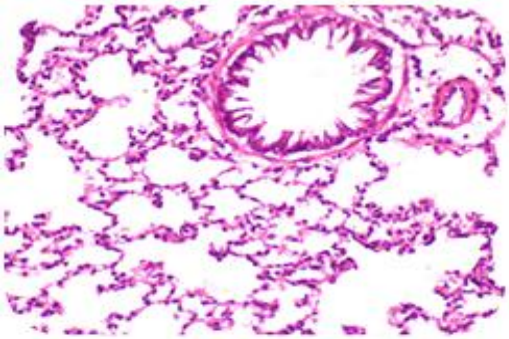

Photo. (23): Photomicrograph of lung of rat from group 9 showing no histopathological lesions (H & E, X 200).

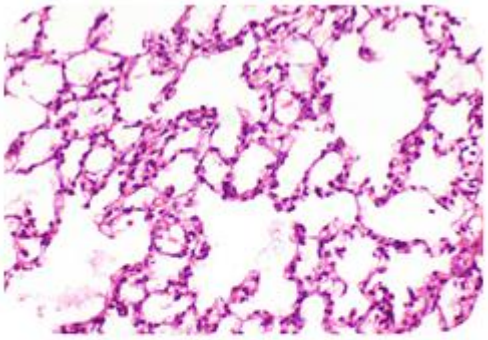

Photo. (24): Photomicrograph of lung of rat from group 9 showing no histopathological lesions (H & E, X 200).

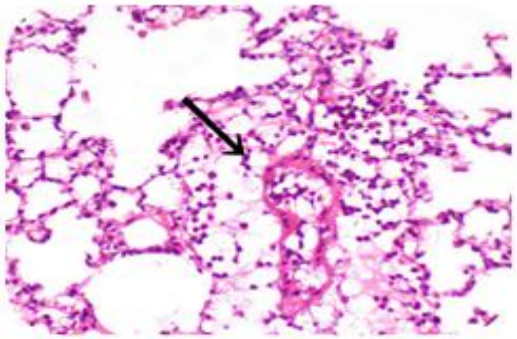

Photo. (25): Photomicrograph of lung of rat from group 9 showing perivascular inflammatory cells infiltration (black arrow) (H & E, X 200).

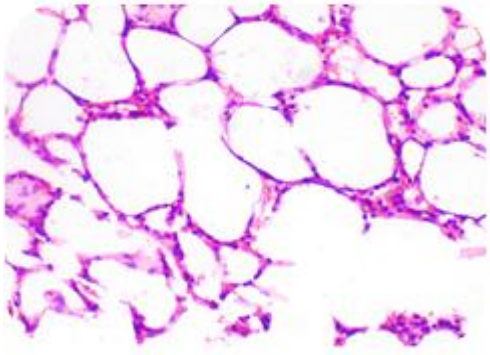

Photo. (26): Photomicrograph of lung of rat from group 10 showing no histopathological lesions (H & E, X 200).

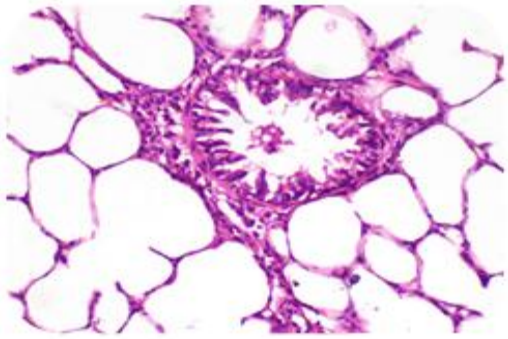

Photo. (27): Photomicrograph of lung of rat from group 10 showing no histopathological lesions (H & E, X 200).

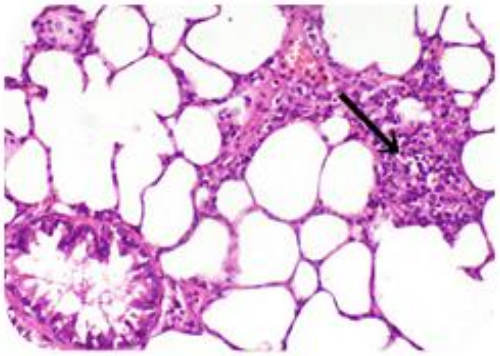

Photo. (28): Photomicrograph of lung of rat from group 10 showing focal interstitial pneumonia (black arrow) (H & E, X 200).

Conclusion

To conclude, when tested on the employed animal models, all suggested dietary formulae restored antioxidant levels, particularly the meal comprising 10% (prickly pear peel, celery leaves, and cabbage leaves) (1:1:1) powder. Furthermore, such animal models have been improved based on their measured lipid profiles, hematology parameters, CRP, and liver function. These formulas are highly suggested for assisting smokers; however, much more human research is required.

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إستعادة مستويات مضادات الأكسدة لدى الفئران المحقونة بالنيكوتين باستخدام تركيبات غذائية مقترحة

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الملخص العربى

تهدف هذه الدراسة إلى معرفة تأثير بعض التركيبات الغذائية على استعادة مستويات مضادات الأكسدة فى الفئران التى تم حقنها بالنيكوتين. تم تقسيم خمسين من ذكور الفئران من سلالة سبراج داولى إلى مجموعتين رئيسيتين: الأولى وهي المجموعة الضابطة السالبة (-C) ٥ فئران، والثانية تم حقنها بالنيكوتين. وقسمت المجموعة الثانية إلى تسع مجموعات فرعية المجموعة الضابطة الموجبة (+C) وثمان مجموعات أخرى تم تغذيتها على نظام غذائي أساسي مكمل بمسحوق (بذور التين الشوكى + بذور الخروب + وبذور الكرفس)، (بذور التين الشوكى المنبتة + بذور الخروب المنبتة + وبذور الكرفس المنبتة)،(ثمار الحرنكش+ ثمار الدوم+ ثمار الخروب) و(قشور التين الشوكي + أوراق الكرنب + أوراق الكرفس) بنسب (٥% و ١٠٪ على التوالي) ، وفي نهاية التجربة تم تقدير وزن الجسم المكتسب والمأخوذ الغذائي ومعدل الاستفاد من الغذاء و مصل الدم لقياس مستويات انزيمات الاكسدة ومستوى البروتين التفاعلي C ودهون الدم ووظائف الكبد كما تم إجراء الفحص الهستوباثولوجي للرئتين. أظهرت البيانات التي تم جمعها أن حقن النيكوتين تسبب في انخفاض معنوي في وزن الجسم المكتسب و المأخوذ الغذائى و معدل الاستفادة من الغذاء و انزيمات (سوبرأكسيد ديسموتاز، وجلوتاثيون بيروكسيداز وكتاليز) و الليبوبروتينات مرتفعة الكثافة ، بينما ارتفع كل من مالون داي ألدهيد، ومستوى البروتين التفاعلي C و الكوليسترول الكلي والجليسريدات الثلاثية و والليبوبروتينات منخفضة الكثافة والليبوبروتينات منخفضة الكثافة جدا) وظائف الكبد مثل (الجلوتاميك أوكسالو أستيك ترانس أمينيز، الجلوتاميك بيرفيك ترانس أمينيز والألكالين فوسفاتيز). عند استخدام التركيبات الغذائية المقترحة أدت الى تحسن جميع النتائج السابقة

الخلاصة: أظهرت الفئران التي عولجت بالنباتات المختبرة تحسنًا في مستويات مضادات الأكسدة وخاصة (قشور التين الشوكي، أوراق الكرفس، أوراق الكرنب) بتركيز ١٠%. لذلك يوصى باستخدام هذه التركيبات لمساعدة المدخنين، مع اجراء المزيد من الدراسات البشرية فى المستقبل.

الكلمات المفتاحية: إنزيمات الأكسدة، النيكوتين، التين الشوكي، الكرفس، الكرنب، الحرنكش، الخروب، الدوم، بذور دوار الشمس.