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Protective Effect of Essential oil of *Pelargonium graveolens* Against Paracetamol Induced Toxicity on Hematological and Hepatic Parameters in Wistar Rats

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nitrobluetetrazolium; PBS, phosphatebuffer saline; SOD, superoxide dismutase; TCA, trichloroaceticacid; Tris, 1,1,1-(trishydroxymethyl) aminomethane

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Introduction

The liver is considered one of the most important organ in the body it plays a central role in the regulation of various physiological processes [1]. It is the center of metabolism of nutrients such as carbo-

as one of the medicinal herbs with the highest antioxidant activity [7]. Pelargonium graveolens L' Herit is an aromatic and hairy herbaceous shrub, up to 1m high. Leaves are prickly and carved; flowers are small, usually pink. P. graveolens (geranium) is native to South Africa (Comoros Islands) and it is widely cultivated in Russia, Egypt, Tunisia Algeria, Morocco, Congo, Japan, Central America and Europe (Spain, Italy, France). [8] Essential oils are natural mixtures of terpenes, mainly monoterpenes and sesquiterpenes, which have been increasingly used in complementary therapies because essential oils are usually rich sources of phytochemical mixtures [9]. Essential oils are a folk medicine and recently their use has expanded worldwide to include therapy against various kinds of inflammatory diseases. [10, 11]. Natural products have been increas-

mixture (streptomycin, penicillin) and trypan blue solution were purchased from Lonza(Cologne Gmbh, Germany)., 1,1-Diphenyl-2-picrylhydrazyl (DPPH), Ascorbic acid, Folin-Ciocalteus's phenol reagent, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT), Nitrobluetetrazolium (NBT), Trichloroaceticacid (TCA), Tris,1,1,1-(trishydroxymethyl) aminomethane, Dimethylsulfoxide (DMSO), Methionine, Ethylenediamine Tetraacetic Acid (EDTA), Riboflavin were purchased from Sigma Chemicals Co. (St. Louis, MO, USA). Additionally, other chemicals including solvents such as methanol, hexane and ethanol were used.

Plant material

The aerial parts of *Pelargonium graveolens* were collected during October and November 2016 from the region of SidiAich, Gafsa,

in acute dose 900 mg/kg (1/5 DL50 of rats). (EOP + A) group was made up of rats pre-treated with essential oil of Pelargonium graveolens for 42days, and then given acetaminophen for 4 days. EOP group consisted of rats given orally the essential oil of Pelargonium graveolens(65 mg/Kg).

At the end of the experimental period, the rats in each group were rapidly sacrificed by decapitation in order to minimize the handling stress. Blood serum was obtained by centrifugation (1500 x g, 15 min, and 4 C). Liver and kidney were removed, cleaned of fat, weighed and stored at 80°C until use.

Tissue homogenate preparation

0.5g of the organ was homogenized in 1 mL of tris buffer solution (TBS) using an Ultra-Turax Homogenizer. The extract was then cen-

albumin (BSA) as standard.

Hepatic histology

Liver slices were fixed and included in paraffin. 6 m thick tissue sections were prepared and colored with hematoxyline - eosine. The tissue preparations were observed under an optical microscope (AC 85V-265V). [21].

Gas chromatography/mass spectrometry (GC–MS) analysis

The analysis of the essential oils of Pelargonium graveolens was performed on a GC–MS HP model 5975B inert MSD (Agilent Technologies, J&W Scientific Products, Palo Alto, CA, USA), equipped

with an Agilent Technologies capillary DB-5MS column (30 m length; 0.25 mm i.d.; 0.25 mm film thickness), and coupled to a mass selective detector (MSD5975B, ionization voltage 70 eV; all Agilent,

the mixture was kept under constant gentle agitation for 1h. Absorbance was read at 765 nm using a spectrophotometer. Gallic acid was used as standard phenol with concentration (0-0.3 mg/mL). All the experiments were performed in triplicate and the results were calculated as gallic acid equivalent (GAE) from a calibration curve of gallic acid standard solution expressed as mg of gallic acid per 100 µL of essential oil.

Statistical Analysis

Statistical analyses were performed using a software program (SPSS 18 for windows). The comparisons between groups were performed using one-way ANOVA followed by a Tukey post hoc test. $p< 0.05$ was considered statistically significant. The results are presented in the form of mean ± standard error of the mean

showing normal hepatic architecture; (B): Paracetamol-treated group showing significant sinusoids congestion, ballooning of hepatocytes, as well as enlargement of nuclei and lymphocytic infiltration in the portal triads and sinusoids; (C): EOP treated rats show normal structure of liver. (D): Paracetamol + EOP showing marked improvement in the section structure of liver.

N°	TRB	Compound	KIa	Composi-tion
29	25,745	α-Muurolol	1755	0,18%
30	25,84	α-Cadinol	1745	0,22%
31	26,02	Geranylpentanoate	1766	0,93%
32	26,12	(E)-Citronellyltiglate	1790	0,3%
33	26,43	Unidentified	1800	0,5%
34	26,73	Cadalene	1865	0,33%
35	28,03	cis-Citronellyltiglate	1890	0,6%
36	28,19	Geranyltiglate	1900	3,99%
37	28,17	Geranyl ester	1910	2,72%

Table 1: *Composition of the essential oil of Pelargonium graveolens.*

Phytochemical studies

ALT	87.33 ± 10.41	182.57 ± 38.27*	84 ± 8.89+	108.67 ± 16.17+
Glycaemia	33.78 ± 2.34	48.67 ± 1.15*	32.67 ± 4.51+	36.78 ± 2.09+
Triglycerides	4.87 ± 0.97	8.03 ± 2.08*	4.83 ± 1.82	5.73 ± 1.33+
Cholesterol	62.67 ± 3.21	50.67 ± 13.8	60± 2.65	60.33 ± 16.17

Table 2: *Effect of Paracetamol and/or EOP on LDH (U/L), ALP (U/L), AST (U/L), ALT (U/L), Glycaemia (µmoles/L), Cholesterol(mmoles/L) and Triglycerides (g/L) levels in serum.*

Values are the mean of 9 measurements ± SD; * p≤0.05: compared to control group (C); + p≤0.05: compared to Paracetamol-treated group (Paracetamol).

Treatment	C	P	EOP	P+EOP
WBC	8.89 ± 1.12	5.9 ± 2.41**	8.25 ± 0.49+	7.6 ± 0.85++
RBC	10.32 ± 0.41	8.35± 0.27*	10.06 ± 0.33+ +	9.09 ± 0.55++

Total polyphenols

moglobin concentration (Hb), hematocrit (HCT), while there is no change of mean corpuscular hemoglobin concentration (MCHC) and mean cell volume (MCV) in Paracetamol-treated rats. The administration of Paracetamol-treated rats with EPG for 6 weeks protected against the alteration of WBC and Pl while the HCT did not seem to be significantly different of Paracetamol-treated group. The treatment of rats with essential oil *Pelargonium graveolens* alone did not cause any significant alteration in haematological parameters.

SOD	1.81 ± 0.3	0.84 ± 0.12*	1.78 ± 0.04+	1.33 ± 0.19+
GPx	15.52 ± 1.01	10.18 ± 0.62*	14.43 ± 2.7+	13.97 ± 0.87+
CAT	11.09 ± 0.75	5.67 ± 0.72*	10.28 ± 1.71+	9.74 ± 1.7+

Table 5: *Effect of Paracetamol and/or EOP on TBARS level and activities of SOD, GPx and CAT in liver tissue.*

Values are the mean of 6 measurements ± SD; Values are the mean of 8 measurements ± SD; * p≤0.05: compared to control group (C); + p≤0.05: compared to Paracetamol-treated group (Paracetamol); TBARS: Lipid peroxidation level (nmoles MDA/mg proteins); SOD:

non-volatiles [25]. Upon GC/MS analysis, the EOP was found to contain 37 constituents eluted from 8 to 30 min, accounting for 96.4% of the essential oil were identified (Table 1). All the volatiles were monoterpenes, sesquiterpenes and diterpenes, both hydro-

from monoterpenes, flavonoids, and phenols. [23] Pelargonium-species are the most popular fruits containing essential oils, citric acid, ascorbic acid, carotenoids, and mineral. These substances prevent damage to cell membrane and other structures by neutralizing free radicals [24] Then, the phenolic acids and flavonoids have been proven to be able to (1) liberate hydrogen proton from their hydroxyl group, (2) scavenge free radicals; and (3) prevent cells from oxidative damage.

Moreover, Pelargonium oil generally contains over 90% of monoterpenes, about 6% of oxygenated compounds and less than 1% of

These results are in agreement with those reported in study of Džamić [31] which showed that the essential oils of Pelargonium graveolens had much lower antioxidant activity resulting in DPPH inhibition percentages of 25.19%, while BHT yielded activity reaching 85.42%. Comparing this Pelargonium graveolens oil activity with other DPPH scavenging activity of essential oil Pelargonium graveolens from Serbia and Egypt respectively, we found that IC50 of EOP than in essential oil (IC50 = 0.802 µg/Ml, IC50 = 0.468µg/mL). However, the IC50 of EOP is higher than in essential oil of Pelargonium from Spain (IC50 = 1.80 mg/mL) [32]. Therefore, the

antiradical scavenging activity of the oil might be attributed to the replacement of hydroxyl groups in the aromatic ring systems of the phenolic compounds as a result of their hydrogen donating ability and thus stopping the chain reaction of lipid oxidation at the initial

Paracetamol hepatotoxicity was evidenced also by disorder in the blood profile. In fact, in blood, the administration of acetaminophen induced a significant decrease of platelet leukocytes, the erythrocyte count hemoglobin concentration (Hb), and hematocrit

agreement with those reached by El-Sayed et al. [37]. They found that the administration of acetaminophen aspirin at a high dose for 3 days in rats resulted in significant elevation of total cholesterol, glycaemia and aspartate transaminase activity. Such high dose (850 mg/kg) of aspirin has been reported to cause also damage in other organs; Also, our results are similar to those reported in the study of Zhang et al [38] which proved that analgesic such acetaminophen, may alter the function of theliver's, causing elevation of serum aspartate as well as alanineaminotransferases and necrosis of hepatic cell.

is a hemeprotein found in peroxisomes of eukaryotic cells that catalyses the conversion of hydrogen peroxide to water and oxygen. [45] GPx plays a critical role in maintaining balance in the redox status of animals under acute oxidative stress and protect against chemically induced oxidative destruction of lipid and proteins. Indeed, our study showed that the administration of paracetamol induced significant increase of lipid peroxidation (TBARS) in the liver. [46] The increase of TBARS was confirmed by the peroxidative effect of aspirin. Lipid peroxidation has been postulated to be

the destructive process in liver injury due to paracetamol administration. The increase in MDA level of liver suggests enhanced lipid peroxidation leading to tissue damage and failure of antioxidant de-

liver damage when compared with the APAP-treated rat. The liver histopathological analysis in groups pre-treated with essential oil of Pelargonium showed hepatocytes preserved, infiltrated cells

data were confirmed by Ben Slima [51]. et al indicating that the administration of essential prevented hepatic alterations.

In general, the hepatoprotective activity of plants can be considered as an expression of the functional improvement of hepatocytes that results from accelerated cellular regeneration Therefore, EOP that has been employed as a protective treatment of liver damage by its antioxidant properties deriving from the phenolic nature of Pelargonium graveolens. In this context, our results showed that pretreatment with EOP was able to reduce levels of AST, ALT, ALP, glucose, cholesterol and triglycerides at all doses employed, improving

ministration [56]. The mechanism of hepatoprotection by EOP of leaves is due to their antioxidant potential. This suggests that leaf extracts can reduce ROS that may lessen the oxidative damage to the hepatocytes and improve the activities of the liver antioxidant enzymes, thus protecting the liver from paracetamol induced damage. Also, the possible mechanism could be by the stimulation of hepatic regeneration through an improved synthesis of protein or accelerated detoxification and excretion.

Mativandlela [57] demonstrated the hepatoprotective effect juice of Pelargonium against paracetamol induced liver injury in rats. Due to the fact that lemon contains a variety of bioactive ingredi-

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