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Investigation of Chemical Composition of Oriental plane (*Platanus orientalis* L.) Hydrosol and its Effects on Tissue Damage Markers and Plasma Enzymes in Short-term Consumption

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Abstract

Oriental plane hydrosol (distillate), as a remedy for weight gain and asthma treatment is popular in ethnomedicine. Phytochemicals of medicinal plants could have side effects or serious damages. In this study, the oriental plane hydrosol was prepared by steam distillation. Also, tree oriental plane hydrosol samples from different companies were purchased from herbal market to compare the constituents. The phytochemicals in hexane and chloroform extracts of the hydrosols were identified by GC-MS analysis. In order to investigate subacute toxicity, the hydrosol was given to groups of 6 of male mice at doses of 10, 50, 100, 300 or 500 µl/ mouse/ twice a day by gavage for 14 consecutive days (subacute toxicity) or just for one day (acute toxicity). Serologic and pathologic samples were prepared. Chloroform extracts contained mostly (*Z*) -3-hexenol, thymol, carvacrol, camphor and the main constituents of hexane extracts include decane, dodecane and hexadecane. The results showed lack of serologic toxicity in subacute consumption of the hydrosol. In acute toxicity study, the levels of ALT, LDH, and BUN increased significantly. Other enzymes did not change significantly in compare to the control group. No significant pathologic damage was seen in heart or lung tissues, but the liver and kidney showed mild inflammation in acute toxicity study and inflammation in subacute toxicity studies. Determination of compounds which are responsible for the observed effects and especially safety of this hydrosol consumption for the longer periods can prevent side effects or possible toxicities.

Keywords: Aromatic Water, Oriental Plane Distillate, *Platanus orientalis*, Toxicity.

1. Introduction

Platanus orientalis L. (Platanaceae) with the common names oriental plane, plantain or the Old World sycamore is a large tree, growing to 30 m or more. The tree has longevity and spreading crown which is deciduous in autumn. And although they are drought tolerant, they usually grow along riverine settings and wetlands. Plantain leaves are hairy and felt at a young age and their hairs gradually fade. These claw leaves with 5-7 lobes and each lobe has large spaced and pointed sinus teeth 25 to 40 cm in size, with a gut-shaped leaf tail that hides the bud at its base in the snout. Its inflorescence is spherical and has a base and is placed on a tall pike and hung (1, 2). The fruit is spherical and up to 2 cm in diameter. Its name is Chenar in Persian. The tree was known as platane in ancient Greek literature. In Asian countries it is called chinar. It was mentioned in Traditional Persian Medicine with the names of Johar, Sanar, Eitham, Delb, Chanal, Chenar, Ras and Delba. Cold and dry na-

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ture is considered for the fruit and bark of the tree. In Iranian traditional medicine and folk medicine, the poultice from its leaves is also applied topically to treat the conjunctiva of the eye, to prevent watery eyes, to remove phlegm and inflammation of the knee and other organs and hot swellings, skin blemishes or burns, to treat infectious wounds and varicose veins (3, 4). Its formulations is traditionally used in Eastern Europe and the Middle East to treat various ailments, including wound healing, analgesic and anti-inflammatory (1, 2, 5), toothache (6, 7) conjunctivitis, skin problems (1) and antidote to snake venom (2). Plantain leaf decoction is also used orally to treat simple diarrhea and dysentery. Plantain distillate (hydrosol, aromatic water) is used orally to gain weight. Although the plant pollen has been reported in many sources as a pulmonary allergen (8, 9) but, the leaf hydrosol is orally ingested as a treatment for asthma and shortness of breath and strengthens the heart and stomach in folk medicine, especially in Fars province (3, 10). Recently, some studies have reported biological activities and phytochemicals from fruits and buds of this plant (1, 11).

So far, with the exception of a few preliminary studies, including the study of anti-inflammatory, anti-oxidant and analgesic effects of plant leaves (2, 5, 12-14), few studies have been done on the compounds or biological effects, as well as the safety of consumption and possible side effects of oriental plane hydrosol.

The present *in vivo* study, designed to study phytochemicals and the possible toxicity of oriental plane leaf hydrosol, enzymatic and pathological changes in the body tissues to determine the side effects that may occur following short-term oral consumption of the plant leaf.

2. Materials and methods

2.1. Phytochemical investigation

The leaves of the oriental plane were collected from Fars province between July and September 2015. The plant was authenticated and a herbarium sample (No. 2638) was kept in the Herbarium museum, School of pharmacy, Shiraz University of Medical Sciences. The leaves were dried in the shade and its powder was used to prepare hydrosol by distillation method in clevenger apparatus. In addition, three samples of oriental plane hydrosol (Aragh chenar) were purchased from different companies in Fars province, Iran. The volatile compounds of hydrosol (distillate) were isolated from using n-hexane solvent and chloroform by liquid-liquid extraction method and after concentration with a rotary evaporator the compounds were identified by Gas Chromatography-Mass spectroscopy (15-17).

Gas Chromatography–Mass Spectrometry (Agilent Technologies 7890 Gas Chromatograph) for analysis of the chemical compositions equipped with HP-5MS capillary column (Agilent Technologies 19091 S-433., 30×0.25 mm inner diameter) and Mass detector (Agilent Technologies model 5975 C in EI mode at 70 eV). The thermal ramp rates were increasing temperature from 60 °C to 220 °C (rate of 5 °C/min) and held at 220 °C for 10 minutes. The interface temperature and mass range was set up to 280 °C and 30 to 600 m/z, respectively. Identification of the volatile compounds was based on NIST (National Institute of Standards and Technology) or Wiley libraries, pervious articles, and by comparing the retention times and mass spectra of the reference compounds (15-17).

2.2 Animal study for acute and subacute toxicity

For the study of acute toxicity, groups of 6 of male mice received the oriental plane hydrosol at doses of 10, 50, 100, 300, or 500 µl/mouse/ twice a day (just for one day) and 14 days after the experiment serologic and pathologic samples were prepared.

In order to investigate acute toxicity, the oriental plane hydrosol was given to groups of 6 of male mice at doses of 10, 50, 100, 300 or 500 µl/ mouse/ twice a day by gavage for 14 consecutive days. One group received only normal saline as control group. Twenty four hours after the last dose of the hydrosol, pathological lesions of liver, kidney, lung, and heart tissues, as well as plasma levels of tissue damage markers was measured. During these 14 days, mice were examined for behavior, nutrition, body weight, and mortality. Blood (1 mL) was taken from the abdominal vein and carefully transferred to a test tube containing anticoagulant. Plasma was then prepared by cen-

trifugation of the samples. The obtained plasma was stored at -20 ° C for further experiments.

For pathological study, after separating the samples and washing with 0.9% sodium chloride, they were fixed with 10% formalin. The paraffin blocks, and then sections with a thickness of 5 microns were prepared and stained by hematoxylin and eosin.

To analyze the plasma levels of enzymes including AST (aspartate aminotransferase), ALT (Alanine Aminotransferase), CK-MB (Creatine kinase-MB), Creatinin, BUN (Blood urea nitrogen), LDH (lactate dehydrogenase) was performed by the commercial kit of Pars Azmoun Company (Iran) and an autoanalyzer (18, 19).

2.3. Statistical analysis

Data were presented as mean±standard deviation from 6 samples and ANOVA with Tukey's test was used for statistical analysis. $P<0.05$ was considered as a statistically significant difference.

3. Results and discussion

3.1. Result of the phytochemical study

The results of GC-MS analysis of prepared hydrosol in the laboratory and the purchased hydrosols are shown in Table 1. The major compounds in the essential oil of the oriental plane leaves were hydrocarbons such as decane, dodecane. As expected, the compounds in the chloroform and hexane extracts of the hydrosol were different.

In the study of 4 n-hexane extracts of oriental plane hydrsols, the identified major compounds, were mostly hydrocarbons including decane, dodecane, undecane. Also compounds that are repeated in hexane extracts include ethylcyclohexane, cis-1,2-dimethylcyclohexane, Decane, Dodecane.

In the chloroform extracts the major compounds were (*Z*) -3-hexenol; 2-Butanone, 3-phenyl-; Benzaldehyde; Acetophenone; thymol; *alpha*-Terpinene; carvacrol; camphor; *beta*-eudesmol; carvone; piperitenone; elemicin. Also the compounds repeated in the chloroform extracts include carvacrol, (*Z*) -3-hexenol, pulegone, thymol and 4-Vinylguaiacol. The compounds in chloroform extract were mostly polar and semi-polar compounds such as monoterpenes, sesquiterpenes, alcohols, acids and ketones.

The compounds in hexane extract were mostly non-polar compounds such as hydrocarbons.

Some identified compounds of the essential oil was not detected in the hydrosol extracts.

Table 1. The phytochemical constituents of essential oil and hydrosol of oriental plane leaf. Hexane and chloroform extracts of the hydrosol prepared in the laboratory and the hydrosols purchased from 3 different companies were analyzed by GC-MS analysis.

		Hexane extract of oriental plane hydrosol				Chloroform extract of oriental plane hydrosol			
Compound	Essential oil	Laboratory prepared hydrosol	Company 1	Company 2	Company 3	Laboratory prepared hydrosol	Company 1	Company 2	Company 3
Acetophenone	2.63%		3.11%						
Acetosol			1.89%	1.02%					
3-Allylguaiacol				15.57%	1.68%				
Benzalaceton	3.03%								
Benzaldehyde	4.13%	6.41%							
Benzeneethanol			1.77%	0.63%					
Benzene, 1,3-dimethyl-									0.65%
Benzenemethanol		2.73%		1.93%					

Continued Table 1.

		Hexane extract of oriental plane hydrosol				Chloroform extract of oriental plane hydrosol			
Compound	Essential oil	Laboratory prepared hydrosol	Company 1	Company 2	Company 3	Laboratory prepared hydrosol	Company 1	Company 2	Company 3
Benzenemethanol,.*alpha*.-methyl-		0.67%							
Benzenemethanol, .*alpha*.-methyl-, (S)-			3.42%						
Benzenepropanoic acid		0.27%							
Ethylbenzene								1.95%	0.38%
2,3-Dihydrobenzofuran			1.16%						
Benzoic acid				0.59%					
alpha.-Bisabolol			1.10%						
L-Borneol			1.83%						
2-Butanone, 3-phenyl-		7.29%							
Camphor				0.35%					
(-)-Camphor			20.84%						
Carvacrol		0.50%	6.22%	4.89%	2.49%				
(-)-Carvone			4.21%						
1,8-Cineole			1.05%						
beta.-Citronellol			1.10%						
E-Citral		2.51%							
Z-Citral		1.60%							
Clovane diol			1.31%						
Coumaran				2.16%					
Coumarin			0.48%						
Cumic acid			3.78%	3.70%					
beta-Cyclocitral	0.60%	0.75%							
(*Z*)-Cyclodecene	0.81%								
1,2-Cyclohexanediol				0.34%					
Ethylcyclohexane						0.53%	0.34%	0.33%	0.35%
cis-1,2-Dimethylcyclohexane							1.75%	1.25%	1.80%
Propylcyclopentane	0.68%					0.84%			
Decane	36.04%					51.15%	4.99%	15.10%	5.12%
Dihydroactinidiolide		2.92%	1.64%						

Continued Table 1.

		Hexane extract of oriental plane hydrosol				Chloroform extract of oriental plane hydrosol			
Compound	Essential oil	Laboratory prepared hydrosol	Company 1	Company 2	Company 3	Laboratory prepared hydrosol	Company 1	Company 2	Company 3
Dihydroactinolide				0.42%					
cis-Dihydrocarvone			1.85%						
trans-Dihydrocarvone				0.60%					
Dihydrocarveol			1.82%						
Dihydrodehydro-β-ionone	0.56%	1.47%							
Dillapiole				4.44%					
3,8-Dimethyldecane						0.99%			
Docosane								0.51%	
Dodecane	10.16%					18.38%	22.18%	17.06%	21.13%
Eicosane								0.93%	0.51%
Elemicin					6.02%				
Estragole				0.51%					
4-Ethyloctane	0.83%					1.72%			
alpha.-Eudesmol	1.11%	1.59%							
beta.-Eudesmol	1.83%	1.88%	6.96%						
Eugenol			1.62%						
Farnesylacetone	1.45%								
2-Furanmethanol				0.50%					
Furfural		0.21%							
Geranyl acetone	1.91%	1.33%							
beta-Gurjunene	1.43%	0.77%							
(*E,E*)-2,4-Heptadienal	1.38%	3.82%							
6-Methyl-3,5-heptadien-2-one		0.67%							
Heptanal		0.24%							
(*Z*)-4-Heptenal		0.39%							
Hexadecane	1.05%					1.93%	1.69%	2.80%	1.89%
Hexadecanoic acid	1.49%								
Hexahydrofarnesyl acetone	2.44%								
Hexanedioic acid, bis(2-ethylhexyl) ester							0.93%		1.01%

Continued Table 1.

Compound	Essential oil	Hexane extract of oriental plane hydrosol: Laboratory prepared hydrosol	Company 1	Company 2	Company 3	Chloroform extract of oriental plane hydrosol: Laboratory prepared hydrosol	Company 1	Company 2	Company 3
Hexanoic acid				0.93%					
1-Hexanol	1.09%	1.09%							
(*E*)-2-Hexenal	3.77%								
2-Hexen-1-ol		0.80%							
(*Z*)-3-hexenol		12.94%	0.46%	0.55%					
3-Hexenyl-benzoate		1.16%							
cis-3-Hexenyl benzoate	2.60%								
2-hydroxycyclo-hexanone				3.47%					
p-hydroxystyrene		0.36%							
(*E*)-beta-Ionene	1.59%								
3-Methylcatechol					2.85%				
methylethylmaleimide		0.58%							
3-Methylnonane	2.36%					4.34%		0.87%	
5-Methylnonane						2.67%		0.52%	
5-Methylundecane						0.86%			
Myristicin				0.84%					
Nonadecane							0.51%		
trans,trans,trans-Nona-2,4,6-trienal		0.25%							
Octadecane						0.53%	0.98%	1.62%	0.98%
1-Octene, 3,7-dimethyl	0.89%								
4-Methyl-2-pentenolide			0.69%	0.91%					
Dibutyl phthalate			0.70%						
Piperitenone					7.35%				
Phenol		1.30%							
Phenylethyl Alcohol				4.70%					
trans-Phytol	2.10%								
Pulegone			0.34%	1.20%	2.55%				
Safranal		0.36%							
Tridecane							14.71%	9.51%	14.32%
alpha-Terpinene				2.62%					
alpha-Terpineol			0.93%	0.42%					
Terpinen-4-ol		0.39%							

Continued Table 1.

Compound	Essential oil	Hexane extract of oriental plane hydrosol				Chloroform extract of oriental plane hydrosol			
		Laboratory prepared hydrosol	Company 1	Company 2	Company 3	Laboratory prepared hydrosol	Company 1	Company 2	Company 3
alpha.-Terpinolene			0.79%						
Tetradecane	2.89%					5.70%	3.03%	3.84%	3.07%
Thymol		0.65%	4.95%	28.01%	46.83%				
Undecane							11.35%	7.13%	11.16%
4-Vinylguaiacol		0.47%	0.44%	3.30%					

It is also possible that these compounds dose not enter the hydrosol due to their insolubility in water. On the other hand, the volatile compounds has different solubility in hexane and chloroform. Although in most previous reports on distillates, hexane has been used to extract compounds in distillates (hydrosol), the results of the present study show that the use of semi-polar or polar solvents is also necessary to extract and identify compounds in distillates.

The low percentage of some compounds such as thymol, carvacrol and camphor in laboratory prepared hydrosol and their high percentage in purchased hydrosol, shows that these compounds might not originated from the oriental plane leaves. Two factors can play a role in the presence of these compounds in purchased hydrosols: 1- the contamination of the device used in the hydro industrial hydrodistillation system. In other words, in the previous days, hydrosols of other plants containing compounds such as thymol and carvacrol were prepared but the devices were not washed well. 2-It is possible that some companies add some essential oils or herbs such as thyme to the hydrosols in order to improve their taste or essence.

A few studies can be found on the essential oil of the oriental plane leaf. Only one report was found on oriental plane hydrosol, the compounds in the hydrosol were in accordance with the report by Hamedi et al (15). Another study was found on the oriental plane leaf infusion that reported benzaldehyde and fatty acids as the major component of the leaf infusion (13). Some of the identified compounds were reported from other plant species for example, (Z) -3-hexenol has been reported as a leaf alcohol from Farfugium japonicum and it has also been mentioned as an insect repellent (20). Among the compounds observed in this study is benzaldehyde, which has been reported previously in cabbage species as well as in plants from Anthurium and ، Arum species, some plants of Lamiaceae family as well as bitter almonds (21, 22). Heptanal has been previously reported in lemon and orange essential oils (23).

Furan, 2-methyl-5- (1,1,5-trimethyl-5-hexenyl) – was detected in Zygophyllum album (24) and geranyl acetone as volatile compounds in tomato species (25). Benzenemethanol was found in Bunium persicum (26) and benzoic acid in Zizyphus mauritiana (27). Pyrocatechol is derived from the rhubarb species as well as in reports of destructive distillation of plants containing catechins (28).

3.2. Acute and subacute toxicity

The result of the *in vivo* study of acute and subacute toxicity is shown in Figures 1-3.

The results of the present study showed no toxicity in subacute consumption of oriental plane leaf hydrosol in male mice (Figure 2). On the other hand, acute studies have shown that levels of liver enzymes such as ALT and LDH have increased. Also, markers of kidney tissue damage such as BUN has increased. Other enzymes had no significant compared to the control group (Figure 1). It is thought that at first, when a substance enters the body, the body responds to the substance and the plasma level of the enzymes increases, or these

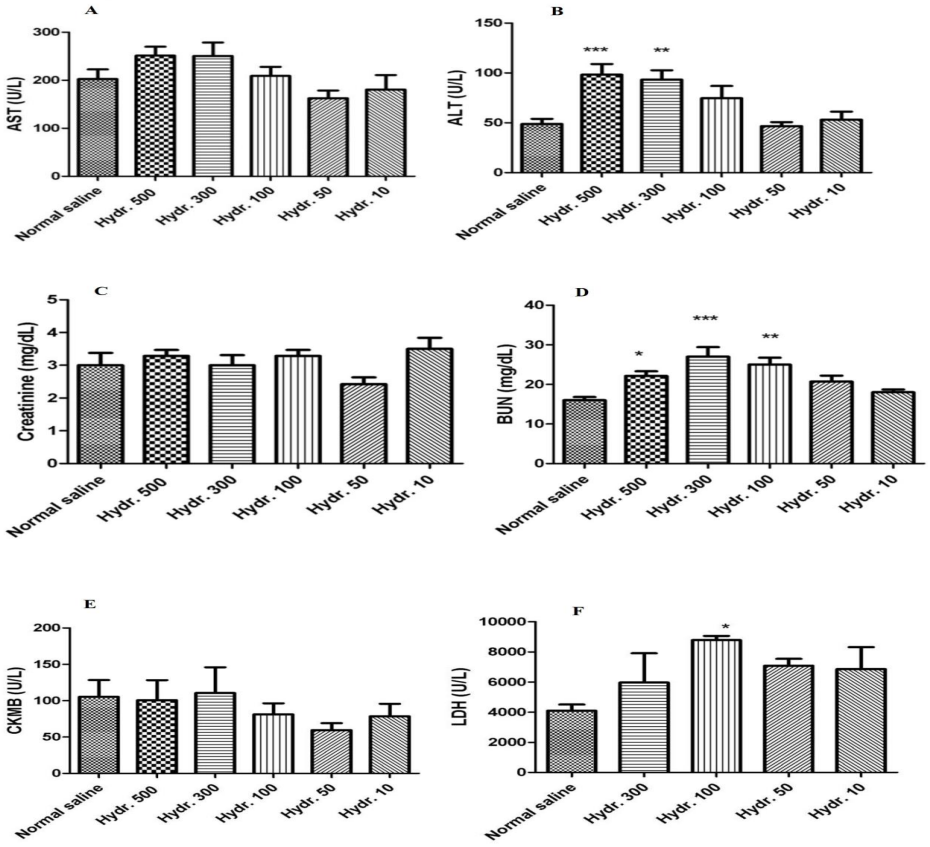

Figure 1. Biomarker plasma levels in acute toxicity test. A: AST; B: ALT; C: creatinine; D: BUN; E: CKMB; F: LDH in groups of 6 mice received hydrosol of P.s orientalis leaf (hydr) at doses of 10, 50, 100, 300 or 500 µl/ kg of body weight. Data are shown as Mean±SEM. Control group received normal saline.
*Significantly different with control group (P<0/05)
**Significantly different with control group (P<0/01)
***Significantly different with control group (P<0/001)

changes may be due to sudden damage to these organs in the short term. No significant changes were observed in the level of markers of tissue damage such as heart in the acute or subacute studies.

In subacute studies, no significant increase was observed in any of the serum indices of tissue damage compared to the control group. This issue may be related to the adaptation of the organs and regeneration of tissues damaged by the compounds in the hydrosol. In other words, over a longer period of time, tissues such as the liver adapt to new conditions with their cell defense mechanisms or effectively detoxify some substances.

Although the present study shows no specific side effects on tissues such as liver, kidney and heart, it should be noted that in some people, (especially in chronic consumption) cellular defense mechanisms in the liver or other tissues may not work well (for example due to alcoholism, liver disease and etc.) (29). Therefore, these people may be more sensitive to the consumption of the hydrosol. Also, in tissues such as the kidneys where cellular defense systems are weaker (for example, than in liver tissue), chronic damage may not be compensated and may eventually lead to organ failure.

In the study, the animals were monitored for 14 consecutive days after receiving the dose and no deaths due to oriental plane hydrosol consumption were observed in the animals. These animals showed no signs of toxicity during the study period. Overall appearance, body care, posture, gait, behavior, and other observational parameters were normal. During the study, the body weight of the animals did not differ significantly between days 1, 7 and 14 of the study.

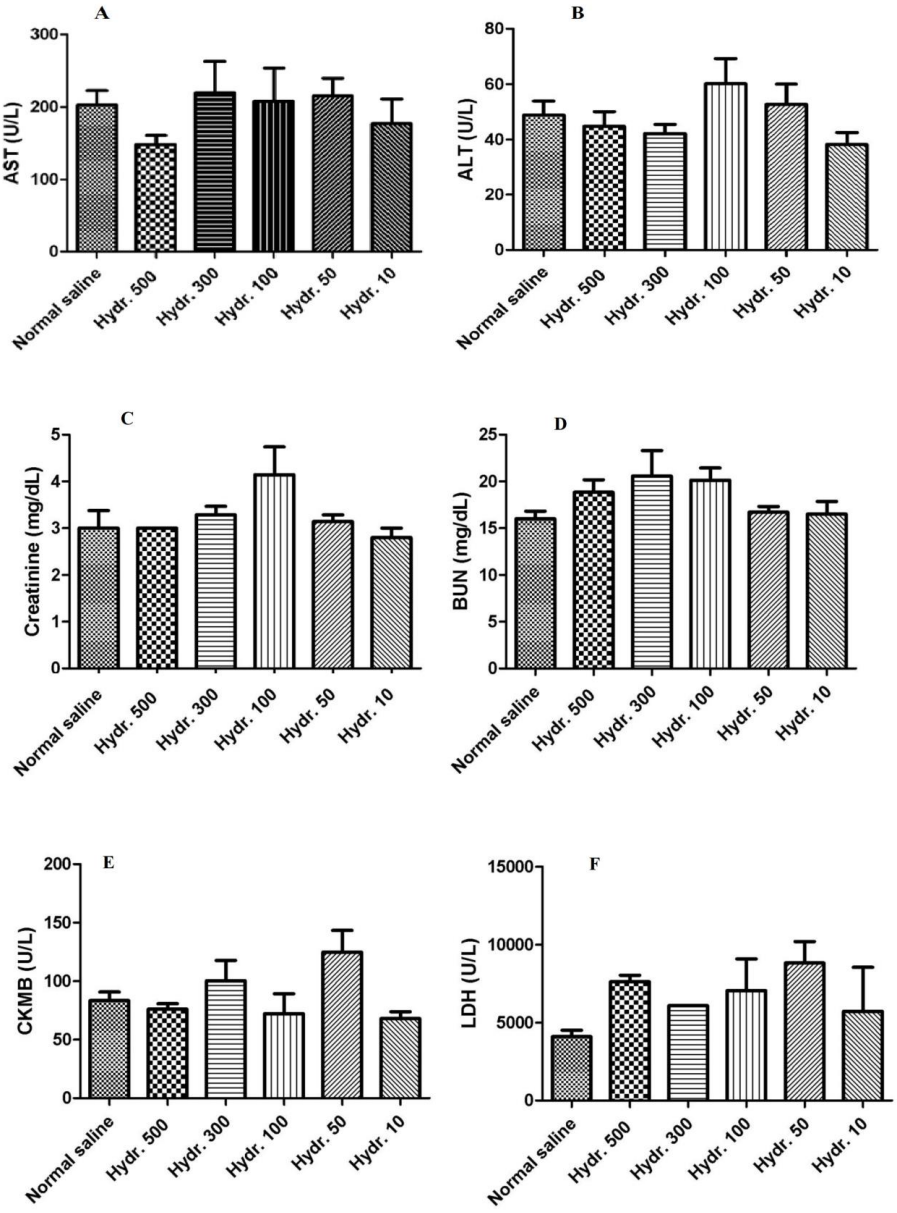

Figure 2. Biomarker plasma levels in subacute toxicity test. A: AST; B: ALT; C: creatinine; D: BUN; E: CKMB; F: LDH in groups of 6 mice received hydrosol of P. orientalis leaf (hydr) at doses of 10, 50, 100, 300 or 500 µl/ kg of body weight. Data are shown as Mean±SEM. Control group received normal saline.

Pathological examination at the end of this study for acute toxicity test, did not show any specific pathological damage in lung and heart organs compared to the control group, but in the study of subacute toxicity, liver and kidney had slight inflammation (Figure 3).

This inflammation and mild tissue damage in the present study may be related to the presence of benzaldehyde in the oriental plane hydrosol. The toxicity of aldehyde compounds as active species and reactants have been reported previously. These substances may cause cytotoxicity and organ damages. It is clear that identification of the oriental plane hydrosol substances which are responsible for cell damage will require more detailed study in the future.

4. Conclusion

T (*Z*) -3-hexenol, thymol, carvacrol, camphor, decane, dodecane and hexadecane were

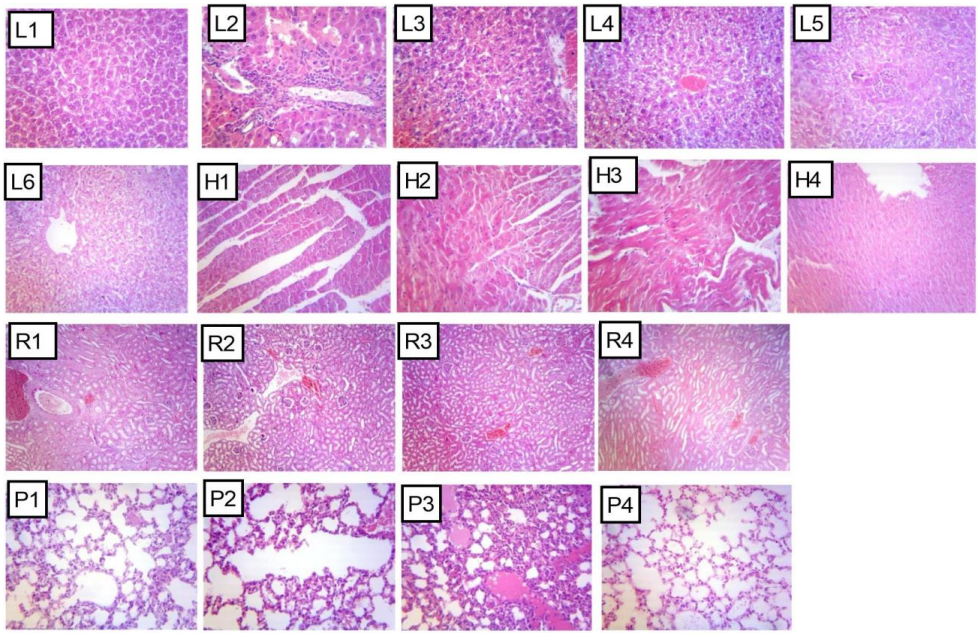

Figure 3. Histopathologic study of liver (L1-L5), Heart (H1-H4), kidney (R1-R4) and lung (P1-P4) in mice received hydrosol of P. orientalis leaf or normal saline.
L1: Control group with no pathological changes. L2: Portal inflammation in liver, L3: Inflammatory cell infiltration in liver, L4: fatty tissue changes in liver (in acute toxicity group), L5: Focal necrosis and L6: Ballooning degeneration in liver of subacute toxicity group (subacute toxicity group). No histopathological changes was observed in the heart of control group (H1) or hydrosol groups (H2-H4). Mild vascular congestion was observed in kidney of mice in control group (R1) and mice received different doses of hydrosol (R2, R3, R4) in both acute and subs cute toxicity studies.
P1: lung tissue in control group with no pathological changes. P2 and P4: lung section with no pathological change was observed in subacute toxicity group. P3: Intra-alveolar edema and hemorrhage was observed in mice received 500 µl/ kg/one day (acute toxicity study).

identified as major constituents of the oriental plane hydrosol.

Lack of serologic toxicity was observed in subacute consumption of the hydrosol but the levels of ALT, LDH, and BUN increased significantly in acute consumption. No significant pathologic damage was seen in heart or lung tissues, but the liver and kidney showed mild inflammation in acute toxicity study and inflammation in subacute toxicity studies. Determination of compounds which are responsible for the observed effects and especially safety of this hydrosol consumption for the longer periods can prevent possible side effects.

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Conflict of Interest

None declared.

References

1. Thai QD, Tchoumtchoua J, Makropoulou M, Boulaka A, Meligova AK, Mitsiou DJ, Mitakou S, Michel S, Halabalaki M, Alexis MN, Skaltsounis LA. Phytochemical study and biological evaluation of chemical constituents of Platanus orientalis and Platanus × acerifolia buds. *Phytochemistry.* 2016 Oct;130:170-81. doi: 10.1016/j.phytochem.2016.04.006. Epub 2016 May 11. PMID: 27179684.

2. Haider S, Nazreen S, Alam MM, Hamid H, Alam MS. Anti-inflammatory and anti-nociceptive activities of Platanus orientalis Linn. and its ulcerogenic risk evaluation. *J Ethnopharmacol.* 2012 Aug 30;143(1):236-40. doi: 10.1016/j.jep.2012.06.029. Epub 2012 Jul 6. PMID: 22771315.

3. Aghili M. Gharabadin Kabir (Republished

by Institute of Medical History, Islamic and Complementary Medicine). Iran University Of Medical Sciencess, Tehran, Iran. 2008.
4. Mahdizadeh S, Khaleghi Ghadiri M, Gorji A. Avicenna's Canon of Medicine: a review of analgesics and anti-inflammatory substances. *Avicenna J Phytomed.* 2015;5(3):182-202.
5. Torkan S, Mohajeri N, Khamesipour F. A comparison study of anti food allergy of plane tree leaves extract with the chemical drug therapy in affected dogs. *Marmara Pharm J*. 2016;20:86-91.
6. Tantry MA, Akbar S, Dar JA, Irtiza S, Galal A, Khuroo MA, et al. Acylated flavonol glycoside from Platanus orientalis. *Fitoterapia*. 2012;83(2):281-5.
7. Yang C-H, Yang Y, Liu J-H. Platachromone A–D: Cytotoxic 2-styrylchromones from the bark of Platanus× acerifolia (Aiton) Willd. *Phytochemistry Letters.* 2013;6(3):387-91.
8. Pazouki N, Sankian M, Nejadsattari T, Khavari-Nejad RA, Varasteh AR. Oriental plane pollen allergy: identification of allergens and cross-reactivity between relevant species. *Allergy Asthma Proc.* 2008 Nov-Dec;29(6):622-8. doi: 10.2500/aap.2008.29.3178. PMID: 19173789.
9. Pazouki N, Sankian M, Leung PT, Nejadsattari T, Khavari-Nejad RA, Varasteh AR. Identification of cyclophilin as a novel allergen from Platanus orientalis pollens by mass spectrometry. *J Biosci Bioeng.* 2009 Feb;107(2):215-7. doi: 10.1016/j.jbiosc.2008.10.016. PMID: 19217563.
10. Mirsadraee M, Tavakoli A, Ghorani V, Ghaffari S. Effects of Rosmarinus officinalis and Platanus orientalis extracts on asthmatic subjects resistant to routine treatments. *Avicenna J Phytomed*. 2018 Sep-Oct;8(5):399-407. PMID: 30345227; PMCID: PMC6190250.
11. Chatzigeorgiou S, Thai QD, Tchoumtchoua J, Tallas K, Tsakiri EN, Papassideri I, Halabalaki M, Skaltsounis AL, Trougakos IP. Isolation of natural products with anti-ageing activity from the fruits of Platanus orientalis. *Phytomedicine.* 2017 Sep 15;33:53-61. doi: 10.1016/j.phymed.2017.07.009. Epub 2017 Jul 31. PMID: 28887920.
12. SICAK Y, Eliuz EAE. Determination of the phytochemical profile, in vitro the antioxidant and antimicrobial activities of essential oil from Arbutus andrachne L. wood growing in Turkey. *Türkiye Ormancılık Dergisi*. 2019;20(1):57-61.
13. Dogan A, Anuk OO. Investigation of the phytochemical composition and antioxidant properties of chinar (Platanus orientalis L.) leaf infusion against ethanol-induced oxidative stress in rats. *Mol Biol Rep*. 2019 Jun;46(3):3049-3061. doi: 10.1007/s11033-019-04741-7. Epub 2019 Mar 12. PMID: 30864112.
14. Hajhashemi V, Ghannadi A, Mousavi S. Antinociceptive study of extracts of Platanus orientalis leaves in mice. *Res Pharm Sci.* 2011 Jul;6(2):123-8. PMID: 22224096; PMCID: PMC3249775.
15. Hamedi A, Pasdaran A, Zebarjad Z, Moein M. A Survey on Chemical Constituents and Indications of Aromatic Waters Soft Drinks (Hydrosols) Used in Persian Nutrition Culture and Folk Medicine for Neurological Disorders and Mental Health. *J Evid Based Complementary Altern Med.* 2017 Oct;22(4):744-752. doi: 10.1177/2156587217714145. Epub 2017 Jun 21. PMID: 28633539; PMCID: PMC5871290.
16. Hamedi A, Moheimani SM, Sakhteman A, Etemadfard H, Moein M. An Overview on Indications and Chemical Composition of Aromatic Waters (Hydrosols) as Functional Beverages in Persian Nutrition Culture and Folk Medicine for Hyperlipidemia and Cardiovascular Conditions. *J Evid Based Complementary Altern Med.* 2017 Oct;22(4):544-561. doi: 10.1177/2156587216686460. Epub 2017 Feb 9. PMID: 29228785; PMCID: PMC5871258.
17. Hamedi A, Afifi M, Etemadfard H. Investigating Chemical Composition and Indications of Hydrosol Soft Drinks (Aromatic Waters) Used in Persian Folk Medicine for Women's Hormonal and Reproductive Health Conditions. *J Evid Based Complementary Altern Med.* 2017 Oct;22(4):824-839. doi: 10.1177/2156587217717413.
18. Heidari R, Niknahad H, Sadeghi A, Mohammadi H, Ghanbarinejad V, Ommati MM, et al. Betaine treatment protects liver through regulating mitochondrial function and counteracting oxidative stress in acute and chronic animal models of hepatic injury. *Biomed Pharmacother.* 2018 Jul;103:75-86. doi: 10.1016/j.biopha.2018.04.010. Epub 2018 Apr 7. PMID: 29635131.
19. Hamedi A, Jamshidzadeh A, Dana M, Pasdaran A, Heidari R. Effects of the essential oil from Citrus aurantium flowers on liver health parameters in a laboratory animal model. *Feyz.*

2020;24(1):38-47
20. Hatanaka A, Sekiya J, Kajiwara T. Distribution of an enzyme system producing cis-3-hexenal and n-hexanal from linolenic and linoleic acids in some plants. *Phytochemistry.* 1978;17(5):869-72.
21. Tollsten L, Bergström G. Headspace volatiles of whole plants and macerated plant parts of Brassica and Sinapis. *Phytochemistry*. 1988;27(7):2073-7.
22. Remaud G, Debon AA, Martin Y-l, Martin GG, Martin GJ. Authentication of bitter almond oil and cinnamon oil: application of the SNIF-NMR method to benzaldehyde. *J Agric Food Chem*. 1997;45(10):4042-8.
23. Kula J, Sadowska H. One-pot synthesis of (E)-2-nonenal from castor oil. *J Am Oil Chem Soc*. 1993;70(6):643-4.
24. Tigrine-Kordjani N, Meklati BY, Chemat F. Contribution of microwave accelerated distillation in the extraction of the essential oil of Zygophyllum album L. *Phytochem Anal.* 2011 Jan-Feb;22(1):1-9. doi: 10.1002/pca.1236. Epub 2010 Sep 7. PMID: 20821807.
25. Tieman DM, Zeigler M, Schmelz EA, Taylor MG, Bliss P, Kirst M, Klee HJ. Identification of loci affecting flavour volatile emissions in tomato fruits. *J Exp Bot.* 2006;57(4):887-96. doi: 10.1093/jxb/erj074. Epub 2006 Feb 10. PMID: 16473892.
26. Pourmortazavi SM, Ghadiri M, Hajimirsadeghi SS. Supercritical fluid extraction of volatile components from Bunium persicum Boiss.(black cumin) and Mespilus germanica L.(medlar) seeds. *J Food Compost Anal*. 2005;18(5):439-46.
27. Memon A, Memon N, Luthria D, Pitafi A, Bhanger M. Phenolic compounds and seed oil composition of Ziziphus mauritiana L. fruit. *Polish J Food Nutr Sci.* 2012;62(1):15-21.
28. Öztürk M, Aydoğmuş-Öztürk F, Duru ME, Topçu G. Antioxidant activity of stem and root extracts of Rhubarb (Rheum ribes): An edible medicinal plant. *Food Chem.* 2007;103(2):623-30.
29. Kawase T, Kato S, Lieber CS. Lipid peroxidation and antioxidant defense systems in rat liver after chronic ethanol feeding. *Hepatology*. 1989 Nov;10(5):815-21. doi: 10.1002/hep.1840100511. PMID: 2807160.